

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

TAKEDA PHARMACEUTICALS U.S.A., INC.,

Plaintiff,

v.

AMNEAL PHARMACEUTICALS, LLC,

Defendant.

Civil Action No. 13-cv-493 (SLR)

THIRD AMENDED COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Takeda Pharmaceuticals U.S.A., Inc. (“Takeda”) files this Third Amended Complaint for patent infringement against Defendant Amneal Pharmaceuticals, LLC (“Amneal”) and, in support thereof, alleges as follows.

NATURE OF THE ACTION

1. This is an action for patent infringement under the Food and Drug and Patent Laws of the United States, U.S.C. Titles 21 and 35 respectively, arising from Amneal’s submission of an Abbreviated New Drug Application (“ANDA”) to the United States Food and Drug Administration (“FDA”), seeking approval to market commercially a generic version of the drug product COLCRYS® (colchicine, USP) prior to the expiration of United States Patent Nos. 7,619,004; 7,601,758; 7,820,681; 7,915,269; 7,964,647; 7,964,648; 7,981,938; 8,093,296; 8,093,297; 8,097,655; 8,415,395; 8,415, 396; 8,440,721; and 8,440,722 which cover, *inter alia* the use of the COLCRYS® to treat and prevent gout flares.

THE PARTIES

2. Takeda Pharmaceuticals U.S.A., Inc. (“Takeda”) is a Delaware corporation with its principal place of business at One Takeda Parkway, Deerfield, Illinois 60015. Takeda holds all right, title and interest in each patent asserted in this action.

3. On information and belief, Amneal Pharmaceuticals, LLC (“Amneal”) is a limited liability company organized under the laws of the State of Delaware, with its principal place of business at 440 U.S. Highway 22 East, Suite 104, Bridgewater, New Jersey, 08807-2477. On information and belief, Amneal is the business of making and selling generic pharmaceutical products, including generic versions of popular brand name prescription drug products, which it distributes in the State of Delaware and throughout the United States.

JURISDICTION AND VENUE

4. This Court has jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331 and 1338(a), 35 U.S.C. § 271, and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

5. This Court has personal jurisdiction over Amneal because, among other reasons, it is a Delaware corporation, it has extensive contacts with the State of Delaware, and Amneal regularly does business in this district. Upon information and belief, Amneal has previously consented to the personal jurisdiction of this Court on multiple occasions and has previously availed itself of this Court by filing suit and asserting counterclaims in other civil actions initiated in this jurisdiction.

6. Venue is proper in this District under 28 U.S.C. §§ 1391(b) and (c), and 1400(b).

STATEMENT OF FACTS RELEVANT TO ALL COUNTS

7. COLCRYS® is used to prevent and treat gout. Gout is a type of severe arthritis typically characterized by extremely painful “flares” (severe and sudden attacks of pain, redness, inflammation, and tenderness in joints) resulting from a build-up of uric acid. COLCRYS® is

the only single active ingredient oral colchicine product approved by the FDA both to treat and prevent painful gout flares.

8. In 2009, as a result of extensive research by Mutual Pharmaceutical Company (“Mutual” – formerly an affiliate of Takeda), the FDA for the first time approved an oral single active ingredient colchicine product: COLCRYS®. Through groundbreaking research, Mutual discovered important new information about colchicine, including previously unknown information concerning safety and efficacy, tolerability, dangerous side effects, and interactions with other medicines.

9. The FDA approved COLCRYS® for marketing in the United States under New Drug Application (“NDA”) Nos. 22-351, 22-352, and 22-353, pursuant to section 505(b) of the Federal Food Drug and Cosmetics Act (“FFDCA”), 21 U.S.C. § 355(b).

10. Takeda is the lawful owner of all right, title, and interest in and to the following United States patents, including the right to sue and to recover for infringement thereof, which patents contain one or more claims covering methods of use of COLCRYS®.

A. United States Patent Number 7,619,004 (“the ‘004 Patent”), entitled “METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND MACROLIDE ANTIBIOTICS,” a copy of which is attached hereto as Exhibit A and incorporated herein by reference as though set forth in full, which was duly and legally issued November 17, 2009, naming Matthew Davis as the inventor.

B. United States Patent Number 7,601,758 (“the ‘758 Patent”), entitled “METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND MACROLIDE ANTIBIOTICS IN THE TREATMENT OF GOUT FLARES,” a copy of which

is attached hereto as Exhibit B and incorporated herein by reference as though set forth in full, which was duly and legally issued October 13, 2009, naming Matthew Davis as the inventor.

C. United States Patent Number 7,820,681 (“the ‘681 Patent”), entitled “METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND A SECOND ACTIVE AGENT,” a copy of which is attached hereto as Exhibit C and incorporated herein by reference as though set forth in full, which was duly and legally issued October 26, 2010, naming Matthew Davis as the inventor.

D. United States Patent Number 7,915,269 (“the ‘269 Patent”), entitled “METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND A SECOND ACTIVE AGENT,” a copy of which is attached hereto as Exhibit D and incorporated herein by reference as though set forth in full, which was duly and legally issued March 29, 2011, naming Matthew Davis as the inventor.

E. United States Patent Number 7,964,647 (“the ‘647 Patent”), entitled “COLCHICINE COMPOSITIONS AND METHODS,” a copy of which is attached hereto as Exhibit E and incorporated herein by reference as though set forth in full, which was duly and legally issued June 21, 2011, naming Matthew Davis as the inventor.

F. United States Patent Number 7,964,648 (“the ‘648 Patent”), entitled “METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND A SECOND ACTIVE AGENT,” a copy of which is attached hereto as Exhibit F and incorporated herein by reference as though set forth in full, which was duly and legally issued June 21, 2011, naming Matthew Davis as the inventor.

G. United States Patent Number 7,981,938 (“the ‘938 Patent”), entitled “COLCHICINE COMPOSITIONS AND METHODS,” a copy of which is attached hereto as

Exhibit G and incorporated herein by reference as though set forth in full, which was duly and legally issued July 19, 2011, naming Matthew Davis as the inventor.

H. United States Patent Number 8,093,296 (“the ‘296 Patent”), entitled “METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND MACROLIDE ANTIBIOTICS,” a copy of which is attached hereto as Exhibit H and incorporated herein by reference as though set forth in full, which was duly and legally issued January 10, 2012, naming Matthew Davis as the inventor.

I. United States Patent Number 8,093,297 (“the ‘297 Patent”), entitled “METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND A SECOND ACTIVE AGENT,” a copy of which is attached hereto as Exhibit I and incorporated herein by reference as though set forth in full, which was duly and legally issued January 10, 2012, naming Matthew Davis as the inventor.

J. United States Patent Number 8,097,655 (“the ‘655 Patent”), entitled “METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND MACROLIDE ANTIBIOTICS,” a copy of which is attached hereto as Exhibit J and incorporated herein by reference as though set forth in full, which was duly and legally issued January 17, 2012, naming Matthew Davis as the inventor.

K. United States Patent Number 8,415,395 (“the ‘395 Patent”), entitled “COLCHICINE COMPOSITIONS AND METHODS,” a copy of which is attached hereto as Exhibit K and incorporated herein by reference as though set forth in full, which was duly and legally issued April 9, 2013, naming Matthew Davis and Hengsheng Feng as inventors.

L. United States Patent Number 8,415,396 (“the ‘396 Patent”), entitled “COLCHICINE COMPOSITIONS AND METHODS,” a copy of which is attached hereto as

Exhibit L and incorporated herein by reference as though set forth in full, which was duly and legally issued April 9, 2013, naming Matthew Davis and Hengsheng Feng as inventors

M. United States Patent Number 8,440,721 (“the ‘721 Patent”), entitled “METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND A SECOND ACTIVE AGENT” a copy of which is attached hereto as Exhibit M and incorporated herein by reference as though set forth in full, which was duly and legally issued May 14, 2013, naming Matthew Davis as inventor.

N. United States Patent Number 8,440,722 (“the ‘722 Patent”), entitled “METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND A SECOND ACTIVE AGENT” a copy of which is attached hereto as Exhibit N and incorporated herein by reference as though set forth in full, which was duly and legally issued May 14, 2013, naming Matthew Davis as inventor.

11. The ‘004, ‘758, ‘681, ‘269, ‘647, ‘648, ‘938, ‘296, ‘297, ‘655, ‘395, ‘396, ‘721, and ‘722 Patents are collectively referred to herein as the “Patents.”

12. Patent information has been submitted to the FDA in connection with NDA Nos. 22-351, 22-352, and 22-353 for COLCRYS®, and the FDA has published the same in “Approved Drug Products with Therapeutic Equivalence Evaluations” (commonly referred to as the “Orange Book”).

13. Takeda is informed and believes, and based thereon alleges, that Amneal has submitted ANDA 204711 to the FDA seeking to market a 0.6 mg oral tablet generic version of COLCRYS® prior to the expiration of the Takeda’s patent rights.

14. Takeda’s FDA approved product label for COLCRYS® contains, *inter alia*, the methods of using COLCRYS® as disclosed and claimed in the Patents, including the use of

colchicine to treat and prevent gout flares with or without concomitant administration of another substance.

15. Under the FDCA, drug products submitted to the FDA for approval via an ANDA are required to have the same labeling as the reference listed drug, here COLCRYS®, except for changes required because of differences approved under a suitability petition (21 U.S.C. § 355(j)(2)(c); 21 C.F.R. § 314.93) or because the generic drug product and reference listed drug are produced or distributed by different manufacturers (21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. §314.94(a)(8)(iv)).

16. On November 26, 2010, Mutual submitted a Citizen Petition (FDA Docket No. FDA-2010-P-0614) to the FDA regarding requirements for ANDA and other applications for single-ingredient oral colchicine tablets in view of the patents and exclusivity granted to COLCRYS®. Mutual's Citizen Petition requested, *inter alia*, that the FDA require the labeling for any single-ingredient oral colchicine product to include all information related to drug-drug interactions that appears in the COLCRYS® labeling, including relevant dose adjustments needed to prevent unnecessary toxicity.

17. On May 25, 2011, the FDA issued its decision on Mutual's Citizen Petition, stating in part: "FDA grants in part Mutual's request regarding labeling requirements for single-ingredient oral colchicine products. FDA agrees that product labeling for any single-ingredient oral colchicine product needs to include adequate information on drug-drug interactions, including relevant dose adjustments needed to prevent unnecessary toxicity. In addition, the labeling for a single-ingredient colchicine product seeking approval for prophylaxis of gout flares must inform healthcare providers that the lower dose colchicine regimen evaluated in the AGREE trial is adequate to treat an acute gout flare that may occur during chronic colchicine

use, and thus, the approval of such a product must await expiration of Colcrys' 3-year exclusivity for acute gout flares on July 30, 2012."

18. Additionally, the FDA noted in its response to Mutual's Citizen Petition that "Mutual's drug-drug interaction studies provided new, quantitative information about the extent of changes in exposure that can occur with co-administration of certain drugs with colchicine."

19. Takeda is informed and believes, and based thereon alleges, that Amneal's proposed label for its generic single active ingredient colchicine product will be the same as the labeling for COLCRYS® except for changes with respect to production, distribution and manufacture, as permitted by the FFDCA and the FDA.

20. Takeda is informed and believes, and based thereon alleges, that if Amneal's generic colchicine product is approved by the FDA, Amneal will infringe and/or induce others to infringe the Patents.

21. On or about February 22, 2013, Takeda received a letter dated February 20, 2013, and signed by a representative of Amneal, purporting to be notice of Amneal's filing of ANDA No. 204711 seeking to market a 0.6 mg generic version of COLCRYS® and allegedly containing a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV Certification") required by 21 U.S.C. § 355(j)(2)(b)(i) and (ii), with respect to the '004, '758, '681, '269, '647, '648, '938, '296, '297, and '655 Patents (Amneal's "First Paragraph IV Notice Letter"). Amneal asserts in its First Paragraph IV Notice Letter that the '004, '758, '681, '269, '647, '648, '938, '296, '297, and '655 Patents are invalid or would not be infringed.

22. On or about June 3, 2013, Takeda received a letter dated May 31, 2013, and signed by a representative of Amneal, purporting to be notice of Amneal's filing of ANDA No. 204711 seeking to market a 0.6 mg generic version of COLCRYS® and allegedly containing a

certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) required by 21 U.S.C. § 355(j)(2)(b)(i) and (ii), with respect to the ‘395 and ‘396 Patents (Amneal’s “Second Paragraph IV Notice Letter”). Amneal asserts in its Second Paragraph IV Notice Letter that the ‘395 and ‘396 Patents are invalid or would not be infringed

23. On or about June 28, 2013, Takeda received a letter dated June 25, 2013, and signed by a representative of Amneal, purporting to be notice of Amneal’s filing of ANDA No. 204711 seeking to market a 0.6 mg generic version of COLCRYS® and allegedly containing a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) required by 21 U.S.C. § 355(j)(2)(b)(i) and (ii), with respect to the ‘721 and ‘722 Patents (Amneal’s “Third Paragraph IV Notice Letter”). Amneal asserts in its Third Paragraph IV Notice Letter that the ‘721 and ‘722 Patents would not be infringed.

24. Amneal has made, and continues to make, substantial preparation in the United States to manufacture, offer to sell, sell, and/or import a 0.6 mg generic version of COLCRYS® prior to Takeda’s Patents expiry.

25. Amneal’s actions, including, but not limited to, the development of its 0.6 mg generic version of COLCRYS® and the filing of an ANDA with a Paragraph IV certification, indicate a refusal to change the course of its actions despite its knowledge of Takeda’s unexpired Patents.

26. Amneal continues to seek approval of ANDA No. 204711 from the FDA for the treatment and prevention of gout flares using 0.6 mg colchicine tablets prior to the expiry of Takeda’s Patents

COUNT I

(Infringement of the ‘004 Patent Under 35 U.S.C. § 271 against Amneal)

27. Paragraphs 1 to 26 are incorporated herein as set forth above.

28. Amneal has committed an act of infringement of the '004 Patent that creates a justiciable case or controversy between Takeda and Amneal. Pursuant to 35 U.S.C. § 271(e)(2)(A), Amneal committed an act of infringement by submitting an ANDA with a Paragraph IV certification that seeks FDA marketing approval for Amneal's generic copy of COLCRYS® prior to expiration of Takeda's '004 Patent.

29. Healthcare providers administering and/or patients using Amneal's proposed generic version of COLCRYS® within the United States in the manner and for the indications described in Amneal's ANDA will be direct infringers of Takeda's '004 Patent under 35 U.S.C. § 271(a). Takeda is informed and believes, and based thereon alleges, that the healthcare providers' and/or patients' infringing use of Amneal's proposed generic version of COLCRYS® in the methods claimed in Takeda's '004 Patent will occur at Amneal's behest and with Amneal's intent, knowledge, and encouragement and Amneal would be liable as infringers under 35 U.S.C. § 271(b) and/or (c).

30. Takeda is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an order of this Court that the effective date of approval for Amneal's ANDA be a date which is not earlier than the expiration date of the '004 Patent.

31. Takeda is entitled to a declaration that commercial manufacture, use, offer for sale, sale, and/or importation of Amneal's generic version of COLCRYS® before the patent expires will directly infringe, and/or infringe under the doctrine of equivalents, and/or indirectly infringe one or more claims of the '004 Patent under 35 U.S.C. § 271 (a), (b) and/or (c).

32. Takeda will be irreparably harmed by Amneal's infringing activities unless those activities are enjoined by this Court. Takeda does not have an adequate remedy at law.

33. This is an exceptional case and Takeda is entitled to an award of reasonable attorneys fees from Amneal.

COUNT II

(Infringement of the '758 Patent Under 35 U.S.C. § 271 against Amneal)

34. Paragraphs 1 to 33 are incorporated herein as set forth above.

35. Amneal has committed an act of infringement of the '758 Patent that creates a justiciable case or controversy between Takeda and Amneal. Pursuant to 35 U.S.C. § 271(e)(2)(A), Amneal committed an act of infringement by submitting an ANDA with a Paragraph IV certification that seeks FDA marketing approval for Amneal's generic copy of COLCRYS® prior to expiration of Takeda's '758 Patent.

36. Healthcare providers administering and/or patients using Amneal's proposed generic version of COLCRYS® within the United States in the manner and for the indications described in Amneal's ANDA will be direct infringers of Takeda's '758 Patent under 35 U.S.C. § 271(a). Takeda is informed and believes, and based thereon alleges, that the healthcare providers' and/or patients' infringing use of Amneal's proposed generic version of COLCRYS® in the methods claimed in Takeda's '758 Patent will occur at Amneal's behest and with Amneal's intent, knowledge, and encouragement and Amneal would be liable as infringers under 35 U.S.C. § 271(b) and/or (c).

37. Takeda is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an order of this Court that the effective date of approval for Amneal's ANDA be a date which is not earlier than the expiration date of the '758 Patent.

38. Takeda is entitled to a declaration that commercial manufacture, use, offer for sale, sale, and/or importation of Amneal's generic version of COLCRYS® before the patent

expires will directly infringe, and/or infringe under the doctrine of equivalents, and/or indirectly infringe one or more claims of the '758 Patent under 35 U.S.C. § 271 (a), (b) and/or (c).

39. Takeda will be irreparably harmed by Amneal's infringing activities unless those activities are enjoined by this Court. Takeda does not have an adequate remedy at law.

40. This is an exceptional case and Takeda is entitled to an award of reasonable attorneys fees from Amneal.

COUNT III

(Infringement of the '681 Patent Under 35 U.S.C. § 271 against Amneal)

41. Paragraphs 1 to 40 are incorporated herein as set forth above.

42. Amneal has committed an act of infringement of the '681 Patent that creates a justiciable case or controversy between Takeda and Amneal. Pursuant to 35 U.S.C. § 271(e)(2)(A), Amneal committed an act of infringement by submitting an ANDA with a Paragraph IV certification that seeks FDA marketing approval for Amneal's generic copy of COLCRYS® prior to expiration of Takeda's '681 Patent.

43. Healthcare providers administering and/or patients using Amneal's proposed generic version of COLCRYS® within the United States in the manner and for the indications described in Amneal's ANDA will be direct infringers of Takeda's '681 Patent under 35 U.S.C. § 271(a). Takeda is informed and believes, and based thereon alleges, that the healthcare providers' and/or patients' infringing use of Amneal's proposed generic version of COLCRYS® in the methods claimed in Takeda's '681 Patent will occur at Amneal's behest and with Amneal's intent, knowledge, and encouragement and Amneal would be liable as infringers under 35 U.S.C. § 271(b) and/or (c).

44. Takeda is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an order of this Court that the effective date of approval for Amneal's ANDA be a date which is not earlier than the expiration date of the '681 Patent.

45. Takeda is entitled to a declaration that commercial manufacture, use, offer for sale, sale, and/or importation of Amneal's generic version of COLCRYS® before the patent expires will directly infringe, and/or infringe under the doctrine of equivalents, and/or indirectly infringe one or more claims of the '681 Patent under 35 U.S.C. § 271 (a), (b) and/or (c).

46. Takeda will be irreparably harmed by Amneal's infringing activities unless those activities are enjoined by this Court. Takeda does not have an adequate remedy at law.

47. This is an exceptional case and Takeda is entitled to an award of reasonable attorneys fees from Amneal.

COUNT IV

(Infringement of the '269 Patent Under 35 U.S.C. § 271 against Amneal)

48. Paragraphs 1 to 47 are incorporated herein as set forth above.

49. Amneal has committed an act of infringement of the '269 Patent that creates a justiciable case or controversy between Takeda and Amneal. Pursuant to 35 U.S.C. § 271(e)(2)(A), Amneal committed an act of infringement by submitting an ANDA with a Paragraph IV certification that seeks FDA marketing approval for Amneal's generic copy of COLCRYS® prior to expiration of Takeda's '269 Patent.

50. Healthcare providers administering and/or patients using Amneal's proposed generic version of COLCRYS® within the United States in the manner and for the indications described in Amneal's ANDA will be direct infringers of Takeda's '269 Patent under 35 U.S.C. § 271(a). Takeda is informed and believes, and based thereon alleges, that the healthcare providers' and/or patients' infringing use of Amneal's proposed generic version of COLCRYS®

in the methods claimed in Takeda's '269 Patent will occur at Amneal's behest and with Amneal's intent, knowledge, and encouragement and Amneal would be liable as infringers under 35 U.S.C. § 271(b) and/or (c).

51. Takeda is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an order of this Court that the effective date of approval for Amneal's ANDA be a date which is not earlier than the expiration date of the '269 Patent.

52. Takeda is entitled to a declaration that commercial manufacture, use, offer for sale, sale, and/or importation of Amneal's generic version of COLCRYS® before the patent expires will directly infringe, and/or infringe under the doctrine of equivalents, and/or indirectly infringe one or more claims of the '269 Patent under 35 U.S.C. § 271 (a), (b) and/or (c).

53. Takeda will be irreparably harmed by Amneal's infringing activities unless those activities are enjoined by this Court. Takeda does not have an adequate remedy at law.

54. This is an exceptional case and Takeda is entitled to an award of reasonable attorneys fees from Amneal.

COUNT V

(Infringement of the '647 Patent Under 35 U.S.C. § 271 against Amneal)

55. Paragraphs 1 to 54 are incorporated herein as set forth above.

56. Amneal has committed an act of infringement of the '647 Patent that creates a justiciable case or controversy between Takeda and Amneal. Pursuant to 35 U.S.C. § 271(e)(2)(A), Amneal committed an act of infringement by submitting an ANDA with a Paragraph IV certification that seeks FDA marketing approval for Amneal's generic copy of COLCRYS® prior to expiration of Takeda's '647 Patent.

57. Healthcare providers administering and/or patients using Amneal's proposed generic version of COLCRYS® within the United States in the manner and for the indications

described in Amneal's ANDA will be direct infringers of Takeda's '647 Patent under 35 U.S.C. § 271(a). Takeda is informed and believes, and based thereon alleges, that the healthcare providers' and/or patients' infringing use of Amneal's proposed generic version of COLCRYS® in the methods claimed in Takeda's '647 Patent will occur at Amneal's behest and with Amneal's intent, knowledge, and encouragement and Amneal would be liable as infringers under 35 U.S.C. § 271(b) and/or (c).

58. Takeda is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an order of this Court that the effective date of approval for Amneal's ANDA be a date which is not earlier than the expiration date of the '647 Patent.

59. Takeda is entitled to a declaration that commercial manufacture, use, offer for sale, sale, and/or importation of Amneal's generic version of COLCRYS® before the patent expires will directly infringe, and/or infringe under the doctrine of equivalents, and/or indirectly infringe one or more claims of the '647 Patent under 35 U.S.C. § 271 (a), (b) and/or (c).

60. Takeda will be irreparably harmed by Amneal's infringing activities unless those activities are enjoined by this Court. Takeda does not have an adequate remedy at law.

61. This is an exceptional case and Takeda is entitled to an award of reasonable attorneys fees from Amneal.

COUNT VI

(Infringement of the '648 Patent Under 35 U.S.C. § 271 against Amneal)

62. Paragraphs 1 to 61 are incorporated herein as set forth above.

63. Amneal has committed an act of infringement of the '648 Patent that creates a justiciable case or controversy between Takeda and Amneal. Pursuant to 35 U.S.C. § 271(e)(2)(A), Amneal committed an act of infringement by submitting an ANDA with a

Paragraph IV certification that seeks FDA marketing approval for Amneal's generic copy of COLCRYS® prior to expiration of Takeda's '648 Patent.

64. Healthcare providers administering and/or patients using Amneal's proposed generic version of COLCRYS® within the United States in the manner and for the indications described in Amneal's ANDA will be direct infringers of Takeda's '648 Patent under 35 U.S.C. § 271(a). Takeda is informed and believes, and based thereon alleges, that the healthcare providers' and/or patients' infringing use of Amneal's proposed generic version of COLCRYS® in the methods claimed in Takeda's '648 Patent will occur at Amneal's behest and with Amneal's intent, knowledge, and encouragement and Amneal would be liable as infringers under 35 U.S.C. § 271(b) and/or (c).

65. Takeda is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an order of this Court that the effective date of approval for Amneal's ANDA be a date which is not earlier than the expiration date of the '648 Patent.

66. Takeda is entitled to a declaration that commercial manufacture, use, offer for sale, sale, and/or importation of Amneal's generic version of COLCRYS® before the patent expires will directly infringe, and/or infringe under the doctrine of equivalents, and/or indirectly infringe one or more claims of the '648 Patent under 35 U.S.C. § 271 (a), (b) and/or (c).

67. Takeda will be irreparably harmed by Amneal's infringing activities unless those activities are enjoined by this Court. Takeda does not have an adequate remedy at law.

68. This is an exceptional case and Takeda is entitled to an award of reasonable attorneys fees from Amneal.

COUNT VII

(Infringement of the '938 Patent Under 35 U.S.C. § 271 against Amneal)

69. Paragraphs 1 to 68 are incorporated herein as set forth above.

70. Amneal has committed an act of infringement of the '938 Patent that creates a justiciable case or controversy between Takeda and Amneal. Pursuant to 35 U.S.C. § 271(e)(2)(A), Amneal committed an act of infringement by submitting an ANDA with a Paragraph IV certification that seeks FDA marketing approval for Amneal's generic copy of COLCRYS® prior to expiration of Takeda's '938 Patent.

71. Healthcare providers administering and/or patients using Amneal's proposed generic version of COLCRYS® within the United States in the manner and for the indications described in Amneal's ANDA will be direct infringers of Takeda's '938 Patent under 35 U.S.C. § 271(a). Takeda is informed and believes, and based thereon alleges, that the healthcare providers' and/or patients' infringing use of Amneal's proposed generic version of COLCRYS® in the methods claimed in Takeda's '938 Patent will occur at Amneal's behest and with Amneal's intent, knowledge, and encouragement and Amneal would be liable as infringers under 35 U.S.C. § 271(b) and/or (c).

72. Takeda is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an order of this Court that the effective date of approval for Amneal's ANDA be a date which is not earlier than the expiration date of the '938 Patent.

73. Takeda is entitled to a declaration that commercial manufacture, use, offer for sale, sale, and/or importation of Amneal's generic version of COLCRYS® before the patent expires will directly infringe, and/or infringe under the doctrine of equivalents, and/or indirectly infringe one or more claims of the '938 Patent under 35 U.S.C. § 271 (a), (b) and/or (c).

74. Takeda will be irreparably harmed by Amneal's infringing activities unless those activities are enjoined by this Court. Takeda does not have an adequate remedy at law.

75. This is an exceptional case and Takeda is entitled to an award of reasonable attorneys fees from Amneal.

COUNT VIII

(Infringement of the '296 Patent Under 35 U.S.C. § 271 against Amneal)

76. Paragraphs 1 to 75 are incorporated herein as set forth above.

77. Amneal has committed an act of infringement of the '296 Patent that creates a justiciable case or controversy between Takeda and Amneal. Pursuant to 35 U.S.C. § 271(e)(2)(A), Amneal committed an act of infringement by submitting an ANDA with a Paragraph IV certification that seeks FDA marketing approval for Amneal's generic copy of COLCRYS® prior to expiration of Takeda's '296 Patent.

78. Healthcare providers administering and/or patients using Amneal's proposed generic version of COLCRYS® within the United States in the manner and for the indications described in Amneal's ANDA will be direct infringers of Takeda's '296 Patent under 35 U.S.C. § 271(a). Takeda is informed and believes, and based thereon alleges, that the healthcare providers' and/or patients' infringing use of Amneal's proposed generic version of COLCRYS® in the methods claimed in Takeda's '296 Patent will occur at Amneal's behest and with Amneal's intent, knowledge, and encouragement and Amneal would be liable as infringers under 35 U.S.C. § 271(b) and/or (c).

79. Takeda is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an order of this Court that the effective date of approval for Amneal's ANDA be a date which is not earlier than the expiration date of the '296 Patent.

80. Takeda is entitled to a declaration that commercial manufacture, use, offer for sale, sale, and/or importation of Amneal's generic version of COLCRYS® before the patent

expires will directly infringe, and/or infringe under the doctrine of equivalents, and/or indirectly infringe one or more claims of the '296 Patent under 35 U.S.C. § 271 (a), (b) and/or (c).

81. Takeda will be irreparably harmed by Amneal's infringing activities unless those activities are enjoined by this Court. Takeda does not have an adequate remedy at law.

82. This is an exceptional case and Takeda is entitled to an award of reasonable attorneys fees from Amneal.

COUNT IX

(Infringement of the '297 Patent Under 35 U.S.C. § 271 against Amneal)

83. Paragraphs 1 to 82 are incorporated herein as set forth above.

84. Amneal has committed an act of infringement of the '297 Patent that creates a justiciable case or controversy between Takeda and Amneal. Pursuant to 35 U.S.C. § 271(e)(2)(A), Amneal committed an act of infringement by submitting an ANDA with a Paragraph IV certification that seeks FDA marketing approval for Amneal's generic copy of COLCRYS® prior to expiration of Takeda's '297 Patent.

85. Healthcare providers administering and/or patients using Amneal's proposed generic version of COLCRYS® within the United States in the manner and for the indications described in Amneal's ANDA will be direct infringers of Takeda's '297 Patent under 35 U.S.C. § 271(a). Takeda is informed and believes, and based thereon alleges, that the healthcare providers' and/or patients' infringing use of Amneal's proposed generic version of COLCRYS® in the methods claimed in Takeda's '297 Patent will occur at Amneal's behest and with Amneal's intent, knowledge, and encouragement and Amneal would be liable as infringers under 35 U.S.C. § 271(b) and/or (c).

86. Takeda is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an order of this Court that the effective date of approval for Amneal's ANDA be a date which is not earlier than the expiration date of the '297 Patent.

87. Takeda is entitled to a declaration that commercial manufacture, use, offer for sale, sale, and/or importation of Amneal's generic version of COLCRYS® before the patent expires will directly infringe, and/or infringe under the doctrine of equivalents, and/or indirectly infringe one or more claims of the '297 Patent under 35 U.S.C. § 271 (a), (b) and/or (c).

88. Takeda will be irreparably harmed by Amneal's infringing activities unless those activities are enjoined by this Court. Takeda does not have an adequate remedy at law.

89. This is an exceptional case and Takeda is entitled to an award of reasonable attorneys fees from Amneal.

COUNT X

(Infringement of the '655 Patent Under 35 U.S.C. § 271 against Amneal)

90. Paragraphs 1 to 89 are incorporated herein as set forth above.

91. Amneal has committed an act of infringement of the '655 Patent that creates a justiciable case or controversy between Takeda and Amneal. Pursuant to 35 U.S.C. § 271(e)(2)(A), Amneal committed an act of infringement by submitting an ANDA with a Paragraph IV certification that seeks FDA marketing approval for Amneal's generic copy of COLCRYS® prior to expiration of Takeda's '655 Patent.

92. Healthcare providers administering and/or patients using Amneal's proposed generic version of COLCRYS® within the United States in the manner and for the indications described in Amneal's ANDA will be direct infringers of Takeda's '655 Patent under 35 U.S.C. § 271(a). Takeda is informed and believes, and based thereon alleges, that the healthcare providers' and/or patients' infringing use of Amneal's proposed generic version of COLCRYS®

in the methods claimed in Takeda's '655 Patent will occur at Amneal's behest and with Amneal's intent, knowledge, and encouragement and Amneal would be liable as infringers under 35 U.S.C. § 271(b) and/or (c).

93. Takeda is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an order of this Court that the effective date of approval for Amneal's ANDA be a date which is not earlier than the expiration date of the '655 Patent.

94. Takeda is entitled to a declaration that commercial manufacture, use, offer for sale, sale, and/or importation of Amneal's generic version of COLCRYS® before the patent expires will directly infringe, and/or infringe under the doctrine of equivalents, and/or indirectly infringe one or more claims of the '655 Patent under 35 U.S.C. § 271 (a), (b) and/or (c).

95. Takeda will be irreparably harmed by Amneal's infringing activities unless those activities are enjoined by this Court. Takeda does not have an adequate remedy at law.

96. This is an exceptional case and Takeda is entitled to an award of reasonable attorneys fees from Amneal.

COUNT XI

(Infringement of the '395 Patent Under 35 U.S.C. § 271 against Amneal)

97. Paragraphs 1 to 96 are incorporated herein as set forth above.

98. Amneal has committed an act of infringement of the '395 Patent that creates a justiciable case or controversy between Takeda and Amneal. Pursuant to 35 U.S.C. § 271(e)(2)(A), Amneal committed an act of infringement by submitting an ANDA with a Paragraph IV certification that seeks FDA marketing approval for Amneal's generic copy of COLCRYS® prior to expiration of Takeda's '395 Patent.

99. Healthcare providers administering and/or patients using Amneal's proposed generic version of COLCRYS® within the United States in the manner and for the indications

described in Amneal's ANDA will be direct infringers of Takeda's '395 Patent under 35 U.S.C. § 271(a). Takeda is informed and believes, and based thereon alleges, that the healthcare providers' and/or patients' infringing use of Amneal's proposed generic version of COLCRYS® in the methods claimed in Takeda's '395 Patent will occur at Amneal's behest and with Amneal's intent, knowledge, and encouragement and Amneal would be liable as infringers under 35 U.S.C. § 271(b) and/or (c).

100. Takeda is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an order of this Court that the effective date of approval for Amneal's ANDA be a date which is not earlier than the expiration date of the '395 Patent.

101. Takeda is entitled to a declaration that commercial manufacture, use, offer for sale, sale, and/or importation of Amneal's generic version of COLCRYS® before the patent expires will directly infringe, and/or infringe under the doctrine of equivalents, and/or indirectly infringe one or more claims of the '395 Patent under 35 U.S.C. § 271 (a), (b) and/or (c).

102. Takeda will be irreparably harmed by Amneal's infringing activities unless those activities are enjoined by this Court. Takeda does not have an adequate remedy at law.

103. This is an exceptional case and Takeda is entitled to an award of reasonable attorneys fees from Amneal.

COUNT XII

(Infringement of the '396 Patent Under 35 U.S.C. § 271 against Amneal)

104. Paragraphs 1 to 103 are incorporated herein as set forth above.

105. Amneal has committed an act of infringement of the '396 Patent that creates a justiciable case or controversy between Takeda and Amneal. Pursuant to 35 U.S.C. § 271(e)(2)(A), Amneal committed an act of infringement by submitting an ANDA with a

Paragraph IV certification that seeks FDA marketing approval for Amneal's generic copy of COLCRYS® prior to expiration of Takeda's '396 Patent.

106. Healthcare providers administering and/or patients using Amneal's proposed generic version of COLCRYS® within the United States in the manner and for the indications described in Amneal's ANDA will be direct infringers of Takeda's '396 Patent under 35 U.S.C. § 271(a). Takeda is informed and believes, and based thereon alleges, that the healthcare providers' and/or patients' infringing use of Amneal's proposed generic version of COLCRYS® in the methods claimed in Takeda's '396 Patent will occur at Amneal's behest and with Amneal's intent, knowledge, and encouragement and Amneal would be liable as infringers under 35 U.S.C. § 271(b) and/or (c).

107. Takeda is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an order of this Court that the effective date of approval for Amneal's ANDA be a date which is not earlier than the expiration date of the '396 Patent.

108. Takeda is entitled to a declaration that commercial manufacture, use, offer for sale, sale, and/or importation of Amneal's generic version of COLCRYS® before the patent expires will directly infringe, and/or infringe under the doctrine of equivalents, and/or indirectly infringe one or more claims of the '396 Patent under 35 U.S.C. § 271 (a), (b) and/or (c).

109. Takeda will be irreparably harmed by Amneal's infringing activities unless those activities are enjoined by this Court. Takeda does not have an adequate remedy at law.

110. This is an exceptional case and Takeda is entitled to an award of reasonable attorneys fees from Amneal.

COUNT XIII

(Infringement of the '721 Patent Under 35 U.S.C. § 271 against Amneal)

111. Paragraphs 1 to 110 are incorporated herein as set forth above.

112. Amneal has committed an act of infringement of the '721 Patent that creates a justiciable case or controversy between Takeda and Amneal. Pursuant to 35 U.S.C. § 271(e)(2)(A), Amneal committed an act of infringement by submitting an ANDA with a Paragraph IV certification that seeks FDA marketing approval for Amneal's generic copy of COLCRYS® prior to expiration of Takeda's '721 Patent.

113. Healthcare providers administering and/or patients using Amneal's proposed generic version of COLCRYS® within the United States in the manner and for the indications described in Amneal's ANDA will be direct infringers of Takeda's '721 Patent under 35 U.S.C. § 271(a). Takeda is informed and believes, and based thereon alleges, that the healthcare providers' and/or patients' infringing use of Amneal's proposed generic version of COLCRYS® in the methods claimed in Takeda's '721 Patent will occur at Amneal's behest and with Amneal's intent, knowledge, and encouragement and Amneal would be liable as infringers under 35 U.S.C. § 271(b) and/or (c).

114. Takeda is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an order of this Court that the effective date of approval for Amneal's ANDA be a date which is not earlier than the expiration date of the '721 Patent.

115. Takeda is entitled to a declaration that commercial manufacture, use, offer for sale, sale, and/or importation of Amneal's generic version of COLCRYS® before the patent expires will directly infringe, and/or infringe under the doctrine of equivalents, and/or indirectly infringe one or more claims of the '721 Patent under 35 U.S.C. § 271 (a), (b) and/or (c).

116. Takeda will be irreparably harmed by Amneal's infringing activities unless those activities are enjoined by this Court. Takeda does not have an adequate remedy at law.

117. This is an exceptional case and Takeda is entitled to an award of reasonable attorneys fees from Amneal.

COUNT XIV

(Infringement of the ‘722 Patent Under 35 U.S.C. § 271 against Amneal)

118. Paragraphs 1 to 117 are incorporated herein as set forth above.

119. Amneal has committed an act of infringement of the ‘722 Patent that creates a justiciable case or controversy between Takeda and Amneal. Pursuant to 35 U.S.C. § 271(e)(2)(A), Amneal committed an act of infringement by submitting an ANDA with a Paragraph IV certification that seeks FDA marketing approval for Amneal’s generic copy of COLCRYS® prior to expiration of Takeda’s ‘722 Patent.

120. Healthcare providers administering and/or patients using Amneal’s proposed generic version of COLCRYS® within the United States in the manner and for the indications described in Amneal’s ANDA will be direct infringers of Takeda’s ‘722 Patent under 35 U.S.C. § 271(a). Takeda is informed and believes, and based thereon alleges, that the healthcare providers’ and/or patients’ infringing use of Amneal’s proposed generic version of COLCRYS® in the methods claimed in Takeda’s ‘722 Patent will occur at Amneal’s behest and with Amneal’s intent, knowledge, and encouragement and Amneal would be liable as infringers under 35 U.S.C. § 271(b) and/or (c).

121. Takeda is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an order of this Court that the effective date of approval for Amneal’s ANDA be a date which is not earlier than the expiration date of the ‘722 Patent.

122. Takeda is entitled to a declaration that commercial manufacture, use, offer for sale, sale, and/or importation of Amneal’s generic version of COLCRYS® before the patent

expires will directly infringe, and/or infringe under the doctrine of equivalents, and/or indirectly infringe one or more claims of the '722 Patent under 35 U.S.C. § 271 (a), (b) and/or (c).

123. Takeda will be irreparably harmed by Amneal's infringing activities unless those activities are enjoined by this Court. Takeda does not have an adequate remedy at law.

124. This is an exceptional case and Takeda is entitled to an award of reasonable attorneys fees from Amneal.

EXCEPTIONAL CASE

125. Takeda is informed and believes, and based thereon alleges, that Amneal was aware of at least the '004, '758, '681, '269, '647, '648, '938, '296, '297, and '655 patents and that they were listed in the Orange Book as covering COLCRYS® before submitting its ANDA 204711 seeking to market a generic copy of COLCRYS®.

126. Amneal had no basis to submit its ANDA and Paragraph IV Certifications. Amneal's actions render this an exceptional case under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Takeda requests entry of judgment in its favor and against Amneal as follows:

A. A judgment and decree that Amneal has infringed Takeda's '004, '758, '681, '269, '647, '648, '938, '296, '297, '655, '395, '396, '721, and '722 Patents under 35 U.S.C. § 271(e)(2)(A) by submitting its ANDA No. 204711 with a Paragraph IV Certification seeking to market Amneal's generic version of Colcris® prior to the expiration of the Patents;

B. Declaring and entering judgment that Amneal will infringe one of more claims of the '004, '758, '681, '269, '647, '648, '938, '296, '297, '655, '395, '396, '721, and '722 Patents under one or more of 35 U.S.C. § 271 (a), (b) and/or (c) by its manufacture, use,

offering to sell, and sale in, and importation into the United States of Amneal's generic colchicine product prior to the expiration of those patents;

C. A judgment, pursuant to 35 U.S.C. § 271(e)(4)(B), preliminarily and permanently enjoining Amneal, its officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with it or acting on its behalf, from any commercial manufacture, use, offer to sell or sale within the United States, or importation into the United States, of any drug product that infringes the '004, '758, '681, '269, '647, '648, '938, '296, '297, '655, '395, '396, '721 or '722 Patents;

D. Preliminarily and permanently enjoining Amneal, its officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with it or acting on its behalf, from any commercial manufacture, use, offer to sell or sale within the United States, or importation into the United States, of any drug product that infringes the '004, '758, '681, '269, '647, '648, '938, '296, '297, '655, '395, '396, '721 or '722 Patents;

E. That if Amneal engages in the commercial manufacture, use, importation into the United States, sale, or offer for sale of an oral single-ingredient colchicine before the expiration of the Patents, a judgment be awarded to Takeda for damages resulting from such infringement, together with interest, in an amount to be determined at trial;

F. Declaring this an exceptional case under 35 U.S.C. § 285, and that Takeda be awarded reasonable attorneys' fees and costs; and

G. Such other and further relief as the Court may deem just and proper.

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Attorneys for Takeda Pharmaceuticals U.S.A., Inc.

Dated: August 19, 2013

EXHIBIT A

(12) **United States Patent**
Davis

(10) **Patent No.:** **US 7,619,004 B1**
(45) **Date of Patent:** ***Nov. 17, 2009**

(54) **METHODS FOR CONCOMITANT
ADMINISTRATION OF COLCHICINE AND
MACROLIDE ANTIBIOTICS**

(75) Inventor: **Matthew W. Davis**, Erwinna, PA (US)

(73) Assignee: **Mutual Pharmaceutical Company,
Inc.**, Philadelphia, PA (US)

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-
claimer.

(21) Appl. No.: **12/327,258**

(22) Filed: **Dec. 3, 2008**

Related U.S. Application Data

(60) Provisional application No. 61/190,053, filed on Oct.
15, 2008.

(51) **Int. Cl.**
A61K 31/167 (2006.01)
C07C 233/23 (2006.01)
C07C 211/41 (2006.01)

(52) **U.S. Cl.** **514/629**; 564/123; 564/308;
564/427; 568/306

(58) **Field of Classification Search** 514/629;
564/123, 308, 427; 568/306
See application file for complete search history.

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Primary Examiner—Sreeni Padmanabhan

Assistant Examiner—Umamaheswari Ramachandran

(74) *Attorney, Agent, or Firm*—Cantor Colburn LLP

(57) **ABSTRACT**

Methods for concomitant administration of colchicine together with one or more macrolide antibiotics, e.g., clarithromycin or erythromycin, are disclosed. Such methods reduce the dangers commonly associated with such concomitant administration and provide additional benefits. Methods of notifying health care practitioners and patients regarding appropriate dosing for co-administration of colchicine together with macrolide antibiotics are also provided.

8 Claims, 2 Drawing Sheets

U.S. Patent

Nov. 17, 2009

Sheet 1 of 2

US 7,619,004 B1

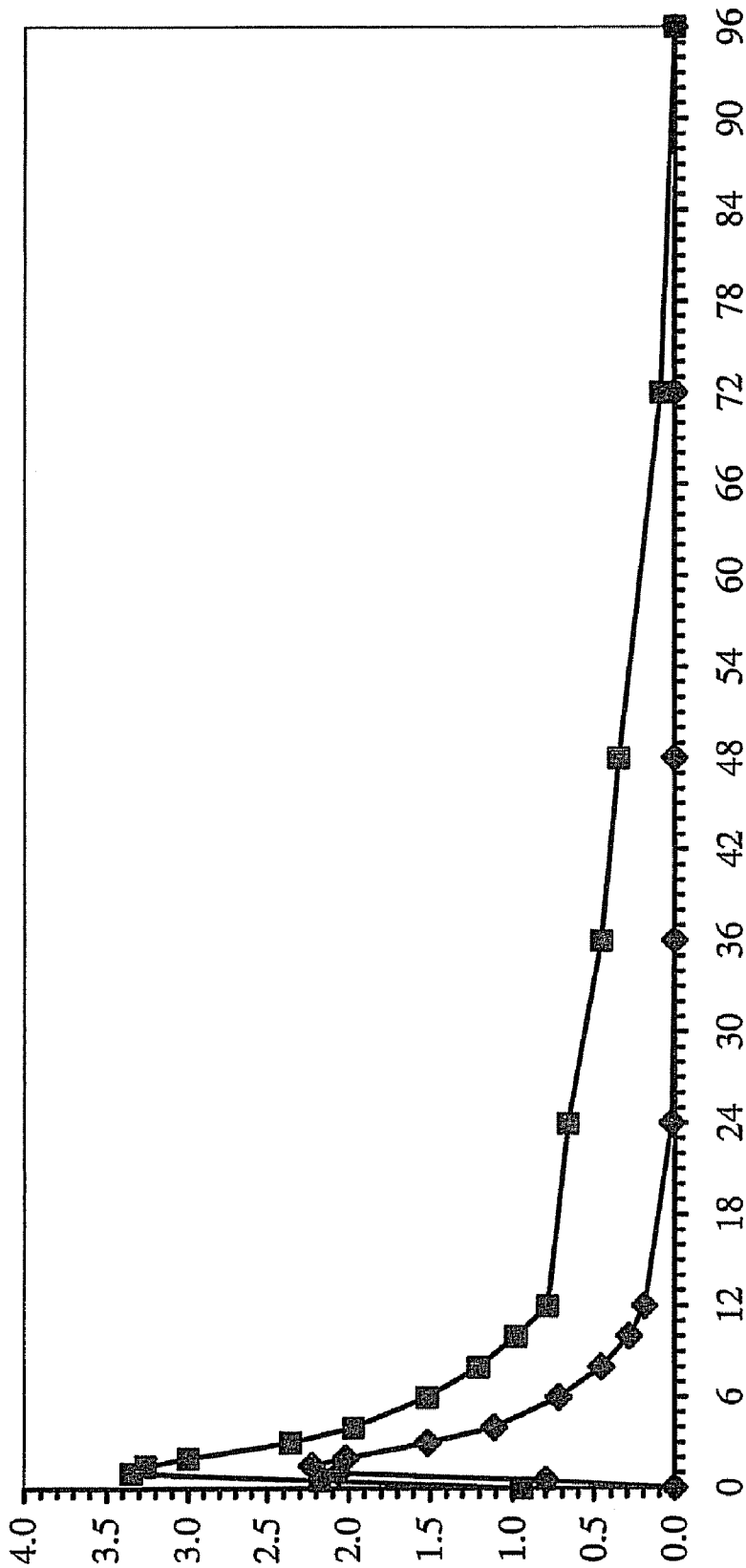


Fig. 1

U.S. Patent

Nov. 17, 2009

Sheet 2 of 2

US 7,619,004 B1

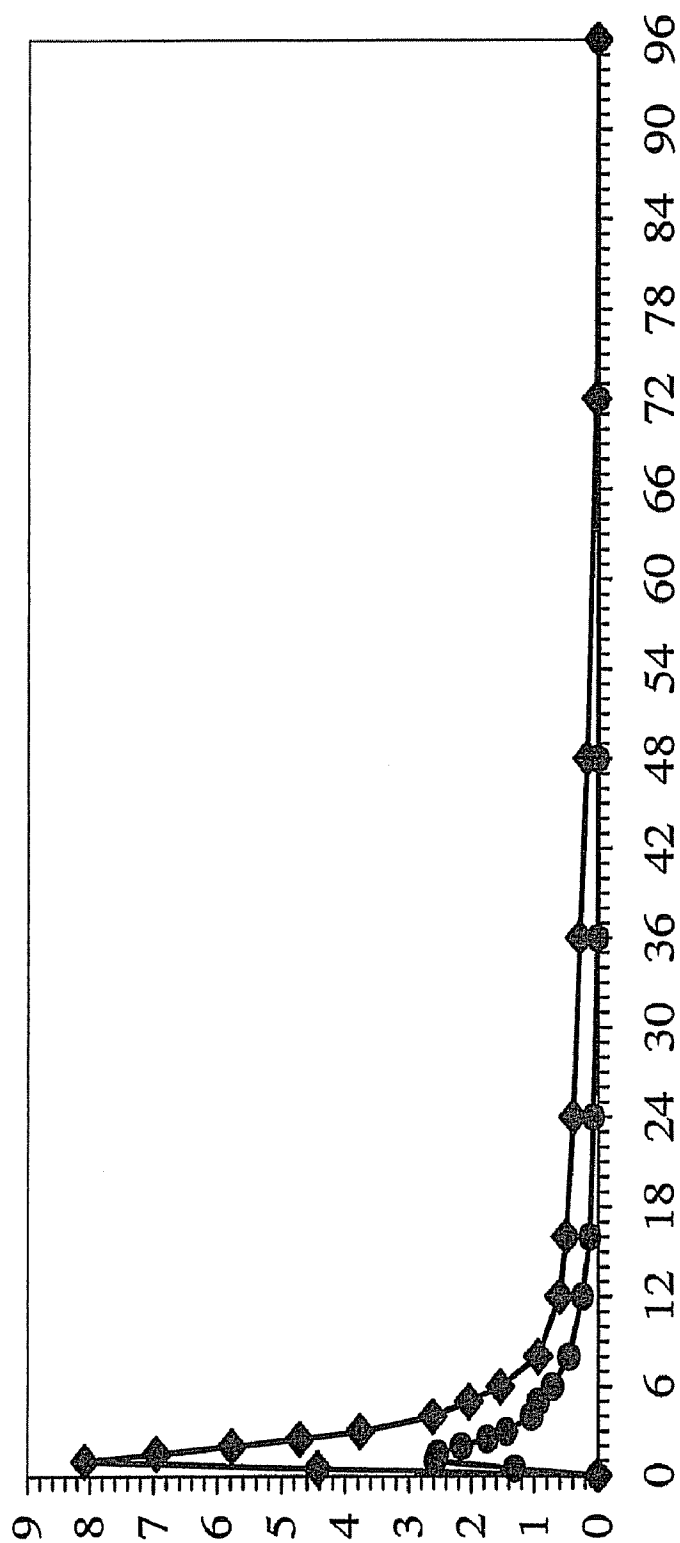


Fig. 2

US 7,619,004 B1

1

METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND MACROLIDE ANTIBIOTICS

CLAIM FOR PRIORITY

This application claims the benefit of Provisional Patent Application Ser. No. 61/190,053, filed Oct. 15, 2008.

BACKGROUND

This application relates to methods allowing for the co-administration of colchicine together with one or more macrolide antibiotics for therapeutic purposes with less danger than is associated with prior methods of administration.

Colchicine:

Colchicine, chemical name (–)-N-[(7S,12aS)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide, is a pale yellow powder soluble in water in 1:25 dilution.

Colchicine is an alkaloid found in extracts of *Colchicum autumnale*, *Gloriosa superba*, and other plants. Among its many biological activities, colchicine blocks microtubule polymerization and arrests cell division. It has adversely affected spermatogenesis in humans and in some animal species under certain conditions.

Colchicine is a microtubule-disrupting agent used in the treatment of gout and other conditions that may be treated, relieved or prevented with anti-inflammatory treatment. Colchicine impairs the motility of granulocytes and can prevent the inflammatory phenomena that initiate an attack (or flare) of gout. Colchicine also inhibits mitosis, thus affecting cells with high turnover such as those in the gastrointestinal tract and bone marrow; therefore, the primary adverse side effects include gastrointestinal upset such as diarrhea and nausea.

Colchicine has a low therapeutic index. The margin between an effective dose and a toxic dose of colchicine is much narrower than that of most other widely used drugs. Consequently, actions that result in increased colchicine levels in patients receiving colchicine therapy are particularly dangerous. Co-administration of colchicine to patients along with certain other drugs can have the effect of increasing colchicine levels. Such drug-drug interactions with colchicine have been reported to result in serious morbid complications and, in some cases, death.

Colchicine is rapidly absorbed from the gastrointestinal tract. Peak concentrations occur in 0.5 to 2 hours. The drug and its metabolites are distributed in leukocytes, kidneys, liver, spleen and the intestinal tract. Colchicine is metabolized in the liver and excreted primarily in the feces with 10 to 20% eliminated unchanged in the urine.

Gout:

Gout (or gouty arthritis) is a disease caused by a build up of uric acid. Such a build up is typically due to an overproduction of uric acid or to a reduced ability of the kidney to excrete uric acid. Gout is more common in certain groups of patients, including adult males, postmenopausal women, and hypertensives. Heavy alcohol use, diabetes, obesity, sickle cell anemia, and kidney disease also increase the risk of developing gout. The condition may also develop in people who take drugs that interfere with uric acid excretion.

In gout, crystals of monosodium urate (a salt of uric acid) are deposited in joints, e.g., on articular cartilage, as well as in and on tendons and surrounding tissues. These deposits correlate with elevated concentrations of uric acid in the blood

2

stream and are believed to provoke the painful inflammatory reaction that occurs in affected tissues. Gout is characterized by excruciating, sudden, unexpected, burning pain, as well as by swelling, redness, warmth, and stiffness in the affected joint. Low-grade fever may also be present. The patient usually suffers from two sources of pain. The patient experiences intense pain whenever an affected joint is flexed. The inflammation of the tissues around the joint also causes the skin to be swollen, tender and sore if it is even slightly touched. For example, a blanket or even the lightest sheet draping over the affected area could cause extreme pain.

A gout flare is a sudden attack of pain in affected joints, especially in the lower extremities, and most commonly in the big toe. In afflicted individuals, the frequency of gout flares typically increases over time. In this fashion, gout progresses from acute gout to chronic gout, which involves repeated episodes of joint pain.

In acute gout flares, symptoms develop suddenly and usually involve only one or a few joints. The big toe, knee, or ankle joints are most often affected. The pain frequently starts during the night and is often described as throbbing, crushing, or excruciating. The joint appears infected, with signs of warmth, redness, and tenderness. Flares of painful joints may go away in several days, but may return from time to time. Subsequent flares usually last longer. Acute gout may progress to chronic gout flares, or may resolve without further attacks.

The chronic appearance of several attacks of gout yearly can lead to joint deformity and limited joint motion. Nodular uric acid deposits, called tophi, may eventually develop in cartilage tissue, tendons, and soft tissues. These tophi are a hallmark of chronic gout, which usually develop only after a patient has suffered from the disease for many years. Deposits of monosodium urate can also occur in the kidneys of gout sufferers, potentially leading to chronic kidney failure.

Use of Colchicine to Treat Gout:

Colchicine can reduce pain in attacks of acute gout flares and also can be used beneficially for treating adults for prophylaxis of gout flares. Although its exact mode of action in the relief of gout is not completely understood, colchicine is known to decrease the inflammatory response to urate crystal deposition by inhibiting migration of leukocytes, to interfere with urate deposition by decreasing lactic acid production by leukocytes, to interfere with kinin formation and to diminish phagocytosis and subsequent inflammatory responses.

The anti-inflammatory effect of colchicine is relatively selective for gouty arthritis. However, other types of arthritis occasionally respond. It is neither an analgesic nor a uricosuric and will not prevent progression of acute gout to chronic gout. It does have a prophylactic, suppressive effect that helps to reduce the incidence of acute attacks as well as to relieve the residual pain and mild discomfort that patients with gout occasionally experience between attacks.

Macrolide Antibiotics:

Macrolide compounds are natural products and natural product derivatives characterized by the presence of a macrocyclic (large) lactone ring known as a macrolide ring. The macrolide antibiotics are important therapeutic agents. Commercially available macrolide antibiotics include azithromycin, clarithromycin, dirithromycin, erythromycin, and roxithromycin.

Clarithromycin is a semi-synthetic macrolide antibiotic with in vitro activity against a variety of aerobic and anaerobic gram-positive and gram-negative microorganisms, as well as most *Mycobacterium avium* complex (MAC) microorganisms. The drug is believed to exert its antibacterial

US 7,619,004 B1

3

action by binding to 50S ribosomal subunits in susceptible microorganisms, resulting in inhibition of protein synthesis.

Clarithromycin is indicated in the treatment of mild to moderate infections in adults and children caused by susceptible strains of microorganisms, such as *Legionella pneumophila*, *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Neisseria gonorrhoeae*. Clarithromycin is also used to treat pharyngitis (tonsillitis), sinusitis, bronchitis, community-acquired pneumonia, uncomplicated skin infections, and disseminated mycobacterial infections. The usual adult dose is 250 or 500 mg every 12 hours (500 or 100 mg per day) for 7 to 14 days, taken without regard to food.

Clarithromycin is rapidly absorbed from the gastrointestinal tract following oral administration, with an absolute bioavailability of approximately 50%. Peak plasma concentrations with single doses are reached within 2 to 3 hours and steady-state plasma concentrations are reached within 3 to 4 days. Food slightly delays the onset of absorption and time to peak concentration and increases the peak concentration by about 24%, but does not affect the extent of exposure. Clarithromycin distributes readily into body tissues and fluids and is not highly bound to plasma proteins (65 to 75%).

Cytochrome p450 (CYP) Enzymes:

CYP enzymes are agents of drug metabolism that are found in the liver, the gastrointestinal tract and other locations in the body. CYP enzymes occur in a variety of closely related proteins referred to as isozymes. Some of these that have been identified as important in drug metabolism are CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Different CYP isozymes may preferentially metabolize different drugs. For example, phenytoin and fosphenytoin have been reported to be preferentially metabolized by CYP2C9, CYP2C19, and CYP3A4, while CYP2D6 has been reported to be responsible for the metabolism of many psychotherapeutic agents, such as thioridazine.

CYP Isozymes and Drug-Drug Interactions:

Examples of CYP-mediated drug-drug interactions include those involving CYP1A2 and CYP2E1 isozymes, which have been reported to be involved in drug-drug interactions involving theophylline, and those involving CYP2C9, CYP1A2, and CYP2C19, which have been reported to be involved in drug-drug interactions involving warfarin.

The 3A family of CYP isozymes, particularly CYP3A4, is also known to be involved in many clinically significant drug-drug interactions, including those involving colchicine and macrolide antibiotics, as well as those involving non-sedating antihistamines and cisapride. CYP3A5 shares very similar protein structure, function and substrate specificity with CYP3A4. The CYP3A5*3 allele is a gene variant that does not express CYP3A5 enzyme. As a result of this genetic variation, about half of African-American subjects and 70-90% of Caucasian subjects do not express CYP3A5, while expression is more common in other ethnic groups.

While drugs are often targets of CYP-mediated metabolism, some may also alter the expression and activity of such enzymes, thus impacting the metabolism of other drugs.

Colchicine is both a target of and a modulator of CYP isozymes. The biotransformation of colchicine in human liver microsomes involves formation of 3-demethylcolchicine and 2-demethylcolchicine. As shown by experiments using antibodies against CYP3A4 and experiments using chemical inhibition of CYP3A4, this transformation is correlated with (and thus apparently mediated by) CYP3A4 activity. CYP2A6, CYP2C9, CYP2C19, CYP2D6, and CYP2E1 do not appear to catalyze this biotransformation.

4

Studies on the effect of colchicine on expression of selected CYP isozymes in primary cultures of human hepatocytes have been reported. Dvorak et al. (Acta Univ. Palacki. Olomuc., Fac. Med. (2000) 143:47-50) provided preliminary data on the effect of colchicine and several of its derivatives on protein levels of CYP1A2, CYP2A6, CYP2C9/19, CYP2E1, and CYP3A4 as assessed by immunoblotting. Colchicine caused an increase in CYP2E1 protein levels and appeared to decrease protein levels of CYP1A2, CYP2C9/19, and CYP3A4, with 10 μ M colchicine causing a greater reduction in each isozyme than 1 μ M colchicine. The 3-demethylcolchicine metabolite was reported to cause a decrease in protein for CYP1A2, CYP2C9/19, CYP2E1, and CYP3A4. The levels of CYP2A6 appeared unaffected by colchicine or any of the tested metabolites. In a more complete report on expression of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2E1, and CYP3A4, Dvorak et al. (Toxicology in Vitro (2002) 16:219-227) concluded that CYP1A2 protein content in 1 μ M colchicine treated cells was not different from that in control cells, while the inducer TCDD increased the level of CYP1A2 protein by an average of three-fold. The levels of CYP2A6 protein were apparently unaffected by colchicine, while enzyme activities of CYP3A4 and CYP2C9 were significantly decreased by colchicine and activity of CYP2E1 was not affected. Northern blots showed that colchicine suppressed CYP2C9 mRNA levels by about 20% and did not alter CYP3A4 mRNA levels as compared to control cells. A subsequent study by Dvorak et al. (Mol. Pharmacol. (2003) 64:160-169) showed that colchicine decreased both basal and rifampicin-inducible and phenobarbital-inducible expression of CYP2B6, CYP2C8/9, and CYP3A4.

Like colchicine, clarithromycin is a target of metabolism by CYP3A isozymes. In non-fasting healthy human subjects, the elimination half-life of clarithromycin is about 3 to 4 hours with 250 mg administered every 12 hours, but increases to 5 to 7 hours with 500 mg administered every 8 to 12 hours. Approximately 20% and 30% of the dose, respectively, is excreted as unchanged drug in urine following oral administration of 250 and 500 mg clarithromycin given every 12 hours. Approximately 10 to 15% of the dose is excreted in urine as 14-hydroxyclearithromycin, an active metabolite of clarithromycin with substantial antibacterial activity. About 40% of an oral clarithromycin dose is excreted in feces.

Clarithromycin is also a potent inhibitor of CYP3A isozymes, as are other macrolide antibiotics. This inhibition is not rapidly reversible. Due to the limited reversibility of the inhibition of CYP3A isozymes by clarithromycin, CYP3A activity may not return to normal after a course of treatment with clarithromycin until the body produces adequate amounts of CYP3A isozymes to replace those irreversibly inhibited by the clarithromycin. Thus, it may take one to two weeks for CYP3A metabolic activity to return to normal following treatment with clarithromycin or other macrolide antibiotics.

P-glycoprotein (Pgp) is an ATP-dependent cell surface transporter molecule. Pgp actively pumps certain compounds, notably including drugs such as colchicine, out of cells. Pgp is encoded by the Adenosine triphosphate-binding cassette subfamily B member 1 (ABCB1) gene, also referred to as the multiple drug resistance 1 gene (MDR1).

Clarithromycin is an inhibitor of Pgp, as are other macrolide antibiotics. Thus clarithromycin and other macrolide antibiotics, in addition to inhibiting the metabolic breakdown of colchicine by inhibiting CYP 3A4 isozymes, can block a mechanism by which colchicine is pumped out of cells. Both the inhibition of colchicine breakdown by CYP 3A4 and the

US 7,619,004 B1

5

inhibition of the pumping of colchicine out of cells by Pgp have the effect of increasing the intracellular levels of colchicine.

Since colchicine acts intracellularly, the combined effects of CYP 3A4 inhibition and Pgp inhibition by clarithromycin (and related macrolide antibiotics) can cause colchicine toxicity in patients taking what would be a safe dose of colchicine in the absence of concomitant macrolide antibiotic administration.

Drug-drug interactions, such as the enhancement of colchicine toxicity by macrolide antibiotics, present a health risk to patients and a medical challenge for all medical care workers. Various studies of adverse reactions from exposure to multiple drugs have found that 6.5-23% of the adverse reactions result from drug-drug interactions. Unfortunately, each year a number of deaths occur as the direct result of patients adding a concomitant prescription pharmaceutical product to their existing medication regimen.

With regard to co-administration of colchicine with clarithromycin and other macrolide antibiotics, warnings have recently been published urging caution, or arguing that the two drugs should not be co-administered. For example, on Jul. 5, 2006 the US Food and Drug Administration (the FDA) approved safety labeling changes for clarithromycin tablets, extended-release tablets, and oral suspension to warn of the risk for increased exposure to colchicine in patients receiving both drugs. The Warnings section of the prescribing information for clarithromycin now includes the following statement: "There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients." In addition, the following was added to the Precautions section of the prescribing information: "[c]olchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Patients should be monitored for clinical symptoms of colchicine toxicity."

A 2006 report entitled "Life-threatening Colchicine Drug Interactions" cautioned that "[c]olchicine should not be used with clarithromycin or erythromycin, and given the potential for fatal outcomes, it would be prudent to avoid all PGP inhibitors with colchicine" (Horn, J. R. and Hansten, P. D., Pharmacy Times, May 2006, p. 111).

More recently, a publication in May, 2008 ended with the conclusion that "[t]he combined prescription of clarithromycin or other CYP3A4 inhibitors and colchicine should be avoided." Van der Velden, et al., (Neth. J. Med. 2008 May; 66(5):204-6).

There accordingly remains a need in the art for improved methods for administering colchicine to patients who are concomitantly being treated with macrolide antibiotics so as to reduce the occurrence of dangerous colchicine toxicity. The present disclosure addresses this need and provides further advantages.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows mean colchicine plasma concentrations following administration of single and multiple oral doses of colchicine 0.6 mg in healthy adults, N=13, Y axis=colchicine concentration, ng/mL, X axis=time in hours, ◆=day 1, ■=day 25. See Example 1.

6

FIG. 2 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin in healthy adults, Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=23, ●=day 1, ◆=day 29. See Example 2.

SUMMARY

Disclosed herein are methods for more safely administering colchicine concomitantly with administration of macrolide antibiotics such as clarithromycin or erythromycin. It has now been discovered that certain reduced or limited colchicine dosage amounts, when administered with concomitantly administered recommended doses of macrolide antibiotics, achieve plasma colchicine levels that are therapeutically effective, but are not significantly higher, and therefore not significantly more toxic, than plasma levels achieved by administration of manufacturers' recommended colchicine dosage amounts in the absence of concomitant macrolide antibiotic administration. Thus, in spite of recent published warnings that the two should not be concomitantly administered, colchicine and macrolide antibiotics can be administered concomitantly without undue hazard when colchicine is administered as disclosed herein.

In one embodiment, colchicine treatment is administered to a patient in suffering from a condition treatable with colchicine, and the patient is concomitantly receiving administration of a macrolide antibiotic to treat an infection. The colchicine therapy may involve either palliative or prophylactic treatment, or both.

In particularly preferred embodiments, the patient is a human gout patient and is administered the colchicine to prevent gout flares. Preferably the method comprises determining a first colchicine dosage amount adapted for daily oral administration to the gout patient to prevent gout flares in the absence of concomitant administration of clarithromycin or erythromycin, determining a second colchicine dosage amount that is a 50% to 75% reduction of the first colchicine dosage amount, and orally administering the second colchicine dosage amount to the gout patient who is concomitantly receiving administration of clarithromycin or erythromycin. Preferably the second colchicine dosage amount is administered to the patient in one or more doses one or more times per day every day, or double the second colchicine dosage amount is administered to the patient in one or more doses per day every other day.

Preferably, in this method, the 50% to 75% reduction comprises one or more of 1) reducing the number of doses of colchicine administered per day, 2) reducing the amount of colchicine administered per dose, and 3) reducing the administration of colchicine from administration every day to administration every other day. For example, in this method, the 50% to 75% reduction may comprise reducing both the number of doses of colchicine administered per day and the amount of colchicine administered per dose.

In other aspects of these embodiments, it is preferred that one or more (where not mutually exclusive) of the following apply: 1) the patient is administered each dose of colchicine as one 0.6 mg colchicine tablet or as one half of a 0.6 mg colchicine tablet, 2) the patient is an adult, 3) the adult patient is less than 70 years old, 4) the patient is receiving concomitant administration of clarithromycin, 6) the second colchicine dosage amount is a one-half reduction of the first colchicine dosage amount, 7) the second colchicine dosage amount is a two-thirds reduction of the first colchicine dosage amount, 8) the second colchicine dosage amount is a three-

US 7,619,004 B1

7

quarters reduction of the first colchicine dosage amount, 9) the first colchicine dosage amount is about 1.2 mg per day and the second colchicine dosage amount is about 0.3 mg per day, 10) the first colchicine dosage amount is about 0.6 mg per day and the second colchicine dosage amount is about 0.15 mg per day.

In preferred aspects of these embodiments the second colchicine dosage amount of about 0.3 mg per day is administered as one half of a 0.6 mg colchicine tablet once a day every day, and the second colchicine dosage amount of about 0.15 mg per day is administered as one half of a 0.6 mg colchicine tablet once a day every other day.

In a distinct preferred embodiment, the patient is administered the colchicine according to a colchicine dosing regimen of a single starting colchicine dose of no more than about 0.6 mg colchicine, followed by either no additional colchicine doses within about 12, 24, 48, or 72 hours, or followed by at least one additional colchicine dose within 12 hours and no more frequently than once every hour (e.g., every 3, 4, 6, 8, or 12 hours). In this embodiment, each additional colchicine dose is preferably no greater than about 0.3 mg and the patient may be an adult patient or a pediatric patient. Preferably the starting colchicine dose is about 0.6 mg or about 0.3 mg, and each additional colchicine dose is about 0.3 mg. When additional doses are administered, it is preferred that only two, three, or four additional colchicine doses are administered within about 24 hours. Preferably, the patient is an adult patient and the starting colchicine dose is about 0.6 mg and each additional colchicine dose, if any, is about 0.3 mg. In one embodiment only three additional colchicine doses are administered within about 24 hours.

In another distinct preferred embodiment, colchicine is administered to a patient in suffering from a condition treatable with colchicine, and the concomitant macrolide antibiotic is administered concurrently, or the patient has recently completed a dosing regimen of a macrolide antibiotic to treat an infection, and the patient is (immediately or within a period of two weeks, preferably three days, more preferably within 48 hours or 24 hours after completion of the macrolide antibiotic dosing regimen) administered a single dose of no more than about 0.6 mg of colchicine, preferably 0.3 mg or 0.6 mg of colchicine. For example, the starting colchicine dose is about 0.6 mg and only one additional colchicine dose is administered within about 24 hours and the additional colchicine dose is about 0.6 mg.

A preferred antibiotic for use in the disclosed methods is one that is an inhibitor of either or both of CYP3A and P-glycoprotein, preferably both. Preferably the antibiotic is dirithromycin, erythromycin, roxithromycin, or more preferably, clarithromycin or erythromycin. The clarithromycin may, for example, be administered to the patient at a dosage amount of about 500 mg daily and the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by 0, 1, 2, 3, or 4 additional colchicine doses of about 0.6 mg every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. Alternately, the clarithromycin may be administered to the patient at a dosage amount of about 1000 mg daily and the colchicine dosing regimen is one about 0.3 mg colchicine dose to start, followed by 0, 1, 2, 3, or 4 additional colchicine doses of about 0.3 mg each every 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 3, 4, 5, or 6 hours) after the preceding colchicine dose. In a preferred regimen for treatment of acute gout flares, ingestion of colchicine is continued until a total of no more than about 1.2, 1.4, 1.6, 1.8, 2, or 2.4 mg of colchicine has been ingested, after which ingestion of colchicine is stopped until a subsequent acute gout flare occurs. In still another

8

preferred regimen, clarithromycin may be administered to a patient, e.g., at a dosage amount of about 250 mg B.I.D. for a period of about 7 to 10 days, and the colchicine dosing regimen is administered to the patient upon completion of the clarithromycin dosing regimen, wherein the colchicine dosing regimen consists of the administration of no more than one dose of no more than 0.6 mg of colchicine. More preferably, the colchicine is administered as a dosage form of 0.6 mg (e.g., one 0.6 mg colchicine tablet), or 0.3 mg (e.g., one half of a 0.6 mg tablet) of colchicine and administration of the dosage form is not repeated within a period of at least about two days, preferably at least about three days.

In various of these and other embodiments, the colchicine-responsive condition is gout (e.g. a gout flare in a chronic gout sufferer), familial Mediterranean fever (FMF), thrombocytopenic purpura, pericarditis, scleroderma, or Behcet's disease. The gout may be an acute gout flare or chronic gout. For gout, the dosing regimen is preferably continued until a total of no more than 2.4 mg of colchicine has been ingested, after which ingestion of colchicine is preferably stopped until a subsequent gout flare occurs.

Another embodiment comprises administering colchicine to a patient also taking clarithromycin, or having completed treatment with clarithromycin within the prior 14 days, the patient being administered a single dose of about 0.6 mg or about 0.3 mg of colchicine to treat a gout flare, which administration is not repeated within any 3-day period.

In another aspect, herein disclosed is a method for increasing the blood plasma levels of colchicine in a patient to whom colchicine is being administered to treat or prevent a colchicine-responsive condition. This method comprises the concomitant dosing of the patient with a sufficient amount of a macrolide antibiotic to increase the C_{max} of colchicine by about 167% to 200%, or to increase the AUC of colchicine in the patient by about 240% to 250%, or to increase the plasma half-life of colchicine by about 233%, or to decrease the clearance of colchicine by about 75%, compared to the C_{max} , AUC, plasma half-life, or clearance in the same or a matched patient when not being administered a concomitant macrolide antibiotic. In a preferred embodiment, the patient is being administered no more than hourly doses of about 0.6 mg of colchicine or less, the macrolide antibiotic is clarithromycin, and the amount of macrolide antibiotic is from about 500 mg to about 1000 mg, with about 500 mg being preferred.

In another aspect, herein disclosed are methods for using colchicine which methods involve the use of pharmacy management systems.

In a preferred aspect one such method comprises a pharmacy receiving a prescription for colchicine for a patient who is suffering from gout (e.g., acute gout flares or chronic gout) and who is concomitantly being treated with a macrolide antibiotic that is an inhibitor of CYP3A and P-glycoprotein, followed by the pharmacy dispensing colchicine in response to receipt of the prescription, wherein the dispensing is preceded by entry into a first computer readable storage medium, in functional communication with a computer, of a unique patient identifier for said patient and at least one drug identifier for colchicine linked to the patient identifier so as to indicate that colchicine is to be administered to the patient. The computer is programmed to issue a drug-drug interaction alert when the at least one drug identifier for colchicine is entered linked to the patient identifier so as to indicate that colchicine is to be administered to the patient and when the patient identifier is also linked to an identifier indicating that a macrolide antibiotic that is an inhibitor of CYP3A or P-glycoprotein is being concomitantly administered to the patient. Upon entry of the at least one drug identifier for colchicine

US 7,619,004 B1

9

linked to the patient identifier, a drug-drug interaction alert is issued to one or more of a pharmacy technician, a pharmacist, or a pharmacy customer obtaining the colchicine, said alert indicating that a macrolide antibiotic is being concomitantly administered to the patient and that prior to the colchicine being dispensed, the colchicine dosing regimen must be reviewed and, if necessary adjusted, so that when the colchicine is delivered to the pharmacy customer obtaining the colchicine it is delivered along with instructions for the colchicine to be taken in accordance with a dosing regimen of no more than one about 0.6 mg colchicine dose to start (e.g., following the onset of the acute gout attack or the first sign of a gout flare) followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours and no more frequently than once every hour and wherein each additional colchicine dose is no greater than about 0.6 mg, and wherein the patient ingests the colchicine as instructed.

The drug-drug interaction alert is preferably issued as one or both of a written warning on a display screen of the pharmacy management computer system, and a printed warning. The printed warning may be attached to or packaged with the dispensed prescription.

In a preferred aspect, the identifier indicating that a macrolide antibiotic is being concomitantly administered to the patient is an identifier indicating that the macrolide antibiotic is clarithromycin and is linked to at least one further identifier indicating that the clarithromycin is prescribed so that 500 mg of clarithromycin is to be ingested by the patient daily, in which case the dosing regimen for colchicine is preferably one about 0.6 mg colchicine dose to start, optionally followed by additional colchicine doses, e.g., 0, 1, 2, 3, or 4 additional colchicine doses within 24 hours of about 0.3 mg ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In another embodiment, the identifier indicating that a macrolide antibiotic is being concomitantly administered to the patient is an identifier indicating that the macrolide antibiotic is clarithromycin is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the clarithromycin is prescribed so that about 500 mg of clarithromycin is to be ingested by the patient daily, in which case the colchicine dosing regimen is (preferably) one about 0.6 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every six to eight hours) after the preceding colchicine dose.

In yet another preferred aspect, the identifier indicating that a macrolide antibiotic is being concomitantly administered to the patient is an identifier indicating that the macrolide antibiotic is clarithromycin and is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the clarithromycin is prescribed so that about 1000 mg of clarithromycin is to be ingested by the patient daily and the dosing regimen is one about 0.3 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 2, 3, 4, 5, 6, 7, or 8 hours (e.g., every eight to twelve hours) after the preceding colchicine dose.

A preferred dosing regimen calls for ingestion of colchicine to be continued until a total of no more than 1.2 mg or 2.4 mg of colchicine has been ingested, after which ingestion of

10

colchicine is to be stopped, e.g., for at least 2, 3, 4, 5, 6, or 7 days, or until a subsequent acute gout flare, or the first sign of a subsequent gout flare, occurs.

Also disclosed herein is a dosage amount adjustment method for administering colchicine to a patient to treat a medical condition, the patient concomitantly suffering from an infection amenable to treatment with a macrolide antibiotic. The method comprises determining a first, a second, and a subsequent monotherapy colchicine dose and a colchicine treatment schedule; and determining an antibiotic dose and an antibiotic treatment schedule; and administering the macrolide antibiotic to the patient at the antibiotic dose according to the antibiotic treatment schedule while concomitantly administering colchicine to the patient according to the colchicine treatment schedule at a first, a second, and a subsequent polytherapy colchicine dose, each of which is a fraction of each of the corresponding first, second, and subsequent monotherapy colchicine doses, the fraction being less than or equal to about $\frac{2}{3}$.

An alternate embodiment of this method comprises determining a monotherapy colchicine dose and a colchicine treatment schedule, each adapted so that, when colchicine is administered to the patient in the absence of concomitant administration of the antibiotic at the monotherapy colchicine dose according to the colchicine treatment schedule, a therapeutic circulating plasma level of colchicine is predicted to be achieved in the patient that is safe and effective to treat the condition in the patient while posing an acceptable adverse effect risk; and determining an antibiotic dose and an antibiotic treatment schedule, each adapted so that, when the antibiotic is administered to the patient at the antibiotic dose according to the antibiotic treatment schedule, a circulating level of the antibiotic is predicted to be achieved in the patient that is safe and therapeutically effective to treat the infection in the patient and administering the antibiotic to the patient at the antibiotic dose according to the antibiotic treatment schedule while concomitantly administering colchicine to the patient at a polytherapy colchicine dose that is a fraction less than or equal to $\frac{1}{2}$ of the monotherapy colchicine dose to the patient according to the colchicine treatment schedule.

According to this embodiment, upon the administering of the antibiotic to the patient at the antibiotic dose according to the antibiotic treatment schedule while concomitantly administering colchicine to the patient at the polytherapy colchicine dose according to the colchicine treatment schedule, the therapeutic circulating level of colchicine is achieved in the patient. Preferably, the fraction is selected from $\frac{1}{12}$, $\frac{1}{6}$, $\frac{1}{4}$, $\frac{1}{3}$, $\frac{5}{12}$, and $\frac{1}{2}$, more preferably, the fraction is $\frac{1}{3}$ or $\frac{1}{2}$. Preferably the antibiotic is selected from clarithromycin, dirithromycin, erythromycin and roxithromycin. The Preferred conditions are selected from gout, FMF, thrombocytopenic purpura, and Behcet's disease. In a preferred embodiment, the gout is an acute gout flare and the colchicine treatment schedule is an acute treatment schedule adapted for treatment of acute gout flares, or the gout is chronic gout, and the colchicine treatment schedule is a chronic treatment schedule adapted for prophylaxis of flares. In another preferred embodiment, the fraction is $\frac{1}{3}$ or $\frac{1}{2}$ and treatment with colchicine is initiated subsequent to initiation of treatment with clarithromycin.

Preferably, each of the monotherapy colchicine doses and the colchicine treatment schedule are each adapted so that, when colchicine is administered to the patient at the monotherapy colchicine doses according to the colchicine treatment schedule in the absence of concomitant administration of the antibiotic, a therapeutic circulating level of colchicine is predicted to be achieved in the patient that is predicted to be

US 7,619,004 B1

11

safe and effective to treat the condition in the patient while posing an acceptable adverse effect risk.

Alternately, the antibiotic dose and the antibiotic treatment schedule are each adapted so that, when the antibiotic is administered to the patient at the antibiotic dose according to the antibiotic treatment schedule a circulating level of the antibiotic is predicted to be achieved in the patient that is therapeutically effective to treat the infection in the patient.

Preferably, upon the administration of the antibiotic to the patient at the antibiotic dose according to the antibiotic treatment schedule while concomitantly administering colchicine to the patient according to the colchicine treatment schedule at the polytherapy colchicine dose, a therapeutic circulating level of colchicine is predicted to be achieved in the patient that is predicted to be safe and effective to treat the condition in the patient while posing an acceptable adverse effect risk. In one embodiment, each subsequent colchicine dose is the same as the second colchicine dose. In another, each of the second and subsequent colchicine doses are the same as the first colchicine dose. In another, the fraction is selected from about $\frac{1}{12}$, about $\frac{1}{6}$, about $\frac{1}{4}$, about $\frac{1}{3}$, about $\frac{5}{12}$, about $\frac{1}{2}$, and about $\frac{7}{12}$, e.g., about $\frac{1}{2}$ or about $\frac{2}{3}$. Preferably the colchicine treatment schedule is once-a-day, twice-a-day, three-times-a-day or four-times-a-day.

Colchicine is one of the most widely used drugs for treating familial Mediterranean fever (FMF). It has been reported that 5-10% of FMF patients do not show a beneficial response to colchicine administration. A polymorphism in the ABCB1 gene, the "ABCB1 3435 C to T polymorphism" has been reported to correlate with this lack of response to colchicine treatment, with patients with the homozygous TT genotype exhibiting the most pronounced "non-responder" phenotypes.

Accordingly, in another aspect, provided herein is a method for treating a patient suffering from FMF, which patient is a colchicine non-responder. Preferably, the patient is homozygous for the TT genotype of the ABCB1 3435 C to T polymorphism. The method entails the concomitant administration of a Pgp inhibitor and colchicine to the patient. A preferred Pgp inhibitor for use in this method is verapamil or cyclosporine-A, more preferably a macrolide antibiotic, preferably dirithromycin, erythromycin or roxithromycin, or, more preferably clarithromycin. Preferred dosage amounts of the Pgp inhibitor for this purpose correspond to those called for in the prescribing information for the drug in question. For clarithromycin, preferred dosage amounts are 500 to 1000 mg per day and duration of clarithromycin dosing is preferably one, two, or three days, repeated weekly or bi-weekly. Preferred colchicine dosing regimens for this purpose are the same as used for treatment of FMF in responders, though the doses of colchicine administered may be increased as tolerated, e.g., up to two to three times the typical doses.

These and other embodiments, advantages and features of the present invention are further elaborated herein below.

DETAILED DESCRIPTION

Following multiple oral doses (0.6 mg twice daily), the mean elimination half-life of colchicine in young healthy volunteers (mean age 25 to 28 years of age) is 26.6 to 31.2 hours.

In the specification and claims that follow, references will be made to a number of terms which shall be defined to have the following meaning.

The terms "a" and "an" do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The term "or" means "and/or". The terms

12

"comprising", "having", "including", and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to").

"Concomitant" and "concomitantly" as used herein refer to the administration of at least two drugs to a patient either simultaneously or within a time period during which the effects of the first administered drug are still operative in the patient. Thus, if the first drug is, e.g., clarithromycin and the second drug is colchicine, the concomitant administration of the second drug can occur as much as one to two weeks, preferably within one to seven days, after the administration of the first drug. This is because clarithromycin can exert a long-lasting inhibition of CYP3A isozymes so that CYP3A activity in the patient may not return to pre-clarithromycin-administration levels for as much as two weeks after the cessation of clarithromycin administration. If colchicine is the first drug, administration of a second drug would be concomitant if done within 1 to 2 days, preferably 12 to 24 hours.

"Dosage amount" means an amount of a drug to suitable to be taken during a fixed period, usually during one day (i.e., daily). A daily dosage amount may be administered as a single daily dose or as smaller multiple doses during a single day. A daily dosage amount may also be result from larger doses administered at intervals of more than one day (e.g., double the dosage amount administered in one or more doses per day every other day) so that on average the daily dosage amount is achieved.

"Dosage amount adapted for daily oral administration" means a daily dosage amount that is of an amount deemed safe and effective for the particular patient under the conditions specified. As used herein and in the claims, this dosage amount is determined by following the recommendations of the drug manufacturer's Prescribing Information as approved by the US Food and Drug Administration.

"Dosing regimen" means the dose of a drug taken at a first time by a patient and the interval (time or symptomatic) and dosage amounts at which any subsequent doses of the drug are taken by the patient. Each dose may be of the same or a different dosage amount.

A "dose" means the measured quantity of a drug to be taken at one time by a patient.

A "patient" means a human or non-human animal in need of medical treatment. Medical treatment can include treatment of an existing condition, such as a disease or disorder, prophylactic or preventative treatment, or diagnostic treatment. In preferred embodiments the patient is human.

"Providing" means giving, administering, selling, distributing, transferring (for profit or not), manufacturing, compounding, or dispensing.

"Risk" means the probability or chance of adverse reaction, injury, or other undesirable outcome arising from a medical treatment. An "acceptable risk" means a measure of the risk of harm, injury, or disease arising from a medical treatment that will be tolerated by an individual or group. Whether a risk is "acceptable" will depend upon the advantages that the individual or group perceives to be obtainable in return for taking the risk, whether they accept whatever scientific and other advice is offered about the magnitude of the risk, and numerous other factors, both political and social. An "acceptable risk" of an adverse reaction means that an individual or a group in society is willing to take or be subjected to the risk that the adverse reaction might occur since the adverse reaction is one whose probability of occurrence is small, or whose consequences are so slight, or the benefits (perceived or real) of the active agent are so great. An "unacceptable risk" of an adverse reaction means that an individual

US 7,619,004 B1

13

or a group in society is unwilling to take or be subjected to the risk that the adverse reaction might occur upon weighing the probability of occurrence of the adverse reaction, the consequences of the adverse reaction, and the benefits (perceived or real) of the active agent. "At risk" means in a state or condition marked by a high level of risk or susceptibility.

Pharmacokinetic parameters referred to herein describe the in vivo characteristics of drug (or a metabolite or a surrogate marker for the drug) over time. These include plasma concentration (C), as well as C_{max} , C_n , C_{24} , T_{max} , and AUC. " C_{max} " is the measured plasma concentration of the active agent at the point of maximum, or peaks, concentration. " C_{min} " is the measured plasma concentration of the active agent at the point of minimum concentration. " C_n " is the measured plasma concentration of the active agent at about n hours after administration. " C_{24} " is the measured plasma concentration of the active agent at about 24 hours after administration. The term " T_{max} " refers to the time from drug administration until C_{max} is reached. "AUC" is the area under the curve of a graph of the measured plasma concentration of an active agent vs. time, measured from one time point to another time point. For example AUC_{0-t} is the area under the curve of plasma concentration versus time from time 0 to time t, where time 0 is the time of initial administration of the drug. Time t can be the last time point with measurable plasma concentration for an individual formulation. The $AUC_{0-\infty}$ or AUC_{0-INF} is the calculated area under the curve of plasma concentration versus time from time 0 to time infinity. In steady-state studies, $AUC_{0-\tau}$ is the area under the curve of plasma concentration over the dosing interval (i.e., from time 0 to time τ (tau), where tau is the length of the dosing interval. Other pharmacokinetic parameters are the parameter K_c or K_{cl} , the terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve; $t_{1/2}$ the terminal elimination half-life, calculated as $0.693/K_{cl}$; CL/F denotes the apparent total body clearance after administration, calculated as Total Dose/Total AUC_{∞} ; and V_{area}/F denotes the apparent total volume of distribution after administration, calculated as Total Dose/(Total $AUC_{\infty} \times K_{cl}$).

"Side effect" means a secondary effect resulting from taking a drug. The secondary effect can be a negative (unfavorable) effect (i.e., an adverse side effect) or a positive (favorable) effect.

The most frequently reported adverse side effects to colchicine therapy are gastrointestinal, specifically abdominal pain with cramps, diarrhea, nausea, and vomiting. Less frequently or rarely reported adverse side effects associated with colchicine therapy include anorexia, agranulocytosis, allergic dermatitis, allergic reactions, alopecia, angioedema, aplastic anemia, bone marrow depression, myopathy, neuropathy, skin rash, thrombocytopenic disorder, and urticaria.

Whether a patient experiences an adverse side effect can be determined by obtaining information from the patient regarding onset of certain symptoms which may be indicative of the adverse side effect, results of diagnostic tests indicative of the adverse side effect, and the like.

Pharmacy management systems are computer-based systems that are widely used by commercial pharmacies to manage prescriptions and to provide pharmacy and medical personnel with warnings and guidance regarding drugs being administered to patients. Such systems typically provide alerts warning either or both of health care providers and patients when a drug that may be harmful to the particular patient is prescribed. For example, such systems can provide alerts warning that a patient has an allergy to a prescribed drug, or is receiving concomitant administration of a drug that can have a dangerous interaction with a prescribed drug. U.S.

14

Pat. Nos. 5,758,095, 5,833,599, 5,845,255, 6,014,631, 6,067, 524, 6,112,182, 6,317,719, 6,356,873, and 7,072,840, each of which is incorporated herein by reference, disclose various pharmacy management systems and aspects thereof. Many pharmacy management systems are now commercially available, e.g., CENTRICITY Pharmacy from BDM Information Systems Ltd., General Electric Healthcare, Waukesha, Wis., Rx30 Pharmacy Systems from Transaction Data Systems, Inc., Ocoee, Fla., SPEED SCRIPT from Digital Simplistics, Inc., Lenexa, Kans., and various pharmacy management systems from OPUS-ISM, Hauppauge, N.Y.

The following examples further illustrate aspects of this disclosure but should not be construed as in any way limiting its scope. In particular, the conditions are merely exemplary and can be readily varied by one of ordinary skill in the art.

EXAMPLES

Example 1

Pharmacokinetic Study in Healthy Adults of Single Vs. Multiple Oral Doses of Colchicine Tablets

This study was a single-center, open-label, single-sequence, two-period study to evaluate the pharmacokinetic profile of colchicine following single and multiple oral doses of colchicine tablets, 0.6 mg, in healthy volunteers.

In Period 1, study subjects received a 0.6-mg dose of colchicine after an overnight fast of at least 10 hours. In Period 2, subjects received a 0.6-mg dose of colchicine in the morning and the evening (approximately 12 hours later) for 10 days (steady state regimen). Subjects received a light breakfast served 60 minutes following dose administration in the morning and the evening dose was administered 90 minutes after an evening meal on Days 15 through 24 only. On Day 25, the colchicine dose was administered after an overnight fast of at least 10 hours and lunch was served 4 hours post-dose. Study periods were separated by a 14-day wash-out. Following the single dose and the last dose of the multiple dose regimen (beginning on the mornings of Day 1 and Day 25, respectively), blood samples were collected (6 mL each) from each subject within 1 hour prior to dosing and after dose administration at study hours 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 (while confined) and 36, 48, 72, and 96 (on an outpatient basis). Plasma concentrations of colchicine and its metabolites were determined using validated LC/MS-MS methods.

Thirteen healthy, non-smoking subjects with a mean age of 25.5 years (range 19 to 38 years) and within 15% of ideal body weight were enrolled in this study. All subjects completed both dosing periods according to protocol.

After a single dose, plasma concentrations are no longer quantifiable 24 hours post-dose in all but 1 subject. After the last dose of the steady state regimen, concentrations remained quantifiable for 48 to 72 hours. Review of individual subject data shows that no subject experienced a secondary colchicine peak, either following a single dose or upon multiple dosing.

All 2-O-demethylcolchicine (2-DMC) concentrations were below the level of quantitation (LOQ, 0.2 ng/mL) and only one sample from 1 subject (of 13 subjects) had a detectable 3-O-demethylcolchicine (3-DMC) concentration which was near the level of quantitation. Therefore, metabolites are not discussed further.

In healthy adults, colchicine appears to be readily absorbed when given orally, reaching a mean maximum plasma concentration of 2.5 ng/mL in 1.5 hours after a single dose. The

US 7,619,004 B1

15

drug is distributed widely, with an apparent volume of distribution of 540 L, greatly exceeding total body water. The elimination half-life as calculated following a single oral dose is approximately 5 hours. Levels were not detectable by 24 hours post-dose and this is therefore not an accurate estimate. Pharmacokinetic parameter values are summarized in the table below.

Review of trough plasma concentrations indicates that steady state was attained by approximately the eighth day of dosing for most subjects. Colchicine may have a diurnal variation reflected in the observed Cmin concentrations at steady state. Cmin concentrations prior to the morning dose are approximately 12% higher than the Cmin concentrations prior to the evening dose (Day 23 and Day 24). The mean Cmin concentration observed on Day 25 was 0.907 ng/mL.

Colchicine accumulated following administration of multiple doses to an extent greater than expected. Exposure was nearly two-fold higher (approximately 1.7 based on AUC [Day 25 AUC_{0-∞}/Day 1 AUC_{0-∞}] and approximately 1.5 based on Cmax [Day 25 C_{max}/Day 1 C_{max}]). This observation could be attributable to an underestimation of AUC_∞ following a single dose. With the higher plasma levels that occur with repeated dosing, a longer terminal elimination half life is apparent, 26.6 hours. Pharmacokinetic parameter values are summarized in the tables below.

TABLE 1

| Colchicine Pharmacokinetic Parameter Values Following Administration of A Single Oral Dose of Colchicine 0.6 mg in Healthy Adults (N = 13) | | | | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|------------------------------------|-----------------------------|--------------------------|---------------------------|--------------------------|
| | AUC _{0-∞} (pg-hr/mL) | AUC _{0-inf} (pg-hr/mL) | C _{max} (pg/mL) | T _{max} (hr) | K _{el} (1/hr) | T _{1/2} (hr) |
| MEAN | 10508.54 | 12281.90 | 2470.77 | 1.50 | 0.1829 | 4.95 |
| STDEV | 3544.82 | 4423.34 | 706.98 | 0.54 | 0.0592 | 4.43 |
| % CV | 33.73 | 36.02 | 28.61 | 36.00 | 32.39 | 89.54 |
| MEDIAN | 10560.90 | 11451.45 | 2714.00 | 1.50 | 0.1992 | 3.48 |
| MIN | 4812.88 | 7252.66 | 1584.00 | 1.00 | 0.0359 | 2.84 |
| MAX | 18128.65 | 23838.48 | 3977.00 | 3.00 | 0.2443 | 19.29 |

TABLE 2

| Colchicine Pharmacokinetic Parameter Values Following Administration of Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults (N = 13) | | | | | | | | | |
|------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|----------------------------------|------------------------------------|-----------------------------|-----------------------------|-----------------------------|--------------------------|---------------------------|--------------------------|
| | AUC _{0-∞} (pg-hr/mL) | AUC _{0-τ} (pg-hr/mL) | AUC _{0-inf} (pg-hr/mL) | C _{max} (pg/mL) | C _{min} (pg/mL) | C _{ave} (pg/mL) | T _{max} (hr) | K _{el} (1/hr) | T _{1/2} (hr) |
| MEAN | 43576.96 | 29056.23 | 54198.77 | 3553.15 | 906.51 | 1210.68 | 1.31 | 0.03 | 26.60 |
| STDEV | 9333.26 | 4531.30 | 9214.54 | 843.45 | 152.19 | 188.80 | 0.60 | 0.00 | 4.33 |
| % CV | 21.42 | 15.59 | 17.00 | 23.74 | 16.79 | 15.59 | 45.61 | 16.34 | 16.26 |
| MEDIAN | 41925.10 | 28452.15 | 54113.43 | 3734.00 | 903.50 | 1185.51 | 1.00 | 0.03 | 26.51 |
| MIN | 29328.78 | 20791.98 | 37599.76 | 1977.00 | 636.23 | 866.33 | 0.50 | 0.02 | 20.82 |
| MAX | 58265.35 | 36083.95 | 67944.65 | 4957.00 | 1149.67 | 1503.50 | 3.00 | 0.03 | 33.65 |

TABLE 3

| Mean (% CV) Colchicine Pharmacokinetic Parameter Values Following Administration of Single and Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|----------------|
| | Vd/F (L) | CL/F (L/hr) |
| Colchicine 0.6-mg Single Dose (N = 13) | | |
| Day 1 | 341 (54.4) | 54.1 (31.0) |

16

TABLE 3-continued

| Mean (% CV) Colchicine Pharmacokinetic Parameter Values Following Administration of Single and Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|----------------|
| | Vd/F (L) | CL/F (L/hr) |
| Colchicine 0.6 mg b.i.d. × 10 days | | |
| Day 25 | 1150 (18.73) | 30.3 (19.0) |

CL = Dose/AUC₀₋₁ (Calculated from mean values)Vd = CL/K_e (Calculated from mean values)

In the above table, the parameter CL/F denotes the apparent total body clearance after administration, calculated as Total Dose/Total AUC_{0-τ}; and V_d/F denotes the apparent total volume of distribution after administration, calculated as Total Dose/(Total AUC_∞ × K_{cl}).

Example 2

Clinical Drug-Drug Interaction Study of Colchicine and Clarithromycin

A single-center, open-label, one sequence, two-period study was carried out in 23 healthy subjects. On Day 1, a single 0.6-mg dose of colchicine was administered. After completing a 21-day washout period, all subjects received 250 mg of clarithromycin administered twice daily for 7 days (Days 22 through 29), a sufficient dose and duration to inhibit CYP3A4 and Pgp. On the final day (Day 29), a single dose of colchicine was co-administered with the clarithromycin dose.

When combined with steady-state clarithromycin, there is a significant increase in exposure to colchicine as compared

to when colchicine is given alone: the mean C_{max} and AUC_{0-∞} concentrations increased 167% and 250%, respectively. In addition, co-administration of clarithromycin and colchicine resulted in an increase of 233% in the plasma elimination half-life (t_{1/2}) of colchicine and a 75% decrease in apparent clearance (CL/F). A summary of the mean (% CV) colchicine pharmacokinetic parameters for Day 1 (colchicine administered alone) and Day 29 (colchicine co-administered with steady-state clarithromycin) are given in the table below and illustrated in the table that follows.

US 7,619,004 B1

17

18

TABLE 4

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Clarithromycin in Healthy Adults | | | | | | | | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|--------------------|----------------------------|-------------------------------|--------------------------|----------------|----------------|------------------|
| DAY | C_{max} (ng/mL) | T_{max}^1 (h) | AUC_{0-t} (ng · h/mL) | AUC_{∞} (ng · h/mL) | Ke (h ⁻¹) | Vd/F (L) | CL/F (L/hr) | $t_{1/2}$ (h) |
| Colchicine Alone (n = 23) | | | | | | | | |
| 1 | 3 (30.97) | 1.00 (0.5-2.0) | 12 (37.6) | 16 (49.6) | 0.132 (46.87) | 432 (56.1) | 46.8 (43.7) | 9 (126.4) |
| Colchicine + Clarithromycin (n = 23) | | | | | | | | |
| 29 | 8 (23.74) | 1.0 (1.0-5.0) | 42 (23.3) | 53 (22.8) | 0.0298 (90.82) | 493 (33.69) | 12 (23.8) | 30 (41.37) |
| p value | | | | | | | | |
| | <0.0001 | 0.05061 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.0001 |

¹ T_{max} mean (range)

Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges directed to the same component or property are inclusive and independently combinable.

All methods described herein can be performed in a suitable order unless otherwise indicated or clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") herein is intended to better illuminate the disclosure and is non-limiting unless otherwise specified. No language in the specification should be construed as indicating that any non-claimed element as essential to the practice of the claimed embodiments. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this disclosure belongs. The terms wt %, weight percent, percent by weight, etc. are equivalent and interchangeable.

Embodiments are described herein, including the best modes known to the inventors. Variations of such embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The skilled artisan is expected to employ such variations as appropriate, and the disclosed methods are expected to be practiced otherwise than as specifically described herein. Accordingly, all modifications and equivalents of the subject matter recited in the claims appended hereto are included to the extent permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed unless otherwise indicated herein or otherwise clearly contradicted by context.

What is claimed is:

1. A method of using colchicine for prophylactic treatment of gout flares in a human gout patient so as to reduce the occurrence of colchicine toxicity when said patient is receiving concomitant administration of clarithromycin, said method comprising:

orally administering a second colchicine daily dosage amount for prophylactic treatment of gout flares to the human gout patient who is concomitantly receiving administration of clarithromycin, wherein the second colchicine daily dosage amount is a 75% reduction of a first colchicine daily dosage amount suitable for daily

oral administration for the prophylactic treatment of gout flares in the absence of concomitant administration of clarithromycin, wherein concomitant administration of clarithromycin is administration within 1 to 2 days of orally administering the second colchicine dosage amount, and

wherein the first colchicine daily dosage amount is 1.2 mg administered as two 0.6 mg doses per day, and the second colchicine daily dosage amount is 0.3 mg per day, or wherein the first colchicine daily dosage amount is 0.6 mg per day and the second colchicine daily dosage amount is 0.15 mg per day administered as 0.3 mg every other day, or wherein the first colchicine daily dosage amount is 0.6 mg per day and the second colchicine daily dosage amount is 0.15 mg per day.

2. The method of claim 1 wherein the patient is administered each dose of colchicine as one 0.6 mg colchicine tablet or as one half of a 0.6 mg colchicine tablet.

3. The method of claim 1 wherein the patient is an adult.

4. The method of claim 3 wherein the patient is less than 70 years old.

5. A method of using colchicine for prophylactic treatment of gout flares in an adult human gout patient so as to reduce the occurrence of colchicine toxicity when said patient is receiving concomitant administration of clarithromycin, said method comprising: administering a reduced colchicine daily dosage amount to the patient for prophylactic treatment of gout flares, wherein the reduced colchicine daily dosage amount is 75% of a manufacturers' recommended colchicine daily dosage amount for the prophylactic treatment of gout flares in the absence of concomitant clarithromycin administration, wherein concomitant administration of clarithromycin is administration within 1 to 2 days of orally administering the second colchicine dosage amount.

6. The method of claim 5 wherein the reduced colchicine daily dosage amount is about 0.3 mg per day.

7. The method of claim 5 wherein the reduced colchicine daily dosage amount is about 0.15 mg per day, which is administered as 0.3 mg of colchicine once a day every other day.

8. The method of claim 1 wherein the clarithromycin is administered concurrently with the second colchicine daily dosage amount.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

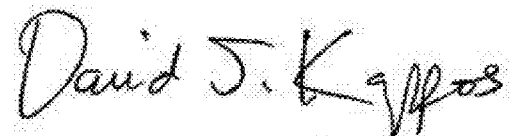
PATENT NO. : 7,619,004 B1
APPLICATION NO. : 12/327258
DATED : November 17, 2009
INVENTOR(S) : Matthew W. Davis

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 18 line 49, DELETE “is 75% of a manufacturer’s recommended”, and replace with
--is a 75% reduction of a manufacturer’s recommended--.

Signed and Sealed this
Twenty-fifth Day of October, 2011

A handwritten signature in black ink that reads "David J. Kappos". The signature is written in a cursive, flowing style with a large initial 'D' and a stylized 'K'.

David J. Kappos
Director of the United States Patent and Trademark Office

EXHIBIT B

US007601758B1

(12) **United States Patent**
Davis

(10) **Patent No.:** **US 7,601,758 B1**
(45) **Date of Patent:** **Oct. 13, 2009**

(54) **METHODS FOR CONCOMITANT
ADMINISTRATION OF COLCHICINE AND
MACROLIDE ANTIBIOTICS IN THE
TREATMENT OF GOUT FLARES**

(75) Inventor: **Matthew W. Davis**, Erwinna, PA (US)

(73) Assignee: **Mutual Pharmaceutical Company,
Inc.**, Philadelphia, PA (US)

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

(21) Appl. No.: **12/368,700**

(22) Filed: **Feb. 10, 2009**

Related U.S. Application Data

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Oct. 15, 2008.

(51) **Int. Cl.**
A61K 31/167 (2006.01)
C07C 233/23 (2006.01)
C07C 211/41 (2006.01)

(52) **U.S. Cl.** **514/629**; 564/123; 564/308;
564/427; 568/306

(58) **Field of Classification Search** None
See application file for complete search history.

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Primary Examiner—Shaojia Anna Jiang

Assistant Examiner—Eric S Olson

(74) *Attorney, Agent, or Firm*—Cantor Colburn LLP

(57) **ABSTRACT**

Methods for treating gout flares comprising concomitant
administration of colchicine together with one or more mac-
rolide antibiotics, e.g., clarithromycin or erythromycin, are
disclosed. Such methods reduce the dangers commonly asso-
ciated with such concomitant administration and provide
additional benefits. Methods of notifying health care practi-
tioners and patients regarding appropriate dosing for co-ad-
ministration of colchicine together with macrolide antibiotics
are also provided.

11 Claims, 2 Drawing Sheets

U.S. Patent

Oct. 13, 2009

Sheet 1 of 2

US 7,601,758 B1

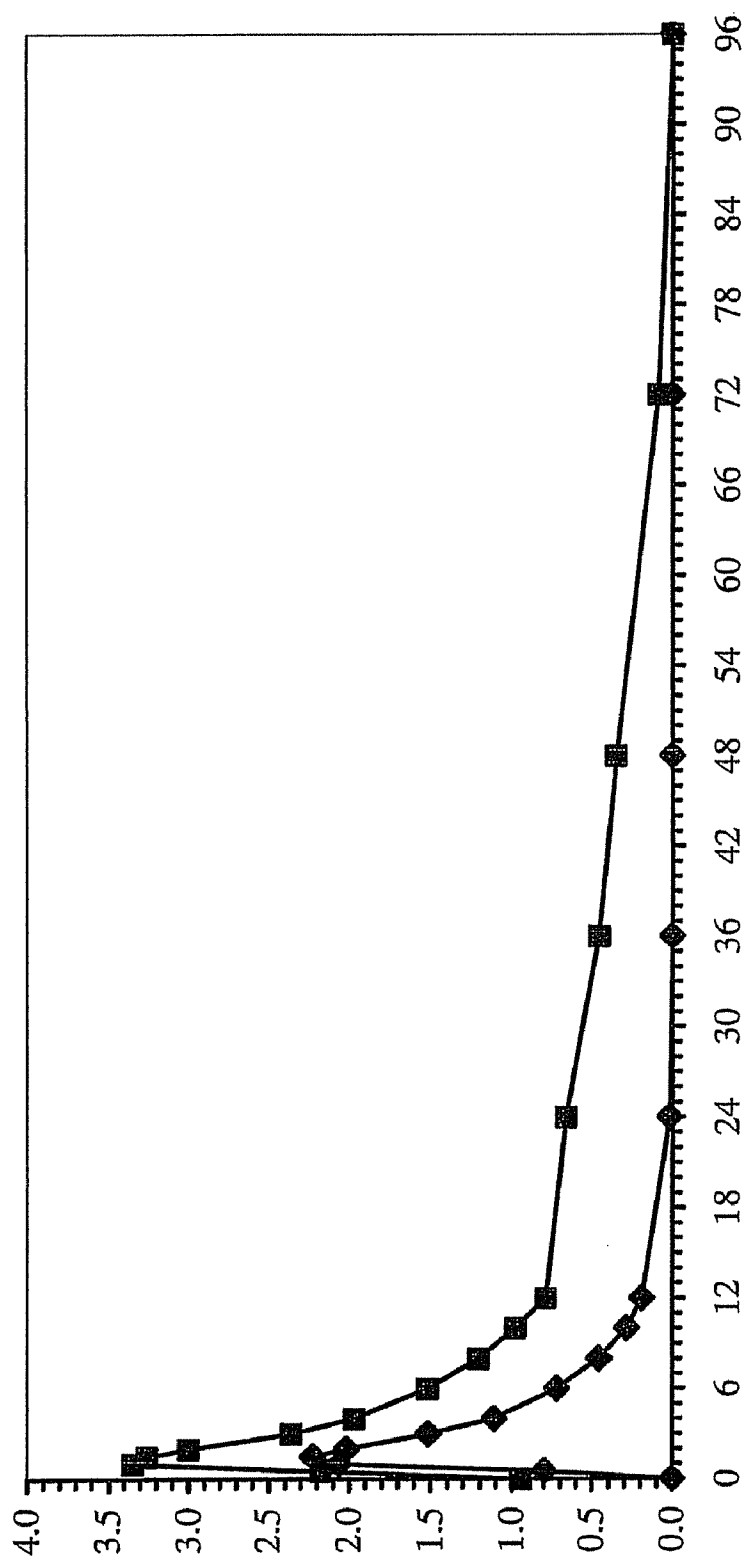


Fig. 1

U.S. Patent

Oct. 13, 2009

Sheet 2 of 2

US 7,601,758 B1

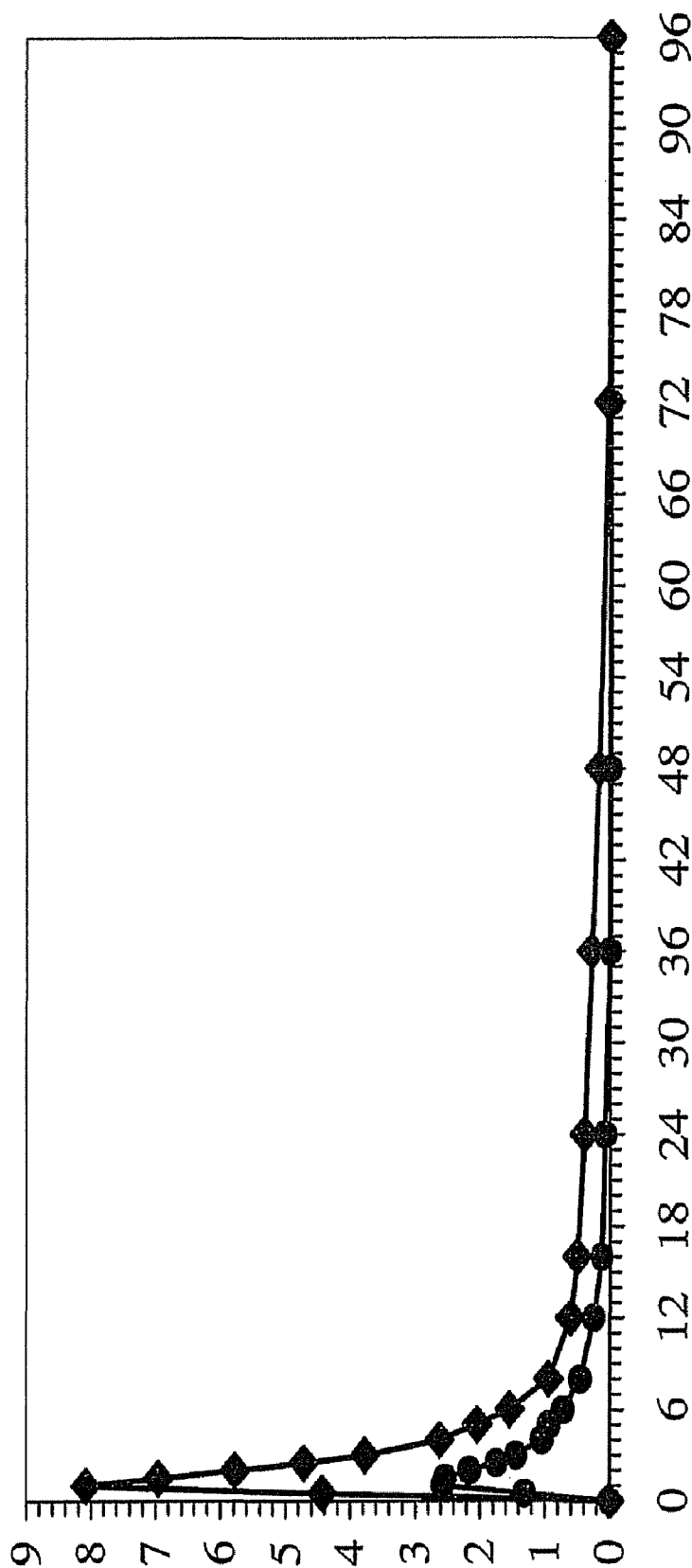


Fig. 2

US 7,601,758 B1

1

METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND MACROLIDE ANTIBIOTICS IN THE TREATMENT OF GOUT FLARES

CLAIM FOR PRIORITY

This application claims the benefit of Provisional Patent Application Ser. No. 61/190,053, filed Oct. 15, 2008.

BACKGROUND

This application relates to methods allowing for the co-administration of colchicine together with one or more macrolide antibiotics for therapeutic purposes with less danger than is associated with prior methods of administration.

Colchicine:

Colchicine, chemical name (–)-N-[(7S, 12aS)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide, is a pale yellow powder soluble in water in 1:25 dilution.

Colchicine is an alkaloid found in extracts of *Colchicum autumnale*, *Gloriosa superba*, and other plants. Among its many biological activities, colchicine blocks microtubule polymerization and arrests cell division. It has adversely affected spermatogenesis in humans and in some animal species under certain conditions.

Colchicine is a microtubule-disrupting agent used in the treatment of gout and other conditions that may be treated, relieved or prevented with anti-inflammatory treatment. Colchicine impairs the motility of granulocytes and can prevent the inflammatory phenomena that initiate an attack (or flare) of gout. Colchicine also inhibits mitosis, thus affecting cells with high turnover such as those in the gastrointestinal tract and bone marrow; therefore, the primary adverse side effects include gastrointestinal upset such as diarrhea, nausea and vomiting. More serious side effects include morbid complications such as myopathy, neuropathy, bone marrow suppression and drug-induced cytopenia. Particular expressions of these morbid complications may include neuromuscular toxicity with paresthesias, pancytopenia, and seizures.

Colchicine has a low therapeutic index. The margin between an effective dose and a toxic dose of colchicine is much narrower than that of most other widely used drugs. Consequently, actions that result in increased colchicine levels in patients receiving colchicine therapy are particularly dangerous. Co-administration of colchicine to patients along with certain other drugs can have the effect of increasing colchicine levels. Such drug-drug interactions with colchicine have been reported to result in serious morbid complications and, in some cases, death.

Colchicine is rapidly absorbed from the gastrointestinal tract. Peak concentrations occur in 0.5 to 2 hours. The drug and its metabolites are distributed in leukocytes, kidneys, liver, spleen and the intestinal tract. Colchicine is metabolized in the liver and excreted primarily in the feces with 10 to 20% eliminated unchanged in the urine.

Gout:

Gout (or gouty arthritis) is a disease caused by a build up of uric acid. Such a build up is typically due to an overproduction of uric acid or to a reduced ability of the kidney to excrete uric acid. Gout is more common in certain groups of patients, including adult males, postmenopausal women, and hypertensives. Heavy alcohol use, diabetes, obesity, sickle cell anemia, and kidney disease also increase the risk of developing gout. The condition may also develop in people who take drugs that interfere with uric acid excretion.

In gout, crystals of monosodium urate (a salt of uric acid) are deposited in joints, e.g., on articular cartilage, as well as in

2

and on tendons and surrounding tissues. These deposits correlate with elevated concentrations of uric acid in the blood stream and are believed to provoke the painful inflammatory reaction that occurs in affected tissues. Gout is characterized by excruciating, sudden, unexpected, burning pain, as well as by swelling, redness, warmth, and stiffness in the affected joint. Low-grade fever may also be present. The patient usually suffers from two sources of pain. The patient experiences intense pain whenever an affected joint is flexed. The inflammation of the tissues around the joint also causes the skin to be swollen, tender and sore if it is even slightly touched. For example, a blanket or even the lightest sheet draping over the affected area could cause extreme pain.

A gout flare is a sudden attack of pain in affected joints, especially in the lower extremities, and most commonly in the big toe. In afflicted individuals, the frequency of gout flares typically increases over time. In this fashion, gout progresses from acute gout to chronic gout, which involves repeated episodes of joint pain. In acute gout flares, symptoms develop suddenly and usually involve only one or a few joints. The big toe, knee, or ankle joints are most often affected. The pain frequently starts during the night and is often described as throbbing, crushing, or excruciating. The joint appears infected, with signs of warmth, redness, and tenderness. Gout flares appear substantially more frequently with more intensive urate-lowering regimens and are a common consequence of therapy with allopurinol. Flares of painful joints may go away in several days, but may return from time to time. Subsequent flares usually last longer. Acute gout may progress to chronic gout flares, or may resolve without further attacks.

The chronic appearance of several attacks of gout yearly can lead to joint deformity and limited joint motion. Nodular uric acid deposits, called tophi, may eventually develop in cartilage tissue, tendons, and soft tissues. These tophi are a hallmark of chronic gout, which usually develop only after a patient has suffered from the disease for many years. Deposits of monosodium urate can also occur in the kidneys of gout sufferers, potentially leading to chronic kidney failure.

Use of Colchicine to Treat Gout:

Colchicine can reduce pain in attacks of acute gout flares and also can be used beneficially for treating adults for prophylaxis of gout flares. Although its exact mode of action in the relief of gout is not completely understood, colchicine is known to decrease the inflammatory response to urate crystal deposition by inhibiting migration of leukocytes, to interfere with urate deposition by decreasing lactic acid production by leukocytes, to interfere with kinin formation and to diminish phagocytosis and subsequent inflammatory responses.

The anti-inflammatory effect of colchicine is relatively selective for gouty arthritis. However, other types of arthritis occasionally respond. It is neither an analgesic nor a uricosuric and will not prevent progression of acute gout to chronic gout. It does have a prophylactic, suppressive effect that helps to reduce the incidence of acute attacks as well as to relieve the residual pain and mild discomfort that patients with gout occasionally experience between attacks.

Macrolide Antibiotics:

Macrolide compounds are natural products and natural product derivatives characterized by the presence of a macrocyclic (large) lactone ring known as a macrolide ring. The macrolide antibiotics are important therapeutic agents. Commercially available macrolide antibiotics include azithromycin, clarithromycin, dirithromycin, erythromycin, and roxithromycin.

Clarithromycin is a semi-synthetic macrolide antibiotic with in vitro activity against a variety of aerobic and anaerobic gram-positive and gram-negative microorganisms, as well as most *Mycobacterium avium* complex (MAC) micro-

US 7,601,758 B1

3

organisms. The drug is believed to exert its antibacterial action by binding to 50S ribosomal subunits in susceptible microorganisms, resulting in inhibition of protein synthesis.

Clarithromycin is indicated in the treatment of mild to moderate infections in adults and children caused by susceptible strains of microorganisms, such as *Legionella pneumophila*, *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Neisseria gonorrhoeae*. Clarithromycin is also used to treat pharyngitis (tonsillitis), sinusitis, bronchitis, community-acquired pneumonia, uncomplicated skin infections, and disseminated mycobacterial infections. The usual adult dose is 250 or 500 mg every 12 hours (500 or 100 mg per day) for 7 to 14 days, taken without regard to food.

Clarithromycin is rapidly absorbed from the gastrointestinal tract following oral administration, with an absolute bioavailability of approximately 50%. Peak plasma concentrations with single doses are reached within 2 to 3 hours and steady-state plasma concentrations are reached within 3 to 4 days. Food slightly delays the onset of absorption and time to peak concentration and increases the peak concentration by about 24%, but does not affect the extent of exposure. Clarithromycin distributes readily into body tissues and fluids and is not highly bound to plasma proteins (65 to 75%).

Cytochrome p450 (CYP) enzymes:

CYP enzymes are agents of drug metabolism that are found in the liver, the gastrointestinal tract and other locations in the body. CYP enzymes occur in a variety of closely related proteins referred to as isozymes. Some of these that have been identified as important in drug metabolism are CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Different CYP isozymes may preferentially metabolize different drugs. For example, phenytoin and fosphenytoin have been reported to be preferentially metabolized by CYP2C9, CYP2C19, and CYP3A4, while CYP2D6 has been reported to be responsible for the metabolism of many psychotherapeutic agents, such as thioridazine.

CYP Isozymes and Drug-Drug Interactions:

Examples of CYP-mediated drug-drug interactions include those involving CYP1A2 and CYP2E1 isozymes, which have been reported to be involved in drug-drug interactions involving theophylline, and those involving CYP2C9, CYP1A2, and CYP2C19, which have been reported to be involved in drug-drug interactions involving warfarin.

The 3A family of CYP isozymes, particularly CYP3A4, is also known to be involved in many clinically significant drug-drug interactions, including those involving colchicine and macrolide antibiotics, as well as those involving non-sedating antihistamines and cisapride. CYP3A5 shares very similar protein structure, function and substrate specificity with CYP3A4. The CYP3A5*3 allele is a gene variant that does not express CYP3A5 enzyme. As a result of this genetic variation, about half of African-American subjects and 70-90% of Caucasian subjects do not express CYP3A5, while expression is more common in other ethnic groups.

While drugs are often targets of CYP-mediated metabolism, some may also alter the expression and activity of such enzymes, thus impacting the metabolism of other drugs.

Colchicine is both a target of and a modulator of CYP isozymes. The biotransformation of colchicine in human liver microsomes involves formation of 3-demethylcolchicine and 2-demethylcolchicine. As shown by experiments using antibodies against CYP3A4 and experiments using chemical inhibition of CYP3A4, this transformation is correlated with (and thus apparently mediated by) CYP3A4 activity. CYP2A6, CYP2C9, CYP2C19, CYP2D6, and CYP2E1 do not appear to catalyze this biotransformation.

Studies on the effect of colchicine on expression of selected CYP isozymes in primary cultures of human hepa-

4

cytes have been reported. Dvorak et al. (Acta Univ. Palacki. Olomuc, Fac. Med. (2000) 143:47-50) provided preliminary data on the effect of colchicine and several of its derivatives on protein levels of CYP1A2, CYP2A6, CYP2C9/19, CYP2E1, and CYP3A4 as assessed by immunoblotting. Colchicine caused an increase in CYP2E1 protein levels and appeared to decrease protein levels of CYP1A2, CYP2C9/19, and CYP3A4, with 10 μ M colchicine causing a greater reduction in each isozyme than 1 μ M colchicine. The 3-demethylcolchicine metabolite was reported to cause a decrease in protein for CYP1A2, CYP2C9/19, CYP2E1, and CYP3A4. The levels of CYP2A6 appeared unaffected by colchicine or any of the tested metabolites. In a more complete report on expression of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2E1, and CYP3A4, Dvorak et al. (Toxicology in Vitro (2002) 16:219-227) concluded that CYP1A2 protein content in 1 μ M colchicine treated cells was not different from that in control cells, while the inducer TCDD increased the level of CYP1A2 protein by an average of three-fold. The levels of CYP2A6 protein were apparently unaffected by colchicine, while enzyme activities of CYP3A4 and CYP2C9 were significantly decreased by colchicine and activity of CYP2E1 was not affected. Northern blots showed that colchicine suppressed CYP2C9 mRNA levels by about 20% and did not alter CYP3A4 mRNA levels as compared to control cells. A subsequent study by Dvorak et al. (Mol. Pharmacol. (2003) 64:160-169) showed that colchicine decreased both basal and rifampicin-inducible and phenobarbital-inducible expression of CYP2B6, CYP2C8/9, and CYP3A4.

Like colchicine, clarithromycin is a target of metabolism by CYP3A isozymes. In non-fasting healthy human subjects, the elimination half-life of clarithromycin is about 3 to 4 hours with 250 mg administered every 12 hours, but increases to 5 to 7 hours with 500 mg administered every 8 to 12 hours. Approximately 20% and 30% of the dose, respectively, is excreted as unchanged drug in urine following oral administration of 250 and 500 mg clarithromycin given every 12 hours. Approximately 10 to 15% of the dose is excreted in urine as 14-hydroxyclearithromycin, an active metabolite of clarithromycin with substantial antibacterial activity. About 40% of an oral clarithromycin dose is excreted in feces.

Clarithromycin is also a potent inhibitor of CYP3A isozymes, as are other macrolide antibiotics. This inhibition is not rapidly reversible. Due to the limited reversibility of the inhibition of CYP3A isozymes by clarithromycin, CYP3A activity may not return to normal after a course of treatment with clarithromycin until the body produces adequate amounts of CYP3A isozymes to replace those irreversibly inhibited by the clarithromycin. Thus, it may take one to two weeks for CYP3A metabolic activity to return to normal following treatment with clarithromycin or other macrolide antibiotics.

P-glycoprotein (Pgp) is an ATP-dependent cell surface transporter molecule. Pgp actively pumps certain compounds, notably including drugs such as colchicine, out of cells. Pgp is encoded by the Adenosine triphosphate-binding cassette subfamily B member 1 (ABCB1) gene, also referred to as the multiple drug resistance 1 gene (MDR1).

Clarithromycin is an inhibitor of Pgp, as are other macrolide antibiotics. In vitro, agents that inhibit CYP 3A4 typically also inhibit Pgp, and the magnitude of Pgp inhibition in vitro generally trends proportionally with magnitude of CYP 3A4 inhibition. However, equipotent CYP 3A4 inhibitors can exhibit different degrees of Pgp inhibition.

Thus clarithromycin and other macrolide antibiotics, in addition to inhibiting the metabolic breakdown of colchicine by inhibiting CYP 3A4 isozymes, can block a mechanism by which colchicine is pumped out of cells. Both the inhibition of colchicine breakdown by CYP 3A4 and the inhibition of

US 7,601,758 B1

5

the pumping of colchicine out of cells by Pgp have the effect of increasing the intracellular levels of colchicine.

Since colchicine acts intracellularly, the combined effects of CYP 3A4 inhibition and Pgp inhibition by clarithromycin (and related macrolide antibiotics) can cause colchicine toxicity in patients taking what would be a safe dose of colchicine in the absence of concomitant macrolide antibiotic administration.

Drug-drug interactions, such as the enhancement of colchicine toxicity by macrolide antibiotics, present a health risk to patients and a medical challenge for all medical care workers. Various studies of adverse reactions from exposure to multiple drugs have found that 6.5-23% of the adverse reactions result from drug-drug interactions. Unfortunately, each year a number of deaths occur as the direct result of patients adding a concomitant prescription pharmaceutical product to their existing medication regimen.

With regard to co-administration of colchicine with clarithromycin and other macrolide antibiotics, warnings have recently been published urging caution, or arguing that the two drugs should not be co-administered. For example, on Jul. 5, 2006 the US Food and Drug Administration (the FDA) approved safety labeling changes for clarithromycin tablets, extended-release tablets, and oral suspension to warn of the risk for increased exposure to colchicine in patients receiving both drugs. The Warnings section of the prescribing information for clarithromycin now includes the following statement: "There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients." In addition, the following was added to the Precautions section of the prescribing information: "[c]olchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Patients should be monitored for clinical symptoms of colchicine toxicity."

A 2006 report entitled "Life-threatening Colchicine Drug Interactions" cautioned that "[c]olchicine should not be used with clarithromycin or erythromycin, and given the potential for fatal outcomes, it would be prudent to avoid all PGP inhibitors with colchicine" (Horn, J. R. and Hansten, P. D., Pharmacy Times, May 2006, p. 111).

More recently, a publication in May, 2008 ended with the conclusion that "[t]he combined prescription of clarithromycin or other CYP3A4 inhibitors and colchicine should be avoided." Van der Velden, et al., (Neth. J. Med. 2008 May; 66(5):204-6).

There accordingly remains a need in the art for improved methods for administering colchicine to patients who are concomitantly being treated with macrolide antibiotics so as to reduce the occurrence of dangerous colchicine toxicity. The present disclosure addresses this need and provides further advantages.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows mean colchicine plasma concentrations following administration of single and multiple oral doses of colchicine 0.6 mg in healthy adults, N=13, Y axis=colchicine concentration, ng/mL, X axis=time in hours, ◆=day 1, ■=day 25. See Example 1.

FIG. 2 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin in healthy adults, Y-axis=colchicine concentration, ng/mL, X-axis=time in hours, N=23, •=day 1, ◆=day 29. See Example 2.

6

SUMMARY

Disclosed herein are methods for more safely administering colchicine concomitantly with administration of macrolide antibiotics such as clarithromycin or erythromycin. It has now been discovered that certain reduced or limited colchicine dosage amounts, when administered with concomitantly administered recommended doses of macrolide antibiotics, certain "colchicine plus macrolide" dosing regimens, achieve plasma colchicine levels that are therapeutically effective, but are not significantly higher, and therefore not significantly more toxic, than plasma levels achieved by administration of manufacturers' recommended colchicine dosage amounts in the absence of concomitant macrolide antibiotic administration. Thus, in spite of recent published warnings that the two should not be concomitantly administered, colchicine and macrolide antibiotics can be administered concomitantly without undue hazard when colchicine is administered as disclosed herein.

In one embodiment, colchicine treatment is administered to a patient in suffering from a condition treatable with colchicine, and the patient is concomitantly receiving administration of a macrolide antibiotic to treat an infection. The colchicine therapy may involve either palliative or prophylactic treatment, or both.

In particularly preferred embodiments, the patient is a human gout patient and is administered the colchicine to treat or prevent a gout flare. Preferably the method comprises determining a first colchicine dosage amount adapted for oral administration to the gout patient to treat gout flares in the absence of concomitant administration of clarithromycin or erythromycin, determining a second colchicine dosage amount that is a 50% to 75% reduction, preferably a two-thirds or three quarters reduction, of the first colchicine dosage amount, and orally administering the second colchicine dosage amount to the gout patient who is concomitantly receiving administration of clarithromycin or erythromycin.

Preferably, in this method, the 50% to 75% reduction comprises one or more of 1) reducing the number of doses of colchicine administered (e.g., per day), 2) reducing the amount of colchicine administered per dose (i.e., reducing the size of at least one colchicine dose), and 3) reducing the administration of colchicine from administration every day to administration every other day. For example, in this method, the 50% to 75% reduction may comprise reducing both the number of doses of colchicine administered per day and the amount of colchicine administered per dose.

In other aspects of these embodiments, it is preferred that one or more (where not mutually exclusive) of the following apply: 1) the patient is administered each dose of colchicine as one 0.6 mg colchicine tablet or as one half of a 0.6 mg colchicine tablet (e.g. one half a scored 0.6 mg colchicine tablet), 2) the patient is an adult, 3) the adult patient is less than 70 years old, 4) the patient is receiving concomitant administration of clarithromycin, 5) the second colchicine dosage amount is about a one-half reduction of the first colchicine dosage amount, 6) the second colchicine dosage amount is about a two-thirds reduction of the first colchicine dosage amount, 7) the second colchicine dosage amount is about a three-quarters reduction of the first colchicine dosage amount, 8) the first colchicine dosage amount is about 1.8 mg per day and the second colchicine dosage amount is about 0.6 mg per day, 9) the second colchicine dosage amount is a single dose of about 0.6 mg, and after administration of the single dose ingestion of colchicine is stopped until a subsequent gout flare occurs, 10) the second colchicine dosage amount is a single dose of about 0.6 mg of colchicine, and after administration of the single dose ingestion of colchicine is not repeated within a 3-day period.

US 7,601,758 B1

7

In other aspects of these embodiments the second colchicine dosage amount of about 0.3 mg per day is administered as one half of a 0.6 mg colchicine tablet once a day every day, and the second colchicine dosage amount of about 0.15 mg per day is administered as one half of a 0.6 mg colchicine tablet once a day every other day.

In an additional embodiment the first colchicine dosage amount is about 1.8 mg per day and the second colchicine dosage amount is a single 0.6 mg dose, and preferably ingestion of colchicine is not repeated for at least three days after the single dose is administered.

In an additional embodiment, the patient is administered the colchicine according to a colchicine dosing regimen of a single starting colchicine dose of no more than about 0.6 mg colchicine, followed by either no additional colchicine doses within about 12, 24, 48, or 72 hours, or followed by at least one additional colchicine dose within 12 hours and no more frequently than once every hour (e.g., every 3, 4, 6, 8, or 12 hours). In this embodiment, each additional colchicine dose is preferably no greater than about 0.3 mg and the patient may be an adult patient or a pediatric patient. Preferably the starting colchicine dose is about 0.6 mg or about 0.3 mg, and each additional colchicine dose (if any) is about 0.3 mg. When additional doses are administered, it is preferred that only two, three, or four additional colchicine doses are administered within about 24 hours. Preferably, the patient is an adult patient and the starting colchicine dose is about 0.6 mg and each additional colchicine dose, if any, is about 0.3 mg. In one embodiment only three additional colchicine doses are administered within about 24 hours.

In another embodiment, colchicine is administered to a patient in suffering from a condition treatable with colchicine, and the concomitant macrolide antibiotic is administered concurrently, or the patient has recently completed a dosing regimen of a macrolide antibiotic to treat an infection, and the patient is (immediately or within a period of two weeks, preferably three days, more preferably within 48 hours or 24 hours after completion of the macrolide antibiotic dosing regimen) administered a single dose of no more than about 0.6 mg of colchicine, preferably 0.3 mg or 0.6 mg of colchicine. For example, an initial dose of about 0.6 mg is administered and ingestion of colchicine is not repeated for at least three days, or only one additional colchicine dose is administered within about 24 hours and the additional colchicine dose is about 0.6 mg.

A preferred antibiotic for use in the disclosed methods is one that is an inhibitor of either or both of CYP3A and P-glycoprotein. Preferably the antibiotic is dirithromycin, erythromycin, roxithromycin, or more preferably, clarithromycin or erythromycin. The clarithromycin may, for example, be administered to the patient at a dosage amount of about 500 mg daily and the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by 0, 1, 2, 3, or 4 additional colchicine doses of about 0.6 mg every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. Alternately, the clarithromycin may be administered to the patient at a dosage amount of about 1000 mg daily and the colchicine dosing regimen is one about 0.3 mg colchicine dose to start, followed by 0, 1, 2, 3, or 4 additional colchicine doses of about 0.3 mg each every 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 3, 4, 5, or 6 hours) after the preceding colchicine dose. In a preferred regimen for treatment of acute gout flares, ingestion of colchicine is continued until a total of no more than about 1.2, 1.4, 1.6, 1.8, 2, or 2.4 mg of colchicine has been ingested, after which ingestion of colchicine is stopped until a subsequent acute gout flare occurs. In still another preferred regimen, clarithromycin may be administered to a patient, e.g., at a dosage amount of about 250 mg B.I.D. for a period of about 7 to 10 days, and the colchicine dosing regimen is adminis-

8

tered to the patient upon completion of the clarithromycin dosing regimen, wherein the colchicine dosing regimen consists of the administration of no more than one dose of no more than 0.6 mg of colchicine. More preferably, the colchicine is administered as a dosage form of 0.6 mg (e.g., one 0.6 mg colchicine tablet), or 0.3 mg (e.g., one half of a 0.6 mg tablet) of colchicine and administration of the dosage form is not repeated within a period of at least about two days, preferably at least about three days.

In various of these and other embodiments, the colchicine-responsive condition is gout (e.g. a gout flare in a chronic gout sufferer), familial Mediterranean fever (FMF), thrombocytopenic purpura, pericarditis, scleroderma, or Behçet's disease. The gout may be an acute gout flare or chronic gout. For acute gout, the dosing regimen is preferably continued until a total of no more than about 1.8 mg to about 4.8 mg of colchicine has been ingested, after which ingestion of colchicine is preferably stopped, for at least 2, 3, 4, 5, 6, or 7 days, until a subsequent gout flare occurs, or until the first signs of a subsequent gout flare.

Another embodiment comprises administering colchicine to a patient also taking clarithromycin, or having completed treatment with clarithromycin or erythromycin within the prior 14 days, the patient being administered a single dose of about 0.6 mg or about 0.3 mg of colchicine to treat a gout flare, which administration is not repeated within any 3-day period.

In another aspect, herein disclosed is a method for increasing the blood plasma levels of colchicine in a patient to whom colchicine is being administered to treat or prevent a colchicine-responsive condition. This method comprises the concomitant dosing of the patient with a sufficient amount of a macrolide antibiotic to increase the C_{max} of colchicine by about 167% to 200%, or to increase the AUC of colchicine in the patient by about 240% to 250%, or to increase the plasma half-life of colchicine by about 233%, or to decrease the clearance of colchicine by about 75%, compared to the C_{max} , AUC, plasma half-life, or clearance in the same or a matched patient when not being administered a concomitant macrolide antibiotic. In a preferred embodiment, the patient is being administered no more than hourly doses of about 0.6 mg of colchicine or less, the macrolide antibiotic is clarithromycin, and the amount of macrolide antibiotic is from about 500 mg to about 1000 mg, with about 500 mg being preferred.

In another aspect, herein disclosed are methods for using colchicine which methods involve the use of pharmacy management systems.

One such method comprises a pharmacy receiving a prescription for colchicine for a patient who is suffering from gout (e.g., acute gout flares or chronic gout) and who is concomitantly being treated with a macrolide antibiotic that is an inhibitor of CYP3A and P-glycoprotein, followed by the pharmacy dispensing colchicine in response to receipt of the prescription, wherein the dispensing is preceded by entry into a first computer readable storage medium, in functional communication with a computer, of a unique patient identifier for said patient and at least one drug identifier for colchicine linked to the patient identifier so as to indicate that colchicine is to be administered to the patient. The computer is programmed to issue a drug-drug interaction alert when the at least one drug identifier for colchicine is entered linked to the patient identifier so as to indicate that colchicine is to be administered to the patient and when the patient identifier is also linked to an identifier indicating that a macrolide antibiotic that is an inhibitor of CYP3A or P-glycoprotein is being concomitantly administered to the patient. Upon entry of the at least one drug identifier for colchicine linked to the patient identifier, a drug-drug interaction alert is issued to one or more of a pharmacy technician, a pharmacist, or a pharmacy customer obtaining the colchicine, said alert indicating that a

US 7,601,758 B1

9

macrolide antibiotic is being concomitantly administered to the patient and that prior to the colchicine being dispensed, the colchicine dosing regimen must be reviewed and, if necessary adjusted, so that when the colchicine is delivered to the pharmacy customer obtaining the colchicine it is delivered along with instructions for the colchicine to be taken in accordance with a dosing regimen of no more than one about 0.6 mg colchicine dose to start (e.g., following the onset of the acute gout attack or the first sign of a gout flare) followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours and no more frequently than once every hour and wherein each additional colchicine dose is no greater than about 0.6 mg, and wherein the patient ingests the colchicine as instructed.

The drug-drug interaction alert is preferably issued as one or both of a written warning on a display screen of the pharmacy management computer system, and a printed warning. The printed warning may be attached to or packaged with the dispensed prescription.

In a preferred aspect, the identifier indicating that a macrolide antibiotic is being concomitantly administered to the patient is an identifier indicating that the macrolide antibiotic is clarithromycin and is linked to at least one further identifier indicating that the clarithromycin is prescribed so that 500 mg of clarithromycin is to be ingested by the patient daily, in which case the dosing regimen for colchicine is preferably one about 0.6 mg colchicine dose to start, optionally followed by additional colchicine doses, e.g., 0, 1, 2, 3, or 4 additional colchicine doses within 24 hours of about 0.3 mg ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In another embodiment, the identifier indicating that a macrolide antibiotic is being concomitantly administered to the patient is an identifier indicating that the macrolide antibiotic is clarithromycin is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the clarithromycin is prescribed so that about 500 mg of clarithromycin is to be ingested by the patient daily, in which case the colchicine dosing regimen is (preferably) one about 0.6 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every six to eight hours) after the preceding colchicine dose.

In yet another preferred aspect, the identifier indicating that a macrolide antibiotic is being concomitantly administered to the patient is an identifier indicating that the macrolide antibiotic is clarithromycin and is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the clarithromycin is prescribed so that about 1000 mg of clarithromycin is to be ingested by the patient daily and the dosing regimen is one about 0.3 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 2, 3, 4, 5, 6, 7, or 8 hours (e.g., every eight to twelve hours) after the preceding colchicine dose.

Also disclosed herein is a dosing regimen adjustment method for administering colchicine to a patient to treat a medical condition, the patient concomitantly suffering from an infection amenable to treatment with a macrolide antibiotic. The method comprises determining a first colchicine dosing regimen (the colchicine dosing regimen suitable for administration in the absence of macrolide co-administration, which dosing regimen may consist of one or more doses of colchicine); and determining an antibiotic dosage amount and

10

an antibiotic treatment schedule; and administering the macrolide antibiotic to the patient in the antibiotic dosage amount according to the antibiotic treatment schedule while concomitantly administering the colchicine to the patient according to a second colchicine dosing regimen, which may consist of one or more reduced colchicine doses. The second colchicine dosing regimen is a fraction of the first colchicine dosing regimen, where the fraction is obtained by administering reduced colchicine doses or by reducing the frequency of colchicine doses, and wherein the fraction is less than or equal to about $\frac{2}{3}$ or less than or equal to about $\frac{1}{2}$.

According to this embodiment, upon the administering of the antibiotic to the patient at the antibiotic dosage amount according to the antibiotic treatment schedule while concomitantly administering colchicine to the patient at the second colchicine dosing regimen, the therapeutic circulating level of colchicine is achieved in the patient. Preferably, the fraction is selected from $\frac{1}{12}$, $\frac{1}{6}$, $\frac{1}{4}$, $\frac{1}{3}$, $\frac{5}{12}$, and $\frac{1}{2}$, more preferably, the fraction is $\frac{1}{3}$ or $\frac{1}{2}$. In one embodiment, if the second colchicine dosing regimen comprises a "first" colchicine dose, and one or more "subsequent" colchicine doses, each subsequent colchicine dose may be the same as the first dose, or a fraction of the first dose. The fraction is selected from about $\frac{1}{12}$, about $\frac{1}{6}$, about $\frac{1}{4}$, about $\frac{1}{3}$, about $\frac{5}{12}$, about $\frac{1}{2}$, and about $\frac{7}{12}$, e.g., about $\frac{1}{2}$ or about $\frac{2}{3}$. In one example, the second colchicine dosing regimen is once-a-day, twice-a-day, three-times-a-day or four-times-a-day. In a variation of this example, the initial treatment day in, a second colchicine dosing regimen that lasts for more than one day, has one more dose administered than are administered each subsequent day.

Preferably the antibiotic is selected from clarithromycin, dirithromycin, erythromycin and roxithromycin. The Preferred conditions are selected from gout, FMF, thrombocytopenic purpura, and Behçet's disease. The first and second colchicine dosing regimens may differ, depending on the condition being treated. In a preferred embodiment, the gout is an acute gout flare and the colchicine treatment schedule is an acute treatment schedule adapted for treatment of acute gout flares, or the gout is chronic gout, and the colchicine treatment schedule is a chronic treatment schedule adapted for prophylaxis of flares. In another preferred embodiment, the fraction is $\frac{1}{3}$ or $\frac{1}{2}$ and treatment with colchicine is initiated subsequent to initiation of treatment with clarithromycin.

Colchicine is one of the most widely used drugs for treating familial Mediterranean fever (FMF). In an embodiment for the treatment of FMF, each colchicine dosing regimen is:

| Age | Daily Dose | |
|-------------------------------|------------|---------|
| | Usual | Maximum |
| Adults and children >12 years | 1.2 mg | 2.4 mg |
| Children >6 to 12 years | 0.9 mg | 1.8 mg |
| Children 4 to 6 years | 0.3 mg | 1.8 mg |

and the colchicine dosing regimen during concomitant administration with a macrolide antibiotic for the treatment of FMF is no greater than a maximum of 0.3 mg twice daily.

It has been reported that 5-10% of FMF patients do not show a beneficial response to colchicine administration. A polymorphism in the ABCB1 gene, the "ABCB1 3435 C to T polymorphism" has been reported to correlate with this lack of response to colchicine treatment, with patients with the homozygous TT genotype exhibiting the most pronounced "non-responder" phenotypes.

US 7,601,758 B1

11

Accordingly, in another aspect, provided herein is a method for treating a patient suffering from FMF, which patient is a colchicine non-responder. Preferably, the patient is homozygous for the TT genotype of the ABCB1 3435 C to T polymorphism. The method entails the concomitant administration of a Pgp inhibitor and colchicine to the patient. A preferred Pgp inhibitor for use in this method is verapamil or cyclosporine-A, more preferably a macrolide antibiotic, preferably dirithromycin, erythromycin or roxithromycin, or, more preferably clarithromycin. Preferred dosage amounts of the Pgp inhibitor for this purpose correspond to those called for in the prescribing information for the drug in question. For clarithromycin, preferred dosage amounts are 500 to 1000 mg per day and duration of clarithromycin dosing is preferably one, two, or three days, repeated weekly or bi-weekly. Preferred colchicine dosing regimens for this purpose are the same as used for treatment of FMF in responders, though the doses of colchicine administered may be increased as tolerated, e.g., up to two to three times the typical doses.

These and other embodiments, advantages and features of the present invention are further elaborated herein below.

DETAILED DESCRIPTION

Following multiple oral doses (0.6 mg twice daily), the mean elimination half-life of colchicine in young healthy volunteers (mean age 25 to 28 years of age) is 26.6 to 31.2 hours.

In the specification and claims that follow, references will be made to a number of terms which shall be defined to have the following meaning.

The terms “a” and “an” do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The term “or” means “and/or”. The terms “comprising”, “having”, “including”, and “containing” are to be construed as open-ended terms (i.e., meaning “including, but not limited to”).

“Concomitant”, “concomitantly”, “co-administration” and “co-administered” as used herein refer to the administration of at least two drugs to a patient either simultaneously or within a time period during which the effects of the first administered drug are still operative in the patient. Thus, if the first drug is, e.g., clarithromycin or erythromycin and the second drug is colchicine, the concomitant administration of the second drug can occur as much as about one to two weeks, e.g., within one to fourteen or one to seven days, after the administration of the first drug. This is because clarithromycin and erythromycin can exert long-lasting inhibition of CYP3A isozymes so that CYP3A activity in the patient may not return to pre-clarithromycin or erythromycin-administration levels for as much as two weeks after the cessation of clarithromycin or erythromycin administration. If colchicine is the first drug, administration of a second drug would be concomitant if done within 1 to 2 days, preferably 12 to 24 hours.

“Dosage amount” means an amount of a drug suitable to be taken during a fixed period, usually during one day (i.e., daily).

“Dosage amount adapted for oral administration” means a dosage amount that is of an amount deemed safe and effective for the particular patient under the conditions specified. As used herein and in the claims, this dosage amount is determined by following the recommendations of the drug manufacturer’s Prescribing Information as approved by the US Food and Drug Administration.

“Dosing regimen” means the dose of a drug taken at a first time by a patient and the interval (time or symptomatic) and dosage amounts at which any subsequent doses of the drug are taken by the patient. Each dose may be same or a different.

12

A “dose” means the measured quantity of a drug to be taken at one time by a patient.

A “patient” means a human or non-human animal in need of medical treatment. Medical treatment can include treatment of an existing condition, such as a disease or disorder, prophylactic or preventative treatment, or diagnostic treatment. In preferred embodiments the patient is human.

“Risk” means the probability or chance of adverse reaction, injury, or other undesirable outcome arising from a medical treatment. An “acceptable risk” means a measure of the risk of harm, injury, or disease arising from a medical treatment that will be tolerated by an individual or group. Whether a risk is “acceptable” will depend upon the advantages that the individual or group perceives to be obtainable in return for taking the risk, whether they accept whatever scientific and other advice is offered about the magnitude of the risk, and numerous other factors, both political and social. An “acceptable risk” of an adverse reaction means that an individual or a group in society is willing to take or be subjected to the risk that the adverse reaction might occur since the adverse reaction is one whose probability of occurrence is small, or whose consequences are so slight, or the benefits (perceived or real) of the active agent are so great. An “unacceptable risk” of an adverse reaction means that an individual or a group in society is unwilling to take or be subjected to the risk that the adverse reaction might occur upon weighing the probability of occurrence of the adverse reaction, the consequences of the adverse reaction, and the benefits (perceived or real) of the active agent. “At risk” means in a state or condition marked by a high level of risk or susceptibility.

Pharmacokinetic parameters referred to herein describe the in vivo characteristics of drug (or a metabolite or a surrogate marker for the drug) over time. These include plasma concentration (C), as well as C_{max} , C_n , C_{24} , T_{max} , and AUC. “ C_{max} ” is the measured plasma concentration of the active agent at the point of maximum, or peak, concentration. “ C_{min} ” is the measured plasma concentration of the active agent at the point of minimum concentration. “ C_n ” is the measured plasma concentration of the active agent at about n hours after administration. “ C_{24} ” is the measured plasma concentration of the active agent at about 24 hours after administration. The term “ T_{max} ” refers to the time from drug administration until C_{max} is reached. “AUC” is the area under the curve of a graph of the measured plasma concentration of an active agent vs. time, measured from one time point to another time point. For example AUC_{0-t} is the area under the curve of plasma concentration versus time from time 0 to time t, where time 0 is the time of initial administration of the drug. Time t can be the last time point with measurable plasma concentration for an individual formulation. The $AUC_{0-\infty}$ or AUC_{0-INF} is the calculated area under the curve of plasma concentration versus time from time 0 to time infinity. In steady-state studies, $AUC_{0-\tau}$ is the area under the curve of plasma concentration over the dosing interval (i.e., from time 0 to time τ (tau), where tau is the length of the dosing interval. Other pharmacokinetic parameters are the parameter K_e or K_{e1} , the terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve; $t_{1/2}$ the terminal elimination half-life, calculated as $0.693/K_{e1}$. CL/F denotes the apparent total body clearance after administration, calculated as Total Dose/Total AUC $_{\infty}$; and V_{area}/F denotes the apparent total volume of distribution after administration, calculated as Total Dose/(Total AUC $_{\infty} \times K_{e1}$).

“Side effect” means a secondary effect resulting from taking a drug. The secondary effect can be a negative (unfavorable) effect (i.e., an adverse side effect) or a positive (favorable) effect.

The most frequently reported adverse side effects to colchicine therapy are gastrointestinal, specifically abdominal pain with cramps, diarrhea, nausea, and vomiting. Less frequently

US 7,601,758 B1

13

or rarely reported adverse side effects associated with colchicine therapy include anorexia, agranulocytosis, allergic dermatitis, allergic reactions, alopecia, angioedema, aplastic anemia, bone marrow depression, myopathy, neuropathy, skin rash, thrombocytopenic disorder, and urticaria.

Whether a patient experiences an adverse side effect can be determined by obtaining information from the patient regarding onset of certain symptoms which may be indicative of the adverse side effect, results of diagnostic tests indicative of the adverse side effect, and the like.

Pharmacy management systems are computer-based systems that are widely used by commercial pharmacies to manage prescriptions and to provide pharmacy and medical personnel with warnings and guidance regarding drugs being administered to patients. Such systems typically provide alerts warning either or both of health care providers and patients when a drug that may be harmful to the particular patient is prescribed. For example, such systems can provide alerts warning that a patient has an allergy to a prescribed drug, or is receiving concomitant administration of a drug that can have a dangerous interaction with a prescribed drug. U.S. Pat. Nos. 5,758,095, 5,833,599, 5,845,255, 6,014,631, 6,067,524, 6,112,182, 6,317,719, 6,356,873, and 7,072,840, each of which is incorporated herein by reference, disclose various pharmacy management systems and aspects thereof. Many pharmacy management systems are now commercially available, e.g., CENTRICITY Pharmacy from BDM Information Systems Ltd., General Electric Healthcare, Waukesha, Wis., Rx30 Pharmacy Systems from Transaction Data Systems, Inc., Ocoee, Fla., SPEED SCRIPT from Digital Simplistics, Inc., Lenexa, Kans., and various pharmacy management systems from OPUS-ISM, Hauppauge, N.Y.

The following examples further illustrate aspects of this disclosure but should not be construed as in any way limiting its scope. In particular, the conditions are merely exemplary and can be readily varied by one of ordinary skill in the art.

EXAMPLES

Example 1

Pharmacokinetic Study in Healthy Adults of Single vs. Multiple Oral Doses of Colchicine Tablets

This study was a single-center, open-label, single-sequence, two-period study to evaluate the pharmacokinetic profile of colchicine following single and multiple oral doses of colchicine tablets, 0.6 mg, in healthy volunteers.

In Period 1, study subjects received a 0.6-mg dose of colchicine after an overnight fast of at least 10 hours. In Period 2, subjects received a 0.6-mg dose of colchicine in the morning and the evening (approximately 12 hours later) for 10 days (steady state regimen). Subjects received a light breakfast served 60 minutes following dose administration in the morning and the evening dose was administered 90 minutes after an evening meal on Days 15 through 24 only. On Day 25, the colchicine dose was administered after an overnight fast of at least 10 hours and lunch was served 4 hours post-dose. Study periods were separated by a 14-day wash-out. Following the single dose and the last dose of the multiple dose regimen (beginning on the mornings of Day 1 and Day 25, respectively), blood samples were collected (6 mL each) from each subject within 1 hour prior to dosing and after dose administration at study hours 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 (while confined) and 36, 48, 72, and 96 (on an outpatient basis). Plasma concentrations of colchicine and its metabolites were determined using validated LC/MS-MS methods.

Thirteen healthy, non-smoking subjects with a mean age of 25.5 years (range 19 to 38 years) and within 15% of ideal

14

body weight were enrolled in this study. All subjects completed both dosing periods according to protocol.

After a single dose, plasma concentrations are no longer quantifiable 24 hours post-dose in all but 1 subject. After the last dose of the steady state regimen, concentrations remained quantifiable for 48 to 72 hours. Review of individual subject data shows that no subject experienced a secondary colchicine peak, either following a single dose or upon multiple dosing.

All 2-O-demethylcolchicine (2-DMC) concentrations were below the level of quantitation (LOQ, 0.2 ng/mL) and only one sample from 1 subject (of 13 subjects) had a detectable 3-O-demethylcolchicine (3-DMC) concentration, which was near the level of quantitation. Therefore, metabolites are not discussed further.

In healthy adults, colchicine appears to be readily absorbed when given orally, reaching a mean maximum plasma concentration of 2.5 ng/mL in 1.5 hours after a single dose. The drug is distributed widely, with an apparent volume of distribution of 540 L, greatly exceeding total body water. The elimination half-life as calculated following a single oral dose is approximately 5 hours. Levels were not detectable by 24 hours post-dose and this is therefore not an accurate estimate. Pharmacokinetic parameter values are summarized in the table below.

Review of trough plasma concentrations indicates that steady state was attained by approximately the eighth day of dosing for most subjects. Colchicine may have a diurnal variation reflected in the observed C_{min} concentrations at steady state. C_{min} concentrations prior to the morning dose are approximately 12% higher than the C_{min} concentrations prior to the evening dose (Day 23 and Day 24). The mean C_{min} concentration observed on Day 25 was 0.907 ng/mL.

Colchicine accumulated following administration of multiple doses to an extent greater than expected. Exposure was nearly two-fold higher (approximately 1.7 based on AUC [Day 25 AUC_{0-∞}/Day 1 AUC_{0-∞}] and approximately 1.5 based on C_{max} [Day 25 C_{max}/Day 1 C_{max}]). This observation could be attributable to an underestimation of AUC_∞ following a single dose. With the higher plasma levels that occur with repeated dosing, a longer terminal elimination half life is apparent, 26.6 hours. Pharmacokinetic parameter values are summarized in the tables below.

TABLE 1

Colchicine Pharmacokinetic Parameter Values Following Administration of A Single Oral Dose of Colchicine 0.6 mg in Healthy Adults (N = 13)

| | AUC _{0-t} (pg-hr/mL) | AUC _{0-inf} (pg-hr/mL) | C _{max} (pg/mL) | T _{max} (hr) | K _{el} (1/hr) | T _{1/2} (hr) |
|--------|----------------------------------|------------------------------------|-----------------------------|--------------------------|---------------------------|--------------------------|
| MEAN | 10508.54 | 12281.90 | 2470.77 | 1.50 | 0.1829 | 4.95 |
| STDEV | 3544.82 | 4423.34 | 706.98 | 0.54 | 0.0592 | 4.43 |
| % CV | 33.73 | 36.02 | 28.61 | 36.00 | 32.39 | 89.54 |
| MEDIAN | 10560.90 | 11451.45 | 2714.00 | 1.50 | 0.1992 | 3.48 |
| MIN | 4812.88 | 7252.66 | 1584.00 | 1.00 | 0.0359 | 2.84 |
| MAX | 18128.65 | 23838.48 | 3977.00 | 3.00 | 0.2443 | 19.29 |

US 7,601,758 B1

15

16

TABLE 2

| Colchicine Pharmacokinetic Parameter Values Following Administration of Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults (N = 13) | | | | | | | | | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|----------------------------------|------------------------------------|-----------------------------|-----------------------------|-----------------------------|--------------------------|---------------------------|--------------------------|
| | AUC _{0-t} (pg-hr/mL) | AUC _{0-t} (pg-hr/mL) | AUC _{0-inf} (pg-hr/mL) | C _{max} (pg/mL) | C _{min} (pg/mL) | C _{ave} (pg/mL) | T _{max} (hr) | K _{el} (1/hr) | T _{1/2} (hr) |
| MEAN | 43576.96 | 29056.23 | 54198.77 | 3553.15 | 906.51 | 1210.68 | 1.31 | 0.03 | 26.60 |
| STDEV | 9333.26 | 4531.30 | 9214.54 | 843.45 | 152.19 | 188.80 | 0.60 | 0.00 | 4.33 |
| % CV | 21.42 | 15.59 | 17.00 | 23.74 | 16.79 | 15.59 | 45.61 | 16.34 | 16.26 |
| MEDIAN | 41925.10 | 28452.15 | 54113.43 | 3734.00 | 903.50 | 1185.51 | 1.00 | 0.03 | 26.51 |
| MIN | 29328.78 | 20791.98 | 37599.76 | 1977.00 | 636.23 | 866.33 | 0.50 | 0.02 | 20.82 |
| MAX | 58265.35 | 36083.95 | 67944.65 | 4957.00 | 1149.67 | 1503.50 | 3.00 | 0.03 | 33.65 |

TABLE 3

| Mean (% CV) Colchicine Pharmacokinetic Parameter Values Following Administration of Single and Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|-------------|
| | Vd/F (L) | CL/F (L/hr) |
| Colchicine 0.6-mg Single Dose (N = 13) | | |
| Day 1 | 341 (54.4) | 54.1 (31.0) |
| Colchicine 0.6 mg b.i.d. × 10 days | | |
| Day 25 | 1150 (18.73) | 30.3 (19.0) |

CL = Dose/AUC_{0-t} (Calculated from mean values)

Vd = CL/Ke (Calculated from mean values)

In the above table, the parameter CL/F denotes the apparent total body clearance after administration, calculated as Total Dose/Total AUC_{0- τ} ; and V_d/F denotes the apparent total volume of distribution after administration, calculated as Total Dose/(Total AUC_∞ × K_{e1}).

20

Example 2

Clinical Drug-Drug Interaction Study of Colchicine and Clarithromycin

A single-center, open-label, one sequence, two-period study was carried out in 23 healthy subjects. On Day 1, a single 0.6-mg dose of colchicine was administered. After completing a 21-day washout period, all subjects received 250 mg of clarithromycin administered twice daily for 7 days (Days 22 through 29), a sufficient dose and duration to inhibit CYP3A4 and Pgp. On the final day (Day 29), a single dose of colchicine was co-administered with the clarithromycin dose.

When combined with steady-state clarithromycin, there is a significant increase in exposure to colchicine as compared to when colchicine is given alone: the mean C_{max} and AUC_{0-t} concentrations increased 167% and 250%, respectively. In addition, co-administration of clarithromycin and colchicine resulted in an increase of 233% in the plasma elimination half-life (t_{1/2}) of colchicine and a 75% decrease in apparent clearance (CL/F). A summary of the mean (% CV) colchicine pharmacokinetic parameters for Day 1 (colchicine administered alone) and Day 29 (colchicine co-administered with steady-state clarithromycin) are given in the table below and illustrated in the table that follows.

TABLE 4

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Clarithromycin in Healthy Adults | | | | | | | | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|--------------------------------------|-----------------------------------|---------------------------------|--------------------------|----------------|----------------|-------------------------|
| DAY | C _{max} (ng/mL) | T _{max} ¹ (h) | AUC _{0-t} (ng · h/mL) | AUC _∞ (ng · h/mL) | Ke (h ⁻¹) | Vd/F (L) | CL/F (L/hr) | t _{1/2} (h) |
| Colchicine Alone (n = 23) | | | | | | | | |
| 1 | 3 (30.97) | 1.00 (0.5-2.0) | 12 (37.6) | 16 (49.6) | 0.132 (46.87) | 432 (56.1) | 46.8 (43.7) | 9 (126.4) |
| Colchicine + Clarithromycin (n = 23) | | | | | | | | |
| 29 | 8 (23.74) | 1.0 (1.0-5.0) | 42 (23.3) | 53 (22.8) | 0.0298 (90.82) | 493 (33.69) | 12 (23.8) | 30 (41.37) |
| p value | | | | | | | | |
| | <0.0001 | 0.05061 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.0001 |

¹T_{max} mean (range)

US 7,601,758 B1

17

Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges directed to the same component or property are inclusive and independently combinable.

All methods described herein can be performed in a suitable order unless otherwise indicated or clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") herein is intended to better illuminate the disclosure and is non-limiting unless otherwise specified. No language in the specification should be construed as indicating that any non-claimed element as essential to the practice of the claimed embodiments. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this disclosure belongs. The terms wt %, weight percent, percent by weight, etc. are equivalent and interchangeable.

Embodiments are described herein, including the best modes known to the inventors. Variations of such embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The skilled artisan is expected to employ such variations as appropriate, and the disclosed methods are expected to be practiced otherwise than as specifically described herein. Accordingly, all modifications and equivalents of the subject matter recited in the claims appended hereto are included to the extent permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed unless otherwise indicated herein or otherwise clearly contradicted by context.

What is claimed is:

1. A method of using colchicine to treat a gout flare in a human patient who is receiving concomitant administration of clarithromycin or erythromycin, said method comprising:
 35 determining a first colchicine dosage amount adapted for oral administration to the patient to treat a gout flare in the absence of concomitant administration of clarithromycin or erythromycin,
 40 determining a second colchicine dosage amount that is about a two thirds reduction of the first colchicine dosage amount,
 orally administering the second colchicine dosage amount to the patient who is experiencing a gout flare and is concomitantly receiving administration of clarithromycin-

18

cin or erythromycin, wherein concomitant administration of clarithromycin or erythromycin is administration within 1 to 2 days of orally administering the second colchicine dosage amount, and

not repeating colchicine administration for at least three days.

2. The method of claim 1 wherein the two thirds reduction comprises reducing the number of doses of colchicine administered.

3. The method of claim 1 wherein the two thirds reduction comprises reducing the size of at least one colchicine dose.

4. The method of claim 1 wherein the two thirds reduction comprises reducing both the number of doses of colchicine administered and the size of at least one colchicine dose.

5. The method of claim 1 wherein the patient is an adult.

6. The method of claim 5 wherein the patient is less than 70 years old.

7. The method of claim 1 wherein the patient is receiving concomitant administration of clarithromycin.

8. The method of claim 1 wherein the first colchicine dosage amount is about 1.8 mg per day and the second colchicine dosage amount is about 0.6 mg per day.

9. The method of claim 8 wherein, after administration of the second colchicine dosage amount as a single 0.6 mg dose, ingestion of colchicine is not repeated for at least three days.

10. A method of using colchicine to treat a gout flare in an adult human gout patient so as to reduce the occurrence of colchicine toxicity when said patient is receiving concomitant administration of clarithromycin or erythromycin, said method comprising:

administering a reduced colchicine dosage amount to the patient to treat gout flares, wherein the reduced colchicine dosage amount is about 50% to about 75% of a manufacturer's recommended colchicine dosage amount in the absence of concomitant clarithromycin or erythromycin administration, and

not repeating colchicine administration for at least three days,

wherein concomitant administration of clarithromycin or erythromycin is administration within 1 to 2 days of orally administering the second colchicine dosage amount.

11. The method of claim 10 wherein the reduced colchicine dosage amount is about 0.6 mg per day.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

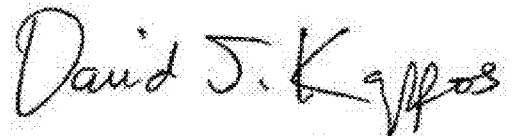
PATENT NO. : 7,601,758 B1
APPLICATION NO. : 12/368700
DATED : October 13, 2009
INVENTOR(S) : Matthew W. Davis

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 18 line 32, DELETE “is about 50% to about 75% of a manufacturer’s recommended”, and replace with --is about a 50% to about a 75% reduction of a manufacturer’s recommended--.

Signed and Sealed this
Fourteenth Day of June, 2011

A handwritten signature in black ink that reads "David J. Kappos". The signature is written in a cursive, flowing style with a large initial "D".

David J. Kappos
Director of the United States Patent and Trademark Office

EXHIBIT C

US007820681B1

(12) **United States Patent**
Davis(10) **Patent No.: US 7,820,681 B1**
(45) **Date of Patent: Oct. 26, 2010**(54) **METHODS FOR CONCOMITANT
ADMINISTRATION OF COLCHICINE AND A
SECOND ACTIVE AGENT**(75) Inventor: **Matthew W. Davis**, Erwinna, PA (US)(73) Assignee: **Mutual Pharmaceutical Company,
Inc.**, Philadelphia, PA (US)(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.(21) Appl. No.: **12/372,046**(22) Filed: **Feb. 17, 2009****Related U.S. Application Data**(60) Provisional application No. 61/152,067, filed on Feb.
12, 2009, provisional application No. 61/138,141,
filed on Jan. 14, 2009.(51) **Int. Cl.****A61K 31/167** (2006.01)**C07C 233/23** (2006.01)**C07C 211/41** (2006.01)(52) **U.S. Cl.** **514/263.31**; 564/123; 564/308;
564/427; 568/306; 514/629(58) **Field of Classification Search** None
See application file for complete search history.(56) **References Cited****U.S. PATENT DOCUMENTS**

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Methods for concomitant administration of colchicine
together with one or more second active agents, e.g., keto-
conazole and ritonavir, are disclosed. Such methods reduce
the dangers commonly associated with such concomitant
administration and provide additional benefits. Methods of
notifying health care practitioners and patients regarding
appropriate dosing for concomitant administration of colchi-
cine together with second active agents are also provided.

4 Claims, 5 Drawing Sheets

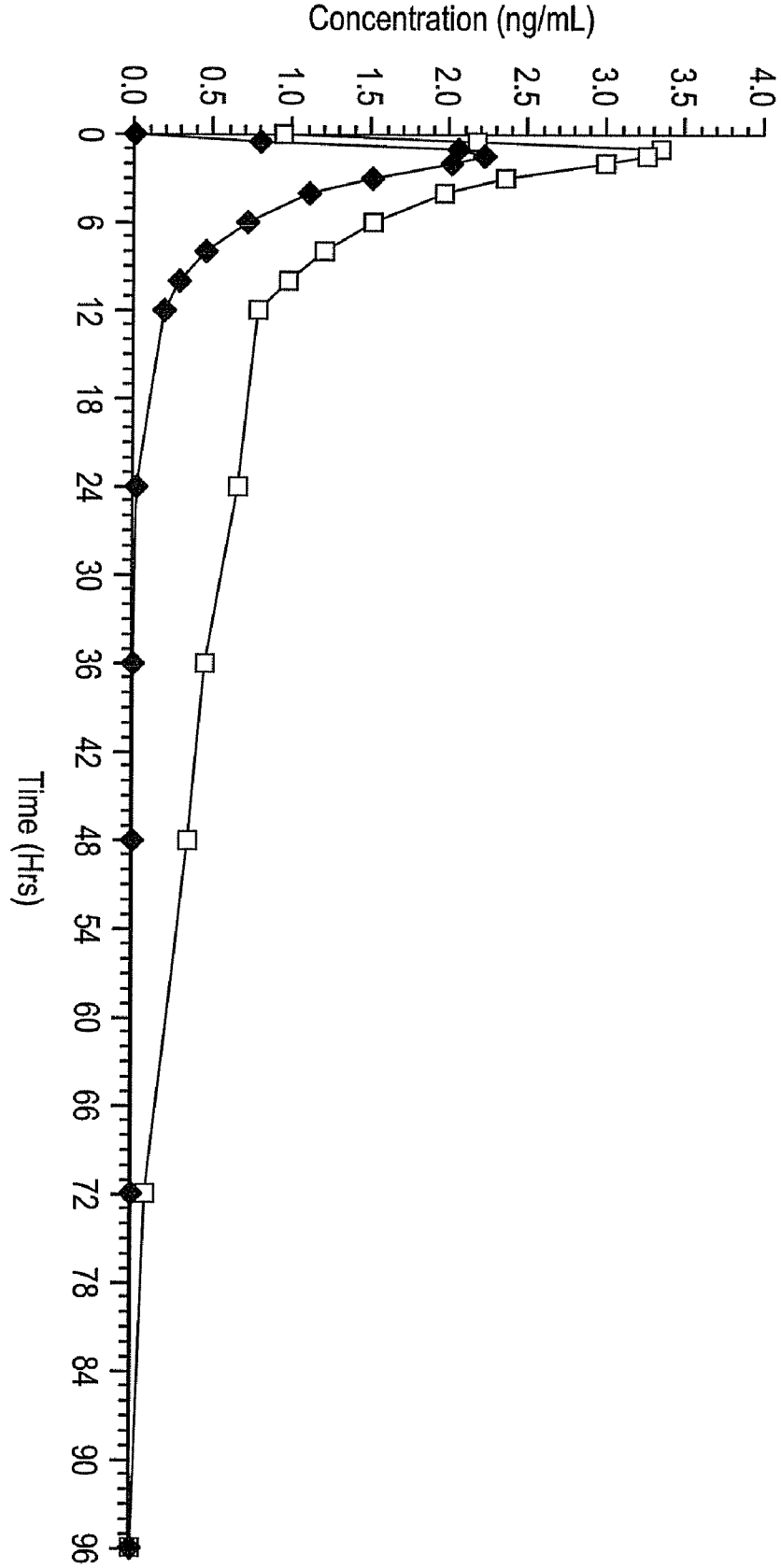


FIG. 1

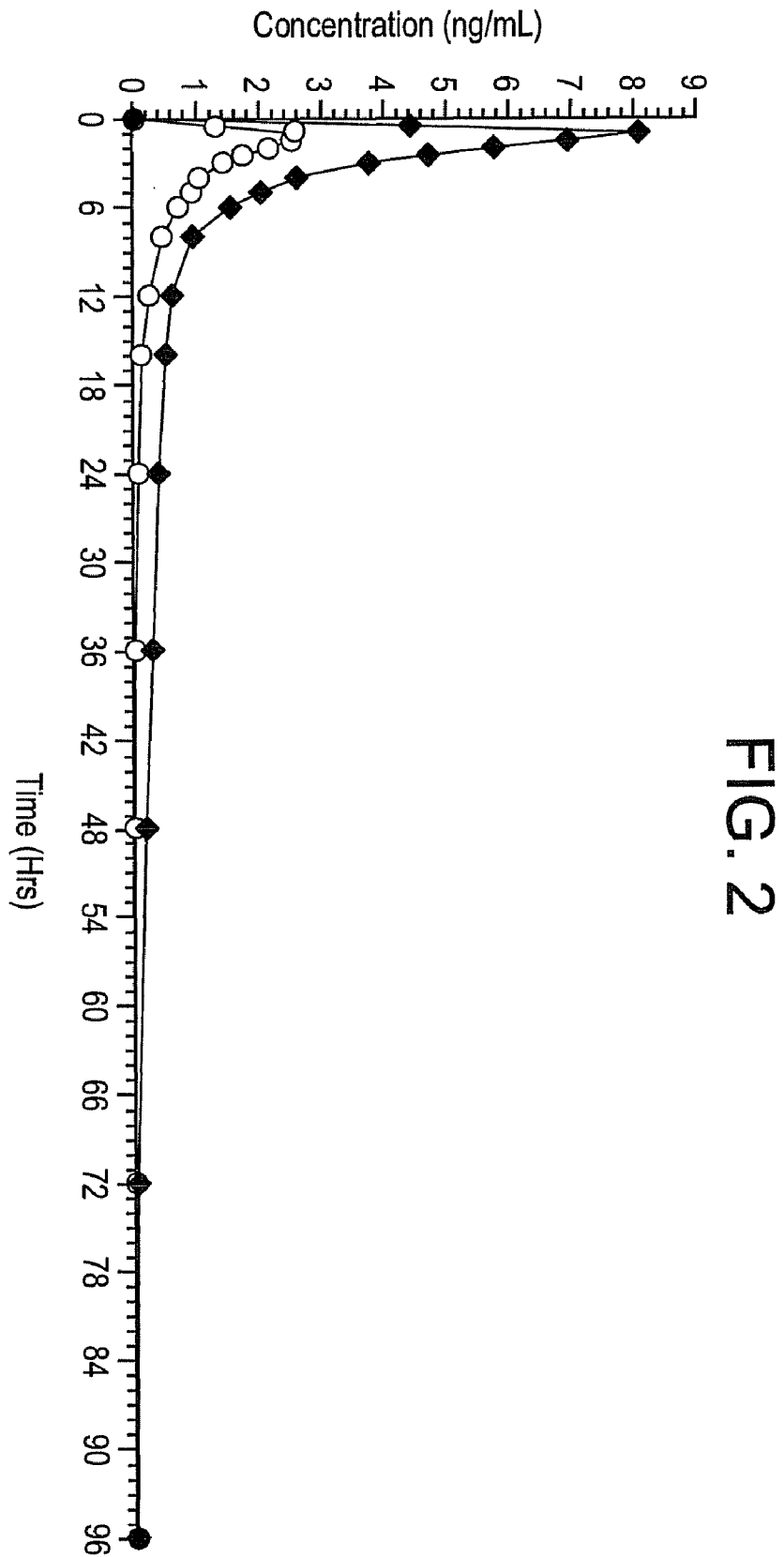


FIG. 2

FIG. 3

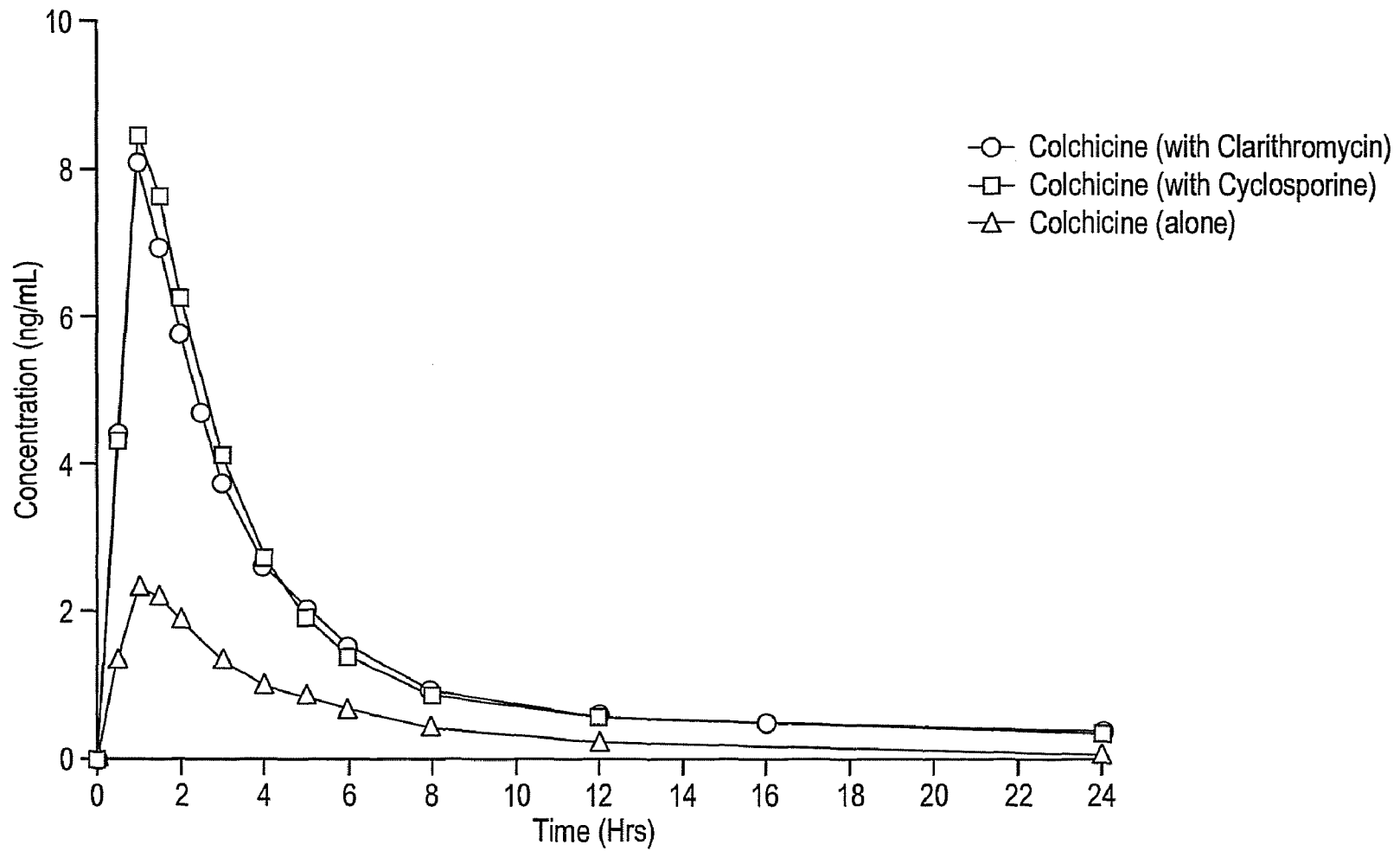


FIG. 4

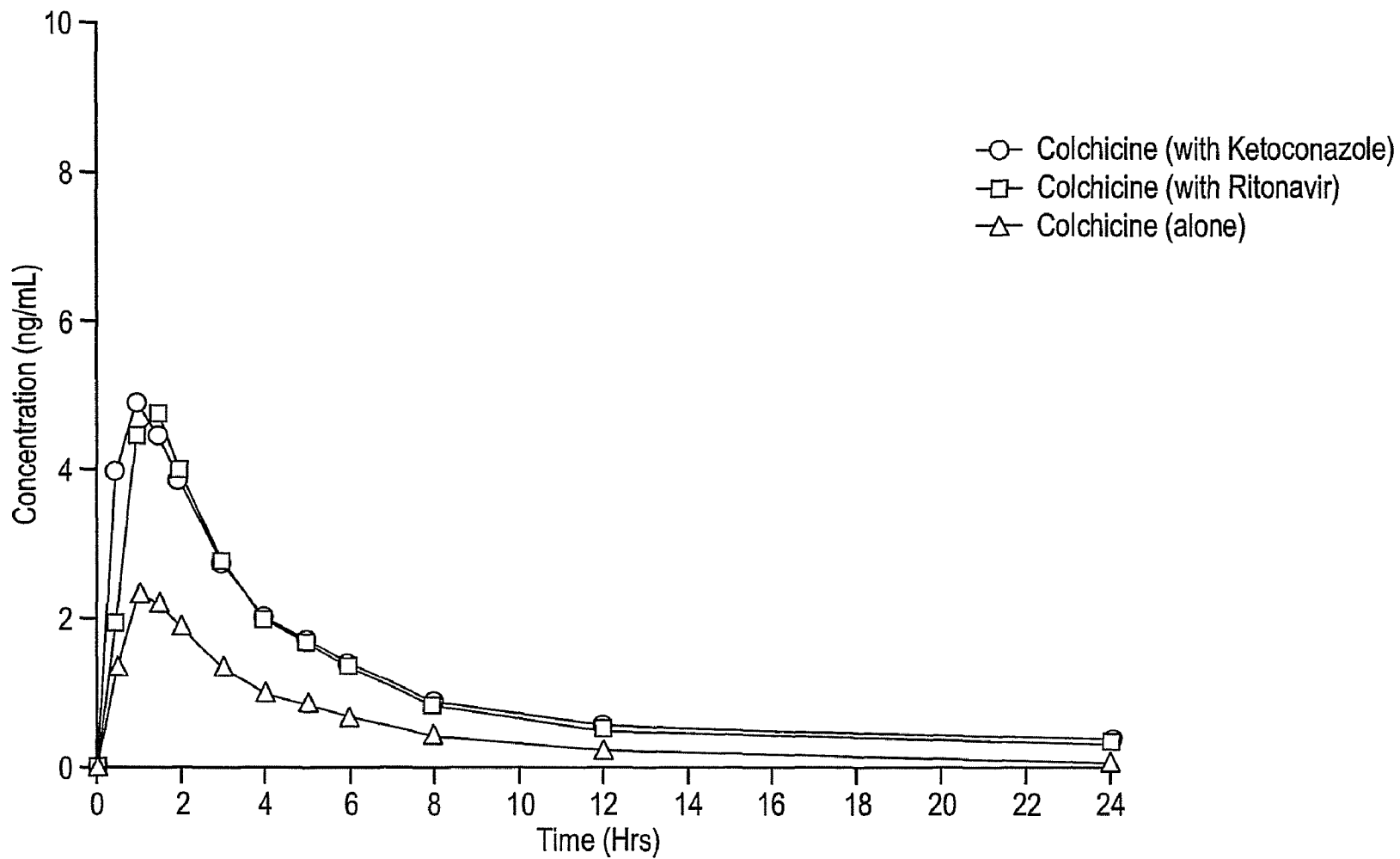
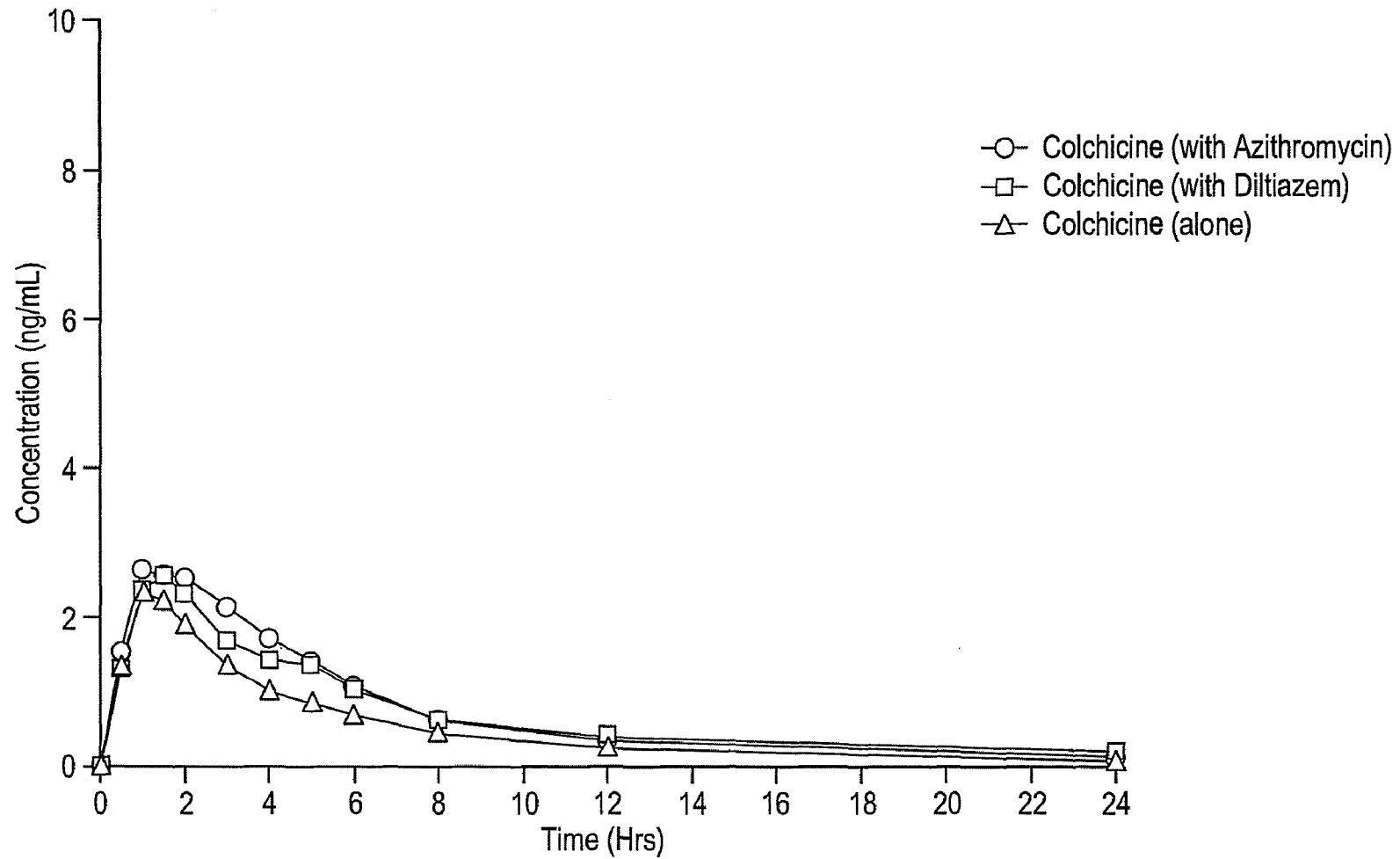


FIG. 5



US 7,820,681 B1

1

METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND A SECOND ACTIVE AGENT

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority from U.S. Provisional Application Ser. Nos. 61/138,141 filed Jan. 14, 2009 and 61/152,067 filed Feb. 12, 2009, both of which are hereby incorporated by reference in their entirety.

FIELD OF THE DISCLOSURE

This disclosure relates to methods allowing for the co-administration of colchicine together with one or more second active agents for therapeutic purposes with improved safety compared to prior methods of administration.

BACKGROUND

Colchicine, chemical name (–)-N-[(7S, 12aS)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide, is an alkaloid found in extracts of *Colchicum autumnale*, *Gloriosa superba*, and other plants. It is a microtubule-disrupting agent used in the treatment of gout and other conditions that may be treated, relieved or prevented with anti-inflammatory treatment. Colchicine impairs the motility of granulocytes and can prevent the inflammatory phenomena that initiate an attack (or flare) of gout. Colchicine also inhibits mitosis, resulting in effects in cells with high turnover rates such as those in the gastrointestinal tract and bone marrow. The primary adverse side effects of colchicine therapy include gastrointestinal upset such as diarrhea and nausea.

Colchicine has a narrow therapeutic index. The margin between an effective dose and a toxic dose of colchicine is much narrower than that of many other widely used drugs. Consequently, actions that result in increased colchicine levels in patients receiving colchicine therapy are particularly dangerous. Co-administration of colchicine to patients along with certain other drugs can have the effect of increasing colchicine levels. Such drug-drug interactions with colchicine have been reported to result in serious morbid complications and, in some cases, death.

Colchicine is rapidly absorbed from the gastrointestinal tract. Peak concentrations occur in 0.5 to 2 hours. The drug and its metabolites are distributed in leukocytes, kidneys, liver, spleen and the intestinal tract. Colchicine is metabolized in the liver and excreted primarily in the feces with 10 to 20% eliminated unchanged in the urine.

Gout (or gouty arthritis) is a disease caused by a build up of uric acid in the joints. Such a build up is typically due to an overproduction of uric acid, or to a reduced ability of the kidney to excrete uric acid. Gout is characterized by excruciating, sudden, unexpected, burning pain, as well as by swelling, redness, warmth, and stiffness in the affected joint. Low-grade fever may also be present. A gout flare is a sudden attack of pain in affected joints, especially in the lower extremities, and most commonly in the big toe. In afflicted individuals, the frequency of gout flares typically increases over time. In this manner, gout progresses from acute gout to chronic gout, which involves repeated episodes of joint pain.

Colchicine can reduce pain in attacks of acute gout flares and also can be used beneficially for treating adults for prophylaxis of gout flares. Although its exact mode of action in the relief of gout is not completely understood, colchicine is

2

known to decrease the inflammatory response to urate crystal deposition by inhibiting migration of leukocytes, to interfere with urate deposition by decreasing lactic acid production by leukocytes, to interfere with kinin formation and to diminish phagocytosis and subsequent inflammatory responses.

Cytochrome p450 (CYP) enzymes are agents of drug metabolism that are found in the liver, the gastrointestinal tract and other locations in the body. CYP enzymes occur in a variety of closely related proteins referred to as isozymes and different CYP isozymes may preferentially metabolize different drugs. The 3A family of CYP isozymes, particularly CYP3A4, is also known to be involved in many clinically significant drug-drug interactions, including those involving colchicine and second active agents. While drugs are often targets of CYP-mediated metabolism, some may also alter the expression and activity of such enzymes, thus impacting the metabolism of other drugs. The biotransformation of colchicine in human liver microsomes involves formation of 3-demethylcolchicine and 2-demethylcolchicine. As shown by experiments using antibodies against CYP3A4 and experiments using chemical inhibition of CYP3A4, this transformation is correlated with (and thus apparently mediated by) CYP3A4 activity.

P-glycoprotein (P-gp) is an ATP-dependent cell surface transporter molecule that acts as an ATPase efflux pump for multiple cytotoxic agents, including colchicine. P-gp actively pumps certain compounds, including drugs such as colchicine, out of cells. P-gp is encoded by the Adenosine triphosphate-binding cassette subfamily B member 1 (ABCB1) gene, also referred to as the multiple drug resistance 1 gene (MDR1).

Since colchicine acts intracellularly, the combined effects of CYP3A4 inhibition and P-gp inhibition by second active agents that also interact with CYP3A4 and P-gp can cause colchicine toxicity in patients taking what would be a safe dose of colchicine in the absence of concomitant second agent administration. Various studies of adverse reactions from exposure to multiple drugs have found that 6.5-23% of the adverse reactions result from drug-drug interactions. Unfortunately, each year a number of deaths occur as the direct result of patients adding a concomitant prescription pharmaceutical product to their existing medication regimen.

There accordingly remains a need for improved methods for administering colchicine to individuals who are concomitantly being treated with second active agents so as to reduce the possibility of colchicine toxicity while maintaining the sometimes life-saving advantages of being able to administer the two (or more) agents concomitantly. The present disclosure addresses this need and provides further advantages.

SUMMARY

In one embodiment, a method of treating an individual in need of treatment with colchicine comprises concomitantly administering to the individual colchicine and another drug, for example, ketoconazole or ritonavir or cyclosporine, wherein the colchicine is administered as a dosing regimen with a starting colchicine dose of no more than about 0.6 mg colchicine, followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours and no more frequently than once every hour wherein each additional colchicine dose is no greater than about 0.6 mg. According to another embodiment, the other drug is, for example, verapamil or diltiazem, and the starting colchicine dose during coadministration with the other drug is no more than about 1.2 mg colchicine, followed by either: no additional colchicine doses within

US 7,820,681 B1

3

about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours.

In another aspect, a method of using colchicine comprises increasing the blood plasma levels of colchicine in an individual being administered doses of about 0.6 mg or less of colchicine to treat a colchicine-treatable condition, said method comprising the concomitant dosing of the individual with a sufficient amount of ketoconazole to increase the C_{max} of colchicine by about 90%, or to increase the AUC_{0-t} of colchicine in the individual by about 190%, or to increase the AUC_{0-inf} of colchicine in the individual by about 205%, or to decrease the clearance of colchicine by about 70%, compared to the C_{max} , AUC_{0-t} , AUC_{0-inf} or clearance in a matched individual not administered concomitant ketoconazole.

In yet another aspect, a method of using colchicine comprises increasing the blood plasma levels of colchicine in an individual being administered doses of about 0.6 mg or less of colchicine to treat a colchicine-treatable condition, said method comprising the concomitant dosing of the individual with a sufficient amount of ritonavir to increase the C_{max} of colchicine by about 170%, or to increase the AUC_{0-t} of colchicine in the individual by about 245%, or to decrease the clearance of colchicine by about 70%, compared to the C_{max} , AUC_{0-t} or clearance in a matched individual not administered concomitant ritonavir.

In another embodiment, a method for using colchicine comprises a pharmacy receiving a prescription for colchicine for a patient who is concomitantly being treated with ketoconazole or ritonavir or verapamil, and the pharmacy dispensing colchicine in response to receipt of the prescription, wherein the dispensing is preceded by: entering, into a first computer readable storage medium in functional communication with a computer, of a unique patient identifier for said patient and at least one drug identifier for colchicine linked to the patient identifier so as to indicate that colchicine is to be administered to the patient, wherein the computer has been programmed to issue a drug-drug interaction alert when the at least one drug identifier for colchicine is entered linked to the patient identifier so as to indicate that colchicine is to be administered to the patient and when the patient identifier is also linked to an identifier indicating that ketoconazole or ritonavir or verapamil is being concomitantly administered to the patient, wherein, upon entry of the at least one drug identifier for colchicine linked to the patient identifier, a drug-drug interaction alert is issued to one or more of a pharmacy technician, a pharmacist, or a pharmacy customer obtaining the colchicine, said alert indicating that that ketoconazole or ritonavir is being concomitantly administered to the patient and that prior to the colchicine being dispensed, the colchicine dosing regimen must be reviewed and, if necessary adjusted, so that when the colchicine is delivered to the pharmacy customer obtaining the colchicine it is delivered along with instructions for the colchicine to be taken in accordance with a dosing regimen of no more than about 0.6 mg colchicine, followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours and no more frequently than once every hour wherein each additional colchicine dose is no greater than about 0.6 mg.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ritonavir, wherein the adjusted daily dosage amount of colchicine is about 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a dose suitable for the patient if the patient were not receiving concomitant ritonavir.

4

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ketoconazole, wherein the adjusted daily dosage amount of colchicine is about 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant ketoconazole.

A method of treating an individual in need of treatment for gout flares, comprises concomitantly administering colchicine and azithromycin, and carefully monitoring the individual for potential toxicity. The method further comprises adjusting the dose of colchicine or azithromycin as necessary to avoid adverse side effects.

A method of treating an individual with colchicine comprises concomitantly administering colchicine and verapamil, and carefully monitoring the individual for signs and symptoms of adverse side effects. The method further comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of verapamil, wherein the adjusted daily dosage amount of colchicine is about 50% to 75% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for a patient if the patient were not receiving concomitant verapamil.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows mean colchicine plasma concentrations following administration of single and multiple oral doses of colchicine 0.6 mg in healthy adults, N=13, Y axis=colchicine concentration, ng/mL, X axis=time in hours, ◆=day 1, ■=day 25. See Example 1.

FIG. 2 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin in healthy adults, Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=23, ●=colchicine alone, ◆=colchicine plus clarithromycin. See Example 2.

FIG. 3 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin and steady-state cyclosporine in healthy adults. Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=18, ▲=colchicine alone, ●=colchicine plus clarithromycin, ■=colchicine plus cyclosporine.

FIG. 4 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state ketoconazole and steady-state ritonavir in healthy adults. Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=18, ▲=colchicine alone, ●=colchicine plus ketoconazole, ■=colchicine plus ritonavir.

FIG. 5 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state azithromycin and steady-state diltiazem in healthy adults. Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=18, ▲=colchicine alone, ●=colchicine plus azithromycin, ■=colchicine plus diltiazem.

US 7,820,681 B1

5

These and other embodiments, advantages and features of the present invention become clear when detailed description is provided in subsequent sections.

DETAILED DESCRIPTION

Disclosed herein are methods for safely administering colchicine concomitantly with a second active agent, wherein the second active agent is a CYP3A4 inhibitor, a P-gp inhibitor, or both. Exemplary second active agents that are CYP3A4 and P-gp inhibitors are azithromycin, ketoconazole, ritonavir, diltiazem, verapamil and cyclosporine. It has now been discovered that certain reduced or limited colchicine dosage amounts, when administered with concomitantly administered recommended dosage amounts of second active agents that are CYP3A4 inhibitors, P-gp inhibitors, or both, achieve plasma colchicine levels that are therapeutically effective, but are not significantly higher, and therefore not significantly more toxic, than plasma levels achieved by administration of manufacturers' recommended colchicine dosages in the absence of concomitant administration with the second active agent. Thus, colchicine and second active agents that are CYP3A4 inhibitors, P-gp inhibitors, or both, can be administered concomitantly with improved safety when colchicine is administered as disclosed herein.

Without being held to theory, it has been hypothesized by the inventors herein that P-gp inhibition is more important in the elimination of colchicine than CYP3A4 inhibition. The CYP3A4 and P-gp inhibition potential of clarithromycin, azithromycin, ketoconazole, ritonavir, diltiazem and cyclosporine are given in Table 1. Based on their level of P-gp inhibition, it was predicted that clarithromycin and cyclosporine will increase colchicine concentrations more than ketoconazole or ritonavir, which will increase colchicine levels more than verapamil, azithromycin or diltiazem. The results presented herein confirm this hypothesis.

TABLE 1

| CYP3A4 and P-gp inhibition potential of second active agents | | |
|--------------------------------------------------------------|----------------------------|---------------------------|
| Drug | CYP3A Inhibition potential | P-gp Inhibition potential |
| Clarithromycin | +++++ | +++++ |
| Cyclosporine | +++++ | +++++ |
| Ketoconazole | +++++ | +++ |
| Ritonavir | +++++ | +++ |
| Verapamil | ++ | ++ |
| Diltiazem | + | + |
| Azithromycin | + | + |

Ritonavir (Norvir®, Abbott Laboratories) is an inhibitor of Human Immunodeficiency Virus (HIV) protease and is approved for the treatment of HIV-infection when used as part of a highly active antiretroviral therapy (HAART) regimen at the recommended dose of 600 mg twice daily. Although a very potent and effective protease inhibitor at the recommended dose, ritonavir is not well tolerated by HIV-infected patients at the approved dose and therefore, is generally not used clinically as a sole, therapeutic protease inhibitor within a HAART regimen. Rather, ritonavir is used more often as a pharmacokinetic enhancer or 'boosting agent' when combined with other approved protease inhibitors that are CYP3A4 and P-gp substrates and also have inherent bioavailability issues, such as poor bioavailability due to first pass effect. Improving the pharmacokinetic disposition of other protease inhibitors is possible due to the potent CYP3A4 and P-gp inhibitory activity ritonavir possesses. Sub-therapeutic ritonavir doses are used to achieve pharmacokinetic enhance-

6

ment of the co-administered protease inhibitors; typically 100 mg of ritonavir administered twice daily is the ritonavir dose used in combination with the primary protease inhibitor. This low-dose ritonavir regimen boosts the bioavailability of the second protease inhibitor without contributing significantly to the adverse event profile of the HAART regimen.

Cyclosporine (Neoral®, Novartis Pharmaceuticals Corporation) is the active principle in Neoral® an oral formulation that immediately forms a microemulsion in an aqueous environment. Cyclosporine is indicated for kidney, liver, and heart transplantation; rheumatoid arthritis and psoriasis. Cyclosporine is extensively metabolized by the CYP3A4 enzyme system in the liver, and to a lesser degree in the gastrointestinal tract, and the kidney. The metabolism of cyclosporine can be altered by the co-administration of a variety of agents.

Ketoconazole is a synthetic broad-spectrum antifungal agent available in scored white tablets, each containing 200 mg ketoconazole base for oral administration. Ketoconazole tablets are indicated for the treatment of the following systemic fungal infections: candidiasis, chronic mucocutaneous candidiasis, oral thrush, candiduria, blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. Ketoconazole is a potent inhibitor of the CYP3A4 enzyme system. Co-administration of ketoconazole and drugs primarily metabolized by the CYP3A4 enzyme may result in increased plasma concentrations of the drugs that could increase or prolong both therapeutic and adverse side effects.

Azithromycin is a macrolide antibiotic indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in specific conditions. Azithromycin remains the sole agent developed and marketed within the azalide macrolide subclass. Due to its dibasic structure, azithromycin has demonstrated unique pharmacokinetic properties that differ significantly from those of classic macrolide agents. Azithromycin's pharmacokinetics are characterized by low concentrations in serum, secondary to rapid and significant uptake by fibroblasts and acute reactant cells such as polymorphonuclear leukocytes (PMNs), monocytes, and lymphocytes. Azithromycin is a weak to moderate CYP3A4 inhibitor.

Diltiazem (Cardizem® CD, Biovail Pharmaceuticals, Inc. [Biovail]) is an extended-release (ER) calcium ion influx inhibitor available in blue capsules, each containing 240 mg diltiazem hydrochloride for oral administration. Diltiazem ER capsules are indicated for the treatment of hypertension and the management of chronic stable angina and angina due to coronary artery spasm. Diltiazem is a CYP3A4 and P-gp inhibitor.

Verapamil HCl ER (Mylan Pharmaceuticals, Inc.) is a calcium ion influx inhibitor available in a pale green, capsule shaped, film-coated tablets, each containing 240 mg verapamil hydrochloride for oral administration. Verapamil HCl ER tablets are indicated for the management of hypertension. Verapamil HCl ER is a potent CYP3A4 and P-gp inhibitor.

In one embodiment, colchicine is administered to an individual suffering from a condition treatable with colchicine, and the concomitant second active agent (e.g., ketoconazole, ritonavir, cyclosporine, verapamil, or diltiazem or any other CYP3A4 or P-gp inhibitor) is administered concurrently while the colchicine administration is reduced, or the individual has recently completed a dosing regimen of the second active agent, in which case the colchicine administration may still be reduced for a period of time.

In one embodiment, disclosed herein is a method of administering colchicine and a second active agent (e.g., ketoconazole).

US 7,820,681 B1

7

zole, ritonavir, or cyclosporine) wherein an individual is administered the colchicine according to a colchicine dosing regimen of a single starting colchicine dose of no more than about 0.6 mg colchicine, followed by either no additional colchicine doses within about 12, 24, 48, or 72 hours, or followed by at least one additional colchicine dose within 12 hours and no more frequently than once every hour (e.g., every 3, 4, 6, 8, or 12 hours). In this embodiment, each additional colchicine dose is specifically no greater than about 0.3 mg and the individual is an adult individual or a pediatric individual. Specifically, the starting colchicine dose is about 0.6 mg or about 0.3 mg, and each additional colchicine dose is about 0.3 mg. In one embodiment, when additional doses are administered, only two, three, or four additional colchicine doses are administered within about 24 hours. Specifically, the individual is an adult individual and the starting colchicine dose is about 0.6 mg, and each additional colchicine dose, if any, is about 0.3 mg. In one embodiment, only three additional colchicine doses are administered within about 24 hours.

In one embodiment, disclosed herein is a method of administering colchicine and a second active agent (e.g., verapamil or diltiazem) wherein an individual is administered the colchicine according to a colchicine dosing regimen of a single starting colchicine dose of no more than about 1.2 mg colchicine, followed by either no additional colchicine doses within about 12, 24, 48, or 72 hours, or followed by at least one additional colchicine dose within 12 hours and no more frequently than once every hour (e.g., every 3, 4, 6, 8, or 12 hours). In this embodiment, each additional colchicine dose is specifically no greater than about 0.3 mg or 0.6 mg and the individual is an adult individual or a pediatric individual. Specifically, the starting colchicine dose is about 0.6 mg or 1.2 mg, and each additional colchicine dose is about 0.3 mg or 0.6 mg. In one embodiment, when additional doses are administered, only two, three, or four additional colchicine doses are administered within about 24 hours. Specifically, the individual is an adult individual and the starting colchicine dose is about 1.2 mg, and each additional colchicine dose, if any, is about 0.3 mg or 0.6 mg. In one embodiment, only three additional colchicine doses are administered within about 24 hours.

In one embodiment, the second active agent is ketoconazole or ritonavir. In one embodiment, the ketoconazole is administered to the individual at a dosage of about 200 mg daily and the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by 0, 1, 2, 3, or 4 additional colchicine doses of about 0.6 mg every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In another embodiment, the ritonavir is administered to the individual at a dosage of about 200 to 1200 mg daily (e.g., in 2x100 mg doses or 2x600 mg doses) and the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by 0, 1, 2, 3, or 4 additional colchicine doses of about 0.6 mg every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In an exemplary regimen for treatment of acute gout flares, ingestion of colchicine is continued until a total of no more than about 1.2, 1.4, 1.6, 1.8, 2, or 2.4 mg of colchicine has been ingested, after which ingestion of colchicine is stopped until a subsequent acute gout flare occurs. More preferably, the colchicine is administered as a dosage form of 0.6 mg (e.g., one 0.6 mg colchicine tablet), or 0.3 mg (e.g., one half of a 0.6 mg tablet) of colchicine and administration of the dosage form is not repeated within a period of at least about two days, preferably at least about three days.

8

In one embodiment, the second active agent (e.g., ketoconazole or ritonavir or cyclosporine) is administered to the individual before the colchicine is administered to the individual, and wherein the administration of second active agent is terminated no more than about fourteen days prior to the initiation of colchicine administration. For example, the method comprises administering colchicine to an individual also taking a second active agent (e.g., ketoconazole or ritonavir or cyclosporine), or having completed treatment with the second active agent within the prior 14 days, the individual being administered a single dose of about 0.6 mg or about 0.3 mg of colchicine to treat a gout flare, which administration is not repeated within any 3-day period. According to this embodiment if the second active agent is instead verapamil or diltiazem, if the second active agent is terminated no more than about fourteen days prior to the initiation of the colchicine administration to treat a gout flare, the single dose of colchicine is about 1.2 mg not to be repeated within a 3-day period.

In another aspect, herein disclosed is a method for increasing the blood plasma levels of colchicine in an individual to whom colchicine is being administered to treat or prevent a colchicine-responsive condition. This method comprises the concomitant dosing of the individual with a sufficient amount of ketoconazole to increase the C_{max} of colchicine by about 90%, or to increase the AUC_{0-t} of colchicine in the individual by about 190%, or to increase the AUC_{0-inf} of colchicine in the individual by about 205%, or to decrease the clearance of colchicine by about 70%, compared to the C_{max} , AUC_{0-t} , or clearance in the same or a matched individual when not being administered a concomitant ketoconazole. In a specific embodiment, the individual is being administered no more than hourly doses of about 0.6 mg of colchicine or less, and the amount of ketoconazole is about 200 mg. In one embodiment, the single dose is one 0.6 mg colchicine tablet.

In yet another aspect, herein disclosed is a method for increasing the blood plasma levels of colchicine in an individual to whom colchicine is being administered to treat or prevent a colchicine-responsive condition. This method comprises the concomitant dosing of the individual with a sufficient amount of ritonavir to increase the C_{max} of colchicine by about 170%, or to increase the AUC_{0-t} of colchicine in the individual by about 245%, or to decrease the clearance of colchicine by about 70%, compared to the C_{max} , AUC_{0-t} , or clearance in the same or a matched individual when not being administered concomitant ritonavir. In a specific embodiment, the individual is being administered no more than hourly doses of about 0.6 mg of colchicine or less, and the amount of ritonavir is about 200 to about 1200 mg. In one embodiment, the single dose is one 0.6 mg colchicine tablet.

In one embodiment, a method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ritonavir, wherein the adjusted daily dosage amount of colchicine is 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant ritonavir. Treating is, for example, to prevent gout flares, to treat acute gout, or to treat familial Mediterranean fever. When the colchicine is administered to prevent gout flares, the adjusted daily dosage amount of colchicine may be reduced from a 0.6 mg twice daily intended dose to a 0.6 mg once daily adjusted dose. Alternatively, when the colchicine is administered to prevent gout flares, wherein the adjusted daily dosage amount of colchicine is reduced from a 0.6 mg once daily intended dose to a 0.3 mg once daily adjusted dose.

US 7,820,681 B1

9

In one embodiment, when treating is for acute gout, the intended daily dosage amount is 1.8 to 2.4 mg, and the maximum adjusted daily dosage amount is 0.6 mg, not to be repeated within 3 days. In another embodiment, treating is for acute gout, the intended daily dosage amount is 2.4 to 4.8 mg and the maximum adjusted daily dosage amount is 0.6 to 1.2 mg, not to be repeated within 3 days. In yet another embodiment, treating is for familial Mediterranean fever and the daily dosage amount 1.2 to 2.4 mg for adults, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. In another embodiment, treating is for familial Mediterranean fever and the intended daily dosage amount is 0.9 to 1.8 mg for children 6-12 years or 4-6 years, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. The concomitantly administered dose of ritonavir is, for example, 200 mg per day. In one embodiment, the ritonavir is administered to the patient before the colchicine is administered to the patient, and wherein the administration of ritonavir is terminated no more than about fourteen days prior to the initiation of colchicine administration. The method optionally further comprises carefully monitoring the individual for potential toxicity. Any 0.3 mg dose contemplated in this method can be a single 0.3 mg dosage form or one-half a 0.6 mg dosage form, e.g. one-half a 0.6 mg colchicine tablet.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ketoconazole, wherein the adjusted daily dosage amount of colchicine is 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant ketoconazole. Treating is, for example, to prevent gout flares, to treat acute gout, or to treat familial Mediterranean fever. When the colchicine is administered to prevent gout flares, the adjusted daily dosage amount of colchicine may reduced from a 0.6 mg twice daily intended dose to a 0.6 mg once daily adjusted dose. Alternatively, when the colchicine is administered to prevent gout flares, wherein the adjusted daily dosage amount of colchicine is reduced from a 0.6 mg once daily intended dose to a 0.3 mg once daily adjusted dose. In one embodiment, when treating is for acute gout, the intended daily dosage amount is 1.8 to 2.4 mg, and the maximum adjusted daily dosage amount is 0.6 mg, not to be repeated within 3 days. In another embodiment, treating is for acute gout, the intended daily dosage amount is 2.4 to 4.8 mg and the maximum adjusted daily dosage amount is 0.6 to 1.2 mg, not to be repeated within 3 days. In yet another embodiment, treating is for familial Mediterranean fever and the daily dosage amount 1.2 to 2.4 mg for adults, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. In another embodiment, treating is for familial Mediterranean fever and the intended daily dosage amount is 0.9 to 1.8 mg for children 6-12 years or 4-6 years, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. The concomitantly administered dose of ketoconazole is, for example, 250 mg per day. In one embodiment, the ketoconazole is administered to the patient before the colchicine is administered to the patient, and wherein the administration of ketoconazole is terminated no more than about fourteen days prior to the initiation of colchicine administration. The method optionally further comprises carefully monitoring the individual for potential toxicity. Any 0.3 mg dose contemplated in this method can be a single 0.3 mg dosage form or one-half a 0.6 mg dosage form, e.g. one-half a 0.6 mg colchicine tablet.

10

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of cyclosporine, wherein the adjusted daily dosage amount of colchicine is 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant cyclosporine. Treating is, for example, to prevent gout flares, to treat acute gout, or to treat familial Mediterranean fever. When the colchicine is administered to prevent gout flares, the adjusted daily dosage amount of colchicine may reduced from a 0.6 mg twice daily intended dose to a 0.3 mg once daily adjusted dose. Alternatively, when the colchicine is administered to prevent gout flares, wherein the adjusted daily dosage amount of colchicine is reduced from a 0.6 mg once daily intended dose to a 0.3 mg once every other day adjusted dose. In one embodiment, when treating is for acute gout, the intended daily dosage amount is 1.8 to 2.4 mg, and the maximum adjusted daily dosage amount is 0.6 mg, not to be repeated within 3 days. In another embodiment, treating is for acute gout, the intended daily dosage amount is 2.4 to 4.8 mg and the maximum adjusted daily dosage amount is 0.6 to 1.2 mg, not to be repeated within 3 days. In yet another embodiment, treating is for familial Mediterranean fever and the daily dosage amount 1.2 to 2.4 mg for adults, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. In another embodiment, treating is for familial Mediterranean fever and the intended daily dosage amount is 0.9 to 1.8 mg for children 6-12 years or 4-6 years, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. The concomitantly administered dose of cyclosporine can be various dosage strengths administered per day, and can be administered as an oral preparation, topically, or intravenously. In one embodiment, the cyclosporine is administered to the patient before the colchicine is administered to the patient, and wherein the administration of cyclosporine is terminated no more than about fourteen days prior to the initiation of colchicine administration. The method optionally further comprises carefully monitoring the individual for potential toxicity. Any 0.3 mg dose contemplated in this method can be a single 0.3 mg dosage form or one-half a 0.6 mg dosage form, e.g. one-half a 0.6 mg colchicine tablet.

In another embodiment, colchicine is concomitantly administered with azithromycin. Concomitant administration of azithromycin with colchicine increases exposure to colchicine approximately 46% and thus has the potential to produce colchicine toxicity. During concomitant use of azithromycin and colchicine, the physician should carefully monitor individuals for any signs or symptoms of colchicine toxicity. Additionally, dosing adjustments to either the colchicine and/or the azithromycin may be necessary to avoid adverse side effects.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of verapamil, wherein the adjusted daily dosage amount of colchicine is 50% to 75% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant verapamil. Treating is, for example, to prevent gout flares, to treat acute gout, or to treat familial Mediterranean fever. When the colchicine is administered to prevent gout flares, the adjusted daily dosage amount of colchicine may reduced from a 0.6 mg twice daily intended dose to a 0.3 mg once daily adjusted

US 7,820,681 B1

11

dose. In one embodiment, when treating is for acute gout, the intended daily dosage amount is 1.8 to 2.4 mg, and the maximum adjusted daily dosage amount is 1.2 mg. In another embodiment, treating is for acute gout, the intended daily dosage amount is 2.4 to 4.8 mg and the maximum adjusted daily dosage amount is about one-third the intended daily dosage amount. In yet another embodiment, treating is for familial Mediterranean fever and the daily dosage amount 1.2 to 2.4 mg for adults, and the maximum adjusted daily dosage amount is 1.2 mg, given, for example, in two 0.6 mg doses. In one embodiment, the verapamil is administered to the patient before the colchicine is administered to the patient, and wherein the administration of verapamil is terminated no more than about fourteen days prior to the initiation of colchicine administration. The method optionally further comprises carefully monitoring the individual for potential toxicity. Any 0.3 mg dose contemplated in this method can be a single 0.3 mg dosage form or one-half a 0.6 mg dosage form, e.g. one-half a 0.6 mg colchicine tablet.

Disclosed herein are specific dosage reductions of colchicine that improve safety when colchicine is co-administered with certain active agents. The dose of colchicine recommended for administration without co-administration of certain other active agents, such as CYP3A4 or P-gp inhibitors, is referred to as an intended daily dosage amount. The reduced or modified daily dosage amount determined from the experiments presented herein is referred to as an adjusted daily dosage amount. An adjusted daily dosage amount is thus a daily dosage amount that can be safely co-administered with a second active agent as disclosed herein. A dose adjustment is thus a dose of colchicine and does not include cessation of colchicine, that is, a dose of 0 mg of colchicine.

In these and other embodiments, the colchicine-responsive condition is gout (e.g., a gout flare in a chronic gout sufferer), familial Mediterranean fever (FMF), thrombocytopenic purpura, pericarditis, scleroderma, or Behçet's disease. In some embodiments, the treatment with colchicine is either palliative or prophylactic. The gout may be acute gout, e.g. a gout flare, or chronic gout.

Acute Gout

Acute gout, or gout flares, can be treated according to the following treatment schedule. This table indicates the original, or intended, dose, i.e., the dose of colchicine recommended absent concomitant administration of the drugs listed below. This table also presents the dose adjustment of the present invention, or the recommended colchicine dose to be administered when the strong and moderate CYP3A4 and P-gp inhibitors are administered concomitantly with colchicine when the patient is being treated for acute gout, or an acute gout flare.

| Colchicine Dose Recommendation | | |
|--------------------------------|-------------------------------------------------------------------------------------------------|---------------------------------------------|
| Drug | Original Intended Dose (Total Dose) | Dose Adjustment |
| Strong CYP3A4 Inhibitors | Regimen Reduced by Two Thirds | |
| Erythromycin | 1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 tablet) one hour later. | 0.6 mg (1 tablet) × 1 dose. |
| Ketoconazole | | Dose to be repeated no earlier than 3 days. |
| Ritonavir | | Dose to be repeated no earlier than 3 days. |

12

-continued

| Colchicine Dose Recommendation | | |
|--------------------------------|-------------------------------------------------------------------------------------------------|---------------------------------------------|
| Drug | Original Intended Dose (Total Dose) | Dose Adjustment |
| Moderate CYP3A4 Inhibitors | Regimen Reduced by One Third | |
| Diltiazem | 1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 tablet) one hour later. | 1.2 mg (2 tablets) × 1 dose. |
| Verapamil | Dose to be repeated no earlier than 3 days. | Dose to be repeated no earlier than 3 days. |
| Strong P-gp Inhibitors | Regimen Reduced by Two Thirds | |
| Cyclosporine | 1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 tablet) one hour later. | 0.6 mg (1 tablet) × 1 dose. |
| | Dose to be repeated no earlier than 3 days. | Dose to be repeated no earlier than 3 days. |

Chronic Gout

For chronic gout, an original intended daily dosage amount is 1.2 mg or 6 mg. Alternatively, an intended daily dosage amount of chronic gout can be as much as 2.4 mg per day. The daily dosage amount for chronic gout can be administered at one time or dosed at intervals throughout the day, e.g. twice daily, three times daily, or four times daily.

Chronic gout, with and without a concomitant dose of another drug, can be treated according to the following treatment schedule:

Colchicine Dose Adjustment for Co-Administration with Interacting Drugs if No Alternative Available

| Colchicine Dose Recommendation | | |
|--------------------------------|------------------------|-----------------------------|
| Drug | Original Intended Dose | Dose Adjustment |
| Clarithromycin | 0.6 mg twice daily | 0.3 mg once daily |
| | 0.6 mg once daily | 0.3 mg once every other day |
| Cyclosporine | 0.6 mg twice daily | 0.3 mg once daily |
| | 0.6 mg once daily | 0.3 mg once every other day |
| Erythromycin | 0.6 mg twice daily | 0.3 mg once daily |
| | 0.6 mg once daily | 0.3 mg once every other day |
| Ritonavir | 0.6 mg twice daily | 0.6 mg once daily |
| | 0.6 mg once daily | 0.3 mg once daily |

Familial Mediterranean Fever

Familial Mediterranean Fever (FMF) can be treated according to the following intended daily dosing schedule:

| Daily dosage amount | | | |
|-------------------------------|--------|---------|--|
| Age | Usual | Maximum | |
| Adults and children >12 years | 1.2 mg | 2.4 mg | |
| Children >6 to 12 years | 0.9 mg | 1.8 mg | |
| Children 4 to 6 years | 0.3 mg | 1.8 mg | |

When colchicine is given to patients with FMF concomitantly with other drugs, the adjusted (reduced) dosage amount of colchicine, according to this embodiment, is provided in the table below:

US 7,820,681 B1

13

14

| Concomitant Drug Class or Food | Noted or Anticipated Outcome | Clinical Comment |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Strong CYP3A4 Inhibitors: atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin | Significant increase in colchicine plasma levels ¹ ; fatal colchicine toxicity has been reported with clarithromycin, a strong CYP3A4 inhibitor. Similarly, significant increase in colchicine plasma levels is anticipated with other strong CYP3A4 inhibitors. | Use colchicine with caution at reduced maximum dose of 0.3 mg twice daily with increased monitoring for adverse effects. In patients with renal or hepatic impairment, use of colchicine in conjunction with these drugs is contraindicated. |
| Moderate CYP3A4 inhibitors: amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, verapamil | Significant increase in colchicine plasma concentration is anticipated. Neuromuscular toxicity has been reported with diltiazem and verapamil interactions. | Use colchicine with caution at reduced maximum dose of 0.6 mg twice daily with increased monitoring for adverse effects. In patients with renal or hepatic impairment, use a maximum dose of 0.3 mg twice daily. |
| Strong P-gp Inhibitors e.g. Cyclosporine, ranolazine. | Significant increase in colchicine plasma levels ¹ ; fatal colchicine toxicity has been reported with cyclosporine, a strong P-gp inhibitor. Similarly, significant increase in colchicine plasma levels is anticipated with other strong P-gp inhibitors. | Use colchicine with caution at reduced maximum dose of 0.3 mg twice daily with increased monitoring for adverse effects. In patients with renal or hepatic impairment, use of colchicine in conjunction with these drugs is contraindicated. |

Pharmacy management systems are computer-based systems that are widely used by commercial pharmacies to manage prescriptions and to provide pharmacy and medical personnel with warnings and guidance regarding drugs being administered to individuals. Such systems typically provide alerts warning either or both of health care providers and patients when a drug that may be harmful to the particular patient is prescribed. For example, such systems can provide alerts warning that a patient has an allergy to a prescribed drug, or is receiving concomitant administration of a drug that can have a dangerous interaction with a prescribed drug. U.S. Pat. Nos. 5,758,095, 5,833,599, 5,845,255, 6,014,631, 6,067, 524, 6,112,182, 6,317,719, 6,356,873, and 7,072,840, each of which is incorporated herein by reference, disclose various pharmacy management systems and aspects thereof. Many pharmacy management systems are now commercially available, e.g., CENTRICITY Pharmacy from BDM Information Systems Ltd., General Electric Healthcare, Waukesha, Wis., Rx30 Pharmacy Systems from Transaction Data Systems, Inc., Ocoee, Fla., SPEED SCRIPT from Digital Simplicities, Inc., Lenexa, Kans., and various pharmacy management systems from OPUS-ISM, Hauppauge, N.Y.

In another aspect, herein disclosed are methods for using colchicine which methods involve the use of pharmacy management systems.

In one aspect, one such method comprises a pharmacy receiving a prescription for colchicine for a patient who is suffering from gout (e.g., acute gout flares or chronic gout) and who is concomitantly being treated with a second active agent (e.g., ketoconazole or ritonavir) that is an inhibitor of CYP3A and P-glycoprotein, followed by the pharmacy dispensing colchicine in response to receipt of the prescription, wherein the dispensing is preceded by entry into a first computer readable storage medium, in functional communication with a computer, of a unique patient identifier for said patient and at least one drug identifier for colchicine linked to the

patient identifier so as to indicate that colchicine is to be administered to the patient. The computer is programmed to issue a drug-drug interaction alert when the at least one drug identifier for colchicine is entered linked to the patient identifier so as to indicate that colchicine is to be administered to the patient and when the patient identifier is also linked to an identifier indicating that a second active agent (e.g., ketoconazole or ritonavir) that is an inhibitor of CYP3A4 or P-glycoprotein is being concomitantly administered to the patient. Upon entry of the at least one drug identifier for colchicine linked to the patient identifier, a drug-drug interaction alert is issued to one or more of a pharmacy technician, a pharmacist, or a pharmacy customer obtaining the colchicine, said alert indicating that a second active agent (e.g., ketoconazole or ritonavir) is being concomitantly administered to the patient and that prior to the colchicine being dispensed, the colchicine dosing regimen must be reviewed and, if necessary adjusted, so that when the colchicine is delivered to the pharmacy customer obtaining the colchicine it is delivered along with instructions for the colchicine to be taken in accordance with a dosing regimen of no more than one about 0.6 mg colchicine dose to start (e.g., following the onset of the acute gout attack or the first sign of a gout flare) followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours and no more frequently than once every hour and wherein each additional colchicine dose is no greater than about 0.6 mg, and wherein the patient ingests the colchicine as instructed.

The drug-drug interaction alert is preferably issued as one or both of a written warning on a display screen of the pharmacy management computer system, and a printed warning. The printed warning may be attached to or packaged with the dispensed prescription.

In one aspect, the identifier indicating that ketoconazole is being concomitantly administered to the patient is an identifier

US 7,820,681 B1

15

fier indicating that the second active agent is ketoconazole and is linked to at least one further identifier indicating that the ketoconazole is prescribed so that 200 mg of ketoconazole is to be ingested by the patient daily, in which case the dosing regimen for colchicine is preferably one about 0.6 mg colchicine dose to start, optionally followed by additional colchicine doses, e.g., 0, 1, 2, 3, or 4 additional colchicine doses within 24 hours of about 0.3 mg ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In another embodiment, the identifier indicating that ketoconazole is being concomitantly administered to the patient is an identifier indicating that the second active agent is ketoconazole is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the ketoconazole is prescribed so that about 200 mg of ketoconazole is to be ingested by the patient daily, in which case the colchicine dosing regimen is one about 0.3 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every six to eight hours) after the preceding colchicine dose. In one embodiment, the dosing regimen calls for the about 0.3 mg colchicine dose every six to eight hours. In another embodiment, the dosing regimen calls for one dose of the colchicine every eight to twelve hours.

In yet another preferred aspect, the identifier indicating that ketoconazole is being concomitantly administered to the patient is an identifier indicating that the second active agent is ketoconazole and is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the ketoconazole is prescribed so that about 200 mg of ketoconazole is to be ingested by the patient daily and the dosing regimen is one about 0.3 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 2, 3, 4, 5, 6, 7, or 8 hours (e.g., every eight to twelve hours) after the preceding colchicine dose.

A preferred dosing regimen calls for ingestion of colchicine to be continued until a total of no more than 1.2 mg or 2.4 mg of colchicine has been ingested, after which ingestion of colchicine is to be stopped, e.g., for at least 2, 3, 4, 5, 6, or 7 days, or until a subsequent acute gout flare, or the first sign of a subsequent gout flare, occurs.

In another aspect, the identifier indicating that ritonavir is being concomitantly administered to the patient is an identifier indicating that the second active agent is ritonavir and is linked to at least one further identifier indicating that the ritonavir is prescribed so that 200 or 1200 mg of ritonavir is to be ingested by the patient daily, in which case the dosing regimen for colchicine is preferably one about 0.6 mg colchicine dose to start, optionally followed by additional colchicine doses, e.g., 0, 1, 2, 3, or 4 additional colchicine doses within 24 hours of about 0.3 mg ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In another embodiment, the identifier indicating that ritonavir is being concomitantly administered to the patient is an identifier indicating that the second active agent is ritonavir is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating

16

that the ritonavir is prescribed so that about 1200 mg of ritonavir is to be ingested by the patient daily, in which case the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every six to eight hours) after the preceding colchicine dose. In one embodiment, the dosing regimen calls for the about 0.3 mg colchicine dose every six to eight hours. In another embodiment, the dosing regimen calls for one dose of the colchicine every eight to twelve hours.

In yet another aspect, the identifier indicating that ritonavir is being concomitantly administered to the patient is an identifier indicating that the second active agent is ritonavir and is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the ritonavir is prescribed so that about 1200 mg of ritonavir is to be ingested by the patient daily and the dosing regimen is one about 0.3 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 2, 3, 4, 5, 6, 7, or 8 hours (e.g., every eight to twelve hours) after the preceding colchicine dose.

Also disclosed herein is a dosage adjustment method for administering colchicine to a patient to treat a medical condition, the patient concomitantly treated with a second active agent. The second active agent may be, for example, ritonavir, ketoconazole, cyclosporine, verapamil, or diltiazem. The method comprises determining a first colchicine dosing regimen (the colchicine dosing regimen suitable for administration in the absence of co-administration with a second active agent, which dosing regimen may consist of one or more doses of colchicine); and determining a second active agent dosing regimen; and administering the second active agent to the patient at the second active agent dosing regimen while concomitantly administering colchicine to the patient according to a second colchicine dosing regimen, which may consist of one or more reduced colchicine doses. The second colchicine dosing regimen is a fraction of the first colchicine dosing regimen, where the fraction is obtained by administering reduced colchicine doses or by reducing the frequency of colchicine doses, and wherein the fraction is less than or equal to about $\frac{2}{3}$ or less than or equal to about $\frac{1}{2}$ or less than or equal to about $\frac{1}{3}$.

According to this embodiment, upon the administering the second active agent to the patient at the second active agent dosing regimen while concomitantly administering colchicine to the patient at the second colchicine dosing regimen, the therapeutic circulating level of colchicine is achieved in the patient. Preferably, the fraction is selected from $\frac{1}{12}$, $\frac{1}{6}$, $\frac{1}{4}$, $\frac{1}{3}$, $\frac{5}{12}$, and $\frac{1}{2}$, more preferably, the fraction is $\frac{1}{3}$ or $\frac{1}{2}$. In one embodiment, if the second colchicine dosing regimen comprises a "first" colchicine dose, and one or more "subsequent" colchicine doses, each subsequent colchicine dose may be the same as the first dose, or a fraction of the first dose. The fraction is selected from about $\frac{1}{12}$, about $\frac{1}{6}$, about $\frac{1}{4}$, about $\frac{1}{3}$, about $\frac{5}{12}$, about $\frac{1}{2}$, and about $\frac{2}{3}$, e.g., about $\frac{1}{2}$ or about $\frac{2}{3}$. In one example, the second colchicine dosing regimen is once-a-day, twice-a-day, three-times-a-day or four-times-a-day. In a variation of this example, the initial treatment day in, a second colchicine dosing regimen that lasts for more than one day, has one more dose administered than are administered each subsequent day.

Preferably the second active agent is selected from ketoconazole, cyclosporine, ritonavir, verapamil, or diltiazem. The specific conditions are selected from gout, FMF, thrombocytopenic purpura, and Behçet's disease. In one embodi-

US 7,820,681 B1

17

ment, the gout is an acute gout flare and the colchicine treatment schedule is an acute treatment schedule adapted for treatment of acute gout flares, or the gout is chronic gout, and the colchicine treatment schedule is a chronic treatment schedule adapted for prophylaxis, or prevention, of flares. In another embodiment, the fraction of colchicine administered to the patient concomitantly with a second active agent that is a CYP3A4 or P-gp inhibitor is $\frac{1}{3}$ or $\frac{1}{2}$ the original intended amount of colchicine and treatment with colchicine is initiated subsequent to or at the same time as initiation of treatment with the second active agent.

Colchicine is one of the most widely used drugs for treating familial Mediterranean fever (FMF). It has been reported that 5-10% of FMF patients do not show a beneficial response to colchicine administration. A polymorphism in the ABCB1 gene, the "ABCB1 3435 C to T polymorphism" has been reported to correlate with this lack of response to colchicine treatment, with patients with the homozygous TT genotype exhibiting the most pronounced "non-responder" phenotypes.

Accordingly, in another aspect, provided herein is a method for treating a patient suffering from FMF, which patient is a colchicine non-responder. Preferably, the patient is homozygous for the TT genotype of the ABCB1 3435 C to T polymorphism. The method entails the concomitant administration of a P-gp inhibitor and colchicine to the patient. Exemplary P-gp inhibitors include ketoconazole and ritonavir. Preferred dosages of the P-gp inhibitor for this purpose correspond to those called for in the prescribing information for the drug in question. For ketoconazole, an exemplary dosage is 200 mg per day. For ritonavir, an exemplary dosage is 200 or 1200 mg per day. Specific colchicine dosing regimens for this purpose are the same as used for treatment of FMF in responders, though the doses of colchicine administered may be increased as tolerated, e.g., up to two to three times the typical doses.

The following examples further illustrate aspects of this disclosure but should not be construed as in any way limiting its scope. In particular, the conditions are merely exemplary and can be readily varied by one of ordinary skill in the art.

EXAMPLES

Example 1

Pharmacokinetic Study in Healthy Adults of Single vs. Multiple Oral Doses of Colchicine Tablets

This study was a single-center, open-label, single-sequence, two-period study to evaluate the pharmacokinetic profile of colchicine following single and multiple oral doses of colchicine tablets, 0.6 mg, in healthy volunteers.

In Period 1, study subjects received a 0.6-mg dose of colchicine after an overnight fast of at least 10 hours. In Period 2, subjects received a 0.6 mg dose of colchicine in the morning and the evening (approximately 12 hours later) for 10 days (steady state regimen). Subjects received a light breakfast served 60 minutes following dose administration in the morning and the evening dose was administered 90 minutes after an evening meal on Days 15 through 24 only. On Day 25, the colchicine dose was administered after an overnight fast of at least 10 hours and lunch was served 4 hours

18

post-dose. Study periods were separated by a 14-day wash-out. Following the single dose and the last dose of the multiple dose regimen (beginning on the mornings of Day 1 and Day 25, respectively), blood samples were collected (6 mL each) from each subject within 1 hour prior to dosing and after dose administration at study hours 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 (while confined) and 36, 48, 72, and 96 (on an outpatient basis). Plasma concentrations of colchicine and its metabolites were determined using validated LC/MS-MS methods.

Thirteen healthy, non-smoking subjects with a mean age of 25.5 years (range 19 to 38 years) and within 15% of ideal body weight were enrolled in this study. All subjects completed both dosing periods according to protocol.

After a single dose, plasma concentrations are no longer quantifiable 24 hours post-dose in all but 1 subject. After the last dose of the steady state regimen, concentrations remained quantifiable for 48 to 72 hours. Review of individual subject data shows that no subject experienced a secondary colchicine peak, either following a single dose or upon multiple dosing.

All 2-O-demethylcolchicine (2-DMC) concentrations were below the level of quantitation (LOQ, 0.2 ng/mL) and only one sample from 1 subject (of 13 subjects) had a detectable 3-O-demethylcolchicine (3-DMC) concentration, which was near the level of quantitation. Therefore, metabolites are not discussed further.

In healthy adults, colchicine appears to be readily absorbed when given orally, reaching a mean maximum plasma concentration of 2.5 ng/mL in 1.5 hours after a single dose. The drug is distributed widely, with an apparent volume of distribution of 540 L, greatly exceeding total body water. The elimination half-life as calculated following a single oral dose is approximately 5 hours. Levels were not detectable by 24 hours post-dose and this is therefore not an accurate estimate. Pharmacokinetic parameter values are summarized in the table below.

Review of trough plasma concentrations indicates that steady state was attained by approximately the eighth day of dosing for most subjects. Colchicine may have a diurnal variation reflected in the observed C_{min} concentrations at steady state. C_{min} concentrations prior to the morning dose are approximately 12% higher than the C_{min} concentrations prior to the evening dose (Day 23 and Day 24). The mean C_{min} concentration observed on Day 25 was 0.907 ng/mL.

Colchicine accumulated following administration of multiple doses to an extent greater than expected. Exposure was nearly two-fold higher (approximately 1.7 based on AUC [Day 25 AUC_{0-τ}/Day 1 AUC_{0-∞}] and approximately 1.5 based on C_{max} [Day 25 C_{max}/Day 1 C_{max}]). This observation could be attributable to an underestimation of AUC_∞ following a single dose. With the higher plasma levels that occur with repeated dosing, a longer terminal elimination half life is apparent, 26.6 hours. Pharmacokinetic parameter values are summarized in Tables 3-5.

US 7,820,681 B1

19

20

TABLE 3

| Colchicine Pharmacokinetic Parameter Values Following Administration of A Single Oral Dose of Colchicine 0.6 mg in Healthy Adults (N = 13) | | | | | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------|----------|---------|-------|----------|---------|----------|
| | MEAN | STDEV | % CV | MEDIAN | MIN | MAX |
| AUC _{0-t} (pg-hr/mL) | 10494.66 | 3544.08 | 33.77 | 10560.90 | 4812.88 | 18091.85 |
| AUC _{0-inf} (pg-hr/mL) | 12268.18 | 4422.08 | 36.05 | 11451.45 | 7252.66 | 23801.68 |
| C _{max} (pg/mL) | 2450.15 | 702.11 | 28.66 | 2480.00 | 1584.00 | 3977.00 |
| T _{max} (hr) | 1.50 | 0.54 | 36.00 | 1.50 | 1.00 | 3.00 |
| K _{el} (1/hr) | 0.1829 | 0.0592 | 32.38 | 0.1992 | 0.0359 | 0.2443 |
| T _{1/2} (hr) | 4.95 | 4.43 | 89.54 | 3.48 | 2.84 | 19.29 |

TABLE 4

| Colchicine Pharmacokinetic Parameter Values Following Administration of Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults (N = 13) | | | | | | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|----------|---------|-------|----------|----------|----------|
| | MEAN | STDEV | % CV | MEDIAN | MIN | MAX |
| AUC _{0-t} (pg-hr/mL) | 43576.96 | 9333.26 | 21.42 | 41925.10 | 29328.78 | 58265.35 |
| AUC _{0-τ} (pg-hr/mL) | 20366.61 | 3322.12 | 16.31 | 20423.08 | 13719.18 | 25495.25 |
| AUC _{0-inf} (pg-hr/mL) | 54198.77 | 9214.54 | 17.00 | 54113.43 | 37599.76 | 67944.65 |
| C _{max} (pg/mL) | 3553.15 | 843.45 | 23.74 | 3734.00 | 1977.00 | 4957.00 |
| C _{min} (pg/mL) | 906.51 | 152.19 | 16.79 | 903.50 | 636.23 | 1149.67 |
| C _{ave} (pg/mL) | 1697.22 | 276.84 | 16.31 | 1701.92 | 1143.26 | 2124.60 |
| T _{max} (hr) | 1.31 | 0.60 | 45.61 | 1.00 | 0.50 | 3.00 |
| K _{el} (1/hr) | 0.0267 | 0.0044 | 16.34 | 0.0261 | 0.0206 | 0.0333 |
| T _{1/2} (hr) | 26.60 | 4.33 | 16.26 | 26.51 | 20.82 | 33.65 |

TABLE 5

| Mean (% CV) Colchicine Pharmacokinetic Parameter Values Following Administration of Single and Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|----------------|
| | Vd/F (L) | CL/F (L/hr) |
| Colchicine 0.6-mg Single Dose (N = 13) | | |
| Day 1 | 341 (54.4) | 54.1 (31.0) |
| Colchicine 0.6 mg b.i.d. × 10 days | | |
| Day 25 | 1150 (18.73) | 30.3 (19.0) |

CL = Dose/AUC_{0-t} (Calculated from mean values)
Vd = CL/Ke (Calculated from mean values)

In tables, the parameter CL/F denotes the apparent total body clearance after administration, calculated as Total Dose/ Total AUC_{0-*tau*}; and V_d/F denotes the apparent total volume of distribution after administration, calculated as Total Dose/ (Total AUC_∞ × K_{el}). FIG. 1 shows mean colchicine plasma

concentrations following administration of single and multiple oral doses of colchicine 0.6 mg in healthy adults.

Example 2

Clinical Drug-Drug Interaction Study of Colchicine and Clarithromycin

A single-center, open-label, one sequence, two-period study was carried out in 23 healthy subjects. On Day 1, a single 0.6-mg dose of colchicine was administered. After completing a 21-day washout period, all subjects received 250 mg of clarithromycin administered twice daily for 7 days (Days 22 through 29), a sufficient dose and duration to inhibit CYP3A4 and Pgp. On the final day (Day 29), a single dose of colchicine was co-administered with the clarithromycin dose. When combined with steady-state clarithromycin, there is a significant increase in exposure to colchicine as compared to when colchicine is given alone: the mean C_{max} and AUC_{0-t} concentrations increased 167% and 250%, respectively. In addition, co-administration of clarithromycin and colchicine resulted in an increase of 233% in the plasma elimination half-life (t_{1/2}) of colchicine and a 75% decrease in apparent clearance (CL/F). A summary of the mean (% CV) colchicine pharmacokinetic parameters for Day 1 (colchicine adminis-

US 7,820,681 B1

21

tered alone) and Day 29 (colchicine co-administered with steady-state clarithromycin) are given in the table below and illustrated in Table 5.

TABLE 6

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Clarithromycin in Healthy Adults | | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|--------------------------------------|
| Arithmetic Mean (% CV) | | |
| Parameter (units) | Colchicine (N = 23) | Colchicine + Clarithromycin (N = 23) |
| AUC ₀₋₄ (ng · hr/mL) | 12.37 (37.64) | 41.95 (23.31) |
| AUC _{0-inf} (ng · hr/mL) | 15.53 (49.6) | 52.62 (22.84) |
| C _{max} (ng/mL) | 2.84 (30.97) | 8.44 (17.63) |
| T _{max} (hr)* | 1.50 (0.50-2.00) | 1.00 (0.50-2.00) |
| CL/F (L/hr) | 46.8 (43.68) | 12.0 (23.75) |

FIG. 2 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin in healthy adults. Based on the foregoing data, it is concluded that the dose of colchicine co-administered with clarithromycin should be reduced by $\frac{2}{3}$.

Example 3

Clinical Drug-Drug Interaction Study of Colchicine and Cyclosporine

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

A single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with cyclosporine on Day 15. Cyclosporine was administered as a single-dose (1×100 mg capsule) on the morning of Day 15. A 14 day washout period was completed after the first colchicine dose on Day 1 and prior to the co-administration of colchicine and cyclosporine doses on Day 15.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 15. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on a confined basis. Subjects were then return to the clinic on a non-confined basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration on Days 2-5 (Period 1) and Days 16-19 (Period 2). Cyclosporine plasma concentrations were not measured.

22

TABLE 7

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Cyclosporine in Healthy Adults | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|------------------------------------|
| Arithmetic Mean (% CV) | | |
| Parameter (units) | Colchicine (N = 23) | Colchicine + Cyclosporine (N = 23) |
| AUC ₀₋₄ (ng · hr/mL) | 12.55 | 39.83 |
| AUC _{0-inf} (ng · hr/mL) | 15.00 | 47.31 |
| C _{max} (ng/mL) | 2.72 | 8.82 |
| T _{max} (hr)* | 1.15 | 1.13 |
| CL/F (L/hr) | 48.24 | 13.42 |

FIG. 3 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin and steady-state cyclosporine in healthy adults. Based on the foregoing data, the dose of colchicine co-administered with cyclosporine should be reduced by approximately $\frac{1}{2}$ to $\frac{3}{4}$.

Example 4

Clinical Drug-Drug Interaction Study of Colchicine and Ritonavir

An open-label, non-randomized, single-center, one-sequence, two-period drug interaction study was conducted in healthy male and female volunteers; there will be a 14-day washout between the two periods. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

All subjects received a single 0.6-mg dose of colchicine on Day 1 administered under standard fasting conditions, followed by a 14-day washout period completed on an outpatient basis. At discharge on Day 2, study subjects were instructed to return to the clinical site on the mornings and evenings of Days 15 through 18 to receive two daily dosage amounts of ritonavir (1×100 mg ritonavir capsule twice daily (every 12 hours) on Days 15-18) in a 'directly-observed' fashion; after taking the first dose of ritonavir, subjects remained in the clinic for observation for 1 hour post-dose administration on Day 15. On the evening of Day 18, study participants remained at the clinic for their final study confinement period. In the morning on Day 19, study subjects received a single 0.6 mg colchicine dose with a single 100 mg ritonavir dose and study subjects received the final 100 mg ritonavir dose 12 hours later in the evening on Day 19 under standard fasting conditions.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 19. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on an inpatient basis. Subjects returned to the clinic on an outpatient basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration. Ritonavir plasma concentrations were not measured.

US 7,820,681 B1

23

TABLE 8

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Ritonovir in Healthy Adults: 1n-transformed data | | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|------------------------|---------|
| | Colchicine Alone | Colchicine + Ritonovir | % Ratio |
| C_{max} (pg/mL), geometric mean | 1798.37 | 4835.39 | 268.88 |
| AUC_{0-t} (pg · h/mL), geometric mean | 7642.71 | 27793.08 | 363.65 |
| AUC_{∞} (pg · h/mL), geometric mean | 9551.74 | 33771.36 | 353.56 |

TABLE 9

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Ritonovir in Healthy Adults | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|---------------------------|--|
| Arithmetic Mean (% CV) Median (Range) for T_{max} | | | |
| Parameter (units) | Colchicine + Ritonovir (N = 18) | Colchicine Alone (N = 18) | |
| AUC_{0-t} (ng · hr/mL) | 29.05 (30.76) | 8.41 (47.46) | |
| $AUC_{0-\infty}$ (ng · hr/mL) | 35.28 (29.79) | 10.41 (45.48) | |
| C_{max} (ng/mL) | 4.99 (25.18) | 1.87 (28.19) | |
| T_{max} (hr) | 1.5 (1-1.5) | 1 (0.5-1.5) | |
| CL/F (L/hr) | 18.59 (31.58) | 67.93 (39.47) | |

Following exposure to 100 mg b.i.d.×5 days, there was a significant increase in exposure to a single 0.6-mg colchicine (approximately 245%). Mean peak colchicine concentration increased by approximately 170%. Total apparent oral clearance was decreased by 70% with co-administration. T_{max} is not affected. Elimination half-life could not be estimated accurately as plasma concentrations were not quantifiable after 24 hours.

FIG. 4 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state ritonavir and steady-state ketoconazole in healthy adults. Based on the foregoing data, the dose of colchicine co-administered with ritonavir should be reduced by approximately $\frac{1}{2}$.

Example 5

Clinical Drug-Drug Interaction Study of Colchicine and Ketoconazole

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers; there will be a 14-day washout between the two periods. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled.

A single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with ketoconazole on Day 19 (AM dose). Ketoconazole was administered for 5 consecutive days [200 mg twice daily (every 12 hours)] beginning on the morning of Day 15, with the last 200 mg ketoconazole dose administered on the evening of Day 19. Total study participation, exclusive of up to 28 days of screening, was approximately 24 days, during which subjects will be confined on two occasions for a total confinement of approximately 3 days.

24

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 19. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on an inpatient basis. Subjects then returned to the clinic on an outpatient basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration. Ketoconazole plasma concentrations were not measured.

TABLE 10

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Ketoconazole in Healthy Adults: 1n-transformed data | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|---------------------------|---------|
| | Colchicine Alone | Colchicine + Ketoconazole | % Ratio |
| C_{max} (pg/mL), geometric mean | 2598.28 | 5078.50 | 195.46 |
| AUC_{0-t} (pg · h/mL), geometric mean | 11087.99 | 33223.80 | 299.64 |
| AUC_{∞} (pg · h/mL), geometric mean | 13185.92 | 42143.00 | 319.61 |

TABLE 11

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Ketoconazole in Healthy Adults | | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|------------------------------------|--|
| Arithmetic Mean (% CV) | | | |
| Parameter (units) | Colchicine (N = 23) | Colchicine + Ketoconazole (N = 23) | |
| AUC_{0-t} (pg · hr/mL) | 11988.61 | 34382.82 | |
| $AUC_{0-\infty}$ (pg · hr/mL) | 14314.09 | 43688.90 | |
| C_{max} (pg/mL) | 2779.08 | 5266.92 | |
| T_{max} (hr)* | 1.00 | 1.02 | |
| CL/F (L/hr) | 49301.09 | 14797.94 | |

*Median (Range) for T_{max}

Following administration of ketoconazole 200 mg b.i.d.×5 days, there was a significant increase in exposure to a single oral dose of colchicine 0.6 mg (C_{max} and AUC_{0-t} increased by 90% and 190%, respectively, and $AUC_{0-\infty}$ increased by about 205%). Total apparent oral clearance decreased by 70% with co-administration. Elimination half-life could not be estimated accurately as plasma concentrations were not quantifiable after 24 hours.

FIG. 4 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state ritonavir and steady-state ketoconazole in healthy adults. Based on the foregoing data, the dose of colchicine co-administered with ketoconazole should be reduced by approximately $\frac{1}{2}$.

Example 6

Clinical Drug-Drug Interaction Study of Colchicine and Azithromycin

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers; there was a 14-day washout between the two periods. Twenty-four (24)

US 7,820,681 B1

25

non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

A single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with the azithromycin on Day 19. Azithromycin was administered for 5 consecutive days (2×250 mg once daily [Day 15 only] and then 1×250 mg once daily Days 16-19) beginning on the morning of Day 15, with the last 250 mg azithromycin dose administered on the morning on Day 19. Total study participation, exclusive of up to 28 days of screening, was approximately 24 days, during which subjects were confined on two occasions for a total confinement of approximately 3 days.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 19. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on an inpatient basis. Subjects returned to the clinic on an outpatient basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration. Azithromycin plasma concentrations were not measured.

TABLE 12

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Azithromycin in Healthy Adults | | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|---------------------------|---------|
| | Colchicine Alone | Colchicine + Azithromycin | % Ratio |
| C_{max} (pg/mL), geometric mean | 2535.94 | 2856.22 | 112.63 |
| AUC_{0-t} (pg · h/mL), geometric mean | 10971.51 | 16090.52 | 146.66 |
| AUC_{∞} (pg · h/mL), geometric mean | 12931.80 | 18312.83 | 141.61 |

TABLE 13

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Azithromycin in Healthy Adults | | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|---------------------------|--|
| Parameter (units) | Arithmetic Mean (% CV) Median (Range) for T_{max} | | |
| | Colchicine + Azithromycin (N = 21) | Colchicine Alone (N = 21) | |
| AUC_{0-t} (ng · hr/mL) | 17.16 (37.78) | 11.98 (45.81) | |
| $AUC_{0-\infty}$ (ng · hr/mL) | 19.61 (39.15) | 14.13 (46.73) | |
| C_{max} (ng/mL) | 3.05 (39.54) | 2.74 (41.52) | |
| T_{max} (hr) | 1.5 (0.5-3) | 1.0 (0.5-3) | |
| $t_{1/2}$ (hr) | 6.71 (68.34) ¹ | 6.07 (66.15) ¹ | |
| CL/F (L/hr) | 35.01 (37.26) | 50.24 (40.31) | |

Following administration of azithromycin 500 mg on Day 1 followed by 250 mg×4 days, exposure to colchicine is increased (approximately 46% for AUC_{0-t} and approximately 40% for $AUC_{0-\infty}$). Mean peak colchicine concentration increased by approximately 12% and total apparent oral clearance decreased approximately 30% with co-administration. T_{max} was not affected.

FIG. 5 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose

26

colchicine (0.6 mg) co-administered with steady-state azithromycin and steady-state diltiazem in healthy adults.

Example 7

Clinical Drug-Drug Interaction study of Colchicine and Diltiazem

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

As single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with diltiazem ER on Day 21. Diltiazem ER was administered for 7 consecutive days (1×240 mg capsule once daily on Days 15-21) beginning on the morning of Day 15, with the last 240 mg diltiazem ER dose administered on the morning on Day 21. A 14-day washout period was completed after the first colchicine dose on Day 1 and prior to the administration of the first diltiazem ER dose on Day 15.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 21. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on an inpatient basis. Subjects returned to the clinic on an outpatient basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration. Diltiazem plasma concentrations were not measured.

TABLE 14

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Diltiazem in Healthy Adults | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|------------------------|---------|
| | Colchicine Alone | Colchicine + Diltiazem | % Ratio |
| C_{max} (pg/mL), geometric mean | 2006.42 | 2583.22 | 128.75 |
| AUC_{0-t} (pg · h/mL), geometric mean | 9154.55 | 15740.37 | 171.94 |
| AUC_{∞} (pg · h/mL), geometric mean | 11022.30 | 19902.98 | 180.57 |

TABLE 15

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Diltiazem in Healthy Adults | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|---------------------------|--|
| Parameter (units) | Arithmetic Mean (% CV) Median (Range) for T_{max} | | |
| | Colchicine + Diltiazem (N = 20) | Colchicine Alone (N = 20) | |
| AUC_{0-t} (ng · hr/mL) | 17.73 | 10.04 | |
| $AUC_{0-\infty}$ (ng · hr/mL) | 22.49 | 12.03 | |
| C_{max} (ng/mL) | 2.80 | 2.17 | |
| T_{max} (hr) | 1.48 | 1.15 | |
| $t_{1/2}$ (hr) | 12.50 | 5.51 | |
| CL/F (L/hr) | 463.49 | 395.83 | |

US 7,820,681 B1

27

FIG. 5 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state azithromycin and steady-state diltiazem in healthy adults.

Example 8

Clinical Drug-Drug Interaction Study of Colchicine and Verapamil

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

A single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with verapamil HCl ER on Day 19. Verapamil HCl ER was administered for 5 consecutive days (1x240 mg tablet once daily on Days 15-19) beginning on the morning of Day 15, with the last 240 mg verapamil HCl ER dose administered on the morning on Day 19. A 14-day washout period was completed after the first colchicine dose on Day 1 and prior to the administration of the first verapamil HCl ER dose on Day 15.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 19. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on a confined basis. Subjects returned to the clinic on a non-confined basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration on Days 2-5 (Period 1) and Days 20-23 (Period 2). Verapamil plasma concentrations were not measured.

TABLE 16

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Verapamil in Healthy Adults | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|------------------------|---------|
| | Colchicine Alone | Colchicine + Verapamil | % Ratio |
| C_{max} (pg/mL), geometric mean | 2768.77 | 3639.68 | 131.45 |
| AUC_{0-t} (pg · h/mL), geometric mean | 12256.40 | 23889.21 | 194.94 |
| AUC_{∞} (pg · h/mL), geometric mean | 14415.79 | 29556.75 | 205.03 |

TABLE 17

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Verapamil in Healthy Adults | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|---------------------------|
| | Arithmetic Mean (% CV) Median (Range) for T_{max} | |
| Parameter (units) | Colchicine + Verapamil (N = 24) | Colchicine Alone (N = 24) |
| AUC_{0-t} (ng · hr/mL) | 24.64 | 13.09 |
| $AUC_{0-\infty}$ (ng · hr/mL) | 30.59 | 15.37 |
| C_{max} (ng/mL) | 3.85 | 2.97 |
| T_{max} (hr) | 1.15 | 1.22 |

28

TABLE 17-continued

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Verapamil in Healthy Adults | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|---------------------------|
| | Arithmetic Mean (% CV) Median (Range) for T_{max} | |
| Parameter (units) | Colchicine + Verapamil (N = 24) | Colchicine Alone (N = 24) |
| $t_{1/2}$ (hr) | 17.17 | 6.24 |
| CL/F (L/hr) | 21.01 | 43.93 |

Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges directed to the same component or property are inclusive and independently combinable.

All methods described herein can be performed in a suitable order unless otherwise indicated or clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., “such as”) herein is intended to better illuminate the disclosure and is non-limiting unless otherwise specified. No language in the specification should be construed as indicating that any non-claimed element as essential to the practice of the claimed embodiments. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this disclosure belongs. The terms wt %, weight percent, percent by weight, etc. are equivalent and interchangeable.

In the specification and claims that follow, references will be made to a number of terms which shall be defined to have the following meaning.

The terms “a” and “an” do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The term “or” means “and/or”. The terms “comprising”, “having”, “including”, and “containing” are to be construed as open-ended terms (i.e., meaning “including, but not limited to”).

“Concomitant” and “concomitantly” as used herein refer to the administration of at least two drugs to a patient either simultaneously or within a time period during which the effects of the first administered drug are still operative in the patient. Thus, if the first drug is, e.g., clarithromycin and the second drug is colchicine, the concomitant administration of the second drug can occur as much as one to two weeks, preferably within one to seven days, after the administration of the first drug. This is because clarithromycin can exert a long-lasting inhibition of CYP3A isozymes so that CYP3A activity in the patient may not return to pre-clarithromycin-administration levels for as much as two weeks after the cessation of clarithromycin administration. If colchicine is the first drug, administration of a second drug would be concomitant if done within 1 to 2 days, preferably 12 to 24 hours.

A “dose” means the measured quantity of a drug to be taken at one time by a patient.

A “dosage amount” means an amount of a drug suitable to be taken during a fixed period, usually during one day (i.e. daily). A “daily dosage amount” is the total dosage amount taken in one day, that is, a 24 hour period.

“Dosing regimen” means the dose of a drug taken at a first time by a patient and the interval (time or symptomatic) and

US 7,820,681 B1

29

dosage amounts at which any subsequent doses of the drug are taken by the patient. Each dose may be of the same or different.

A “patient” means a human or non-human animal in need of medical treatment. Medical treatment can include treatment of an existing condition, such as a disease or disorder, prophylactic or preventative treatment, or diagnostic treatment. In preferred embodiments the patient is human.

“Providing” means giving, administering, selling, distributing, transferring (for profit or not), manufacturing, compounding, or dispensing.

“Risk” means the probability or chance of adverse reaction, injury, or other undesirable outcome arising from a medical treatment. An “acceptable risk” means a measure of the risk of harm, injury, or disease arising from a medical treatment that will be tolerated by an individual or group. Whether a risk is “acceptable” will depend upon the advantages that the individual or group perceives to be obtainable in return for taking the risk, whether they accept whatever scientific and other advice is offered about the magnitude of the risk, and numerous other factors, both political and social. An “acceptable risk” of an adverse reaction means that an individual or a group in society is willing to take or be subjected to the risk that the adverse reaction might occur since the adverse reaction is one whose probability of occurrence is small, or whose consequences are so slight, or the benefits (perceived or real) of the active agent are so great. An “unacceptable risk” of an adverse reaction means that an individual or a group in society is unwilling to take or be subjected to the risk that the adverse reaction might occur upon weighing the probability of occurrence of the adverse reaction, the consequences of the adverse reaction, and the benefits (perceived or real) of the active agent. “At risk” means in a state or condition marked by a high level of risk or susceptibility.

Pharmacokinetic parameters referred to herein describe the in vivo characteristics of drug (or a metabolite or a surrogate marker for the drug) over time. These include plasma concentration (C), as well as C_{max} , C_n , C_{24} , T_{max} , and AUC. “ C_{max} ” is the measured plasma concentration of the active agent at the point of maximum, or peak, concentration. “ C_{min} ” is the measured plasma concentration of the active agent at the point of minimum concentration. “ C_n ” is the measured plasma concentration of the active agent at about n hours after administration. “ C_{24} ” is the measured plasma concentration of the active agent at about 24 hours after administration. The term “ T_{max} ” refers to the time from drug administration until C_{max} is reached. “AUC” is the area under the curve of a graph of the measured plasma concentration of an active agent vs. time, measured from one time point to another time point. For example AUC_{0-t} is the area under the curve of plasma concentration versus time from time 0 to time t, where time 0 is the time of initial administration of the drug. Time t can be the last time point with measurable plasma concentration for an individual formulation. The $AUC_{0-\infty}$, AUC_{∞} or AUC_{0-inf} is the calculated area under the curve of plasma concentration versus time from time 0 to time infinity. In steady-state studies, $AUC_{0-\tau}$ is the area under the curve of plasma concentration over the dosing interval (i.e., from time 0 to time τ (tau), where tau is the length of the dosing interval. Other pharmacokinetic parameters are the parameter K_e or

30

K_{el} , the terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve; $t_{1/2}$ the terminal elimination half-life, calculated as $0.693/K_{el}$. CL/F denotes the apparent total body clearance after administration, calculated as Total Dose/Total AUC_{∞} ; and V_{area}/F denotes the apparent total volume of distribution after administration, calculated as Total Dose/(Total $AUC_{\infty} \times K_{el}$).

“Side effect” means a secondary effect resulting from taking a drug. The secondary effect can be a negative (unfavorable) effect (i.e., an adverse side effect) or a positive (favorable) effect.

The most frequently reported adverse side effects to colchicine therapy are gastrointestinal, specifically abdominal pain with cramps, diarrhea, nausea, and vomiting. Less frequently or rarely reported adverse side effects associated with colchicine therapy include anorexia, agranulocytosis, allergic dermatitis, allergic reactions, alopecia, angioedema, aplastic anemia, bone marrow depression, myopathy, neuropathy, skin rash, thrombocytopenic disorder, and urticaria.

Whether a patient experiences an adverse side effect can be determined by obtaining information from the patient regarding onset of certain symptoms which may be indicative of the adverse side effect, results of diagnostic tests indicative of the adverse side effect, and the like.

Embodiments are described herein, including the best modes known to the inventors. Variations of such embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The skilled artisan is expected to employ such variations as appropriate, and the disclosed methods are expected to be practiced otherwise than as specifically described herein. Accordingly, all modifications and equivalents of the subject matter recited in the claims appended hereto are included to the extent permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed unless otherwise indicated herein or otherwise clearly contradicted by context.

What is claimed is:

1. A method of treating a patient in need of treatment for the prophylaxis of gout flares with colchicine, comprising orally administering to the patient in need of treatment for the prophylaxis of gout flares, an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of 200 mg per day of ritonavir, wherein the adjusted daily dosage amount of colchicine is 25% to 50% of 0.6 mg twice per day or 0.6 mg once per day, which is an amount of colchicine suitable for the patient if the patient were not receiving concomitant ritonavir.
2. The method of claim 1, further comprising carefully monitoring the individual for potential toxicity.
3. The method of claim 1, wherein the adjusted daily dosage amount of colchicine is 25% of an intended daily dosage amount of colchicine.
4. The method of claim 1, wherein the adjusted daily dosage amount of colchicine is 50% of an intended daily dosage amount of colchicine.

* * * * *

EXHIBIT D

US007915269B2

(12) **United States Patent**
Davis(10) **Patent No.:** **US 7,915,269 B2**
(45) **Date of Patent:** ***Mar. 29, 2011**(54) **METHODS FOR CONCOMITANT
ADMINISTRATION OF COLCHICINE AND A
SECOND ACTIVE AGENT**(75) Inventor: **Matthew W. Davis**, Erwinna, PA (US)(73) Assignee: **AR Holding Company, Inc.**,
Wilmington, DE (US)(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.This patent is subject to a terminal dis-
claimer.(21) Appl. No.: **12/858,667**(22) Filed: **Aug. 18, 2010**(65) **Prior Publication Data**

US 2010/0305171 A1 Dec. 2, 2010

Related U.S. Application Data(62) Division of application No. 12/372,046, filed on Feb.
17, 2009, now Pat. No. 7,820,681.(60) Provisional application No. 61/138,141, filed on Jan.
14, 2009, provisional application No. 61/152,067,
filed on Feb. 12, 2009.(51) **Int. Cl.****A61K 31/52** (2006.01)**A61K 31/16** (2006.01)(52) **U.S. Cl.** **514/263.31**; 514/629(58) **Field of Classification Search** 514/263.31
See application file for complete search history.(56) **References Cited****U.S. PATENT DOCUMENTS**

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ABSTRACTMethods for concomitant administration of colchicine
together with one or more second active agents, e.g., keto-
conazole and ritonavir, are disclosed. Such methods reduce
the dangers commonly associated with such concomitant
administration and provide additional benefits. Methods of
notifying health care practitioners and patients regarding
appropriate dosing for concomitant administration of colchi-
cine together with second active agents are also provided.**1 Claim, 5 Drawing Sheets**

US 7,915,269 B2

Page 2

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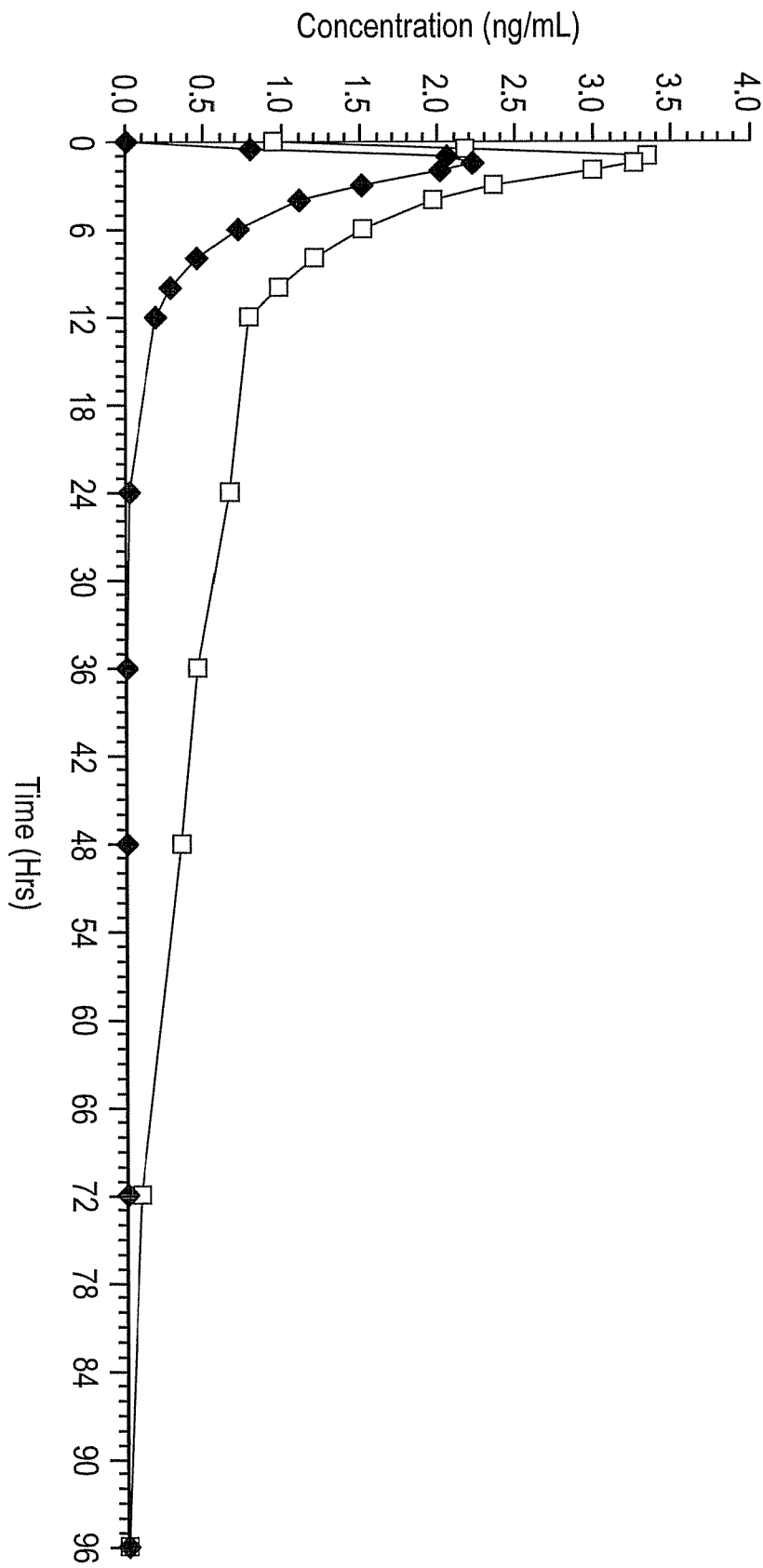


FIG. 1

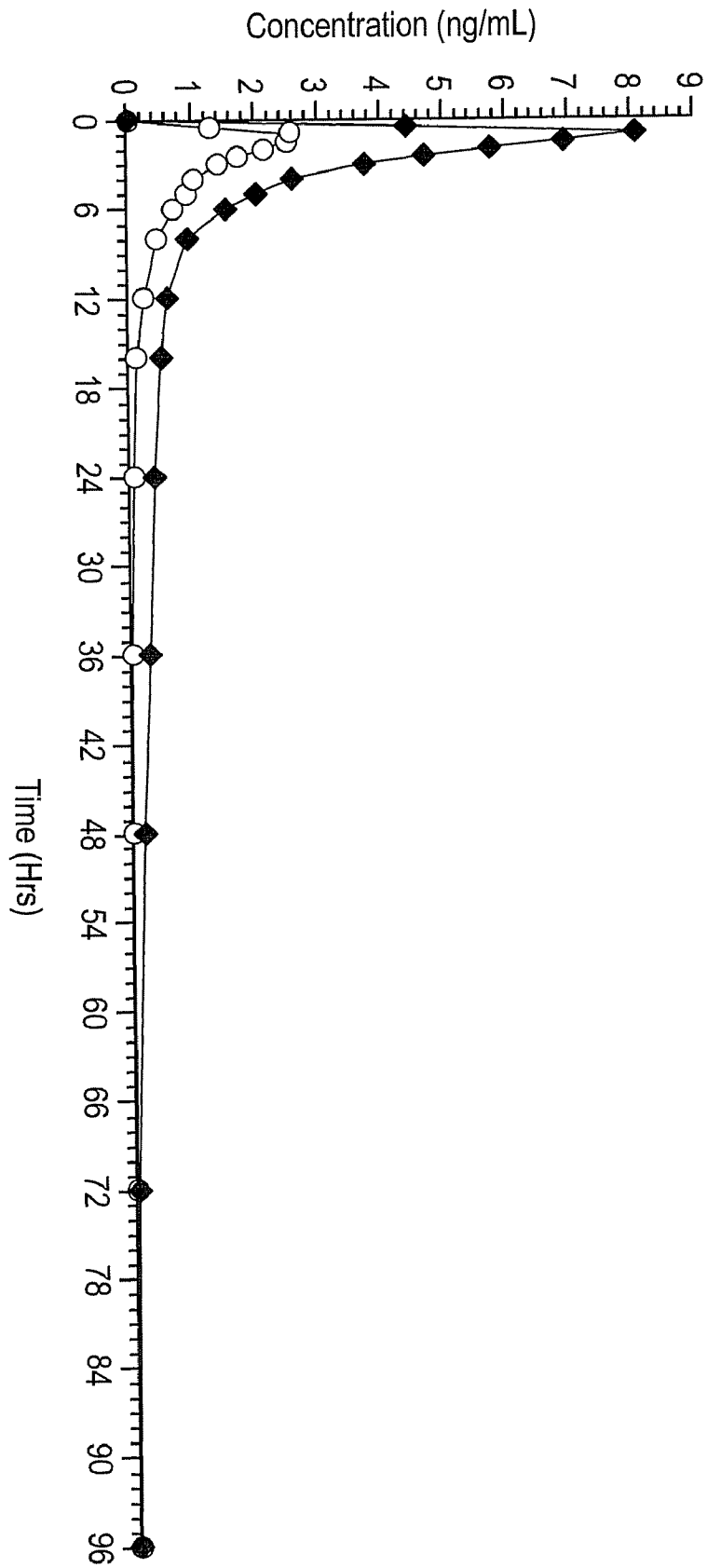


FIG. 2

FIG. 3

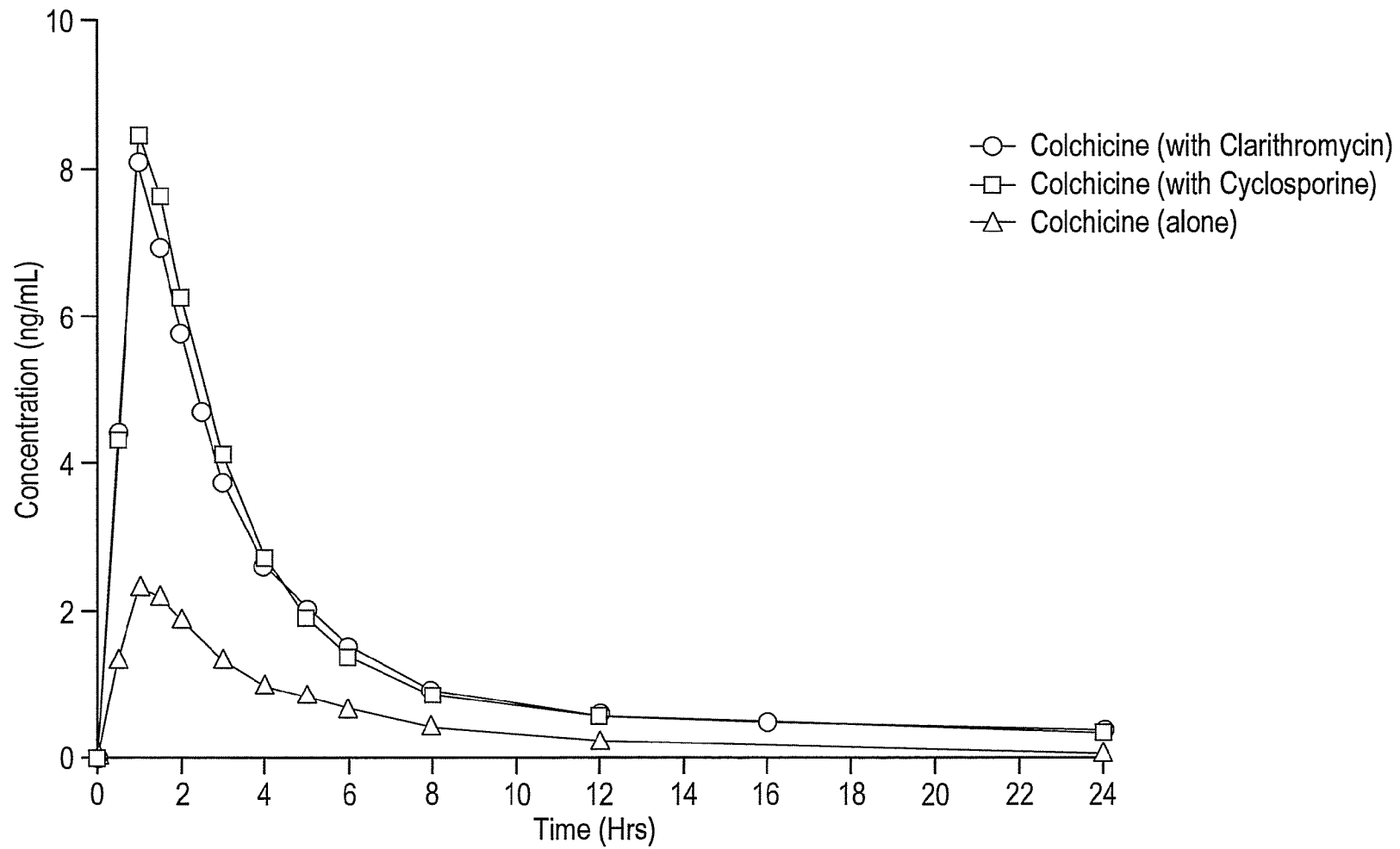


FIG. 4

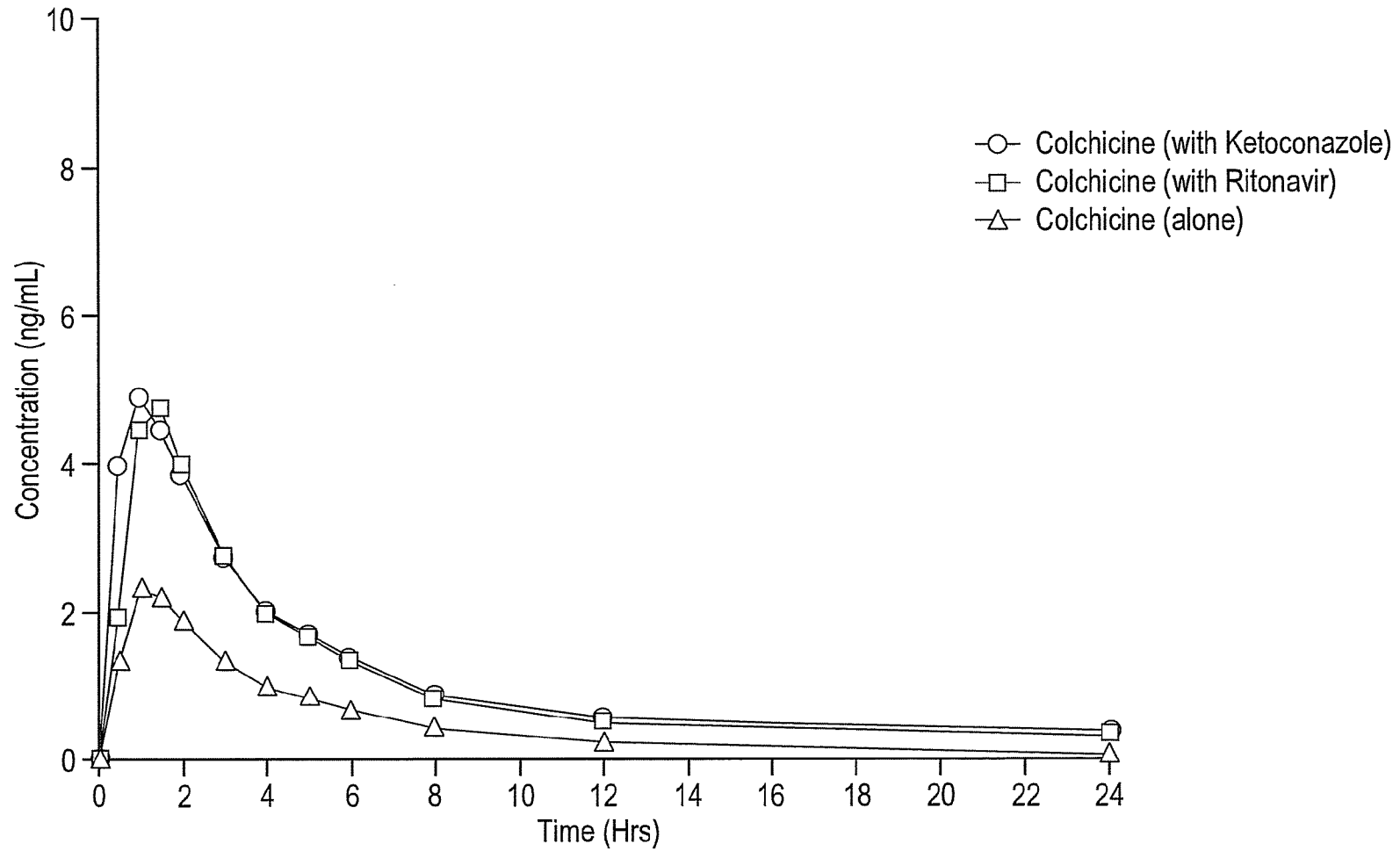
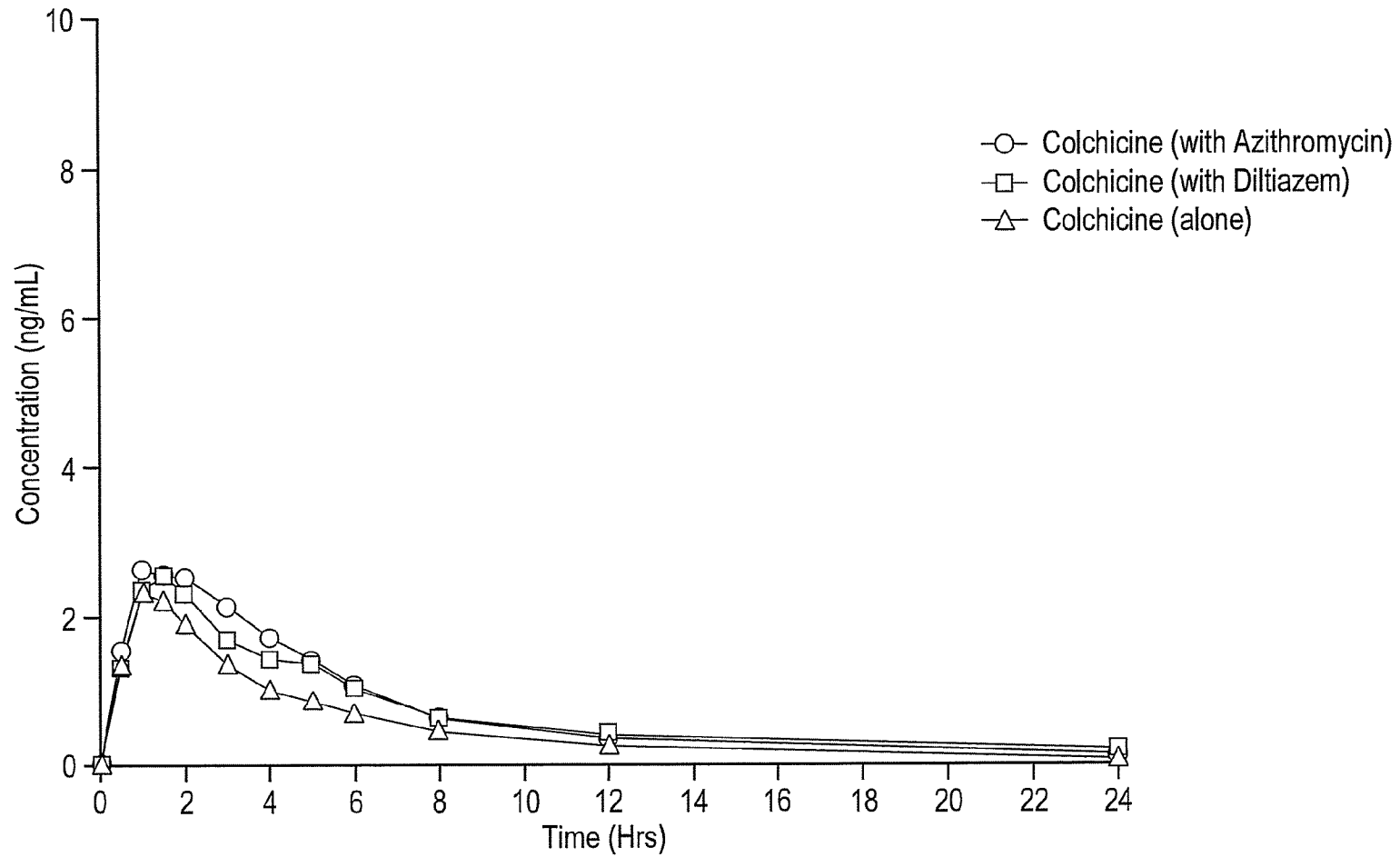


FIG. 5



US 7,915,269 B2

1

METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND A SECOND ACTIVE AGENT

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a Divisional of U.S. application Ser. No. 12/372,046, filed Feb. 17, 2009, which claims priority from U.S. Provisional Application Ser. Nos. 61/138,141 filed Dec. 17, 2008 and 61/152,067 filed Feb. 12, 2009, all of which are hereby incorporated by reference in their entirety.

FIELD OF THE DISCLOSURE

This disclosure relates to methods allowing for the co-administration of colchicine together with one or more second active agents for therapeutic purposes with improved safety compared to prior methods of administration.

BACKGROUND

Colchicine, chemical name (–)-N-[(7S,12aS)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide, is an alkaloid found in extracts of *Colchicum autumnale*, *Gloriosa superba*, and other plants. It is a microtubule-disrupting agent used in the treatment of gout and other conditions that may be treated, relieved or prevented with anti-inflammatory treatment. Colchicine impairs the motility of granulocytes and can prevent the inflammatory phenomena that initiate an attack (or flare) of gout. Colchicine also inhibits mitosis, resulting in effects in cells with high turnover rates such as those in the gastrointestinal tract and bone marrow. The primary adverse side effects of colchicine therapy include gastrointestinal upset such as diarrhea and nausea.

Colchicine has a narrow therapeutic index. The margin between an effective dose and a toxic dose of colchicine is much narrower than that of many other widely used drugs. Consequently, actions that result in increased colchicine levels in patients receiving colchicine therapy are particularly dangerous. Co-administration of colchicine to patients along with certain other drugs can have the effect of increasing colchicine levels. Such drug-drug interactions with colchicine have been reported to result in serious morbid complications and, in some cases, death.

Colchicine is rapidly absorbed from the gastrointestinal tract. Peak concentrations occur in 0.5 to 2 hours. The drug and its metabolites are distributed in leukocytes, kidneys, liver, spleen and the intestinal tract. Colchicine is metabolized in the liver and excreted primarily in the feces with 10 to 20% eliminated unchanged in the urine.

Gout (or gouty arthritis) is a disease caused by a build up of uric acid in the joints. Such a build up is typically due to an overproduction of uric acid, or to a reduced ability of the kidney to excrete uric acid. Gout is characterized by excruciating, sudden, unexpected, burning pain, as well as by swelling, redness, warmth, and stiffness in the affected joint. Low-grade fever may also be present. A gout flare is a sudden attack of pain in affected joints, especially in the lower extremities, and most commonly in the big toe. In afflicted individuals, the frequency of gout flares typically increases over time. In this manner, gout progresses from acute gout to chronic gout, which involves repeated episodes of joint pain.

Colchicine can reduce pain in attacks of acute gout flares and also can be used beneficially for treating adults for prophylaxis of gout flares. Although its exact mode of action in

2

the relief of gout is not completely understood, colchicine is known to decrease the inflammatory response to urate crystal deposition by inhibiting migration of leukocytes, to interfere with urate deposition by decreasing lactic acid production by leukocytes, to interfere with kinin formation and to diminish phagocytosis and subsequent inflammatory responses.

Cytochrome p450 (CYP) enzymes are agents of drug metabolism that are found in the liver, the gastrointestinal tract and other locations in the body. CYP enzymes occur in a variety of closely related proteins referred to as isozymes and different CYP isozymes may preferentially metabolize different drugs. The 3A family of CYP isozymes, particularly CYP3A4, is also known to be involved in many clinically significant drug-drug interactions, including those involving colchicine and second active agents. While drugs are often targets of CYP-mediated metabolism, some may also alter the expression and activity of such enzymes, thus impacting the metabolism of other drugs. The biotransformation of colchicine in human liver microsomes involves formation of 3-demethylcolchicine and 2-demethylcolchicine. As shown by experiments using antibodies against CYP3A4 and experiments using chemical inhibition of CYP3A4, this transformation is correlated with (and thus apparently mediated by) CYP3A4 activity.

P-glycoprotein (P-gp) is an ATP-dependent cell surface transporter molecule that acts as an ATPase efflux pump for multiple cytotoxic agents, including colchicine. P-gp actively pumps certain compounds, including drugs such as colchicine, out of cells. P-gp is encoded by the Adenosine triphosphate-binding cassette subfamily B member 1 (ABCB1) gene, also referred to as the multiple drug resistance 1 gene (MDR1).

Since colchicine acts intracellularly, the combined effects of CYP3A4 inhibition and P-gp inhibition by second active agents that also interact with CYP3A4 and P-gp can cause colchicine toxicity in patients taking what would be a safe dose of colchicine in the absence of concomitant second agent administration. Various studies of adverse reactions from exposure to multiple drugs have found that 6.5-23% of the adverse reactions result from drug-drug interactions. Unfortunately, each year a number of deaths occur as the direct result of patients adding a concomitant prescription pharmaceutical product to their existing medication regimen.

There accordingly remains a need for improved methods for administering colchicine to individuals who are concomitantly being treated with second active agents so as to reduce the possibility of colchicine toxicity while maintaining the sometimes life-saving advantages of being able to administer the two (or more) agents concomitantly. The present disclosure addresses this need and provides further advantages.

SUMMARY

In one embodiment, a method of treating an individual in need of treatment with colchicine comprises concomitantly administering to the individual colchicine and another drug, for example, ketoconazole or ritonavir or cyclosporine, wherein the colchicine is administered as a dosing regimen with a starting colchicine dose of no more than about 0.6 mg colchicine, followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours and no more frequently than once every hour wherein each additional colchicine dose is no greater than about 0.6 mg. According to another embodiment, the other drug is, for example, verapamil or diltiazem, and the starting colchicine dose during coadministration with the other drug is no more than about 1.2 mg colchicine,

US 7,915,269 B2

3

followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours.

In another aspect, a method of using colchicine comprises increasing the blood plasma levels of colchicine in a individual being administered doses of about 0.6 mg or less of colchicine to treat a colchicine-treatable condition, said method comprising the concomitant dosing of the individual with a sufficient amount of ketoconazole to increase the C_{max} of colchicine by about 90%, or to increase the $AUC_{0-\infty}$ of colchicine in the individual by about 190%, or to increase the $AUC_{0-\infty}$ of colchicine in the individual by about 205%, or to decrease the clearance of colchicine by about 70%, compared to the C_{max} , $AUC_{0-\infty}$, $AUC_{0-\infty}$ or clearance in a matched individual not administered concomitant ketoconazole.

In yet another aspect, a method of using colchicine comprises increasing the blood plasma levels of colchicine in an individual being administered doses of about 0.6 mg or less of colchicine to treat a colchicine-treatable condition, said method comprising the concomitant dosing of the individual with a sufficient amount of ritonavir to increase the C_{max} of colchicine by about 170%, or to increase the $AUC_{0-\infty}$ of colchicine in the individual by about 245%, or to decrease the clearance of colchicine by about 70%, compared to the C_{max} , $AUC_{0-\infty}$, or clearance in a matched individual not administered concomitant ritonavir.

In another embodiment, a method for using colchicine comprises a pharmacy receiving a prescription for colchicine for a patient who is concomitantly being treated with ketoconazole or ritonavir or verapamil, and the pharmacy dispensing colchicine in response to receipt of the prescription, wherein the dispensing is preceded by: entering, into a first computer readable storage medium in functional communication with a computer, of a unique patient identifier for said patient and at least one drug identifier for colchicine linked to the patient identifier so as to indicate that colchicine is to be administered to the patient, wherein the computer has been programmed to issue a drug-drug interaction alert when the at least one drug identifier for colchicine is entered linked to the patient identifier so as to indicate that colchicine is to be administered to the patient and when the patient identifier is also linked to an identifier indicating that ketoconazole or ritonavir or verapamil is being concomitantly administered to the patient, wherein, upon entry of the at least one drug identifier for colchicine linked to the patient identifier, a drug-drug interaction alert is issued to one or more of a pharmacy technician, a pharmacist, or a pharmacy customer obtaining the colchicine, said alert indicating that that ketoconazole or ritonavir is being concomitantly administered to the patient and that prior to the colchicine being dispensed, the colchicine dosing regimen must be reviewed and, if necessary adjusted, so that when the colchicine is delivered to the pharmacy customer obtaining the colchicine it is delivered along with instructions for the colchicine to be taken in accordance with a dosing regimen of no more than about 0.6 mg colchicine, followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours and no more frequently than once every hour wherein each additional colchicine dose is no greater than about 0.6 mg.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ritonavir, wherein the adjusted daily dosage amount of colchicine is about 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount

4

of colchicine is a dose suitable for the patient if the patient were not receiving concomitant ritonavir.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ketoconazole, wherein the adjusted daily dosage amount of colchicine is about 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant ketoconazole.

A method of treating an individual in need of treatment for gout flares, comprises concomitantly administering colchicine and azithromycin, and carefully monitoring the individual for potential toxicity. The method further comprises adjusting the dose of colchicine or azithromycin as necessary to avoid adverse side effects.

A method of treating an individual with colchicine comprises concomitantly administering colchicine and verapamil, and carefully monitoring the individual for signs and symptoms of adverse side effects. The method further comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of verapamil, wherein the adjusted daily dosage amount of colchicine is about 50% to 75% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for a patient if the patient were not receiving concomitant verapamil.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows mean colchicine plasma concentrations following administration of single and multiple oral doses of colchicine 0.6 mg in healthy adults, N=13, Y axis=colchicine concentration, ng/mL, X axis=time in hours, ◆=day 1, ■=day 25. See Example 1.

FIG. 2 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin in healthy adults, Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=23, ●=colchicine alone, ◆=colchicine plus clarithromycin. See Example 2.

FIG. 3 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin and steady-state cyclosporine in healthy adults, Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=18, ▲=colchicine alone, ●=colchicine plus clarithromycin, ■=colchicine plus cyclosporine.

FIG. 4 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state ketoconazole and steady-state ritonavir in healthy adults, Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=18, ▲=colchicine alone, ●=colchicine plus ketoconazole, ■=colchicine plus ritonavir.

FIG. 5 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state azithromycin and steady-state diltiazem in healthy adults, Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=18, ▲=colchicine alone, ●=colchicine plus azithromycin, ■=colchicine plus diltiazem.

US 7,915,269 B2

5

These and other embodiments, advantages and features of the present invention become clear when detailed description is provided in subsequent sections.

DETAILED DESCRIPTION

Disclosed herein are methods for safely administering colchicine concomitantly with a second active agent, wherein the second active agent is a CYP3A4 inhibitor, a P-gp inhibitor, or both. Exemplary second active agents that are CYP3A4 and P-gp inhibitors are azithromycin, ketoconazole, ritonavir, diltiazem, verapamil and cyclosporine. It has now been discovered that certain reduced or limited colchicine dosage amounts, when administered with concomitantly administered recommended dosage amounts of second active agents that are CYP3A4 inhibitors, P-gp inhibitors, or both, achieve plasma colchicine levels that are therapeutically effective, but are not significantly higher, and therefore not significantly more toxic, than plasma levels achieved by administration of manufacturers' recommended colchicine dosages in the absence of concomitant administration with the second active agent. Thus, colchicine and second active agents that are CYP3A4 inhibitors, P-gp inhibitors, or both, can be administered concomitantly with improved safety when colchicine is administered as disclosed herein.

Without being held to theory, it has been hypothesized by the inventors herein that P-gp inhibition is more important in the elimination of colchicine than CYP3A4 inhibition. The CYP3A4 and P-gp inhibition potential of clarithromycin, azithromycin, ketoconazole, ritonavir, diltiazem and cyclosporine are given in Table 1. Based on their level of P-gp inhibition, it was predicted that clarithromycin and cyclosporine will increase colchicine concentrations more than ketoconazole or ritonavir, which will increase colchicine levels more than verapamil, azithromycin or diltiazem. The results presented herein confirm this hypothesis.

TABLE 1

| CYP3A4 and P-gp inhibition potential of second active agents | | |
|--------------------------------------------------------------|----------------------------|---------------------------|
| Drug | CYP3A Inhibition potential | P-gp Inhibition potential |
| Clarithromycin | +++++ | +++++ |
| Cyclosporine | +++++ | +++++ |
| Ketoconazole | +++++ | +++ |
| Ritonavir | +++++ | +++ |
| Verapamil | ++ | ++ |
| Diltiazem | + | + |
| Azithromycin | + | + |

Ritonavir (Norvir®, Abbott Laboratories) is an inhibitor of Human Immunodeficiency Virus (HIV) protease and is approved for the treatment of HIV-infection when used as part of a highly active antiretroviral therapy (HAART) regimen at the recommended dose of 600 mg twice daily. Although a very potent and effective protease inhibitor at the recommended dose, ritonavir is not well tolerated by HIV-infected patients at the approved dose and therefore, is generally not used clinically as a sole, therapeutic protease inhibitor within a HAART regimen. Rather, ritonavir is used more often as a pharmacokinetic enhancer or 'boosting agent' when combined with other approved protease inhibitors that are CYP3A4 and P-gp substrates and also have inherent bioavailability issues, such as poor bioavailability due to first pass effect. Improving the pharmacokinetic disposition of other protease inhibitors is possible due to the potent CYP3A4 and P-gp inhibitory activity ritonavir possesses. Sub-therapeutic ritonavir doses are used to achieve pharmacokinetic enhance-

6

ment of the co-administered protease inhibitors; typically 100 mg of ritonavir administered twice daily is the ritonavir dose used in combination with the primary protease inhibitor. This low-dose ritonavir regimen boosts the bioavailability of the second protease inhibitor without contributing significantly to the adverse event profile of the HAART regimen.

Cyclosporine (Neoral®, Novartis Pharmaceuticals Corporation) is the active principle in Neoral® an oral formulation that immediately forms a microemulsion in an aqueous environment. Cyclosporine is indicated for kidney, liver, and heart transplantation; rheumatoid arthritis and psoriasis. Cyclosporine is extensively metabolized by the CYP3A4 enzyme system in the liver, and to a lesser degree in the gastrointestinal tract, and the kidney. The metabolism of cyclosporine can be altered by the co-administration of a variety of agents.

Ketoconazole is a synthetic broad-spectrum antifungal agent available in scored white tablets, each containing 200 mg ketoconazole base for oral administration. Ketoconazole tablets are indicated for the treatment of the following systemic fungal infections: candidiasis, chronic mucocutaneous candidiasis, oral thrush, candiduria, blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. Ketoconazole is a potent inhibitor of the CYP3A4 enzyme system. Co-administration of ketoconazole and drugs primarily metabolized by the CYP3A4 enzyme may result in increased plasma concentrations of the drugs that could increase or prolong both therapeutic and adverse side effects.

Azithromycin is a macrolide antibiotic indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in specific conditions. Azithromycin remains the sole agent developed and marketed within the azalide macrolide subclass. Due to its dibasic structure, azithromycin has demonstrated unique pharmacokinetic properties that differ significantly from those of classic macrolide agents. Azithromycin's pharmacokinetics are characterized by low concentrations in serum, secondary to rapid and significant uptake by fibroblasts and acute reactant cells such as polymorphonuclear leukocytes (PMNs), monocytes, and lymphocytes. Azithromycin is a weak to moderate CYP3A4 inhibitor.

Diltiazem (Cardizem® CD, Biovail Pharmaceuticals, Inc. [Biovail]) is an extended-release (ER) calcium ion influx inhibitor available in blue capsules, each containing 240 mg diltiazem hydrochloride for oral administration. Diltiazem ER capsules are indicated for the treatment of hypertension and the management of chronic stable angina and angina due to coronary artery spasm. Diltiazem is a CYP3A4 and P-gp inhibitor.

Verapamil HCl ER (Mylan Pharmaceuticals, Inc.) is a calcium ion influx inhibitor available in a pale green, capsule shaped, film-coated tablets, each containing 240 mg verapamil hydrochloride for oral administration. Verapamil HCl ER tablets are indicated for the management of hypertension. Verapamil HCl ER is a potent CYP3A4 and P-gp inhibitor.

In one embodiment, colchicine is administered to an individual suffering from a condition treatable with colchicine, and the concomitant second active agent (e.g., ketoconazole, ritonavir, cyclosporine, verapamil, or diltiazem or any other CYP3A4 or P-gp inhibitor) is administered concurrently while the colchicine administration is reduced, or the individual has recently completed a dosing regimen of the second active agent, in which case the colchicine administration may still be reduced for a period of time.

In one embodiment, disclosed herein is a method of administering colchicine and a second active agent (e.g., ketoconazole).

US 7,915,269 B2

7

zole, ritonavir, or cyclosporine) wherein an individual is administered the colchicine according to a colchicine dosing regimen of a single starting colchicine dose of no more than about 0.6 mg colchicine, followed by either no additional colchicine doses within about 12, 24, 48, or 72 hours, or followed by at least one additional colchicine dose within 12 hours and no more frequently than once every hour (e.g., every 3, 4, 6, 8, or 12 hours). In this embodiment, each additional colchicine dose is specifically no greater than about 0.3 mg and the individual is an adult individual or a pediatric individual. Specifically, the starting colchicine dose is about 0.6 mg or about 0.3 mg, and each additional colchicine dose is about 0.3 mg. In one embodiment, when additional doses are administered, only two, three, or four additional colchicine doses are administered within about 24 hours. Specifically, the individual is an adult individual and the starting colchicine dose is about 0.6 mg, and each additional colchicine dose, if any, is about 0.3 mg. In one embodiment, only three additional colchicine doses are administered within about 24 hours.

In one embodiment, disclosed herein is a method of administering colchicine and a second active agent (e.g., verapamil or diltiazem) wherein an individual is administered the colchicine according to a colchicine dosing regimen of a single starting colchicine dose of no more than about 1.2 mg colchicine, followed by either no additional colchicine doses within about 12, 24, 48, or 72 hours, or followed by at least one additional colchicine dose within 12 hours and no more frequently than once every hour (e.g., every 3, 4, 6, 8, or 12 hours). In this embodiment, each additional colchicine dose is specifically no greater than about 0.3 mg or 0.6 mg and the individual is an adult individual or a pediatric individual. Specifically, the starting colchicine dose is about 0.6 mg or 1.2 mg, and each additional colchicine dose is about 0.3 mg or 0.6 mg. In one embodiment, when additional doses are administered, only two, three, or four additional colchicine doses are administered within about 24 hours. Specifically, the individual is an adult individual and the starting colchicine dose is about 1.2 mg, and each additional colchicine dose, if any, is about 0.3 mg or 0.6 mg. In one embodiment, only three additional colchicine doses are administered within about 24 hours.

In one embodiment, the second active agent is ketoconazole or ritonavir. In one embodiment, the ketoconazole is administered to the individual at a dosage of about 200 mg daily and the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by 0, 1, 2, 3, or 4 additional colchicine doses of about 0.6 mg every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In another embodiment, the ritonavir is administered to the individual at a dosage of about 200 to 1200 mg daily (e.g., in 2x100 mg doses or 2x600 mg doses) and the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by 0, 1, 2, 3, or 4 additional colchicine doses of about 0.6 mg every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In an exemplary regimen for treatment of acute gout flares, ingestion of colchicine is continued until a total of no more than about 1.2, 1.4, 1.6, 1.8, 2, or 2.4 mg of colchicine has been ingested, after which ingestion of colchicine is stopped until a subsequent acute gout flare occurs. More preferably, the colchicine is administered as a dosage form of 0.6 mg (e.g., one 0.6 mg colchicine tablet), or 0.3 mg (e.g., one half of a 0.6 mg tablet) of colchicine and administration of the dosage form is not repeated within a period of at least about two days, preferably at least about three days.

8

In one embodiment, the second active agent (e.g., ketoconazole or ritonavir or cyclosporine) is administered to the individual before the colchicine is administered to the individual, and wherein the administration of second active agent is terminated no more than about fourteen days prior to the initiation of colchicine administration. For example, the method comprises administering colchicine to an individual also taking a second active agent (e.g., ketoconazole or ritonavir or cyclosporine), or having completed treatment with the second active agent within the prior 14 days, the individual being administered a single dose of about 0.6 mg or about 0.3 mg of colchicine to treat a gout flare, which administration is not repeated within any 3-day period. According to this embodiment if the second active agent is instead verapamil or diltiazem, if the second active agent is terminated no more than about fourteen days prior to the initiation of the colchicine administration to treat a gout flare, the single dose of colchicine is about 1.2 mg not to be repeated within a 3-day period.

In another aspect, herein disclosed is a method for increasing the blood plasma levels of colchicine in an individual to whom colchicine is being administered to treat or prevent a colchicine-responsive condition. This method comprises the concomitant dosing of the individual with a sufficient amount of ketoconazole to increase the C_{max} of colchicine by about 90%, or to increase the AUC_{0-t} of colchicine in the individual by about 190%, or to increase the AUC_{0-inf} of colchicine in the individual by about 205%, or to decrease the clearance of colchicine by about 70%, compared to the C_{max} , AUC_{0-t} , or clearance in the same or a matched individual when not being administered a concomitant ketoconazole. In a specific embodiment, the individual is being administered no more than hourly doses of about 0.6 mg of colchicine or less, and the amount of ketoconazole is about 200 mg. In one embodiment, the single dose is one 0.6 mg colchicine tablet.

In yet another aspect, herein disclosed is a method for increasing the blood plasma levels of colchicine in an individual to whom colchicine is being administered to treat or prevent a colchicine-responsive condition. This method comprises the concomitant dosing of the individual with a sufficient amount of ritonavir to increase the C_{max} of colchicine by about 170%, or to increase the AUC_{0-t} of colchicine in the individual by about 245%, or to decrease the clearance of colchicine by about 70%, compared to the C_{max} , AUC_{0-t} , or clearance in the same or a matched individual when not being administered concomitant ritonavir. In a specific embodiment, the individual is being administered no more than hourly doses of about 0.6 mg of colchicine or less, and the amount of ritonavir is about 200 to about 1200 mg. In one embodiment, the single dose is one 0.6 mg colchicine tablet.

In one embodiment, a method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ritonavir, wherein the adjusted daily dosage amount of colchicine is 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant ritonavir. Treating is, for example, to prevent gout flares, to treat acute gout, or to treat familial Mediterranean fever. When the colchicine is administered to prevent gout flares, the adjusted daily dosage amount of colchicine may be reduced from a 0.6 mg twice daily intended dose to a 0.6 mg once daily adjusted dose. Alternatively, when the colchicine is administered to prevent gout flares, wherein the adjusted daily dosage amount of colchicine is reduced from a 0.6 mg once daily intended dose to a 0.3 mg once daily adjusted dose.

US 7,915,269 B2

9

In one embodiment, when treating is for acute gout, the intended daily dosage amount is 1.8 to 2.4 mg, and the maximum adjusted daily dosage amount is 0.6 mg, not to be repeated within 3 days. In another embodiment, treating is for acute gout, the intended daily dosage amount is 2.4 to 4.8 mg and the maximum adjusted daily dosage amount is 0.6 to 1.2 mg, not to be repeated within 3 days. In yet another embodiment, treating is for familial Mediterranean fever and the daily dosage amount 1.2 to 2.4 mg for adults, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. In another embodiment, treating is for familial Mediterranean fever and the intended daily dosage amount is 0.9 to 1.8 mg for children 6-12 years or 4-6 years, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. The concomitantly administered dose of ritonavir is, for example, 200 mg per day. In one embodiment, the ritonavir is administered to the patient before the colchicine is administered to the patient, and wherein the administration of ritonavir is terminated no more than about fourteen days prior to the initiation of colchicine administration. The method optionally further comprises carefully monitoring the individual for potential toxicity. Any 0.3 mg dose contemplated in this method can be a single 0.3 mg dosage form or one-half a 0.6 mg dosage form, e.g. one-half a 0.6 mg colchicine tablet.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ketoconazole, wherein the adjusted daily dosage amount of colchicine is 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant ketoconazole. Treating is, for example, to prevent gout flares, to treat acute gout, or to treat familial Mediterranean fever. When the colchicine is administered to prevent gout flares, the adjusted daily dosage amount of colchicine may reduced from a 0.6 mg twice daily intended dose to a 0.6 mg once daily adjusted dose. Alternatively, when the colchicine is administered to prevent gout flares, wherein the adjusted daily dosage amount of colchicine is reduced from a 0.6 mg once daily intended dose to a 0.3 mg once daily adjusted dose. In one embodiment, when treating is for acute gout, the intended daily dosage amount is 1.8 to 2.4 mg, and the maximum adjusted daily dosage amount is 0.6 mg, not to be repeated within 3 days. In another embodiment, treating is for acute gout, the intended daily dosage amount is 2.4 to 4.8 mg and the maximum adjusted daily dosage amount is 0.6 to 1.2 mg, not to be repeated within 3 days. In yet another embodiment, treating is for familial Mediterranean fever and the daily dosage amount 1.2 to 2.4 mg for adults, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. In another embodiment, treating is for familial Mediterranean fever and the intended daily dosage amount is 0.9 to 1.8 mg for children 6-12 years or 4-6 years, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. The concomitantly administered dose of ketoconazole is, for example, 250 mg per day. In one embodiment, the ketoconazole is administered to the patient before the colchicine is administered to the patient, and wherein the administration of ketoconazole is terminated no more than about fourteen days prior to the initiation of colchicine administration. The method optionally further comprises carefully monitoring the individual for potential toxicity. Any 0.3 mg dose contemplated in this method can be a single 0.3 mg dosage form or one-half a 0.6 mg dosage form, e.g. one-half a 0.6 mg colchicine tablet.

10

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of cyclosporine, wherein the adjusted daily dosage amount of colchicine is 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant cyclosporine. Treating is, for example, to prevent gout flares, to treat acute gout, or to treat familial Mediterranean fever. When the colchicine is administered to prevent gout flares, the adjusted daily dosage amount of colchicine may reduced from a 0.6 mg twice daily intended dose to a 0.3 mg once daily adjusted dose. Alternatively, when the colchicine is administered to prevent gout flares, wherein the adjusted daily dosage amount of colchicine is reduced from a 0.6 mg once daily intended dose to a 0.3 mg once every other day adjusted dose. In one embodiment, when treating is for acute gout, the intended daily dosage amount is 1.8 to 2.4 mg, and the maximum adjusted daily dosage amount is 0.6 mg, not to be repeated within 3 days. In another embodiment, treating is for acute gout, the intended daily dosage amount is 2.4 to 4.8 mg and the maximum adjusted daily dosage amount is 0.6 to 1.2 mg, not to be repeated within 3 days. In yet another embodiment, treating is for familial Mediterranean fever and the daily dosage amount 1.2 to 2.4 mg for adults, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. In another embodiment, treating is for familial Mediterranean fever and the intended daily dosage amount is 0.9 to 1.8 mg for children 6-12 years or 4-6 years, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. The concomitantly administered dose of cyclosporine can be various dosage strengths administered per day, and can be administered as an oral preparation, topically, or intravenously. In one embodiment, the cyclosporine is administered to the patient before the colchicine is administered to the patient, and wherein the administration of cyclosporine is terminated no more than about fourteen days prior to the initiation of colchicine administration. The method optionally further comprises carefully monitoring the individual for potential toxicity. Any 0.3 mg dose contemplated in this method can be a single 0.3 mg dosage form or one-half a 0.6 mg dosage form, e.g. one-half a 0.6 mg colchicine tablet.

In another embodiment, colchicine is concomitantly administered with azithromycin. Concomitant administration of azithromycin with colchicine increases exposure to colchicine approximately 46% and thus has the potential to produce colchicine toxicity. During concomitant use of azithromycin and colchicine, the physician should carefully monitor individuals for any signs or symptoms of colchicine toxicity. Additionally, dosing adjustments to either the colchicine and/or the azithromycin may be necessary to avoid adverse side effects.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of verapamil, wherein the adjusted daily dosage amount of colchicine is 50% to 75% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant verapamil. Treating is, for example, to prevent gout flares, to treat acute gout, or to treat familial Mediterranean fever. When the colchicine is administered to prevent gout flares, the adjusted daily dosage amount of colchicine may reduced from a 0.6 mg twice daily intended dose to a 0.3 mg once daily adjusted

US 7,915,269 B2

11

dose. In one embodiment, when treating is for acute gout, the intended daily dosage amount is 1.8 to 2.4 mg, and the maximum adjusted daily dosage amount is 1.2 mg. In another embodiment, treating is for acute gout, the intended daily dosage amount is 2.4 to 4.8 mg and the maximum adjusted daily dosage amount is about one-third the intended daily dosage amount. In yet another embodiment, treating is for familial Mediterranean fever and the daily dosage amount 1.2 to 2.4 mg for adults, and the maximum adjusted daily dosage amount is 1.2 mg, given, for example, in two 0.6 mg doses. In one embodiment, the verapamil is administered to the patient before the colchicine is administered to the patient, and wherein the administration of verapamil is terminated no more than about fourteen days prior to the initiation of colchi-

12

embodiments, the treatment with colchicine is either palliative or prophylactic. The gout may be acute gout, e.g. a gout flare, or chronic gout.

Acute Gout

Acute gout, or gout flares, can be treated according to the following treatment schedule. This table indicates the original, or intended, dose, i.e., the dose of colchicine recommended absent concomitant administration of the drugs listed below. This table also presents the dose adjustment of the present invention, or the recommended colchicine dose to be administered when the strong and moderate CYP3A4 and P-gp inhibitors are administered concomitantly with colchicine when the patient is being treated for acute gout, or an acute gout flare.

| Colchicine Dose Recommendation | | |
|-------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Drug | Original Intended Dose (Total Dose) | Dose Adjustment |
| Strong CYP3A4 Inhibitors | | |
| Regimen Reduced by Two Thirds | | |
| Erythromycin Ketoconazole Ritonavir | 1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 tablet) one hour later. Dose to be repeated no earlier than 3 days. | 0.6 mg (1 tablet) × 1 dose. Dose to be repeated no earlier than 3 days. |
| Moderate CYP3A4 Inhibitors | | |
| Regimen Reduced by One Third | | |
| Diltiazem Verapamil | 1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 tablet) one hour later. Dose to be repeated no earlier than 3 days. | 1.2 mg (2 tablets) × 1 dose. Dose to be repeated no earlier than 3 days. |
| Strong P-gp Inhibitors | | |
| Regimen Reduced by Two Thirds | | |
| Cyclosporine | 1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 tablet) one hour later. Dose to be repeated no earlier than 3 days. | 0.6 mg (1 tablet) × 1 dose. Dose to be repeated no earlier than 3 days. |

cine administration. The method optionally further comprises carefully monitoring the individual for potential toxicity. Any 0.3 mg dose contemplated in this method can be a single 0.3 mg dosage form or one-half a 0.6 mg dosage form, e.g. one-half a 0.6 mg colchicine tablet.

Disclosed herein are specific dosage reductions of colchicine that improve safety when colchicine is co-administered with certain active agents. The dose of colchicine recommended for administration without co-administration of certain other active agents, such as CYP3A4 or P-gp inhibitors, is referred to as an intended daily dosage amount. The reduced or modified daily dosage amount determined from the experiments presented herein is referred to as an adjusted daily dosage amount. An adjusted daily dosage amount is thus a daily dosage amount that can be safely co-administered with a second active agent as disclosed herein. A dose adjustment is thus a dose of colchicine and does not include cessation of colchicine, that is, a dose of 0 mg of colchicine.

In these and other embodiments, the colchicine-responsive condition is gout (e.g., a gout flare in a chronic gout sufferer), familial Mediterranean fever (FMF), thrombocytopenic purpura, pericarditis, scleroderma, or Behcet's disease. In some

Chronic Gout

For chronic gout, an original intended daily dosage amount is 1.2 mg or 6 mg. Alternatively, an intended daily dosage amount of chronic gout can be as much as 2.4 mg per day. The daily dosage amount for chronic gout can be administered at one time or dosed at intervals throughout the day, e.g. twice daily, three times daily, or four times daily.

Chronic gout, with and without a concomitant dose of another drug, can be treated according to the following treatment schedule:

Colchicine Dose Adjustment for Co-Administration with Interacting Drugs if no Alternative Available

| Colchicine Dose Recommendation | | |
|--------------------------------|-----------------------------------------|--------------------------------------------------|
| Drug | Original Intended Dose | Dose Adjustment |
| Clarithromycin | 0.6 mg twice daily 0.6 mg once daily | 0.3 mg once daily 0.3 mg once every other day |

US 7,915,269 B2

13

-continued

| Drug | Colchicine Dose Recommendation | |
|--------------|--------------------------------|-----------------------------|
| | Original Intended Dose | Dose Adjustment |
| Cyclosporine | 0.6 mg twice daily | 0.3 mg once daily |
| | 0.6 mg once daily | 0.3 mg once every other day |
| Erythromycin | 0.6 mg twice daily | 0.3 mg once daily |
| | 0.6 mg once daily | 0.3 mg once every other day |
| Ritonavir | 0.6 mg twice daily | 0.6 mg once daily |
| | 0.6 mg once daily | 0.3 mg once daily |

Familial Mediterranean Fever

Familial Mediterranean Fever (FMF) can be treated according to the following intended daily dosing schedule:

| Age | Daily dosage amount | |
|-------------------------------|---------------------|---------|
| | Usual | Maximum |
| Adults and children >12 years | 1.2 mg | 2.4 mg |
| Children >6 to 12 years | 0.9 mg | 1.8 mg |
| Children 4 to 6 years | 0.3 mg | 1.8 mg |

When colchicine is given to patients with FMF concomitantly with other drugs, the adjusted (reduced) dosage amount of colchicine, according to this embodiment, is provided in the table below:

| Concomitant Drug Class or Food | Noted or Anticipated Outcome | Clinical Comment |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Strong CYP3A4 Inhibitors: atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin | Significant increase in colchicine plasma levels ¹ ; fatal colchicine toxicity has been reported with clarithromycin, a strong CYP3A4 inhibitor. Similarly, significant increase in colchicine plasma levels is anticipated with other strong CYP3A4 inhibitors. | Use colchicine with caution at reduced maximum dose of 0.3 mg twice daily with increased monitoring for adverse effects. In patients with renal or hepatic impairment, use of colchicine in conjunction with these drugs is contraindicated. |
| Moderate CYP3A4 inhibitors: amprevir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, verapamil | Significant increase in colchicine plasma concentration is anticipated. Neuromuscular toxicity has been reported with diltiazem and verapamil interactions. | Use colchicine with caution at reduced maximum dose of 0.6 mg twice daily with increased monitoring for adverse effects. In patients with renal or hepatic impairment, use a maximum dose of 0.3 mg twice daily. |
| Strong P-gp Inhibitors e.g. Cyclosporine, ranolazine. | Significant increase in colchicine plasma levels ¹ ; fatal colchicine toxicity has been reported with cyclosporine, a strong P-gp inhibitor. Similarly, significant increase in colchicine plasma levels is anticipated with other strong P-gp inhibitors. | Use colchicine with caution at reduced maximum dose of 0.3 mg twice daily with increased monitoring for adverse effects. In patients with renal or hepatic impairment, use of colchicine in conjunction with these drugs is contraindicated. |

Pharmacy management systems are computer-based systems that are widely used by commercial pharmacies to manage prescriptions and to provide pharmacy and medical personnel with warnings and guidance regarding drugs being administered to individuals. Such systems typically provide alerts warning either or both of health care providers and

14

patients when a drug that may be harmful to the particular patient is prescribed. For example, such systems can provide alerts warning that a patient has an allergy to a prescribed drug, or is receiving concomitant administration of a drug that can have a dangerous interaction with a prescribed drug. U.S. Pat. Nos. 5,758,095, 5,833,599, 5,845,255, 6,014,631, 6,067, 524, 6,112,182, 6,317,719, 6,356,873, and 7,072,840, each of which is incorporated herein by reference, disclose various pharmacy management systems and aspects thereof. Many pharmacy management systems are now commercially available, e.g., CENTRICITY Pharmacy from BDM Information Systems Ltd., General Electric Healthcare, Waukesha, Wis., Rx30 Pharmacy Systems from Transaction Data Systems, Inc., Ocoee, Fla., SPEED SCRIPT from Digital Simplistics, Inc., Lenexa, Kans., and various pharmacy management systems from OPUS-ISM, Hauppauge, N.Y.

In another aspect, herein disclosed are methods for using colchicine which methods involve the use of pharmacy management systems.

In one aspect, one such method comprises a pharmacy receiving a prescription for colchicine for a patient who is suffering from gout (e.g., acute gout flares or chronic gout) and who is concomitantly being treated with a second active agent (e.g., ketoconazole or ritonavir) that is an inhibitor of CYP3A and P-glycoprotein, followed by the pharmacy dispensing colchicine in response to receipt of the prescription, wherein the dispensing is preceded by entry into a first computer readable storage medium, in functional communication

with a computer, of a unique patient identifier for said patient and at least one drug identifier for colchicine linked to the patient identifier so as to indicate that colchicine is to be administered to the patient. The computer is programmed to issue a drug-drug interaction alert when the at least one drug identifier for colchicine is entered linked to the patient identifier.

US 7,915,269 B2

15

tifier so as to indicate that colchicine is to be administered to the patient and when the patient identifier is also linked to an identifier indicating that a second active agent (e.g., ketoconazole or ritonavir) that is an inhibitor of CYP3A4 or P-glycoprotein is being concomitantly administered to the patient. Upon entry of the at least one drug identifier for colchicine linked to the patient identifier, a drug-drug interaction alert is issued to one or more of a pharmacy technician, a pharmacist, or a pharmacy customer obtaining the colchicine, said alert indicating that a second active agent (e.g., ketoconazole or ritonavir) is being concomitantly administered to the patient and that prior to the colchicine being dispensed, the colchicine dosing regimen must be reviewed and, if necessary adjusted, so that when the colchicine is delivered to the pharmacy customer obtaining the colchicine it is delivered along with instructions for the colchicine to be taken in accordance with a dosing regimen of no more than one about 0.6 mg colchicine dose to start (e.g., following the onset of the acute gout attack or the first sign of a gout flare) followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours and no more frequently than once every hour and wherein each additional colchicine dose is no greater than about 0.6 mg, and wherein the patient ingests the colchicine as instructed.

The drug-drug interaction alert is preferably issued as one or both of a written warning on a display screen of the pharmacy management computer system, and a printed warning. The printed warning may be attached to or packaged with the dispensed prescription.

In one aspect, the identifier indicating that ketoconazole is being concomitantly administered to the patient is an identifier indicating that the second active agent is ketoconazole and is linked to at least one further identifier indicating that the ketoconazole is prescribed so that 200 mg of ketoconazole is to be ingested by the patient daily, in which case the dosing regimen for colchicine is preferably one about 0.6 mg colchicine dose to start, optionally followed by additional colchicine doses, e.g., 0, 1, 2, 3, or 4 additional colchicine doses within 24 hours of about 0.3 mg ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In another embodiment, the identifier indicating that ketoconazole is being concomitantly administered to the patient is an identifier indicating that the second active agent is ketoconazole is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the ketoconazole is prescribed so that about 200 mg of ketoconazole is to be ingested by the patient daily, in which case the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every six to eight hours) after the preceding colchicine dose. In one embodiment, the dosing regimen calls for the about 0.3 mg colchicine dose every six to eight hours. In another embodiment, the dosing regimen calls for one dose of the colchicine every eight to twelve hours.

In yet another preferred aspect, the identifier indicating that ketoconazole is being concomitantly administered to the patient is an identifier indicating that the second active agent is ketoconazole and is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first

16

storage medium, and the further identifier indicating that the ketoconazole is prescribed so that about 200 mg of ketoconazole is to be ingested by the patient daily and the dosing regimen is one about 0.3 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 2, 3, 4, 5, 6, 7, or 8 hours (e.g., every eight to twelve hours) after the preceding colchicine dose.

A preferred dosing regimen calls for ingestion of colchicine to be continued until a total of no more than 1.2 mg or 2.4 mg of colchicine has been ingested, after which ingestion of colchicine is to be stopped, e.g., for at least 2, 3, 4, 5, 6, or 7 days, or until a subsequent acute gout flare, or the first sign of a subsequent gout flare, occurs.

In another aspect, the identifier indicating that ritonavir is being concomitantly administered to the patient is an identifier indicating that the second active agent is ritonavir and is linked to at least one further identifier indicating that the ritonavir is prescribed so that 200 or 1200 mg of ritonavir is to be ingested by the patient daily, in which case the dosing regimen for colchicine is preferably one about 0.6 mg colchicine dose to start, optionally followed by additional colchicine doses, e.g., 0, 1, 2, 3, or 4 additional colchicine doses within 24 hours of about 0.3 mg ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In another embodiment, the identifier indicating that ritonavir is being concomitantly administered to the patient is an identifier indicating that the second active agent is ritonavir is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the ritonavir is prescribed so that about 1200 mg of ritonavir is to be ingested by the patient daily, in which case the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every six to eight hours) after the preceding colchicine dose. In one embodiment, the dosing regimen calls for the about 0.3 mg colchicine dose every six to eight hours. In another embodiment, the dosing regimen calls for one dose of the colchicine every eight to twelve hours.

In yet another aspect, the identifier indicating that ritonavir is being concomitantly administered to the patient is an identifier indicating that the second active agent is ritonavir and is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the ritonavir is prescribed so that about 1200 mg of ritonavir is to be ingested by the patient daily and the dosing regimen is one about 0.3 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 2, 3, 4, 5, 6, 7, or 8 hours (e.g., every eight to twelve hours) after the preceding colchicine dose.

Also disclosed herein is a dosage adjustment method for administering colchicine to a patient to treat a medical condition, the patient concomitantly treated with a second active agent. The second active agent may be, for example, ritonavir, ketoconazole, cyclosporine, verapamil, or diltiazem. The method comprises determining a first colchicine dosing regimen (the colchicine dosing regimen suitable for administration in the absence of co-administration with a second active

US 7,915,269 B2

17

agent, which dosing regimen may consist of one or more doses of colchicine); and determining a second active agent dosing regimen; and administering the second active agent to the patient at the second active agent dosing regimen while concomitantly administering colchicine to the patient according to a second colchicine dosing regimen, which may consist of one or more reduced colchicine doses. The second colchicine dosing regimen is a fraction of the first colchicine dosing regimen, where the fraction is obtained by administering reduced colchicine doses or by reducing the frequency of colchicine doses, and wherein the fraction is less than or equal to about $\frac{2}{3}$ or less than or equal to about $\frac{1}{2}$ or less than or equal to about $\frac{1}{3}$.

According to this embodiment, upon the administering the second active agent to the patient at the second active agent dosing regimen while concomitantly administering colchicine to the patient at the second colchicine dosing regimen, the therapeutic circulating level of colchicine is achieved in the patient. Preferably, the fraction is selected from $\frac{1}{12}$, $\frac{1}{6}$, $\frac{1}{4}$, $\frac{1}{3}$, $\frac{5}{12}$, and $\frac{1}{2}$, more preferably, the fraction is $\frac{1}{3}$ or $\frac{1}{2}$. In one embodiment, if the second colchicine dosing regimen comprises a "first" colchicine dose, and one or more "subsequent" colchicine doses, each subsequent colchicine dose may be the same as the first dose, or a fraction of the first dose. The fraction is selected from about $\frac{1}{12}$, about $\frac{1}{6}$, about $\frac{1}{4}$, about $\frac{1}{3}$, about $\frac{5}{12}$, about $\frac{1}{2}$, and about $\frac{7}{12}$, e.g., about $\frac{1}{2}$ or about $\frac{2}{3}$. In one example, the second colchicine dosing regimen is once-a-day, twice-a-day, three-times-a-day or four-times-a-day. In a variation of this example, the initial treatment day in, a second colchicine dosing regimen that lasts for more than one day, has one more dose administered than are administered each subsequent day.

Preferably the second active agent is selected from ketoconazole, cyclosporine, ritonavir, verapamil, or diltiazem. The specific conditions are selected from gout, FMF, thrombocytopenic purpura, and Behcet's disease. In one embodiment, the gout is an acute gout flare and the colchicine treatment schedule is an acute treatment schedule adapted for treatment of acute gout flares, or the gout is chronic gout, and the colchicine treatment schedule is a chronic treatment schedule adapted for prophylaxis, or prevention, of flares. In another embodiment, the fraction of colchicine administered to the patient concomitantly with a second active agent that is a CYP3A4 or P-gp inhibitor is $\frac{1}{3}$ or $\frac{1}{2}$ the original intended amount of colchicine and treatment with colchicine is initiated subsequent to or at the same time as initiation of treatment with the second active agent.

Colchicine is one of the most widely used drugs for treating familial Mediterranean fever (FMF). It has been reported that 5-10% of FMF patients do not show a beneficial response to colchicine administration. A polymorphism in the ABCB1 gene, the "ABCB1 3435 C to T polymorphism" has been reported to correlate with this lack of response to colchicine treatment, with patients with the homozygous TT genotype exhibiting the most pronounced "non-responder" phenotypes.

Accordingly, in another aspect, provided herein is a method for treating a patient suffering from FMF, which patient is a colchicine non-responder. Preferably, the patient is homozygous for the TT genotype of the ABCB1 3435 C to T polymorphism. The method entails the concomitant administration of a P-gp inhibitor and colchicine to the patient. Exemplary P-gp inhibitors include ketoconazole and ritonavir. Preferred dosages of the P-gp inhibitor for this

18

purpose correspond to those called for in the prescribing information for the drug in question. For ketoconazole, an exemplary dosage is 200 mg per day. For ritonavir, an exemplary dosage is 200 or 1200 mg per day. Specific colchicine dosing regimens for this purpose are the same as used for treatment of FMF in responders, though the doses of colchicine administered may be increased as tolerated, e.g., up to two to three times the typical doses.

The following examples further illustrate aspects of this disclosure but should not be construed as in any way limiting its scope. In particular, the conditions are merely exemplary and can be readily varied by one of ordinary skill in the art.

EXAMPLES

Example 1

Pharmacokinetic Study in Healthy Adults of Single vs. Multiple Oral Doses of Colchicine Tablets

This study was a single-center, open-label, single-sequence, two-period study to evaluate the pharmacokinetic profile of colchicine following single and multiple oral doses of colchicine tablets, 0.6 mg, in healthy volunteers.

In Period 1, study subjects received a 0.6-mg dose of colchicine after an overnight fast of at least 10 hours. In Period 2, subjects received a 0.6 mg dose of colchicine in the morning and the evening (approximately 12 hours later) for 10 days (steady state regimen). Subjects received a light breakfast served 60 minutes following dose administration in the morning and the evening dose was administered 90 minutes after an evening meal on Days 15 through 24 only. On Day 25, the colchicine dose was administered after an overnight fast of at least 10 hours and lunch was served 4 hours post-dose. Study periods were separated by a 14-day wash-out. Following the single dose and the last dose of the multiple dose regimen (beginning on the mornings of Day 1 and Day 25, respectively), blood samples were collected (6 mL each) from each subject within 1 hour prior to dosing and after dose administration at study hours 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 (while confined) and 36, 48, 72, and 96 (on an outpatient basis). Plasma concentrations of colchicine and its metabolites were determined using validated LC/MS-MS methods.

Thirteen healthy, non-smoking subjects with a mean age of 25.5 years (range 19 to 38 years) and within 15% of ideal body weight were enrolled in this study. All subjects completed both dosing periods according to protocol.

After a single dose, plasma concentrations are no longer quantifiable 24 hours post-dose in all but 1 subject. After the last dose of the steady state regimen, concentrations remained quantifiable for 48 to 72 hours. Review of individual subject data shows that no subject experienced a secondary colchicine peak, either following a single dose or upon multiple dosing.

All 2-O-demethylcolchicine (2-DMC) concentrations were below the level of quantitation (LOQ, 0.2 ng/mL) and only one sample from 1 subject (of 13 subjects) had a detectable 3-O-demethylcolchicine (3-DMC) concentration, which was near the level of quantitation. Therefore, metabolites are not discussed further.

In healthy adults, colchicine appears to be readily absorbed when given orally, reaching a mean maximum plasma concentration of 2.5 ng/mL in 1.5 hours after a single dose. The drug is distributed widely, with an apparent volume of distribution of 540 L, greatly exceeding total body water. The elimination half-life as calculated following a single oral dose

US 7,915,269 B2

19

is approximately 5 hours. Levels were not detectable by 24 hours post-dose and this is therefore not an accurate estimate. Pharmacokinetic parameter values are summarized in the table below.

Review of trough plasma concentrations indicates that steady state was attained by approximately the eighth day of dosing for most subjects. Colchicine may have a diurnal variation reflected in the observed C_{min} concentrations at steady state. C_{min} concentrations prior to the morning dose are approximately 12% higher than the C_{min} concentrations

20

prior to the evening dose (Day 23 and Day 24). The mean C_{min} concentration observed on Day 25 was 0.907 ng/mL.

Colchicine accumulated following administration of multiple doses to an extent greater than expected. Exposure was nearly two-fold higher (approximately 1.7 based on AUC [Day 25 AUC_{0-τ}/Day 1 AUC_{0-∞}] and approximately 1.5 based on C_{max} [Day 25 C_{max}/Day 1 C_{max}]). This observation could be attributable to an underestimation of AUC_∞ following a single dose. With the higher plasma levels that occur with repeated dosing, a longer terminal elimination half life is apparent, 26.6 hours. Pharmacokinetic parameter values are summarized in Tables 3-5.

TABLE 3

| Colchicine Pharmacokinetic Parameter Values Following Administration of A Single Oral Dose of Colchicine 0.6 mg in Healthy Adults (N = 13) | | | | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------|----------|---------|-------|----------|---------|----------|
| | MEAN | STDEV | % CV | MEDIAN | MIN | MAX |
| AUC _{0-τ} (pg-hr/mL) | 10494.66 | 3544.08 | 33.77 | 10560.90 | 4812.88 | 18091.85 |
| AUC _{0-∞} (pg-hr/mL) | 12268.18 | 4422.08 | 36.05 | 11451.45 | 7252.66 | 23801.68 |
| C _{max} (pg/mL) | 2450.15 | 702.11 | 28.66 | 2480.00 | 1584.00 | 3977.00 |
| T _{max} (hr) | 1.50 | 0.54 | 36.00 | 1.50 | 1.00 | 3.00 |
| K _{el} (1/hr) | 0.1829 | 0.0592 | 32.38 | 0.1992 | 0.0359 | 0.2443 |
| T _{1/2} (hr) | 4.95 | 4.43 | 89.54 | 3.48 | 2.84 | 19.29 |

TABLE 4

| Colchicine Pharmacokinetic Parameter Values Following Administration of Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults (N = 13) | | | | | | |
|------------------------------------------------------------------------------------------------------------------------------------------------------|----------|---------|-------|----------|----------|----------|
| | MEAN | STDEV | % CV | MEDIAN | MIN | MAX |
| AUC _{0-τ} (pg-hr/mL) | 43576.96 | 9333.26 | 21.42 | 41925.10 | 29328.78 | 58265.35 |
| AUC _{0-∞} (pg-hr/mL) | 20366.61 | 3322.12 | 16.31 | 20423.08 | 13719.18 | 25495.25 |
| AUC _{0-∞} (pg-hr/mL) | 54198.77 | 9214.54 | 17.00 | 54113.43 | 37599.76 | 67944.65 |
| C _{max} (pg/mL) | 3553.15 | 843.45 | 23.74 | 3734.00 | 1977.00 | 4957.00 |
| C _{min} (pg/mL) | 906.51 | 152.19 | 16.79 | 903.50 | 636.23 | 1149.67 |
| C _{ave} (pg/mL) | 1697.22 | 276.84 | 16.31 | 1701.92 | 1143.26 | 2124.60 |
| T _{max} (hr) | 1.31 | 0.60 | 45.61 | 1.00 | 0.50 | 3.00 |
| K _{el} (1/hr) | 0.0267 | 0.0044 | 16.34 | 0.0261 | 0.0206 | 0.0333 |
| T _{1/2} (hr) | 26.60 | 4.33 | 16.26 | 26.51 | 20.82 | 33.65 |

US 7,915,269 B2

21

TABLE 5

| Mean (% CV) Colchicine Pharmacokinetic Parameter Values Following Administration of Single and Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|-------------|
| | Vd/F (L) | CL/F (L/hr) |
| Colchicine 0.6-mg Single Dose (N = 13) | | |
| Day 1 | 341 (54.4) | 54.1 (31.0) |
| Colchicine 0.6 mg b.i.d. × 10 days | | |
| Day 25 | 1150 (18.73) | 30.3 (19.0) |

CL = Dose/AUC_{0-t} (Calculated from mean values)

Vd = CL/Ke (Calculated from mean values)

In tables, the parameter CL/F denotes the apparent total body clearance after administration, calculated as Total Dose/Total AUC_{0-t}; and Vd/F denotes the apparent total volume of distribution after administration, calculated as Total Dose/(Total AUC_{0-t} × K_{el}). FIG. 1 shows mean colchicine plasma concentrations following administration of single and multiple oral doses of colchicine 0.6 mg in healthy adults.

Example 2

Clinical Drug-Drug Interaction Study of Colchicine and Clarithromycin

A single-center, open-label, one sequence, two-period study was carried out in 23 healthy subjects. On Day 1, a single 0.6-mg dose of colchicine was administered. After completing a 21-day washout period, all subjects received 250 mg of clarithromycin administered twice daily for 7 days (Days 22 through 29), a sufficient dose and duration to inhibit CYP3A4 and Pgp. On the final day (Day 29), a single dose of colchicine was co-administered with the clarithromycin dose. When combined with steady-state clarithromycin, there is a significant increase in exposure to colchicine as compared to when colchicine is given alone: the mean C_{max} and AUC_{0-t} concentrations increased 167% and 250%, respectively. In addition, co-administration of clarithromycin and colchicine resulted in an increase of 233% in the plasma elimination half-life (t_{1/2}) of colchicine and a 75% decrease in apparent clearance (CL/F). A summary of the mean (% CV) colchicine pharmacokinetic parameters for Day 1 (colchicine administered alone) and Day 29 (colchicine co-administered with steady-state clarithromycin) are given in the table below and illustrated in Table 5.

TABLE 6

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Clarithromycin in Healthy Adults | | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|--------------------------------------|
| Arithmetic Mean (% CV) | | |
| Parameter (units) | Colchicine (N = 23) | Colchicine + Clarithromycin (N = 23) |
| AUC _{0-t} (ng · hr/mL) | 12.37 (37.64) | 41.95 (23.31) |
| AUC _{0-inf} (ng · hr/mL) | 15.53 (49.6) | 52.62 (22.84) |
| C _{max} (ng/mL) | 2.84 (30.97) | 8.44 (17.63) |
| T _{max} (hr)* | 1.50 (0.50-2.00) | 1.00 (0.50-2.00) |
| CL/F (L/hr) | 46.8 (43.68) | 12.0 (23.75) |

FIG. 2 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state

22

clarithromycin in healthy adults. Based on the foregoing data, it is concluded that the dose of colchicine co-administered with clarithromycin should be reduced by ¾.

Example 3

Clinical Drug-Drug Interaction Study of Colchicine and Cyclosporine

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

A single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with cyclosporine on Day 15. Cyclosporine was administered as a single-dose (1×100 mg capsule) on the morning of Day 15. A 14 day washout period was completed after the first colchicine dose on Day 1 and prior to the co-administration of colchicine and cyclosporine doses on Day 15.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 15. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on a confined basis. Subjects were then return to the clinic on a non-confined basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration on Days 2-5 (Period 1) and Days 16-19 (Period 2). Cyclosporine plasma concentrations were not measured.

TABLE 7

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Cyclosporine in Healthy Adults | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|------------------------------------|
| Arithmetic Mean (% CV) | | |
| Parameter (units) | Colchicine (N = 23) | Colchicine + Cyclosporine (N = 23) |
| AUC _{0-t} (ng · hr/mL) | 12.55 | 39.83 |
| AUC _{0-inf} (ng · hr/mL) | 15.00 | 47.31 |
| C _{max} (ng/mL) | 2.72 | 8.82 |
| T _{max} (hr)* | 1.15 | 1.13 |
| CL/F (L/hr) | 48.24 | 13.42 |

FIG. 3 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin and steady-state cyclosporine in healthy adults. Based on the foregoing data, the dose of colchicine co-administered with cyclosporine should be reduced by approximately ½ to ¾.

Example 4

Clinical Drug-Drug Interaction Study of Colchicine and Ritonavir

An open-label, non-randomized, single-center, one-sequence, two-period drug interaction study was conducted in healthy male and female volunteers; there will be a 14-day washout between the two periods. Twenty-four (24) non-

US 7,915,269 B2

23

smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

All subjects received a single 0.6-mg dose of colchicine on Day 1 administered under standard fasting conditions, followed by a 14-day washout period completed on an outpatient basis. At discharge on Day 2, study subjects were instructed to return to the clinical site on the mornings and evenings of Days 15 through 18 to receive two daily dosage amounts of ritonavir (1×100 mg ritonavir capsule twice daily (every 12 hours) on Days 15-18) in a 'directly-observed' fashion; after taking the first dose of ritonavir, subjects remained in the clinic for observation for 1 hour post-dose administration on Day 15. On the evening of Day 18, study participants remained at the clinic for their final study confinement period. In the morning on Day 19, study subjects received a single 0.6 mg colchicine dose with a single 100 mg ritonavir dose and study subjects received the final 100 mg ritonavir dose 12 hours later in the evening on Day 19 under standard fasting conditions.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 19. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on an inpatient basis. Subjects returned to the clinic on an outpatient basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration. Ritonavir plasma concentrations were not measured.

TABLE 8

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Ritonavir in Healthy Adults: ln-transformed data | | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|------------------------|---------|
| | Colchicine Alone | Colchicine + Ritonavir | % Ratio |
| C_{max} (pg/mL), geometric mean | 1798.37 | 4835.39 | 268.88 |
| AUC_{0-t} (pg · h/mL), geometric mean | 7642.71 | 27793.08 | 363.65 |
| AUC_{∞} (pg · h/mL), geometric mean | 9551.74 | 33771.36 | 353.56 |

TABLE 9

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Ritonavir in Healthy Adults | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|---------------------------|--|
| | Arithmetic Mean (% CV) Median (Range) for T_{max} | | |
| Parameter (units) | Colchicine + Ritonavir (N = 18) | Colchicine Alone (N = 18) | |
| AUC_{0-t} (ng · hr/mL) | 29.05 (30.76) | 8.41 (47.46) | |
| $AUC_{0-\infty}$ (ng · hr/mL) | 35.28 (29.79) | 10.41 (45.48) | |
| C_{max} (ng/mL) | 4.99 (25.18) | 1.87 (28.19) | |
| T_{max} (hr) | 1.5 (1-1.5) | 1 (0.5-1.5) | |
| CL/F (L/hr) | 18.59 (31.58) | 67.93 (39.47) | |

Following exposure to 100 mg b.i.d.×5 days, there was a significant increase in exposure to a single 0.6-mg colchicine (approximately 245%). Mean peak colchicine concentration increased by approximately 170%. Total apparent oral clear-

24

ance was decreased by 70% with co-administration. T_{max} is not affected. Elimination half-life could not be estimated accurately as plasma concentrations were not quantifiable after 24 hours.

FIG. 4 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state ritonavir and steady-state ketoconazole in healthy adults. Based on the foregoing data, the dose of colchicine co-administered with ritonavir should be reduced by approximately $\frac{1}{2}$.

Example 5

Clinical Drug-Drug Interaction Study of Colchicine and Ketoconazole

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers; there will be a 14-day washout between the two periods. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled.

A single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with ketoconazole on Day 19 (AM dose). Ketoconazole was administered for 5 consecutive days [200 mg twice daily (every 12 hours)] beginning on the morning of Day 15, with the last 200 mg ketoconazole dose administered on the evening on Day 19. Total study participation, exclusive of up to 28 days of screening, was approximately 24 days, during which subjects will be confined on two occasions for a total confinement of approximately 3 days.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 19. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on an inpatient basis. Subjects then returned to the clinic on an outpatient basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration. Ketoconazole plasma concentrations were not measured.

TABLE 10

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Ketoconazole in Healthy Adults: ln-transformed data | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|---------------------------|---------|
| | Colchicine Alone | Colchicine + Ketoconazole | % Ratio |
| C_{max} (pg/mL), geometric mean | 2598.28 | 5078.50 | 195.46 |
| AUC_{0-t} (pg · h/mL), geometric mean | 11087.99 | 33223.80 | 299.64 |
| AUC_{∞} (pg · h/mL), geometric mean | 13185.92 | 42143.00 | 319.61 |

US 7,915,269 B2

25

TABLE 11

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Ketoconazole in Healthy Adults | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|------------------------------------------|
| Parameter (units) | Arithmetic Mean (% CV) | |
| | Colchicine (N = 23) | Colchicine + Ketoconazole (N = 23) |
| AUC ₀₋₄ (pg · hr/mL) | 11988.61 | 34382.82 |
| AUC _{0-inf} (pg · hr/mL) | 14314.09 | 43688.90 |
| C _{max} (pg/mL) | 2779.08 | 5266.92 |
| T _{max} (hr)* | 1.00 | 1.02 |
| CL/F (L/hr) | 49301.09 | 14797.94 |

*Median (Range) for T_{max}

Following administration of ketoconazole 200 mg b.i.d.×5 days, there was a significant increase in exposure to a single oral dose of colchicine 0.6 mg (C_{max} and AUC₀₋₄ increased by 90% and 190%, respectively, and AUC_{0-∞} increased by about 205%). Total apparent oral clearance decreased by 70% with co-administration. Elimination half-life could not be estimated accurately as plasma concentrations were not quantifiable after 24 hours.

FIG. 4 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state ritonavir and steady-state ketoconazole in healthy adults. Based on the foregoing data, the dose of colchicine co-administered with ketoconazole should be reduced by approximately ½.

Example 6

Clinical Drug-Drug Interaction Study of Colchicine and Azithromycin

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers; there was a 14-day washout between the two periods. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

A single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with the azithromycin on Day 19. Azithromycin was administered for 5 consecutive days (2×250 mg once daily [Day 15 only] and then 1×250 mg once daily Days 16-19) beginning on the morning of Day 15, with the last 250 mg azithromycin dose administered on the morning on Day 19. Total study participation, exclusive of up to 28 days of screening, was approximately 24 days, during which subjects were confined on two occasions for a total confinement of approximately 3 days.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 19. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on an inpatient basis. Subjects returned to the clinic on an outpatient basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration. Azithromycin plasma concentrations were not measured.

26

TABLE 12

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Azithromycin in Healthy Adults | | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|------------------------------|---------|
| | Colchicine Alone | Colchicine + Azithromycin | % Ratio |
| C _{max} (pg/mL), geometric mean | 2535.94 | 2856.22 | 112.63 |
| AUC ₀₋₄ (pg · h/mL), geometric mean | 10971.51 | 16090.52 | 146.66 |
| AUC _∞ (pg · h/mL), geometric mean | 12931.80 | 18312.83 | 141.61 |

TABLE 13

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Azithromycin in Healthy Adults | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|---------------------------------|
| Parameter (units) | Arithmetic Mean (% CV) Median (Range) for T _{max} | |
| | Colchicine + Azithromycin (N = 21) | Colchicine Alone (N = 21) |
| AUC ₀₋₄ (ng · hr/mL) | 17.16 (37.78) | 11.98 (45.81) |
| AUC _{0-∞} (ng · hr/mL) | 19.61 (39.15) | 14.13 (46.73) |
| C _{max} (ng/mL) | 3.05 (39.54) | 2.74 (41.52) |
| T _{max} (hr) | 1.5 (0.5-3) | 1.0 (0.5-3) |
| t _{1/2} (hr) | 6.71 (68.34) ¹ | 6.07 (66.15) ¹ |
| CL/F (L/hr) | 35.01 (37.26) | 50.24 (40.31) |

Following administration of azithromycin 500 mg on Day 1 followed by 250 mg×4 days, exposure to colchicine is increased (approximately 46% for AUC₀₋₄ and approximately 40% for AUC_{0-∞}). Mean peak colchicine concentration increased by approximately 12% and total apparent oral clearance decreased approximately 30% with co-administration. T_{max} was not affected.

FIG. 5 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state azithromycin and steady-state diltiazem in healthy adults.

Example 7

Clinical Drug-Drug Interaction study of Colchicine and Diltiazem

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

As single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with diltiazem ER on Day 21. Diltiazem ER was administered for 7 consecutive days (1×240 mg capsule once daily on Days 15-21) beginning on the morning of Day 15, with the last 240 mg diltiazem ER dose administered on the morning on Day 21. A 14-day washout period was completed after the first colchicine dose on Day 1 and prior to the administration of the first diltiazem ER dose on Day 15.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day

US 7,915,269 B2

27

1 and Day 21. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on an inpatient basis. Subjects returned to the clinic on an outpatient basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration. Diltiazem plasma concentrations were not measured.

TABLE 14

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Diltiazem in Healthy Adults | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|------------------------|---------|
| | Colchicine Alone | Colchicine + Diltiazem | % Ratio |
| C_{max} (pg/mL), geometric mean | 2006.42 | 2583.22 | 128.75 |
| AUC_{0-t} (pg · h/mL), geometric mean | 9154.55 | 15740.37 | 171.94 |
| AUC_{∞} (pg · h/mL), geometric mean | 11022.30 | 19902.98 | 180.57 |

TABLE 15

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Diltiazem in Healthy Adults | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|---------------------------|
| Parameter (units) | Arithmetic Mean (% CV) Median (Range) for T_{max} | |
| | Colchicine + Diltiazem (N = 20) | Colchicine Alone (N = 20) |
| AUC_{0-t} (ng · hr/mL) | 17.73 | 10.04 |
| $AUC_{0-\infty}$ (ng · hr/mL) | 22.49 | 12.03 |
| C_{max} (ng/mL) | 2.80 | 2.17 |
| T_{max} (hr) | 1.48 | 1.15 |
| $t_{1/2}$ (hr) | 12.50 | 5.51 |
| CL/F (L/hr) | 463.49 | 395.83 |

FIG. 5 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state azithromycin and steady-state diltiazem in healthy adults.

Example 8

Clinical Drug-Drug Interaction Study of Colchicine and Verapamil

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

A single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with verapamil HCl ER on Day 19. Verapamil HCl ER was administered for 5 consecutive days (1x240 mg tablet once daily on Days 15-19) beginning on the morning of Day 15, with the last 240 mg verapamil HCl ER dose administered on the morning on Day 19. A 14-day washout period was completed after the first colchicine dose on Day 1 and prior to the administration of the first verapamil HCl ER dose on Day 15.

28

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 19. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on a confined basis. Subjects returned to the clinic on a non-confined basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration on Days 2-5 (Period 1) and Days 20-23 (Period 2). Verapamil plasma concentrations were not measured.

TABLE 16

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Verapamil in Healthy Adults | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|------------------------|---------|
| | Colchicine Alone | Colchicine + Verapamil | % Ratio |
| C_{max} (pg/mL), geometric mean | 2768.77 | 3639.68 | 131.45 |
| AUC_{0-t} (pg · h/mL), geometric mean | 12256.40 | 23889.21 | 194.94 |
| AUC_{∞} (pg · h/mL), geometric mean | 14415.79 | 29556.75 | 205.03 |

TABLE 17

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Verapamil in Healthy Adults | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|---------------------------|
| Parameter (units) | Arithmetic Mean (% CV) Median (Range) for T_{max} | |
| | Colchicine + Verapamil (N = 24) | Colchicine Alone (N = 24) |
| AUC_{0-t} (ng · hr/mL) | 24.64 | 13.09 |
| $AUC_{0-\infty}$ (ng · hr/mL) | 30.59 | 15.37 |
| C_{max} (ng/mL) | 3.85 | 2.97 |
| T_{max} (hr) | 1.15 | 1.22 |
| $t_{1/2}$ (hr) | 17.17 | 6.24 |
| CL/F (L/hr) | 21.01 | 43.93 |

Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges directed to the same component or property are inclusive and independently combinable.

All methods described herein can be performed in a suitable order unless otherwise indicated or clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") herein is intended to better illuminate the disclosure and is non-limiting unless otherwise specified. No language in the specification should be construed as indicating that any non-claimed element as essential to the practice of the claimed embodiments. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this disclosure belongs. The terms wt %, weight percent, percent by weight, etc. are equivalent and interchangeable.

US 7,915,269 B2

29

In the specification and claims that follow, references will be made to a number of terms which shall be defined to have the following meaning.

The terms “a” and “an” do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The term “or” means “and/or”. The terms “comprising”, “having”, “including”, and “containing” are to be construed as open-ended terms (i.e., meaning “including, but not limited to”).

“Concomitant” and “concomitantly” as used herein refer to the administration of at least two drugs to a patient either simultaneously or within a time period during which the effects of the first administered drug are still operative in the patient. Thus, if the first drug is, e.g., clarithromycin and the second drug is colchicine, the concomitant administration of the second drug can occur as much as one to two weeks, preferably within one to seven days, after the administration of the first drug. This is because clarithromycin can exert a long-lasting inhibition of CYP3A isozymes so that CYP3A activity in the patient may not return to pre-clarithromycin-administration levels for as much as two weeks after the cessation of clarithromycin administration. If colchicine is the first drug, administration of a second drug would be concomitant if done within 1 to 2 days, preferably 12 to 24 hours.

A “dose” means the measured quantity of a drug to be taken at one time by a patient.

A “dosage amount” means an amount of a drug suitable to be taken during a fixed period, usually during one day (i.e. daily). A “daily dosage amount” is the total dosage amount taken in one day, that is, a 24 hour period.

“Dosing regimen” means the dose of a drug taken at a first time by a patient and the interval (time or symptomatic) and dosage amounts at which any subsequent doses of the drug are taken by the patient. Each dose may be of the same or different.

A “patient” means a human or non-human animal in need of medical treatment. Medical treatment can include treatment of an existing condition, such as a disease or disorder, prophylactic or preventative treatment, or diagnostic treatment. In preferred embodiments the patient is human.

“Providing” means giving, administering, selling, distributing, transferring (for profit or not), manufacturing, compounding, or dispensing.

“Risk” means the probability or chance of adverse reaction, injury, or other undesirable outcome arising from a medical treatment. An “acceptable risk” means a measure of the risk of harm, injury, or disease arising from a medical treatment that will be tolerated by an individual or group. Whether a risk is “acceptable” will depend upon the advantages that the individual or group perceives to be obtainable in return for taking the risk, whether they accept whatever scientific and other advice is offered about the magnitude of the risk, and numerous other factors, both political and social. An “acceptable risk” of an adverse reaction means that an individual or a group in society is willing to take or be subjected to the risk that the adverse reaction might occur since the adverse reaction is one whose probability of occurrence is small, or whose consequences are so slight, or the benefits (perceived or real) of the active agent are so great. An “unacceptable risk” of an adverse reaction means that an individual or a group in society is unwilling to take or be subjected to the risk that the adverse reaction might occur upon weighing the probability of occurrence of the adverse reaction, the consequences of the adverse reaction, and the benefits (perceived or real) of the active agent. “At risk” means in a state or condition marked by a high level of risk or susceptibility.

30

Pharmacokinetic parameters referred to herein describe the in vivo characteristics of drug (or a metabolite or a surrogate marker for the drug) over time. These include plasma concentration (C), as well as C_{max} , C_n , C_{24} , T_{max} , and AUC. “ C_{max} ” is the measured plasma concentration of the active agent at the point of maximum, or peak, concentration. “ C_{min} ” is the measured plasma concentration of the active agent at the point of minimum concentration. “ C_n ” is the measured plasma concentration of the active agent at about n hours after administration. “ C_{24} ” is the measured plasma concentration of the active agent at about 24 hours after administration. The term “ T_{max} ,” refers to the time from drug administration until C_{max} is reached. “AUC” is the area under the curve of a graph of the measured plasma concentration of an active agent vs. time, measured from one time point to another time point. For example AUC_{0-t} is the area under the curve of plasma concentration versus time from time 0 to time t, where time 0 is the time of initial administration of the drug. Time t can be the last time point with measurable plasma concentration for an individual formulation. The $AUC_{0-\infty}$, AUC_{∞} or AUC_{0-inf} is the calculated area under the curve of plasma concentration versus time from time 0 to time infinity. In steady-state studies, $AUC_{0-\tau}$ is the area under the curve of plasma concentration over the dosing interval (i.e., from time 0 to time τ (tau), where tau is the length of the dosing interval. Other pharmacokinetic parameters are the parameter K_e or K_{el} , the terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve; $t_{1/2}$ the terminal elimination half-life, calculated as $0.693/K_{el}$. CL/F denotes the apparent total body clearance after administration, calculated as Total Dose/Total AUC_{∞} ; and V_{area}/F denotes the apparent total volume of distribution after administration, calculated as Total Dose/(Total $AUC_{\infty} \times K_{el}$).

“Side effect” means a secondary effect resulting from taking a drug. The secondary effect can be a negative (unfavorable) effect (i.e., an adverse side effect) or a positive (favorable) effect.

The most frequently reported adverse side effects to colchicine therapy are gastrointestinal, specifically abdominal pain with cramps, diarrhea, nausea, and vomiting. Less frequently or rarely reported adverse side effects associated with colchicine therapy include anorexia, agranulocytosis, allergic dermatitis, allergic reactions, alopecia, angioedema, aplastic anemia, bone marrow depression, myopathy, neuropathy, skin rash, thrombocytopenic disorder, and urticaria.

Whether a patient experiences an adverse side effect can be determined by obtaining information from the patient regarding onset of certain symptoms which may be indicative of the adverse side effect, results of diagnostic tests indicative of the adverse side effect, and the like.

Embodiments are described herein, including the best modes known to the inventors. Variations of such embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The skilled artisan is expected to employ such variations as appropriate, and the disclosed methods are expected to be practiced otherwise than as specifically described herein. Accordingly, all modifications and equivalents of the subject matter recited in the claims appended hereto are included to the extent permitted

US 7,915,269 B2

31

by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed unless otherwise indicated herein or otherwise clearly contradicted by context.

What is claimed is:

- 1. A method of treating a patient in need of treatment for gout flares with colchicine, comprising orally administering to the patient in need of treatment for gout flares, an adjusted daily dosage amount of colchi-

32

cine wherein the patient is receiving concomitant administration of 200 mg per day of ritonavir, wherein the adjusted daily dosage amount of colchicine is 25% to 50% of an intended daily dosage amount in the absence of concomitant ritonavir, wherein the intended daily dosage amount in the absence of concomitant ritonavir is 1.2 mg at the first sign of flare, followed by 0.6 mg one hour later, dose to be repeated no earlier than 3 days.

* * * * *

EXHIBIT E

US007964647B2

(12) **United States Patent**
Davis(10) **Patent No.:** **US 7,964,647 B2**
(45) **Date of Patent:** ***Jun. 21, 2011**(54) **COLCHICINE COMPOSITIONS AND METHODS**(75) Inventor: **Matthew W. Davis**, Erwinna, PA (US)(73) Assignee: **Mutual Pharmaceutical Company, Inc.**, Philadelphia, PA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/407,980**(22) Filed: **Mar. 20, 2009**(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation of application No. 12/246,034, filed on Oct. 6, 2008.

(60) Provisional application No. 60/977,796, filed on Oct. 5, 2007, provisional application No. 61/090,965, filed on Aug. 22, 2008.

(51) **Int. Cl.****A01N 37/18** (2006.01)**A61K 31/16** (2006.01)**C07C 233/00** (2006.01)**C07C 235/00** (2006.01)**C07C 237/00** (2006.01)**C07C 239/00** (2006.01)**C07C 211/00** (2006.01)**C07C 205/00** (2006.01)**C07C 207/00** (2006.01)(52) **U.S. Cl.** **514/629**; 564/123; 564/308; 564/427; 568/306(58) **Field of Classification Search** None
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ABSTRACT

Stable ultrapure colchicine compositions comprising ultrapure colchicine and a pharmaceutically acceptable excipient are described. The compositions can be tablets. Methods for preparing such compositions and methods of use are also disclosed. Methods of treating gout flares with colchicine compositions are also disclosed.

1 Claim, 1 Drawing Sheet

US 7,964,647 B2

Page 2

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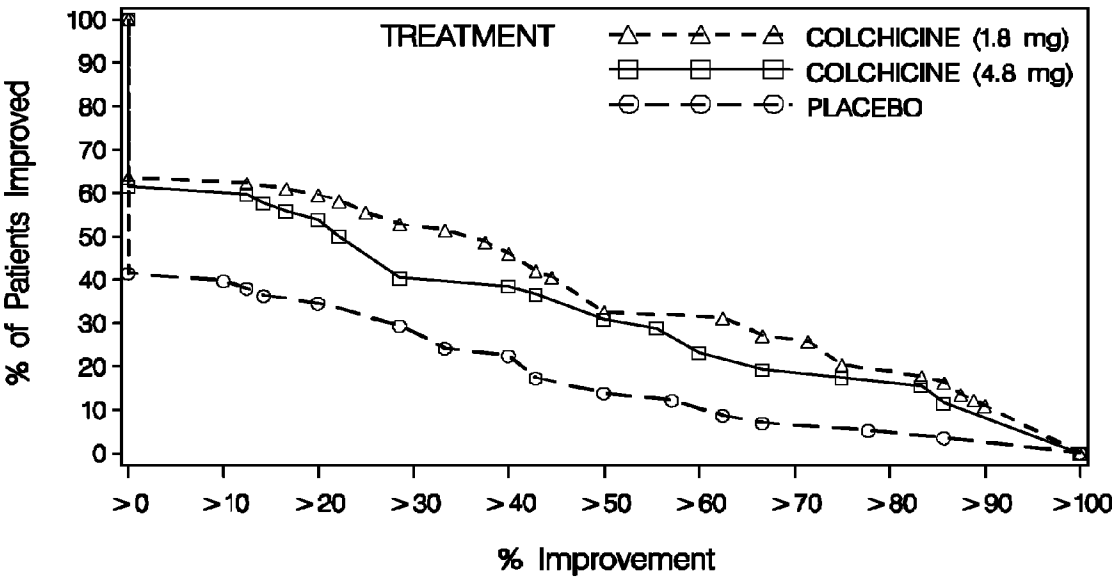
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U.S. Patent

Jun. 21, 2011

US 7,964,647 B2

FIGURE 1



US 7,964,647 B2

1

COLCHICINE COMPOSITIONS AND METHODS

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation of U.S. application Ser. No. 12/246,034, filed Oct. 6, 2008, which claims the benefit of U.S. Provisional Application Ser. No. 60/977,796 filed Oct. 5, 2007 and U.S. Provisional Application Ser. No. 61/090,965 filed Aug. 22, 2008, each of which is hereby incorporated by reference in its entirety.

BACKGROUND

This application relates to colchicine compositions for therapeutic purposes, specifically ultrapure colchicine, and methods of making and using the colchicine compositions.

Colchicine, chemical name (–)-N-[(7S,12aS)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide, is a pale yellow powder soluble in water in 1:25 dilution.

Colchicine is an alkaloid found in extracts of certain plants such as *Colchicum autumnale* and *Gloriosa superba*. Colchicine arrests cell division in animals and plants. It has adversely affected spermatogenesis in humans and in some animal species under certain conditions.

Gout (or gouty arthritis) is a disease caused by a build up of uric acid due to an overproduction of uric acid or a reduced ability of the kidney to get rid of uric acid. It is more common in males, postmenopausal women, and people with high blood pressure. Heavy alcohol use, diabetes, obesity, sickle cell anemia, and kidney disease also increase the risk. The condition may also develop in people who take drugs that interfere with uric acid excretion.

In gout, monosodium urate or uric acid crystals are deposited on the articular cartilage of joints, tendons and surrounding tissues due to elevated concentrations of uric acid in the blood stream. This provokes an inflammatory reaction of these tissues. Gout is characterized by excruciating, sudden, unexpected, burning pain, as well as swelling, redness, warmth, and stiffness in the affected joint. Low-grade fever may also be present. The patient usually suffers from two sources of pain. The crystals inside the joint cause intense pain whenever the affected area is moved. The inflammation of the tissues around the joint also causes the skin to be swollen, tender and sore if it is even slightly touched. For example, a blanket or even the lightest sheet draping over the affected area could cause extreme pain.

Acute gouty arthritis (alternatively referred to as a gout flare or a gout attack) is a sudden attack of pain in affected joints, especially in the feet and legs. Chronic gout involves repeated attacks of joint pain.

In acute gouty arthritis, symptoms develop suddenly and usually involve only one or a few joints. The big toe, knee, or ankle joints are most often affected. The pain frequently starts during the night and is often described as throbbing, crushing, or excruciating. The joint appears infected with signs of warmth, redness, and tenderness. The attacks of painful joints may go away in several days, but may return from time to time. Subsequent attacks usually last longer. Some people may progress to chronic gout (chronic gouty arthritis), while others may have no further attacks.

If several attacks of gout occur each year, it can lead to joint deformity and limited motion in joints. Uric acid deposits, called tophi, develop in cartilage tissue, tendons, and soft tissues. These tophi usually develop only after a patient has

2

suffered from the disease for many years. Deposits also can occur in the kidneys, leading to chronic kidney failure.

Colchicine can be used for treating adults with acute gouty arthritis and pain in attacks of acute gouty arthritis, and also can be used beneficially for treating adults with chronic gout for prophylaxis of acute gout flares. Although its exact mode of action in the relief of gout is not completely understood, colchicine is known to decrease the inflammatory response to urate crystal deposition by inhibiting migration of leukocytes, to interfere with urate deposition by decreasing lactic acid production by leukocytes, to interfere with kinin formation and to diminish phagocytosis and the subsequent anti-inflammatory response. The anti-inflammatory effect of colchicine is relatively selective for acute gouty arthritis. However, other types of arthritis occasionally respond. It is neither an analgesic nor a uricosuric and will not prevent progression to chronic gouty arthritis. It does have a prophylactic, suppressive effect that helps to reduce the incidence of acute attacks and to relieve the residual pain and mild discomfort that patients with gout occasionally experience. In some instances, non-steroidal anti-inflammatory drugs (NSAIDs) may also be prescribed to relieve pain and inflammation in acute gouty arthritis attacks. Strong painkillers, such as codeine, or corticosteroids may also be prescribed to relieve the pain.

Colchicine is rapidly absorbed from the gastrointestinal tract. Peak concentrations occur in 0.5 to 2 hours. The drug and its metabolites are distributed in leukocytes, kidneys, liver, spleen and the intestinal tract. Colchicine is metabolized in the liver and excreted primarily in the feces with 10 to 20% eliminated unchanged in the urine.

There remains a need for pure forms of colchicine having low levels of impurities for pharmaceutical use to minimize the potential for side effects in patients taking colchicine pharmaceutical products and to minimize the need for costly toxicity testing required for approval of pharmaceutical products comprising conventional colchicine having high levels of individual or total impurities. In particular, there is a need for stable compositions comprising ultrapure colchicine.

SUMMARY

Disclosed herein are colchicine compositions.

In one embodiment, the colchicine composition comprises ultrapure colchicine, wherein the ultrapure colchicine comprises no more than about 3.0% total impurities, specifically no more than about 2.0% total impurities, and a pharmaceutically acceptable excipient.

In another embodiment, the colchicine composition comprises ultrapure colchicine, wherein the ultrapure colchicine comprises no more than 3.0% total impurities, specifically no more than about 2.0% total impurities, a filler, a binder, and a disintegrant.

In yet another embodiment, the colchicine composition comprises about 0.6 mgA colchicine, about 12 to about 16 mg pregelatinized starch, about 20 to about 24 mg microcrystalline cellulose, about 3.9 to about 4.7 mg sodium starch glycolate, about 0.5 to about 0.7 mg magnesium stearate, and an amount of lactose monohydrate such that the colchicine dosage form has a total weight of about 100 mg.

In an embodiment, the colchicine composition comprises colchicine; and a pharmaceutically acceptable excipient; wherein the colchicine composition comprises no more than about 3.5% total impurities and no more than 0.42% N-deacetyl-N-formyl colchicine.

In an embodiment, the colchicine composition comprises colchicine; and a pharmaceutically acceptable excipient,

US 7,964,647 B2

3

wherein the colchicine composition has 0.6 mgA colchicine, wherein a single dose of the 0.6 mgA colchicine composition has enhanced bioavailability as compared to a single dose of a pharmaceutical product comprising 0.5 mg colchicine after potency correction for colchicine.

In an embodiment, the colchicine composition comprises colchicine; and a pharmaceutically acceptable excipient, wherein the colchicine composition has equivalent bioavailability when administered in a fed or a fasted state.

In an embodiment, the colchicine composition comprises colchicine; and a pharmaceutically acceptable excipient, wherein administration of a single dose of the colchicine composition to a human provides a Cmax between about 1.3 ng/mL and about 4.0 ng/mL, an AUC_{0-t} between about 4.4 ng-hr/mL and about 30.8 ng-hr/mL, or an AUC_{0-INF} between about 6.7 ng-hr/mL and about 27.8 ng-hr/mL.

Methods of making the colchicine compositions are also disclosed herein.

In an embodiment, the method comprises wet granulating ultrapure colchicine, wherein the ultrapure colchicine comprises no more than about 3.0% of total impurities, with a pharmaceutically acceptable excipient to obtain wet granules, and mixing the granules with a disintegrant to obtain the composition.

In yet another embodiment, the method comprises wet granulating colchicine with a pharmaceutically acceptable excipient to obtain wet granules; drying the wet granules to obtain dried granules; milling the dried granules to obtain milled granules; mixing the milled granules with a disintegrant to obtain the composition; mixing the composition with a lubricant to obtain a tableting blend; and compressing the tableting blend to obtain a colchicine tablet.

Also disclosed herein are methods of making ultrapure colchicine.

In an embodiment, the method comprises subjecting colchicine comprising more than about 3.0% total impurities to column chromatography to obtain a colchicine concentrate, distilling the colchicine concentrate to obtain a colchicine distillate, and crystallizing ultrapure colchicine from the colchicine distillate; wherein the ultrapure colchicine comprises no more than about 3.0% total impurities.

In another embodiment, the method comprises subjecting colchicine comprising more than about 3.0% total impurities to neutral alumina column chromatography to obtain a colchicine concentrate; distilling the colchicine concentrate with ethyl acetate to obtain a colchicine distillate; and crystallizing ultrapure colchicine from the colchicine distillate in ethyl acetate; wherein the ultrapure colchicine comprises no more than about 3.0% total impurities.

In still another embodiment, the method comprises subjecting colchicine comprising more than about 3.0% total impurities to neutral alumina column chromatography to obtain a colchicine concentrate; distilling the colchicine concentrate with ethyl acetate to obtain a colchicine distillate; crystallizing a purified colchicine from the colchicine distillate in ethyl acetate; washing the purified colchicine with ethyl acetate to obtain a washed purified colchicine; and drying the washed purified colchicine to obtain ultrapure colchicine, wherein the ultrapure colchicine comprises no more than about 3.0% total impurities.

Also disclosed are methods of treating a patient with the colchicine compositions.

In an embodiment, the method comprises administering a dosing regimen to a patient having an acute gouty arthritis attack, wherein the dosing regimen consists of two colchicine dosage forms at the onset of the acute gouty arthritis attack,

4

followed by one colchicine dosage form in about one hour, wherein a colchicine dosage form comprises about 0.6 mgA colchicine.

In an embodiment, the method comprises administering less than about 2 mg of colchicine to a patient over a period of about one hour, wherein the patient is experiencing an acute gouty arthritis attack.

In an embodiment, the method comprises administering to a human experiencing an acute gouty arthritis attack a colchicine composition, wherein the composition is effective to provide a colchicine plasma concentration profile having an area under the plasma colchicine concentration curve from time 0 to infinity (AUC_{0-INF}) of about 34.2 ng-hr/mL to about 74.1 ng-hr/mL, an area under the plasma colchicine concentration curve from time 0 to time t (AUC_{0-t}) of about 28.8 ng-hr/mL to about 58.9 ng-hr/mL, or a maximum plasma colchicine concentration (Cmax) of about 3.2 ng/mL to about 11.4 ng/mL for a maximum total dose of about 1.8 mg colchicine.

In an embodiment, the method comprises administering a dosing regimen to a patient having an acute gouty arthritis attack, wherein the dosing regimen consists of two colchicine dosage forms at the onset of the acute gouty arthritis attack, followed by one colchicine dosage form in about one hour, wherein a colchicine dosage form comprises about 0.6 mgA colchicine, wherein the dosing regimen is effective to provide an area under the plasma colchicine concentration curve from time 0 to infinity (AUC_{0-INF}) of about 34.2 ng-hr/mL to about 74.1 ng-hr/mL, an area under the plasma colchicine concentration curve from time 0 to time t (AUC_{0-t}) of about 28.8 ng-hr/mL to about 58.9 ng-hr/mL, or a maximum plasma colchicine concentration (Cmax) of about 3.2 ng/mL to about 11.4 ng/mL.

In an embodiment, the method comprises administering a dosing regimen to a patient having an acute gouty arthritis attack, wherein the dosing regimen consists of two colchicine dosage forms at the onset of the acute gouty arthritis attack, followed by one colchicine dosage form in about one hour, wherein a colchicine dosage form comprises about 0.6 mgA colchicine, wherein the dosing regimen is effective to provide a colchicine plasma concentration profile which has a maximum plasma colchicine concentration (Cmax) which is at least 80% of plasma Cmax provided by a dosing regimen of two dosage forms, followed by one dosage form about every hour later for 6 hours.

In an embodiment, the method comprises administering a dosing regimen to a patient having an acute gouty arthritis attack, wherein the dosing regimen consists of two colchicine dosage forms at the onset of the acute gouty arthritis attack, followed by one colchicine dosage form in about one hour, wherein a colchicine dosage form comprises about 0.6 mgA colchicine, wherein the odds of a patient being a responder to the dosing regimen are not statistically different from the odds of being a responder to a second dosing regimen consisting of two colchicine dosage forms at the onset of the acute gouty arthritis attack, followed by one colchicine dosage form every hour for 6 hours, wherein a responder is a patient obtaining a $\geq 50\%$ improvement in pain at 24 hours after the first dose, without taking an additional active agent for reducing pain of the acute gouty arthritis attack.

In an embodiment, the method comprises administering a dosing regimen to a patient having an acute gouty arthritis attack, wherein the dosing regimen consists of two colchicine dosage forms at the onset of the acute gouty arthritis attack, followed by one colchicine dosage form in about one hour, wherein a colchicine dosage form comprises about 0.6 mgA colchicine, wherein in a randomized, placebo-controlled

US 7,964,647 B2

5

study of the dosing regimen in patients with an acute gouty arthritis attack, the fraction of patients that experienced a given % improvement in pain at 24 hrs after first dose is shown in FIG. 1.

These and other embodiments, advantages and features of the present invention become clear when detailed description and examples are provided in subsequent sections.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the fraction of all patients improved at 24 hrs post-first dose of colchicine, regardless of pain rescue, as a function of the percent improvement in pain determined in the study of Example 3.

DETAILED DESCRIPTION

Disclosed herein are compositions comprising ultrapure colchicine and a pharmaceutically acceptable excipient. Herein, "ultrapure colchicine" means colchicine comprising no more than about 3.0% of total impurities, measured chromatographically as described below, specifically the ultrapure colchicine comprises no more than about 2.0% of total impurities, more specifically no more than about 1.0% of total impurities, or even more specifically no more than about 0.5% of total impurities. In some embodiments, the ultrapure colchicine comprises no more than about 0.10% of N-deacetyl-N-formyl colchicine, measured chromatographically. In some embodiments, the ultrapure colchicine is purified from a botanical source. Methods of making ultrapure colchicine and the compositions comprising the ultrapure colchicine, methods of treating various conditions using the compositions. Dosing regimens are also disclosed.

Not wishing to be bound by theory, it is postulated that the properties of colchicine as an antimitotic agent (e.g. its tubulin binding properties) or its effects on Pgp transporter properties provide the therapeutic effects of colchicine described herein. The methods described herein therefore also contemplate the use of an antimitotic agent with at least one pharmaceutically acceptable excipient. An antimitotic agent can be a drug that prevents or inhibits mitosis, or cell division.

In the specification and claims that follow, references will be made to a number of terms which shall be defined to have the following meaning.

The terms "a" and "an" do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The term "or" means "and/or". The terms "comprising", "having", "including", and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to") unless otherwise noted.

An "active agent" means a compound (including for example, colchicine), element, or mixture that when administered to a patient, alone or in combination with another compound, element, or mixture, confers, directly or indirectly, a physiological effect on the patient. The indirect physiological effect may occur via a metabolite or other indirect mechanism. When the active agent is a compound, then salts, solvates (including hydrates), and co-crystals of the free compound or salt, crystalline forms, non-crystalline forms, and any polymorphs of the compound are contemplated herein. Compounds may contain one or more asymmetric elements such as stereogenic centers, stereogenic axes and the like, e.g., asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. For compounds with two or more asymmetric elements, these compounds can additionally be mixtures of diastereomers.

6

tereomers. For compounds having asymmetric centers, all optical isomers in pure form and mixtures thereof are encompassed. In addition, compounds with carbon-carbon double bonds may occur in Z- and E-forms, with all isomeric forms of the compounds. In these situations, the single enantiomers, i.e., optically active forms can be obtained by asymmetric synthesis, synthesis from optically pure precursors, or by resolution of the racemates. Resolution of the racemates can also be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example, a chiral HPLC column. All forms are contemplated herein regardless of the methods used to obtain them.

"Bioavailability" means the extent or rate at which an active agent is absorbed into a living system or is made available at the site of physiological activity. For active agents that are intended to be absorbed into the bloodstream, bioavailability data for a given formulation may provide an estimate of the relative fraction of the administered dose that is absorbed into the systemic circulation. "Bioavailability" can be characterized by one or more pharmacokinetic parameters.

"Bioequivalence" or "equivalent bioavailability" means the absence of a significant difference in the rate or extent to which the active agent in pharmaceutical equivalents or pharmaceutical alternatives is absorbed into a living system or is made available at the site of physiological activity or the absence of a significant difference in the rate or extent to which the active agent in a pharmaceutical composition is absorbed into a living system or is made available at the site of physiological activity when administered by two different methods (e.g., dosing under non-fasted versus fasted conditions). Bioequivalence can be determined by comparing in vitro dissolution testing data for two dosage forms or two dosing conditions or by comparing pharmacokinetic parameters for two dosage forms or two dosing conditions.

In some embodiments, two products (e.g. an inventive composition and COL-PROBENECID®) or two methods (e.g., dosing under fed (non-fasted) versus fasted conditions) are bioequivalent if the ratio of the geometric mean of logarithmic transformed $AUC_{0-\infty}$, AUC_{0-t} , or C_{max} for the two products or two methods is about 0.80 to about 1.25; specifically if the 90% Confidence Interval (CI) limit for the ratio of the geometric mean of logarithmic transformed $AUC_{0-\infty}$, AUC_{0-t} , or C_{max} for the two products or two methods is about 0.80 to about 1.25; more specifically if the ratios of the geometric mean of logarithmic transformed $AUC_{0-\infty}$, AUC_{0-t} , and C_{max} for the two products or two methods are about 0.80 to about 1.25; yet more specifically if the 90% Confidence Interval (CI) limits for the ratios of the geometric mean of logarithmic transformed $AUC_{0-\infty}$, AUC_{0-t} , and C_{max} for the two products or two methods are about 0.80 to about 1.25.

"Colchicine therapy" refers to medical treatment of a symptom, disorder, or condition by administration of colchicine. Colchicine therapy can be considered optimal when effective plasma levels are reached when required. In addition, peak plasma values (C_{max}) should be as low as possible so as to reduce the incidence and severity of possible side effects.

"Conventional colchicine" means colchicine comprising more than 3% but no more than about 5.0% total impurities, measured chromatographically as described below, and comprising more than about 0.010% of N-deacetyl-N-formyl colchicine.

A "dosage form" means a unit of administration of an active agent. Examples of dosage forms include tablets, cap-

US 7,964,647 B2

7

sules, injections, suspensions, liquids, emulsions, creams, ointments, suppositories, inhalable forms, transdermal forms, and the like.

"Dosing regimen" means the dose of an active agent taken at a first time by a patient and the interval (time or symptomatic) at which any subsequent doses of the active agent are taken by the patient. The additional doses of the active agent can be different from the dose taken at the first time.

A "dose" means the measured quantity of an active agent to be taken at one time by a patient.

"Efficacy" means the ability of an active agent administered to a patient to produce a therapeutic effect in the patient.

As used herein, the term "mgA" refers to milligrams of the active colchicine, or the free base of colchicine, after compensating for the potency of the batch of colchicine (i.e., after compensating for impurities, including solvents, and salts in the colchicine). For example, 0.612 mg of an ultrapure colchicine free base having a total impurity of 2 wt % (thus a purity of 98 wt %) contains 0.6 mgA ($0.612 \text{ mg} \times 0.98 = 0.6 \text{ mgA}$) of colchicine.

An "oral dosage form" means a unit dosage form for oral administration.

A "patient" means a human or non-human animal in need of medical treatment. Medical treatment can include treatment of an existing condition, such as a disease or disorder, prophylactic or preventative treatment, or diagnostic treatment. In some embodiments the patient is a human patient.

"Pharmaceutically acceptable" means that which is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" includes derivatives of colchicine, wherein the colchicine is modified by making acid or base addition salts thereof, and further refers to pharmaceutically acceptable solvates, including hydrates, and co-crystals of such compounds and such salts. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid addition salts of basic residues such as amines; alkali or organic addition salts of acidic residues; and the like, and combinations comprising one or more of the foregoing salts. The pharmaceutically acceptable salts include non-toxic salts and the quaternary ammonium salts of the colchicine. For example, non-toxic acid salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; other acceptable inorganic salts include metal salts such as sodium salt, potassium salt, cesium salt, and the like; and alkaline earth metal salts, such as calcium salt, magnesium salt, and the like, and combinations comprising one or more of the foregoing salts. Pharmaceutically acceptable organic salts includes salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, mesylic, esylic, besylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$ where n is 0-4, and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, $\text{N,N}'$ -dibenzylethylenediamine salt, and the like; and amino acid salts such as arginate, aspartate, glutamate, and the like; and combinations comprising one or more of the foregoing salts; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, $\text{N,N}'$ -dibenzylethylenediamine salt, and the like; and amino acid salts such as arginate, aspartate, glutamate, and the like;

8

and combinations comprising one or more of the foregoing salts. All forms of such derivatives of colchicine are contemplated herein, including all crystalline, amorphous, and polymorph forms. Specific colchicine salts include colchicine hydrochloride, colchicine dihydrochloride, and co-crystals, hydrates or solvates thereof.

"Pharmacokinetic parameters" describe the in vivo characteristics of an active agent (or a metabolite or a surrogate marker for the active agent) over time, such as plasma concentration (C), C_{max} , C_n , C_{24} , T_{max} , and AUC. " C_{max} " is the measured plasma concentration of the active agent at the point of maximum, or peak, concentration. " C_{min} " is the measured plasma concentration of the active agent at the point of minimum concentration. " C_n " is the measured plasma concentration of the active agent at about n hours after administration. " C_{24} " is the measured plasma concentration of the active agent at about 24 hours after administration. The term " T_{max} " refers to the time at which the measured plasma concentration of the active agent is the highest after administration of the active agent. "AUC" is the area under the curve of a graph of the measured plasma concentration of an active agent vs. time, measured from one time point to another time point. For example AUC_{0-t} is the area under the curve of plasma concentration versus time from time 0 to time t , where t can be the last time point with measurable plasma concentration for an individual formulation. The $\text{AUC}_{0-\infty}$ or $\text{AUC}_{0-\text{INF}}$ is the calculated area under the curve of plasma concentration versus time from time 0 to time infinity. In steady-state studies, $\text{AUC}_{0-\tau}$ is the area under the curve of plasma concentration over the dosing interval (i.e., from time 0 to time τ (tau), where tau is the length of the dosing interval. Other pharmacokinetic parameters are the parameter K_e or K_{el} , the terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve; $t_{1/2}$ the terminal elimination half-life, calculated as $0.693/K_{el}$; CL/F denotes the apparent total body clearance after administration, calculated as $\text{Total Dose}/\text{Total AUC}_{\infty}$; and V_{area}/F denotes the apparent total volume of distribution after administration, calculated as $\text{Total Dose}/(\text{Total AUC}_{\infty} \times K_{el})$.

"Adverse event" means any untoward medical occurrence in a patient administered an active agent and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the active agent, whether or not considered related to the active agent.

"Side effect" means a secondary effect resulting from taking an active agent. The secondary effect can be a negative (unfavorable) effect (i.e., an adverse side effect) or a positive (favorable) effect.

The most frequently reported adverse side effects to colchicine therapy are gastrointestinal, specifically diarrhea; abdominal pain with cramps; nausea; and vomiting. Less frequently or rarely reported adverse side effects associated with colchicine therapy include anorexia, agranulocytosis, allergic dermatitis, allergic reactions, alopecia, angioedema, aplastic anemia, bone marrow depression, myopathy, neuropathy, skin rash, thrombocytopenic disorder, and urticaria.

Determining that a patient experiences an adverse side effect can be performed by obtaining information from the patient regarding onset of certain symptoms which may be indicative of the adverse side effect, results of diagnostic tests indicative of the adverse side effect, and the like.

Ultrapure colchicine comprising low levels of individual impurities or total impurities is highly desirable as compared to conventionally available forms of colchicine. Currently,

commercially available forms of colchicine often comprise high levels of impurities. Depending on the source or the preparation process, colchicine may comprise some or all of the common impurities shown in Table 1.

TABLE 1

| Common Impurities | Chemical Name | Other common name |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| Impurity A | N-[(7S,12aS)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]formamide | N-deacetyl-N-formyl colchicine |
| Impurity B | (-)-N-[(7S,12aR)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide | Conformational isomer |
| Impurity C | N-[(7S,7bR,10aS)-1,2,3,9-tetramethoxy-8-oxo-5,6,7,7b,8,10a-hexahydrobenzo[a]cyclopenta[3,4]cyclobuta[1,2-c]cyclohepten-7-yl]-acetamide | β-Lumicolchicine |
| Impurity D | N-[(7S,12aS)-3-(β-D-glucopyranosyloxy)-1,2,10-trimethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide | Colchicoside |
| Impurity E | N-[(7S,12aS)-3-hydroxy-1,2,10-trimethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide | 3-O-demethyl colchicine |
| Impurity F | N-[(7S,12aS)-10-hydroxy-1,2,3-trimethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]acetamide | Colchicine |

In addition to the common impurities listed above, colchicine may also comprise N-[(7S,12aS)-2-hydroxy-1,3,10-trimethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide (“2-O-demethyl colchicine”) impurity. Some analytical methods cannot differentiate 2-O-demethyl colchicine from 3-O-demethyl colchicine.

In addition to the common impurities listed above, colchicine may also comprise other structurally unidentified impurities. In fact, conventional forms of colchicine may comprise as much as 5% of total impurities, determined chromatographically as described below. Such high levels of impurities in conventional colchicine pose several problems. The impurities may cause side effects in patients taking dosage forms comprising conventional colchicine. For example, N-deacetyl-N-formyl-colchicine (Impurity A, also known as Gloriosine) is tumorigenic and has been studied as an anticancer agent. Therefore reduction in the level of N-deacetyl-N-formyl colchicine found in convention colchicine is highly desirable. Additionally, high levels of impurities can also pose a regulatory challenge for pharmaceutical companies using conventional colchicine in products. For a pharmaceutical product comprising an active agent, the United States Food and Drug Administration (FDA) requires “qualification” or toxicity information for any impurity that is greater than the International Conference on Harmonization (ICH) qualification threshold of 0.15% per individual impurity in the active agent substance or 1.0% in the dosage form. Thus, there is a regulatory benefit for a pharmaceutical company to market pharmaceutical products comprising active agents comprising low levels of individual impurities or total impurities in the active agent substance as well as in the dosage form. As a result, for a pharmaceutical composition comprising colchicine, it is in the best interest of both the pharmaceutical company and the patient that impurities be minimized, if possible, in the colchicine and in colchicine compositions or dosage forms.

The ultrapure colchicine disclosed herein comprises no more than (NMT) about 3.0%; specifically NMT about 2.0%, or more specifically, NMT about 1.0%, or even more specifically NMT about 0.5% of total impurities. In one embodiment, “total impurities” includes the common impurities,

Impurities A through F, as well as all structurally unidentified impurities eluting within 1.5 times the retention time of colchicine using an HPLC method as described in more detail below. In another embodiment, other HPLC and HPLC methods, for example, as described in more detail below, can be used to quantify the level of total impurities.

The ultrapure colchicine may also comprise low levels of individual impurities. In one embodiment, the ultrapure colchicine comprises NMT about 2.0%, specifically NMT about 1.5%; more specifically NMT about 1.0%; or yet more specifically, NMT about 0.5%, or even more specifically, NMT about 0.15%, or still more specifically, NMT about 0.10%, of any individual impurity. The impurity can be Impurity A, Impurity B, Impurity C, Impurity D, Impurity E, Impurity F, or an unidentified impurity.

In an embodiment, the ultrapure colchicine comprises no more than (NMT) about 3.0% total impurities and NMT about 0.10% N-deacetyl-N-formyl colchicine.

In another embodiment, the ultrapure colchicine comprises NMT about 3.0% total impurities; NMT about 0.1% per individual impurity of Impurity A, Impurity C, Impurity D, and Impurity E; NMT about 0.15% Impurity F; and NMT about 2.0% of Impurity B.

Not wishing to be bound by theory, it is postulated that the conformational isomer, Impurity B, is in equilibrium with the active colchicine such that even after purification of the colchicine to about 0.5% Impurity B, the purified colchicine re-equilibrates to a level of Impurity B around about 1% to about 1.3%.

The level of an individual impurity or of total impurities in colchicine may be determined by any suitable analytical method known in the art. In one embodiment, the impurity levels are determined using a high performance liquid chromatography (HPLC) assay, for example, the HPLC method described in the Colchicine Official Monograph USP30/NF25, herein fully incorporated by reference.

Exemplary conditions for HPLC or ultra performance liquid chromatography (HPLC) assays that can be used for the impurity analysis of colchicine or of a colchicine pharmaceutical product are listed in Table 2.

TABLE 2

| Exemplary HPLC Conditions For Colchicine Purity Analysis | | | |
|----------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|----------------------------------------------|
| | USP30/NF25 Colchicine Official Monograph Method | HPLC Method | UPLC Method |
| Mobile phase | 0.5 Molar KH ₂ PO ₄ in Methanol:Water (65:45, v:v), pH adjusted to 5.5 with H ₃ PO ₄ | pH 7.2 10 mM Phosphate Buffer:methanol (MeOH) Gradient | pH 4.5 Ammonium Acetate Buffer:MeOH Gradient |
| Column | Octylsilyl silica gel, 4.6 mm × 25 cm, 5 micron | Zorbax SBC(18), 4.6 × 250 mm | Acquity GEH C18, 2.1 × 100 mm, 1.7 μm |
| Flow rate | 1.0 mL/min | 1.0 mL/min | 0.25 mL/min |
| Column Temp | Ambient | Ambient | 30 C. +/- 2 C. |
| Detection | 254 nanometers (nm) | 246 nm | 246 nm |
| Injection volume | 20 microliters (uL) | 75 uL | 7 uL |
| Sample Conc. | 0.006 mg/mL | 0.120 mg/ml | 0.012 mg/ml |
| Run time | 15 minutes (min) | 46 min | 25 min |

US 7,964,647 B2

11

When using one of the above HPLC conditions in Table 2 for colchicine purity analysis, the relative retention time (RRT) of an impurity can be calculated by the following formula:

$$\text{RRT of an impurity} = \text{RT of the impurity} / \text{RT of colchicine},$$

where RT stands for retention time of the impurity or the colchicine at the particular conditions used in the assay.

In one embodiment, using the HPLC method in Table 2, the retention time (RT) of colchicine is about 7 minutes and the relative retention times (RRTs) of the common impurities eluting within 1.5 times the retention time for colchicine are listed in Table 2A:

TABLE 2A

| Relative Retention Times (RRTs) of the Common Impurities | |
|----------------------------------------------------------|------|
| Impurity ID | RRT |
| N-deacetyl-N-formyl colchicine - Impurity A | 0.94 |
| Conformational isomer - Impurity B | 0.8 |
| β -Lumicolchicine - Impurity C | 1.2 |
| Colchicoside - Impurity D | 0.4 |
| 3-O-demethyl colchicine - Impurity E | 0.7 |

In one embodiment, the percent of a particular impurity is calculated by dividing the response (peak area) of the impurity peak by the sum of all responses (total peak area of all peaks, including the colchicine peak and all common and unidentified impurity peaks) eluting within 1.5 times the retention time for colchicine in the HPLC assay and multiplying the result by 100%.

In one embodiment, the level (%) of total impurities is calculated by dividing the sum of responses of any peaks other than that due to colchicine eluting within 1.5 times the retention time for colchicine by the sum of all responses eluting in the HPLC assay and multiplying the result by 100%.

An additional HPLC method for determining the level of impurities other than Impurity F in colchicine or in colchicine pharmaceutical products has been developed and validated for use as an alternative to the methods in Table 2 above. The method is shown in Table 3A below.

TABLE 3A

| Quantitative HPLC Method for determining all impurities other than impurity F in colchicine and colchicine pharmaceutical products. | |
|-------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| Quantitative HPLC Method for colchicine and colchicine products. | |
| Mobile phase | pH 4.5 Ammonium Acetate Buffer: methanol Gradient |
| Column | Waters XBridge C18, 250 mm x 4.6 mm, 5 μ m particle size |
| Flow rate | 0.9 mL/min |
| Column Temp | 10 \pm 3.5 C. (for column)/10 \pm 2 C. (for sample) |
| Detection | 246 nm |
| Injection volume | 75 μ L |
| Sample Conc. | 0.16 mg/ml |
| Run time | 60 min |

In the quantitative HPLC method of Table 3A, the retention time (RT) of colchicine is about 24 minutes and the relative retention times (RRTs) of the common impurities for colchicine are listed in Table 3B:

12

TABLE 3B

| Relative Retention Times (RRTs) of the Common Impurities | |
|----------------------------------------------------------|------|
| Impurity ID | RRT |
| N-deacetyl-N-formyl colchicine - Impurity A | 0.93 |
| Conformational isomer - Impurity B | 0.82 |
| β -Lumicolchicine - Impurity C | 1.76 |
| Colchicoside - Impurity D | 0.18 |
| 3-O-demethyl colchicine - Impurity E | 0.52 |
| 2-O-demethyl colchicine | 0.54 |
| Gamma-Lumicolchicine | 1.37 |

The percentage of individual impurities in the sample solution is calculated as follows:

$$\% \text{ Impurity} = \frac{r_i}{r_s} \times \frac{W_s(\text{mg})}{100 \text{ mL}} \times \frac{6.0 \text{ mL}}{100 \text{ mL}} \times \frac{2.0 \text{ mL}}{100 \text{ mL}} \times P \times \left(\frac{100 - \% RS_s - \% W_s}{100} \right) \times \frac{200 \text{ mL}}{SW(\text{mg}) \times \left(\frac{100 - \% RS_u - \% W_u}{100} \right)} \times \frac{100\%}{RRF}$$

Where:

r_s =The area response of the Colchicine peak in the Working Standard Solution.

r_i =The area response of the impurity peak in the Sample Solution

P=% Purity of the Colchicine Reference Standard divided by 100%.

SW=Weight of Sample taken for Sample Preparation

W_s =Weight of Colchicine in the Stock Standard Solution

RRF=Relative Response Factor for specified and unspecified impurities, 1.0

% RS_{su} =Percent of Residual Solvents in the Colchicine Standard/Sample

% W_{su} =% Water in the Colchicine Standard/Sample

To date, the impurity colchicine (Impurity F or 10-O-Demethyl Colchicine "10-DMC") has been typically analyzed by a qualitative calorimetric test described in the Colchicine Official Monograph USP30/NF25 using ferric chloride solution, rather than chromatographically. The standard for acceptable levels of Impurity F has been absence of production of a definite green color in a solution of colchicine.

However, a chromatographic method has been developed for the determination of Impurity F (Colchicine or 10-O-Demethyl Colchicine "10-DMC"). The chromatographic conditions are as follows:

TABLE 3C

| HPLC parameters for Colchicine determination | |
|----------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| HPLC System: | HPLC equipped with a pump, auto sampler, variable wavelength detector and a suitable data acquisition system. |
| Column: | Phenomenex Gemini C18 150 mm x 4.6 mm 5 μ m, 110 Å |
| Detection: | 245 nm |
| Flow Rate: | About 1.5 mL/min |
| Injection Volume: | 50 μ L |
| Temperature: | Column: 10° C. \pm 3.5° C. Sample: 5° C. \pm 2° C. |
| Needle Rinse Setting: | Double |
| Needle Wash: | Water:Acetonitrile (50:50) |
| Digital Filter Response: | 1.0 |

TABLE 3C-continued

| HPLC parameters for Colchicine determination | |
|----------------------------------------------|------------------------------------------------------------------------------|
| Sampling Rate: | 5.0 |
| Resolution: | 1.2 |
| Mobile Phase: | pH 4.5 Buffer Solution:Acetonitrile (75:25) |
| Run Time: | About 7 minutes for Standard About 20 minutes for first Blank and Samples |

The LQL level for 10-DMC in this method is 0.776304 $\mu\text{g/mL}$. The amount of 10-DMC expressed in percent of Colchicine is calculated as follows:

$$\% \text{ Purity} = \frac{r_i}{r_s} \times \frac{W_s(\text{mg}) \times P}{400 \text{ mL}} \times \left(\frac{100 - \% RS_s - \% W_s}{100} \right) \times \frac{3.0 \text{ mL}}{100 \text{ mL}} \times \frac{50 \text{ mL}}{W_u(\text{mg}) \times \left(\frac{100 - \% RS_u - \% W_u}{100} \right)} \times \frac{100\%}{RRF}$$

Where:

r_i =The peak area response of 10-DMC in the Sample Solution

r_s =The peak area response of Colchicine in the Working Standard Solution

W_s =The weight of Colchicine in the Stock Standard Preparation

W_u =The weight of Colchicine in the Sample Preparation

P =Standard purity factor expressed as labeled (% Purity/100)

$\% RS_{s/u}$ =Percent of Residual Solvents in the Colchicine Standard/Sample

$\% W_{s/u}$ =% Water in the Colchicine Standard/Sample

RRF =Relative response factor for 10-DMC=0.88

Ultrapur colchicine may be obtained by various purification methods starting from colchicine-containing botanical extracts, conventional colchicine, or other partially-purified forms of colchicine. In some embodiments, the colchicine is purified from a botanical source. The botanical source can be any capable of providing colchicine, conventional or ultrapure, in quantities suitable for commercial pharmaceutical product manufacture

The literature from 1884-1997 on methods of isolation and purification of colchicine from various botanic sources, including for example *C. autumnale* corms or leaves and species of *Gloriosa* has been reviewed. (Kiselev & Yavich, 1991, "METHODS OF ISOLATING ALKALOIDS OF THE COLCHICINE SERIES"; Plenum Publishing Co., English translation of article from Khimiya Prirodnykh Soedinenii, No. 5, pp. 592-600, September-October, 1990.). Kiselev & Yavich also review reports in the literature of impurities detected in colchicine stored for various times, as follows. In an article published in 1944 it was reported that chromatography of colchicine corresponding to the requirements of the USP of that time showed the presence of 5% of impurities and various amount of individual impurities. An article published in 1952 reported that colchicine meeting the requirements of the USP contained about 4% of 3-demethylcolchicine. A 1953 article reported 1.5% of N-formyldeacetylcolchicine isolated and the presence of other accompanying alkaloids in a pharmacopeial sample of colchicine. An investigation of a commercial sample by high-resolution liquid chromatography, published in 1986, reported finding 93.4% of colchicine, 2.9% of N-formyldeactylcholchicine, 1.8% of 17-hydroxy-colchicine, and 0.84% of an unknown substance.

Walaszik et al. describes a process of incorporating carbon 14 into *C. autumnale* plants and isolating radioactive colchicine from the radioactive plants (See Walaszik et al., Science (1952) 116:225-227). However, the level of impurities in the isolated radioactive colchicine is not disclosed.

The purification methods disclosed herein produce ultrapure colchicine comprising very low levels of total impurities or individual impurities. In one embodiment, ultrapure colchicine may be obtained from conventional colchicine obtained commercially or produced using solvent extraction of appropriate botanic material as described in more detail below.

In one embodiment, conventional colchicine may be obtained by isolating colchicine from a colchicine chloroform extract. The extract is washed with a mixture of purified water, sodium hydroxide solution, sodium chloride solution and acetic acid. The washed extract is filtered and the resulting concentrate is distilled in two steps, first using methanol, and second using ethyl acetate. The resulting distillate is crystallized. Ethyl acetate can be used to isolate and wash the crystallized colchicine, which is then dried to yield conventional colchicine. The conventional colchicine comprises more than about 3.0% but no more than 5% total impurities.

The conventional colchicine may be used directly in a colchicine composition comprising a pharmaceutically acceptable excipient. It may also be used for further purification to obtain ultrapure forms of colchicine.

In one embodiment of a method of making ultrapure colchicine, the conventional colchicine may be subjected to column chromatography to obtain a purified colchicine concentrate, distilling the purified colchicine concentrate to obtain a colchicine distillate, and crystallizing ultrapure colchicine from the colchicine distillate. The method can further comprise washing the crystallized ultrapure colchicine with a solvent and drying. The ultrapure colchicine comprises no more than about 3.0% of total impurities.

In one embodiment, the column chromatography is carried out using methylene chloride as solvent on a column of neutral alumina. Other solvents or chromatographic media may be used, provided that impurities are removed from the conventional colchicine to the desired level. In another embodiment, distillation of the purified colchicine concentrate is carried out using ethyl acetate. Other organic solvents can be used, provided that impurities are removed from the purified colchicine concentrate. In yet another embodiment, the solvent used to wash the crystallized ultrapure colchicine is ethyl acetate.

In another embodiment, a method of making ultrapure colchicine comprises subjecting colchicine comprising more than about 3.0% total impurities to neutral alumina column chromatography to obtain a colchicine concentrate; distilling the colchicine concentrate with ethyl acetate to obtain a colchicine distillate; crystallizing a purified colchicine from the colchicine distillate in ethyl acetate; washing the purified colchicine with ethyl acetate to obtain a washed purified colchicine; and drying the washed purified colchicine to obtain ultrapure colchicine, wherein the ultrapure colchicine comprises no more than about 3.0% total impurities.

In one embodiment, the ultrapure colchicine obtained in any of the above methods comprises no more than about 2.0% total impurities. In another embodiment, the ultrapure colchicine comprises no more than about 1.5% total impurities. In another embodiment, the ultrapure colchicine comprises no more than about 1.0% total impurities. In another embodiment, the ultrapure colchicine comprises no more than about 0.5% total impurities. In yet another embodiment, the ultrapure colchicine comprises no more than about 0.5% per indi-

US 7,964,647 B2

15

vidual impurity of Impurity A, Impurity B, Impurity C, Impurity D, Impurity E, or Impurity F. In still another embodiment, the ultrapure colchicine comprises no more than about 0.15% per individual impurity of Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F. In another embodiment, the ultrapure colchicine comprises no more than about 1.0% of total unidentified impurities. In yet another embodiment, the ultrapure colchicine comprises no more than about 0.5% of total unidentified impurities. In yet another embodiment, the ultrapure colchicine comprises no more than 1.0% of Impurity B, and no more than 0.1% per individual impurity of any of Impurity A, Impurity C, Impurity D, Impurity E, and Impurity F.

The above methods of making ultrapure colchicine are only examples of suitable methods for its preparation.

The colchicine compositions disclosed herein comprise colchicine and a pharmaceutically acceptable excipient. In one embodiment, the colchicine composition comprises 0.1 wt % to 10 wt % colchicine, specifically 0.1 wt % to 5 wt % colchicine. In one embodiment, the colchicine in the colchicine compositions is ultrapure colchicine. The compositions comprising ultrapure colchicine are stable and provide enhanced safety to patients taking the compositions because the patients are ingesting fewer impurities. In particular, the colchicine compositions contain substantially lower levels of the tumorigenic compound N-deacetyl-N-formyl colchicine.

The pharmaceutically acceptable excipient in the colchicine composition may be a filler (or diluent), a binder, a disintegrant, a lubricant, or a combination comprising two or more of the foregoing excipients.

In one embodiment, the pharmaceutically acceptable excipient comprises a filler. Exemplary fillers may be one or more compounds which are capable of providing compactability and good flow. Exemplary fillers include microcrystalline cellulose, starch, lactose, sucrose, glucose, mannitol, maltodextrin, sorbitol, dextrose, silicic acid, dibasic calcium phosphate, or a combination comprising at least one of the foregoing fillers. Exemplary lactose forms include lactose monohydrate, NF (Fast Flo), lactose spray-dried monohydrate, and lactose anhydrous. Exemplary microcrystalline cellulose (MCC) include, for example, AVICEL® PH101 and AVICELL® PH102, which are commercially available from FMC Biopolymer, Philadelphia, Pa. Exemplary dibasic calcium phosphates include dihydrated and anhydrous dibasic calcium phosphates. In one embodiment, the filler is a combination of microcrystalline cellulose and lactose monohydrate, NF (fast flo).

When present, the amount of the filler in the composition may be about 10 wt % to about 99 wt %, or more specifically, about 30 wt % to about 90 wt %, or even more specifically, about 50 wt % to about 90 wt %, or still more specifically, about 70 wt % to about 85 wt %, based on the total weight of the composition. In one embodiment, the total amount of the filler is about 82 wt %, based on the total weight of the composition.

In one embodiment, the pharmaceutically acceptable excipient comprises a binder. Binders may be used to impart cohesive qualities to a formulation, for example, a tablet formulation, and thus ensure that the tablet remains intact after compaction. Exemplary binders include starches (for example, Starch 1500® or pregelatinized starch), alginates, gelatin, carboxymethylcellulose, sugars (for example, sucrose, glucose, dextrose, and maltodextrin), polyethylene glycol, waxes, natural and synthetic gums, polyvinylpyrrolidone, and cellulosic polymers (for example, microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, and hydroxyethyl cellulose) and

16

combinations comprising one or more of the foregoing binders. In one embodiment, the binder is starch, or more specifically, pregelatinized starch.

When present, the amount of the binder may be about 10 wt % to about 99 wt %, or more specifically, about 10 wt % to about 50 wt %, or even more specifically, about 10 wt % to about 20 wt %, based on the total weight of the composition. In one embodiment, the amount of the binder is about 14 wt %, based on the total weight of the composition.

In another embodiment, the pharmaceutically acceptable excipient comprises a disintegrant. Disintegrants are used to facilitate disintegration or "breakup" of a composition, for example, a tablet, after administration. Exemplary disintegrants include sodium starch glycolate, sodium crosscarmellose (cross-linked carboxy methyl cellulose), crosslinked polyvinylpyrrolidone (PVP-XL), anhydrous calcium hydroxy phosphate, agar-agar, potato or tapioca starch, alginic acid, or a combination comprising one or more of the foregoing disintegrants.

When present, the disintegrant may be present in an amount of about 0.1 to 30 wt %, or more specifically, about 1 to 20 wt %, or even more specifically, about 1 to 10 wt %, based on the total weight of the composition. In one embodiment, the amount of the disintegrant is about 4.5 wt %, based on the total weight of the composition.

In another embodiment, the pharmaceutically acceptable excipient comprises a lubricant. Generally, a lubricant is added just before tableting, and is mixed with the rest of the composition for a minimum period of time to obtain good dispersal. Exemplary lubricants include magnesium stearate, calcium stearate, zinc stearate, stearic acid, talc, glyceryl behenate, polyethylene glycol, polyethylene glycol, polyethylene oxide, sodium lauryl sulfate, magnesium lauryl sulfate, sodium oleate, sodium stearyl fumarate, DL-leucine, colloidal silica, or a combination comprising one or more of the foregoing lubricants. In one embodiment, the lubricant is magnesium stearate, calcium stearate, or zinc stearate.

When present, the lubricant may be present in an amount of about 0.01 wt % to about 10 wt %, or more specifically, about 0.1 wt % to about 5 wt %, or even more specifically, about 0.1 wt % to about 1 wt %, based on the total weight of the composition. In one embodiment, the amount of the lubricant is about 0.6 wt %, based on the total weight of the composition.

If desired, the composition may optionally comprise small amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, or pH buffering agents, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, sodium lauryl sulfate, dioctyl sodium sulfosuccinate, and polyoxyethylene sorbitan fatty acid esters.

In one embodiment, a composition comprises an ultrapure colchicine, wherein the ultrapure colchicine comprises no more than 3.0% of total impurities, a filler, a binder, and a disintegrant.

In another embodiment, a colchicine composition comprises about 0.6 mgA colchicine; about 14 mg pregelatinized starch; about 22 mg microcrystalline cellulose; about 4.3 mg sodium starch glycolate; about 0.6 mg magnesium stearate; and an amount of lactose monohydrate such that the colchicine composition has a total weight of about 100 mg. In one embodiment, the colchicine in the colchicine composition is ultrapure colchicine.

In an embodiment, a colchicine composition comprises colchicine; and a pharmaceutically acceptable excipient; wherein the colchicine composition comprises no more than about 3.5% total impurities, specifically no more than about

US 7,964,647 B2

17

3.0% total impurities, more specifically no more than about 2.0% total impurities, or yet more specifically no more than about 1.0% total impurities. In some of these embodiments, specific limitations on the levels of individual impurities are also met by the colchicine composition. In addition to containing no more than a particular maximum level of total impurities, the colchicine composition can comprise not more than about 0.42% Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F, and not more than about 2.0% Impurity B; specifically not more than about 0.2% Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F, and not more than about 1.5% Impurity B; and more specifically not more than about 0.15% Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F, and not more than about 1.1% Impurity B. In one embodiment the colchicine composition comprises no more than 3.5% total impurities, no more than 0.42% Impurity A, and no more than 2.0% Impurity B. The pharmaceutically acceptable excipient can be one or more discussed previously herein.

In one embodiment, a colchicine composition comprises colchicine and a pharmaceutically acceptable excipient; wherein the colchicine composition comprises no more than about 3.5% total impurities. In some embodiments, the colchicine composition comprises ultrapure colchicine and total impurities in the ultrapure colchicine comprise no more than about 3.0%, or specifically no more than about 2.0%, or more specifically no more than about 1.5%, or yet more specifically, no more than about 1.0%. In addition to containing no more than a particular maximum level of total impurities, the ultrapure colchicine in the colchicine composition can comprise not more than about 0.15% Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F, and not more than about 2.0% Impurity B; specifically not more than about 0.10% Impurity A, Impurity C, Impurity D, or Impurity E; not more than about 0.15% Impurity F, and not more than about 1.5% Impurity B. In one embodiment the colchicine composition comprises ultrapure colchicine comprising no more than 0.10% Impurity A, no more than about 0.15% Impurity F, and no more than 2.0% Impurity B. The pharmaceutically acceptable excipient can be one or more discussed previously herein.

In one embodiment, a colchicine composition comprises colchicine; a filler; a binder; and a disintegrant; wherein the colchicine composition comprises no more than about 3.5% total impurities. In some embodiments, the colchicine composition comprises ultrapure colchicine and total impurities in the composition comprise no more than about 3.5%, or specifically no more than about 3.0%, more specifically no more than about 2.0%, or yet more specifically, no more than about 1.0%; with individual impurity levels of not more than about 0.42% for Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F, and not more than about 2.0% for Impurity B. or specifically with individual impurity levels of not more than about 0.10% for Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F, and not more than about 2.0% for Impurity B.

In one embodiment, the percent total impurities in the composition is determined in an HPLC assay as described in Colchicine Official Monograph USP30/NF25 as 100% times a sum of responses of any peaks other than that due to colchicine, eluting within 1.5 times the retention time for colchicine, relative to a sum of responses of all peaks eluting within 1.5 times the retention time for colchicine and the percent of an individual impurity in the composition is determined in an HPLC assay as described in Colchicine Official Monograph USP30/NF25 as 100% times the responses of the impurity

18

peak relative to a sum of responses of all peaks eluting within 1.5 times the retention time for colchicine.

In yet another embodiment, the percent total and/or individual impurities in the composition is determined in an HPLC assay or HPLC assay in accordance with the methods described in Table 2 or Table 3A or 3C.

In one embodiment, any of the colchicine compositions described above is in the form of a tablet. As used herein, the term "tablet" means a compressed pharmaceutical dosage form of any shape or size. The tablets described herein may be obtained from the compositions comprising colchicine and a pharmaceutically acceptable excipient. Any of the colchicine compositions can be in the form of any other dosage form known in the art, specifically, any oral dosage form, for example a capsule.

Either wet or dry granulation of a colchicine composition may be used prior to compressing the composition into tablets, or direct compression can be used.

In one embodiment, wet granulation is used to prepare wet granules comprising colchicine. A granulating liquid is used in wet granulation process. Both aqueous and non-aqueous liquids may be used as the granulating liquid. In one embodiment, the granulating liquid is an aqueous liquid, or more specifically, de-ionized water. In an embodiment, the colchicine is ultrapure colchicine.

The amount of the granulating liquid used may depend on many factors, for example, the type of the granulating liquid, the amount of the granulating liquid used, whether a hygroscopic excipient is used, the nature of the active agent, and the active agent loading. In one embodiment, the amount of the granulating liquid is in the range of about 5 wt % to about 50 wt %, or more specifically, about 10 wt % to about 40 wt %, based on the dry weight of the granulating particles prior to wet granulation.

Wet granulation time is generally about 5 to 60 minutes. In one embodiment, the colchicine particles and suitable excipients are mixed with the granulating liquid for a period of about 5 to about 45 minutes, or more specifically, about 5 to about 35 minutes. For a small scale, the mixing time is about 1 to about 20 minutes, or more specifically, 3 to 10 minutes. Wet granulation is generally performed at temperatures between about 20° C. to about 35° C., or more specifically, at room temperature (about 25° C.).

Any equipment may be used to contact the granulating liquid with the colchicine and the excipients as long as uniform distribution of the granulating liquid is achieved. For example, small-scale production can be achieved by mixing and wetting the ultrapure colchicine and the excipients in mortars or stainless steel bowls, while for larger quantities, V-blenders with intensifier bars, planetary mixers, rotary granulators, high shear granulators, and fluid-bed granulation equipment may be used. In one embodiment, the granulator is a high shear granulator.

In one embodiment, a method of making a colchicine composition comprises wet granulating colchicine with a pharmaceutically acceptable excipient to obtain wet granules, and mixing the granules with a second excipient to obtain a colchicine composition. In one embodiment, the pharmaceutically acceptable excipient comprises a mixture of a filler and a binder. In another embodiment, the mixture of the filler and the binder comprises pregelatinized starch, lactose monohydrate, and microcrystalline cellulose. In another embodiment, de-ionized water is used as the granulating liquid. In some embodiments, the colchicine is ultrapure colchicine. In an embodiment, the second excipient mixed with the granules is a disintegrant. The colchicine compositions can contain about

US 7,964,647 B2

19

0.1 wt % to about 10 wt %, or more specifically, about 0.1 wt % to about 1 wt %, of colchicine, based on the total weight of the colchicine composition.

In an embodiment, the method of making a composition comprises wet granulating colchicine with a pharmaceutically acceptable excipient to obtain wet granules, and mixing the granules with a disintegrant to obtain a colchicine composition. In some embodiments, the method further comprises drying the mixture. In another embodiment, the wet granules are dried to obtain dried granules; and then the dried granules are mixed with a disintegrant to obtain the composition. In another embodiment, the dried granules can be milled to obtain milled granules before mixing the milled dried granules with the disintegrant. In one embodiment, greater than 50% of the milled granules pass through a 45 micron sieve or mesh screen. The method can further comprise mixing the colchicine composition with a lubricant to obtain a tableting blend or compressing the tableting blend to obtain a tablet. The method can further comprise coating the tablet.

In one embodiment, a method of making a colchicine composition comprises wet granulating ultrapure colchicine with a pharmaceutically acceptable excipient to obtain wet granules; drying the wet granules to obtain dried granules; milling the dried granules to obtain milled granules; and mixing the milled granules with a disintegrant to obtain the composition. The ultrapure colchicine can comprise no more than about 3.0% total impurities, with no more than about 0.10% Impurity A, no more than about 0.15% Impurity F, and no more than about 2.0% Impurity B.

In another embodiment, a method of making a colchicine tablet comprises wet granulating colchicine with a pharmaceutically acceptable excipient to obtain wet granules; drying the wet granules to obtain dried granules; milling the dried granules to obtain milled granules; mixing the milled granules with a disintegrant to obtain the composition; mixing the composition with a lubricant to obtain a tableting blend; and compressing the tableting blend to obtain a colchicine tablet.

In some embodiments, the wet granules are dried to obtain dried granules before mixing with a second excipient, for example a disintegrant. Wet granules can be dried by any suitable means to remove the granulating liquid and to form dried granules containing colchicine and the pharmaceutically acceptable excipient. The conditions and duration of drying depend on factors such as the liquid used and the weight of the granulating particles. Examples of suitable drying methods include, but are not limited to, tray drying, forced air drying, microwave drying, vacuum drying and fluid bed drying.

The extent of drying may be determined by visual observation and manual manipulation, as is common in the art. The extent of drying may also be determined by sieve analysis, moisture measurements, such as loss on drying (LOD) or other suitable methods. In one embodiment, wet granules are dried until the granules lose less than 5 weight percent (wt %), or more specifically, 3 wt % upon drying at 105° C. based on the total weight of the dried granules prior to drying (or LOD of less than 3 wt %).

After drying, dried granules may be mixed directly with an excipient, for example, a filler, a binder, a disintegrant, or a lubricant, for further processing. Alternatively, dried granules may optionally be subjected to additional processing steps prior to mixing with the excipient. For example, dried granules may be sized to reduce particle size prior to mixing with an excipient. Exemplary sizing operations include milling or sieving. Any suitable equipment for reducing the particle size may be used in the present invention. In one embodiment, the

20

dried granules are milled to obtain milled granules so that at least 50% of the milled granules pass through a 45 micron mesh screen.

Suitable excipients may be added extragranularly and mixed with the granules to form colchicine compositions. As used herein, the term “extragranular” or “extragranularly” means that the referenced material, for example, a suitable excipient, is added or has been added as a dry component after wet granulation. In one embodiment, a disintegrant and a lubricant, in that sequence, are added extragranularly to the granules and mixed to form a blend. The blend may be encapsulated directly into capsule shells, for example, hard gelatin shells, to form capsule formulations. Alternatively, the blend may be compressed into tablets. In some embodiments, the granules are dried granules or milled, dried granules. In some embodiments, the colchicine is ultrapure colchicine.

Mixing can be carried out for a sufficient time to produce homogeneous mixtures or blends. Mixing may be accomplished by blending, stirring, shaking, tumbling, rolling, or by any other method to achieve a homogeneous blend. In some embodiments, the components to be mixed are combined under low shear conditions in a suitable apparatus, such as a V-blender, tote blender, double cone blender or any other apparatus capable of functioning under low shear conditions.

The homogenous mixtures or blends are then compressed using any method suitable in the industry.

The colchicine tablets prepared from the above described methods exhibit acceptable physical characteristics including good friability and hardness. The colchicine tablets disclosed herein have friability in the range of about 0% to 3%, specifically about 0 to 1%, more specifically 0% to 0.5%

The colchicine tablet can be coated. Coating the tablet may be performed by any known process. A coating for the colchicine tablet disclosed herein can be any suitable coating, such as, for example, a functional or a non-functional coating, or multiple functional or non-functional coatings. By “functional coating” is meant to include a coating that modifies the release properties of the total formulation, for example, a sustained-release coating. By “non-functional coating” is meant to include a coating that is not a functional coating, for example, a cosmetic coating. A non-functional coating can have some impact on the release of the active agent due to the initial dissolution, hydration, perforation of the coating, etc., but would not be considered to be a significant deviation from the non-coated composition.

In one embodiment, the tablet is coated with a non-functional coating. The coating can be a white or colored OPADRY® or OPADRY® II (both available from Colorcon, West Point, Pa.), optionally with additional ingredients such as carnauba wax, plasticizers, opacifiers, colorants, and antioxidants. In one embodiment, the coating comprises OPADRY® II and carnauba wax.

In an embodiment, a colchicine composition comprises about 0.6 mgA colchicine; about 12 to about 16 mg pregelatinized starch; about 20 to about 24 mg microcrystalline cellulose; about 3.9 to about 4.7 mg sodium starch glycolate; about 0.5 to about 0.7 mg magnesium stearate; and an amount of lactose monohydrate such that the colchicine dosage form has a total weight of about 100 mg. In some embodiments the colchicine composition comprises about 0.6 mgA colchicine, about 14 mg pregelatinized starch, about 22 mg microcrystalline cellulose, about 4.3 mg sodium starch glycolate, about 0.6 mg magnesium stearate, and an amount of lactose monohydrate such that the colchicine dosage form has a total weight of about 100 mg. The colchicine composition can be in the form of a tablet. In some embodiments the tableted

US 7,964,647 B2

21

composition further comprises a coating comprising Opadry® II and carnauba wax. In an embodiment, the colchicine is ultrapure colchicine.

In one embodiment, a colchicine composition comprising ultrapure colchicine is formulated into an immediate-release formulation. By “immediate-release” is meant a conventional or non-modified release in which greater than or equal to about 75% of the active agent is released within two hours of administration, specifically within one hour of administration.

Active agent release from a pharmaceutical formulation can be analyzed in various ways. One exemplary test is in vitro dissolution. A dissolution profile is a plot of the cumulative amount of active agent released from a formulation as a function of time. A dissolution profile can be measured utilizing the Drug Release Test <724>, which incorporates standard test USP 26 (Test <711>). A profile is characterized by the test conditions selected such as, for example, apparatus type, shaft speed, temperature, volume, and pH of the dissolution medium. More than one dissolution profile may be measured. For example, a first dissolution profile can be measured at a pH level approximating that of the stomach, and a second dissolution profile can be measured at a pH level approximating that of one point in the intestine or several pH levels approximating multiple points in the intestine.

In one embodiment, the immediate-release colchicine composition exhibits a dissolution profile such that at ten minutes after combining the composition with 500 ml of purified water at 37° C.±0.5° C. according to USP 28<711> Apparatus 1 (basket), 100 rpm speed, about 90 to about 100 wt. % of the total amount of active agent is released; specifically at 30 minutes after combining the composition with the dissolution medium, about 95 to about 100 wt. % of the total amount of colchicine is released; and more specifically at one hour after combining the composition with the dissolution medium, about 98 to about 100 wt. % of the total amount of colchicine is released.

Potency, or the amount of active colchicine present in a batch of colchicine, can be determined as described in Colchicine Official Monograph USP 30/NF 25 by comparing an assay sample to a colchicine reference standard (e.g., USP Colchicine RS) sample in the chromatographic assay described in Colchicine Official Monograph USP30/NF25. The quantity of active colchicine in the assay sample, in mg, of C₂₂H₂₅NO₆ is calculated by the formula: 10C (r_u/r_s), in which C is the concentration, in µg per mL, of the colchicine reference standard sample; and r_u and r_s are the colchicine peak responses obtained from the assay sample and the colchicine reference standard sample, respectively.

In another embodiment, potency of a batch of colchicine can be determined using the HPLC Potency assay described in the table below by comparing an assay sample to a colchicine reference standard.

| HPLC Potency Assay B | |
|----------------------|------------------------------------------------------------------|
| Mobile phase | 50 mM Potassium Phosphate Buffer:methanol (45:55), pH 5.5 ± 0.05 |
| Column | Phenomenex Luna C8(2), 4.6 mm × 25 cm, 5 µm |
| Flow rate | 1.0 mL/min |
| Column Temperature | Ambient |
| Detection | 254 nm |
| Injection volume | 20 µL |
| Sample Conc. | 0.120 mg/ml |
| Run time | 15 min |

22

The quantity, in percentage, of C₂₂H₂₅NO₆ (active colchicine), on an anhydrous, solvent free basis, in the colchicine assay sample is calculated by the formula:

$$\% \text{ Purity} = \frac{r_u}{r_s} \times \frac{W_s(\text{mg}) \times P \times \left(\frac{100 - M_s - S_s}{100} \right)}{500 \text{ ml}} \times \frac{PV(\text{ml})}{VF(\text{ml})} \times \frac{VF_1(\text{ml})}{SW(\text{mg}) \times \left(\frac{100 - M_u - S_u}{100} \right)} \times \frac{VF_2(\text{ml})}{PV_1(\text{ml})} \times 100$$

Where:

- r_u=The peak area of colchicine in the working sample solution
- r_s=The peak area of colchicine in the working standard solution
- W_s=The weight of colchicine in the standard preparation
- P=Standard purity factor expressed as labeled % Purity
- M_s=Moisture factor in standard expressed as % Moisture
- S_s=Solvent factor in standard expressed as % Solvent
- PV=Pipet volume used for the working standard solution
- VF=Volumetric flask used for the working standard solution
- SW=Sample weight in the stock sample solution
- VF₁=Volumetric flask used for the stock sample solution
- M_u=Moisture factor in sample expressed as % Moisture
- S_u=Solvent factor in sample expressed as % Solvent
- VF₂=Volumetric flask used for the working sample solution
- PV₁=Pipet volume used for the working sample solution.

Alternatively, potency of a batch of colchicine can be determined by comparing an assay sample to a colchicine reference standard in yet another HPLC assay as follows:

| HPLC Potency Assay C | |
|------------------------|-------------------------------------------------------------------------------------------------------------|
| HPLC System: | HPLC equipped with a pump, autosampler, variable wavelength detector and a suitable data acquisition system |
| Column Information: | Phenomenex Gemini C18 150 × 4.6 mm 5 µm 110 Å |
| Detection: | 245 nm |
| Flow Rate: | 1.5 mL/minute |
| Injection Volume: | 20 µL |
| Column Temperature: | 30° C. ± 3° C. |
| Needle Rinse Setting: | Double |
| Sampling Rate: | 2.0 |
| Resolution: | 1.2 |
| Filter Response: | 1.0 |
| Digital Filter: | Enabled |
| Needle Wash/Seal Wash: | Methanol:Water (50:50) |
| Run Time: | About 15 minutes |
| Mobile Phase: | pH 6.0 Buffer Solution (50 mM of Potassium phosphate and 4 mM of EDTA):Methanol (60:40) |
| Diluent: | Water:Methanol (75:25) |

The percent purity of Colchicine (C₂₂H₂₅NO₆), on an anhydrous, solvent-free basis, is calculated as follows:

$$\% \text{ Assay} = \frac{r_u}{r_s} \times \frac{W_s(\text{mg}) \times P}{50 \text{ mL}} \times \left(\frac{100 - \% RS_s - \% W_s}{100} \right) \times$$

-continued

$$\frac{5.0 \text{ mL}}{100 \text{ mL}} \times \frac{500 \text{ mL}}{W_u(\text{mg}) \times \left(\frac{100 - \% RS_u - \% W_u}{100} \right)} \times 100\%$$

Where:
r_u=The peak area response of Colchicine in the Sample Solution.
r_s=The peak area response of Colchicine in the Working Standard Solution.
W_s=The weight of Colchicine in the Stock Standard Preparation.
W_u=The weight of Colchicine in the Sample Preparation.
P=Standard purity factor expressed as labeled (% Purity/100).
% RS_{s/u}=Percent of Residual Solvents in the Colchicine Standard/Sample.
% W_{s/u}=% Water in the Colchicine Standard/Sample.

Disclosed herein are also methods of treatment and dosing regimens.

The compositions comprising ultrapure colchicine disclosed herein may be used to treat or prevent a patient's condition such as acute gouty arthritis, chronic gouty arthritis, acute pericarditis, asthma, Behçet's disease, cancer, chronic gout (prophylaxis), pseudogout cystic disease comprising polycystic kidney disease or cystic fibrosis, demyelinating disease of central or peripheral origin, Dupuytren's contracture, Familial Mediterranean fever, glaucoma, idiopathic pulmonary fibrosis, idiopathic thrombocytopenic purpura, inflammatory disorder comprising rheumatoid arthritis, lentiviral infection, multiple sclerosis, postpericardiotomy syndrome, primary amyloidosis, primary biliary cirrhosis, proliferative vitreoretinopathy, pyoderma gangrenosum, recurrent pericarditis, or a condition in need of enhanced bone formation or bone mineral density.

The traditional dose of colchicine used to treat or prevent an attack of acute gouty arthritis has been about 1.0 to about 1.2 mgA of colchicine, for example, two tablets each comprising about 0.6 mgA colchicine. This dose may be followed by one unit of the composition every hour, or two units every two hours, until pain is relieved or until diarrhea ensues ("diarrheal dose"). After the initial dose, it is sometimes sufficient to take about 0.6 mgA colchicine every two or three hours. The dosing should be stopped if there is gastrointestinal discomfort or diarrhea. (Opiates may be needed to control diarrhea.) In subsequent attacks, the patient should be able to judge his medication requirement accurately enough to stop short of his diarrheal dose. The total amount of colchicine needed to control pain and inflammation during an attack has been believed to be in the range from about 4 mgA to about 8 mgA. An interval of three days between colchicine courses is advised in order to minimize the possibility of cumulative toxicity.

In one embodiment, a method of treating acute gouty arthritis comprises administering two colchicine dosage forms each comprising about 0.6 mgA colchicine at the onset of the acute gout attack, followed by one dosage form every hour for m hours, wherein the value of m is 1 to 8. In one embodiment, the value of m is 1 to 6. In another embodiment, the value of m is 1 (total of 3 tablets). In yet another embodiment, the value of m is 6 (total of 8 tablets). The colchicine in the dosage form can be ultrapure colchicine. The dosage form can be any oral dosage form, specifically a tablet.

In another embodiment, a method of treating Familial Mediterranean Fever comprises administering 1/2 dosage form to four dosage forms daily, each dosage form comprising

ing about 0.6 mgA colchicine (total of about 0.3 to about 2.4 mgA colchicine daily). In another embodiment, a method of prophylactically treating chronic gout comprises administering one-half dosage form, one dosage form, two dosage forms, or three dosage forms, each dosage form comprising about 0.6 mgA of colchicine, daily. In another embodiment, a method of treating Behçet's disease comprises administering one dosage form comprising about 0.6 mgA of colchicine twice daily (total of 2 dosage forms). The colchicine in the dosage form can be ultrapure colchicine. The dosage form can be any oral dosage form, specifically a tablet.

In one embodiment, a method of treating patients with some but not all of the symptoms of acute gout, chronic gout (prophylaxis), or pseudogout, where the patients are not clinically or informally diagnosed with one of these diseases, comprises administering one or more of the dosage forms comprising about 0.6 mgA of colchicine. The colchicine in the dosage form can be ultrapure colchicine.

The invention should not be considered limited to these particular conditions for combining the components and it will be understood, based on this disclosure that the advantageous properties can be achieved through other conditions provided the components retain their basic properties and substantial homogeneity of the blended formulation components of the formulation is otherwise achieved without any significant segregation.

The following examples further illustrate the invention but should not be construed as in any way limiting its scope. In particular, the processing conditions are merely exemplary and can be readily varied by one of ordinary skill in the art.

EXAMPLES

Example 1

Exemplary Ultrapure Colchicine

As discussed above, ultrapure colchicine with reduced levels of individual and total impurities was desired by the inventors for formulation into a new dosage form in order to minimize potential adverse reactions from the impurities in patients taking the dosage form and to reduce the expense of qualification testing during the approval process for marketing the new dosage form. Batches of conventional colchicine were previously obtained from Sanmar Specialty Chemicals Limited (Berigari, India). Conventional colchicine can be further purified to form ultrapure colchicine meeting the following impurity specifications:

TABLE 4

| Purity Specifications for an exemplary batch of Ultrapure Colchicine | | |
|----------------------------------------------------------------------|----------|-------|
| Impurity, Common name | Impurity | NMT % |
| N-deacetyl-N-formyl colchicine | A | 0.10 |
| Conformational isomer | B | 1.0 |
| β-Lumicolchicine | C | 0.10 |
| Colchicoside | D | 0.10 |
| 3-O-demethyl colchicine | E | 0.10 |
| Total Impurities | | 2.0 |

Ultrapure colchicine was prepared to meet the purity specifications in Table 4 as described below.

First, conventional colchicine was obtained from a colchicine chloroform extract. The extract was washed with a mixture of purified water, sodium hydroxide solution, sodium chloride solution and acetic acid. The washed extract was

25

filtered and the resulting concentrate was distilled in two steps, first using methanol, and second using ethyl acetate. The resulting distillate was crystallized. Ethyl acetate was used to isolate and wash the crystallized colchicine, which was then dried, resulting in the conventional colchicine. This process is also referred to herein as the “old process”.

Second, the conventional colchicine was then subjected to column chromatography on neutral alumina using methylene chloride as solvent. The resulting concentrate was distilled using ethyl acetate, crystallized, isolated and washed using ethyl acetate, and dried, resulting in ultrapure colchicine. This method of generating conventional colchicine, followed by the additional chromatography purification step is also referred to herein as the “new process”.

The impurity levels of the lot of ultrapure colchicine and two lots of conventional colchicine were analyzed using the USP30/NF25 Colchicine Official Monograph HPLC method (“USP method”) described in Table 2 above. The impurity levels are shown in Table 5.

TABLE 5

| Colchicine Lot | Impurity Level, % | | | |
|---------------------------|---------------------------------------------|------------------------------------|-------------------------------|------------------|
| | N-Deacetyl-N-formyl colchicine - Impurity A | Conformational Isomer - Impurity B | Total Unidentified Impurities | Total Impurities |
| Ultrapure (RD0600164) | ND* | 0.5 | ND* | 0.5 |
| Conventional-1 (RD060075) | 2.1 | 0.6 | ND* | 2.7 |
| Conventional 2 (RD060055) | 2.2 | 0.6 | ND* | 2.8 |

*ND—None detected.

Table 5 shows that ultrapure colchicine has fewer impurities than each of the conventional colchicine lots. Total impurities of the Ultrapure Lot using the USP method were about 0.5%. On the other hand, total impurities of conventional Lots #1 and 2 were about 2.7% and 2.6%, respectively.

Determined impurity levels may differ depending on the test method used. Table 5B contrasts the determined levels of the conformational isomer, Impurity A (N-deacetyl-N-formyl colchicine), and total impurities for the three colchicine lots using the three methods described in Table 2. The three methods show a maximum absolute variability in the percent determined of 0.8% for N-deacetyl-N-formyl colchicine, of 0.5% for conformational isomer, and 0.7% for total impurities.

TABLE 5B

Levels of impurities in colchicine lots determined using methods of Table 2.

| Lot name (Lot #) | Purification Process | Conformational Isomer | | | N-deacetyl-N-formyl colchicine | | | Total Impurities | | |
|---------------------------|----------------------|-----------------------|-------------|------------|--------------------------------|-------------|------------|------------------|-------------|------------|
| | | UPLC Method | HPLC Method | USP Method | UPLC Method | HPLC Method | USP Method | UPLC Method | HPLC Method | USP Method |
| Conventional-1 (RD060055) | Old | 0.9 | 0.8 | 0.6 | 3.0 | 2.5 | 2.2 | | 3.5 | 2.8 |
| Conventional 2 (RD060075) | Old | 0.9 | 0.8 | 0.6 | 2.7 | 2.3 | 2.1 | | 3.2 | 2.7 |
| Ultrapure (RD0600164) | New | 0.9 | 1.0 | 0.5 | ND* | ND | ND | | 1.1 | 0.5 |

*ND, none detected.

26

Regardless of the testing method used for measuring these impurity levels, the impurity levels for ultrapure colchicine manufactured using the new process remains below the specifications set forth in Table 4.

The ultrapure colchicine of the present invention was prepared to meet the organic volatile impurity specifications (“residual solvents”) in Table 6 as described below. The residual solvents are determined using USP <467> test method. In addition to the known and existing solvents, specifications were also set for residual solvent peaks that were seen in HPLC assay testing as described in Tables 2, 3A, or 3C, which solvents are not expected or previously existing for the residual solvent test methods for colchicine or were not identifiable.

TABLE 6

| Specifications for Organic Volatile Impurities | |
|------------------------------------------------|--------------|
| Organic volatile | NMT |
| Chloroform | 100 ppm |
| Methanol | 3000 ppm |
| Methylene Chloride | 600 ppm |
| Ethanol | 5000 ppm |
| Ethyl Acetate | 6.0% |
| Ethyl Propionate | 5000 ppm |
| Propyl Acetate | 5000 ppm |
| Others | 500 ppm each |

Example 2

Stable Tablets Comprising Ultrapure Colchicine

Stable colchicine compositions comprising the ultrapure colchicine described in Example 1 were manufactured using the following process. Ultrapure colchicine as described in Example 1 was dissolved in purified water. Pregelatinized starch (Starch® 1500), lactose monohydrate, NF (Fast Flo), and microcrystalline cellulose, NF (Avicel PH101) were placed in a 150-liter high shear granulator and mixed. The aqueous ultrapure colchicine solution was added to the granulator while mixing. The wet granules were dried in an oven at 50° C. until the loss on drying of the material was less than 3 wt %. The dried granules were milled through a Fitzmill equipped with a 1A screen.

The milled granules were charged into a 5 cubic foot Gemco Double Cone Blender and blended with screened sodium starch glycolate, NF (GLYCOLYS®). Then,

US 7,964,647 B2

27

screened magnesium stearate, NF was added to the blender. Blending was continued and a final tableting blend was made. This final tableting blend was compressed into core tablets. These core tablets were film-coated with OPADRY®II purple and carnauba wax. The composition of the ultrapure colchicine tablets is shown in Table 7.

TABLE 7

| Ingredient | Amount Per Tablet, mg |
|-----------------------------------------------|-----------------------|
| Ultrapure Colchicine | 0.6 ¹ |
| Pregelatinized starch, NF (Starch 1500) | 14.0 |
| Lactose Monohydrate, NF (Fast Flo) | Varies ² |
| Microcrystalline Cellulose, NF (Avicel PH101) | 21.6 |
| Sodium Starch Glycolate, NF (GLYCOLYS) | 4.3 |
| Magnesium Stearate, NF | 0.6 |
| Total core tablet | 100 |

28

TABLE 7-continued

| Ingredient | Amount Per Tablet, mg |
|------------------------------|-----------------------|
| OPADRY II Purple (#40L10039) | 4.0 |
| Carnauba Wax | 0.01 |

¹Colchicine amount is shown in units of mgA, adjusted for purity of the lot of colchicine.

²Amount adjusted, depending on the actual amount of the colchicine lot added, to maintain an overall core tablet weight of 100 mg.

As a comparison, the lot of conventional colchicine designated in Example 1 as "conventional-2" was substituted in place of ultrapure colchicine in the same tablet formulation shown in Table 7. The same process of making the tablets as described above was used.

The impurities in the tablet comprising the ultrapure colchicine and that comprising the conventional colchicine were analyzed using the HPLC method described in Table 2 above. The impurity levels of both colchicine tablets are shown in Table 8.

TABLE 8

| | | Impurity Content, % | | | | |
|------------------------|----------------|---------------------|---------------------------------------------|----------------------------------|--------------------------|------------------|
| Colchicine Product Lot | Colchicine Lot | Process | N-Deacetyl-N-formyl colchicine (Impurity A) | Conformation Isomer (Impurity B) | Total Unknown Impurities | Total Impurities |
| A | Ultrapure | New | ND* | 1.1 | 0.1 | 1.2 |
| B | Conventional-2 | Old | 2.3 | 1.2 | ND* | 3.6 |

*ND—None detected.

It can be seen from Table 8 that the tablet comprising the ultrapure colchicine has less total impurities than that comprising the conventional colchicine.

The colchicine composition comprising ultrapure colchicine at 6 month stability time points under conditions of 25° C./60% relative humidity and 40° C./60% relative humidity exhibits impurity content ranges of Not Detected to about 0.1% for Impurity A, less than about 1.0% for total unknown impurities compared to a colchicine composition comprising conventional colchicine which exhibits impurity content of greater than about 1.5 for Impurity A and greater than about 2.0% for total unknown impurities when tested under the same conditions.

Table 9 below provides data on impurity levels and stability of impurity levels of colchicine composition batches manufactured using ultrapure and conventional colchicine, and impurity levels for two lots of commercially available COL-PROBENECID® tablets (Watson Laboratories), an FDA-approved combination dosage form comprising colchicine and probenecid.

TABLE 9

| Material | Lot | Colchicine | | Conformational Isomer | | N-Deacetyl peak | |
|--------------------------------------------------|---------|----------------------|-------------------------------|-----------------------|-------------|-----------------|-------------|
| | | purification Process | Conditions of Stability Study | UPLC Method | HPLC Method | UPLC Method | HPLC Method |
| COL-PROBENECID® (Probenecid/Colchicine) Tablets† | L6C0395 | N/A | N/A | 0.8 | — | 2.2 | — |
| | L6M1440 | N/A | N/A | 0.8 | — | 2.5 | — |
| Colchicine Product Lot | B | Old process | room temp, at release | 0.9 | 1.2 | 2.8 | 2.3 |
| | | | 12 mo 25 C./60% RH | 0.9 | 0.9 | 2.7 | 2.6 |
| | | New process | room temp, at release | 1.0 | 1.2 | ND | ND |
| | | | 6 mo 25 C./60% RH | 1.0 | 0.8 | ND | ND |
| | C | New process | 6 mo 40 C./75% RH | 1.0 | 1.1 | ND | ND |
| | | | room temp, at release | 1.0 | 1.1 | ND | ND |
| | | New process | 6 mo 25 C./60% RH | 0.9 | 0.9 | ND | ND |
| | | | 6 mo 40 C./75% RH | 1.0 | 1.1 | ND | ND |

US 7,964,647 B2

29

30

TABLE 9-continued

| Material | Lot | Colchicine | | Conformational Isomer | | N-Deacetyl peak | |
|----------|-----|----------------------|-----------------------------------------------------------------|-----------------------|-------------------|-----------------|----------------|
| | | purification Process | Conditions of Stability Study | UPLC Method | HPLC Method | UPLC Method | HPLC Method |
| | D | New process | room temp, at release 6 mo 25 C./60% RH 6 mo 40 C./75% RH | 1.0 1.0 0.9 | 1.1 1.0 1.1 | ND ND ND | ND ND ND |

—, not analyzed;

†Commercially available;

N/A, not applicable;

ND, none detected.

For comparison, several lots of an FDA-approved colchicine-probenecid combination dosage form and various unapproved commercial colchicine dosage forms were tested for levels of impurities using the HPLC method of Table 2. Results are shown in the tables below.

| Impurities in FDA-Approved Colchicine/Probenecid Combination Product | | | | |
|----------------------------------------------------------------------|---------|---------|---------|---------|
| Watson Laboratories Colchicine/Probenecid Tablets | | | | |
| Impurity | L7G1085 | L7G1085 | L7G1087 | L7E0808 |
| Conformational Isomer | 1.0% | 1.0% | 0.8% | 1.0% |
| N-deacetyl-N-formyl colchicine | 2.0% | 2.0% | 1.5% | 2.0% |
| Largest Unknown | 0.1% | 0.1% | 0.1% | 0.1% |
| Total Impurities | 3.1% | 3.1% | 2.4% | 3.2% |

Summary of Impurities in Marketed Colchicine Products with Batches of colchicine tablets using ultrapure colchicine

| Impurity | Marketed Colchicine Products | | Product Lots with Ultrapure Colchicine |
|--------------------------------|------------------------------|---------|----------------------------------------|
| | Minimum | Maximum | Maximum |
| Conformational Isomer | 0.8% | 1.1% | 1.1% |
| N-deacetyl-N-formyl colchicine | 1.3% | 2.7% | ND |
| Largest Unknown | 0.1% | 1.7% | 0.3% |
| Total Impurities | 2.4% | 5.3% | 1.4% |

ND = none detected

The total impurities found in ultrapure colchicine and colchicine products comprising ultrapure colchicine are significantly lower compared to the approved and unapproved, marketed colchicine products. In addition, the maximum total impurities value observed by testing 14 approved or unapproved marketed products was 5.3%; while the maximum

| Impurities in Unapproved Colchicine Products | | | | | | |
|----------------------------------------------|--------------|----------|----------|--------------|-------------|----------------|
| Impurity | West-Ward | | | Vision | | |
| | 62303A* | 63842A | 63843A | C07003 | C07049 | C07058 |
| Exp Date | January-2009 | May-2011 | May-2011 | January-2009 | August-2009 | September-2009 |
| Conformational Isomer | 1.1/0.9% | 0.9% | 0.9% | 1.1/0.8% | 0.9% | 0.9% |
| N-deacetyl-N-formyl colchicine | 2.5/2.6% | 2.0% | 1.8% | 1.3/1.3% | 2.7% | 2.6% |
| Largest Unknown | 1.7/1.6% | 0.5% | 0.3% | 0.1/0.1% | 0.1% | 0.3% |
| Total Impurities | 5.3/5.3% | 3.5% | 3.1% | 2.5/2.3% | 3.8% | 4.0% |

| Impurity | Qualitest | | Akyma | |
|--------------------------------|-----------|-----------|-------------|--------------|
| | T105G07A | T107G07A | T108G07A | 3A5246004* |
| Exp Date | July-2010 | July-2010 | August-2010 | January-2008 |
| Conformational Isomer | 1.0% | 0.9% | 0.9% | 1.1/0.9% |
| N-deacetyl-N-formyl colchicine | %1.4 | 1.3% | 1.3% | 1.4/1.5% |
| Largest Unknown | 0.3% | 0.2% | 0.2% | 0.2/0.1% |
| Total Impurities | 2.7% | 2.7% | 2.6% | 2.9/2.5% |

*Values from two separate analyses reported

US 7,964,647 B2

31

value seen to date in inventive ultrapure colchicine product batches was 1.4%. This represents a 75% reduction in total impurities.

Of particular significance, the level of the known impurity, N-deacetyl-N-formyl-colchicine (Impurity A, also known as Gloriosine) has been reduced from levels exceeding 2% to levels to undetectable levels that comply with the ICH Q3A (R2) qualification threshold of 0.15% for an active agent. Gloriosine is tumorigenic and has been studied as an anti-cancer agent. Purification of conventional colchicine to obtain ultrapure colchicine has effectively reduced all individual impurity levels in the colchicine to substantially reduce exposure of patients to this tumorigenic impurity.

Example 3

Therapeutic Effects of Ultrapure Colchicine Formulation

The therapeutic effect of the ultrapure colchicine formulation containing 0.6 mgA of colchicine obtained in Example 2 is evaluated in a clinical study that is a multicenter, randomized, double-blind, placebo-controlled, parallel group, 1-week, dose comparison study designed to evaluate the efficacy of ultrapure colchicine in treating an acute gout attack (acute gouty arthritic attack) in patients with acute gout. A sufficient number of patients are screened to enroll and randomize 300 patients (100 patients per treatment group) who meet the criteria of the American College of Rheumatology (ACR) for acute arthritis of gout. The primary objective of the study is to demonstrate the efficacy of colchicine in an acute gout attack (gouty flare) based on pain reduction after 24 hours as a measure of response. Secondary objectives of the study are to compare low-dose and standard-dose dosing regimens of colchicine with respect to pain, time to response and complete pain relief, interference with sleep, and signs and symptoms of inflammation and to determine the safety of colchicine when administered in the two different dosing regimens.

Description of Study

The study will consist of three distinct phases and the number of visits to the study clinic will vary depending on conditions pertaining to an individual patient's acute gout flare experienced in the study as described below. The Pre-Flare Phase will consist of up to two visits to the study clinic (with additional interim visits for clinical laboratory testing every 3 months until acute gout flare onset): Visit 1 (Screening) and Visit 2 (Randomization). The Flare Phase will not include a visit to the study clinic. The Post-Flare Phase will consist of up to three visits to the study clinic: Visit 3 (as soon as possible [ASAP] up to 48 hours post-flare onset; if a patient cannot complete Visit 3 in the first 48 hours post-flare onset, Visit 3 will be waived and the patient should return to the clinic for Visit 4), Visit 4 (>48 to 96 hours post-flare onset in patients who took at least one dose of study drug and in patients who did not qualify for treatment with study drug during the Flare Phase but did not complete Visit 3), and Visit 5 (7 days post-flare onset to be conducted in patients who took at least one dose of study drug and whose acute gout flare was still ongoing at Visit 4). For those patients in whom the acute gout flare is not resolved at Visit 5 (based on the judgment of the Investigator) or in whom there is an unresolved AE or clinically significant treatment-emergent laboratory abnormality, there will be one additional follow-up visit 14 days post-flare onset (Visit 6).

When a patient develops an acute gout flare, the patient will call the trained personnel at the Gout Flare Call Center (avail-

32

able 24 hours/day throughout the duration of the study). The patient will be queried regarding any changes in his/her medical health and concomitant medication use since the time of randomization. In order to establish if the patient's acute gout flare will be eligible for treatment with study drug, a standardized questionnaire will be used to document that the patient has all of the following signs/symptoms of the affected joint(s): swelling, erythema, marked tenderness, and pain. In addition, a patient must have at least one of the following: rapid onset of maximum pain within the prior 4 to 12 hours, decreased range of motion in the joint, warmth, or other symptom similar to a prior gout flare. Patients will be asked to rate the pain severity for each joint affected by the acute gout flare by using a study diary. Patients must have at least one joint affected by an acute gout flare with a pain assessment of ≥ 4 on the PI-NRS at the onset of the acute gout flare during the Flare Phase prior to taking study drug. If signs and symptoms of an acute gout flare are confirmed and the gout flare is considered eligible for treatment with study drug, the patient will also be instructed to begin taking study drug and to continue completing the patient diary. Patients will be instructed to stop taking study drug and to call the investigational site if at any time they experience a severe gastrointestinal event while taking study drug. The Gout Flare Call Center will call the patient in 24 hours from the onset of the acute gout flare to ensure that the patient has completed the patient diary, including assessments for pain at 24 hours.

In the event that the Gout Flare Call Center determines that the patient does not qualify for treatment with study drug, the patient may be asked to call back in 1 hour for re-assessment. Patients who do not qualify for treatment with study drug may seek alternative therapy without prejudice to further study participation should another acute gout flare occur.

The Gout Flare Call Center will contact patients on a monthly basis beginning 1 month after randomization to study drug. These contacts will continue until the patient has an acute gout flare or study completion, whichever occurs first. The purpose of these contacts is to re-educate patients about study participation.

Post-Flare Phase:

Visit 3: After developing an acute gout flare, whether eligible for treatment with study drug or not, all patients will return to the clinic as soon as possible after acute gout flare onset for clinical assessments. If a patient cannot complete Visit 3 in the first 48 hours post-flare onset, Visit 3 will be waived and the patient should return to the clinic for Visit 4. For patients whose acute gout flare was deemed eligible for treatment with study drug and at least one dose of study drug was taken, Investigators will examine the patient and complete clinical assessments, patient diaries will be collected, the patient will be queried for concomitant medication use and Adverse Events (AEs), and the study drug blister pack will be collected. For patients whose acute gout flare was deemed not eligible for treatment with study drug by the Gout Flare Call Center, continued eligibility for the study will be confirmed by the Investigator based on review of the inclusion and exclusion criteria as well as the responses to the standardized questionnaire and examination of the patient. Patient diaries will be collected and patients will be queried for concomitant medication use and AEs.

Visit 4: The second Post-Flare Phase visit is to be conducted >48 to 96 hours following acute gout flare onset. It will take place in patients who took at least one dose of study drug and also in those patients who did not qualify for treatment with study drug during the Flare Phase but did not complete Visit 3. For patients whose acute gout flare was deemed eligible for treatment with study drug and at least one dose of

US 7,964,647 B2

33

study drug was taken, Investigators will examine the patient and complete clinical assessments, patient diaries will be collected, patients will be queried for concomitant medication use and AEs, and the study drug blister pack will be collected (if not previously collected). Patients who took at least one dose of study drug and whose acute gout flare is still ongoing at Visit 4 will return to the clinic for a final visit (Visit 5) 7 days post-flare onset; however, if their acute gout flare is resolved at Visit 4, final study assessments, including collection of samples for laboratory safety and a complete physical examination, will be performed at Visit 4. For patients whose acute gout flare was deemed not eligible for treatment with study drug by the Gout Flare Call Center who did not have a Visit 3, continued eligibility for the study will be confirmed by the Investigator based on review of the inclusion and exclusion criteria as well as the responses to the standardized questionnaire and examination of the patient. Patient diaries will be collected and patients will be queried for concomitant medication use and AEs.

Visit 5/Early Termination: The final visit for the study will take place 7 days after the acute gout flare onset in patients who took at least one dose of study drug and whose acute gout flare was still ongoing at Visit 4. Patients will be examined and clinical assessments will be made. A complete physical examination will be conducted. Samples for clinical laboratory testing will be collected. Patient diaries will be collected and patients will be queried for concomitant medication use and AEs. The study drug blister pack will be collected (if not previously collected).

Visit 6/Follow-up: For those patients in whom the acute gout flare is not resolved at Visit 5 (based on the judgment of the Investigator) or in whom there is an unresolved AE or clinically significant treatment-emergent laboratory abnormality, there will be one additional follow-up visit 14 days post-flare onset (Visit 6).

For inclusion in the study, a patient must be 18 years of age or older, must present with a confirmed diagnosis of gout consistent with the criteria of the ACR, and must have experienced ≥ 2 acute gouty arthritic attacks in the 12 months prior to randomization. Patients on urate-lowering therapy must be on a stable dose and schedule with no changes in therapy for 4 weeks prior to randomization and expected to remain on a stable regimen during study participation.

Patients with acute polyarticular gout (>4 joints); taking colchicine routinely; with a known hypersensitivity to colchicine; with a history of myocardial infarction, unstable angina, cerebrovascular events, or coronary artery bypass grafting; with active myeloid leukemia, obstructive gastrointestinal cancer, or metastatic cancer; with chronic renal dysfunction, with chronic hepatic dysfunction are excluded from the study. Patients using systemic corticosteroid, cyclosporine, adalimumab, etanercept, infliximab, anakinra, abatacept, mycophenolate, azathioprine, or chronic use of non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, tramadol, and other analgesics such as opiates at screening are also be excluded.

The three treatment groups in this study are two ultrapure colchicine tablets (1.2 mgA) administered at the onset of an acute gout attack followed by one tablet (0.6 mgA) after one hour and one placebo tablet every hour thereafter for 5 hours (the "low" dose regimen); two ultrapure colchicine tablets (1.2 mgA) administered at the onset of an acute gout attack followed by one tablet (0.6 mgA) every hour for six (6) hours (the "standard" dose regimen); or two placebo tablets at the onset of an acute gout attack followed by one placebo capsule every hour thereafter for 6 hours (the "placebo" regimen).

34

Efficacy assessment will be made based on patient and Investigator inputs. Patients will record pain severity and sleep interference on a study diary. The severity of pain for each joint affected by the acute gouty arthritic attack will be rated on an 11-point pain intensity numerical rating scale (PI-NRS) that ranges from 0 ("no pain") to 10 ("worst possible pain"). Recordings are to be made prior to each dose of study drug, i.e., pre-treatment with study drug and for the first 8 hours following start of treatment, and every 8 hours thereafter (while awake) until symptoms disappear or 72 hours have passed since the first dose of study drug was taken, whichever occurs first. The patient's pain assessment of each affected joint as reported by the patient at pre-treatment with study drug and at 24 hours post-start of study drug will be documented by a central Study Center to be used in the event the patient fails to provide data on his/her study diary for either of these two key time points. In the morning upon awakening, the patient is to rate sleep interference due to the acute gout flare in the study diary on an 11-point scale that ranges from 0 ("pain did not interfere with sleep") to 10 ("pain completely interfered; patient was unable to sleep"). Investigators will provide clinical assessments in the clinic at all Post-Flare Phase study visits, and at medically necessary intervening visits. For these assessments, each of the patient's joints affected by the acute gouty arthritic attack will be examined and signs and symptoms of inflammation will be rated (erythema [absent, present, or not assessable], swelling [0, "none" to 3, "severe"], and tenderness to touch [0, "none" to 3, "severe"]). At the final clinic visit, the Investigator will also provide a global assessment of response to treatment ranging from 0 ("excellent") to 4 ("none").

The primary efficacy variable is response to treatment in the target joint, based on patient self-assessment of pain at 24 hours post-dose. The target joint is identified during data analysis as that joint affected by the acute gout flare with the highest baseline pain score on the patient diary. Ties among maximum joint scores for an individual are resolved by random selection. A responder is one who provides both a pre-treatment and valid 24-hour pain score and achieves a $\geq 50\%$ reduction in pain score at the 24-hour post-dose assessment relative to the pre-treatment score and does not use rescue medication. Patients who use rescue medication, discontinue prior to the 24-hour post-dose assessment, or do not achieve a $\geq 50\%$ reduction in pain score at the 24 hour post-dose assessment relative to the pre-treatment score are deemed non-responders.

The secondary efficacy variables are assessments of magnitude of pain reduction, time to response, time to complete pain relief, and interference with sleep as recorded on patient diaries by the patient. Signs and symptoms of inflammation per Investigator's clinical assessments of the target joint are evaluated. Time to drop out (use of rescue medications) is also evaluated. Investigator global assessment of response to treatment is assessed.

The primary efficacy analysis will be based on an Intent-to-Treat (ITT) population, defined as all patients who were randomized, contacted the Gout Flare Call Center, took at least one dose of study drug, and had one subsequent contact. The Per Protocol (PP) population is defined as the subset of the ITT population confirmed by the Investigator as continuing to meet all major inclusion and exclusion criteria and initiating treatment within 12 hours of the onset of the acute gout flare. Analyses will also be made on an Evaluable patient population with an Evaluable patient defined as one who, in addition to being included in the PP population, completed the randomized treatment course. The ITT population will be used for the evaluation of safety.

US 7,964,647 B2

35

Statistical tests for efficacy analysis are two-tailed with an alpha significance level of 0.05.

For primary efficacy analysis, the number of responders in the standard-dose colchicine group and the placebo group, as defined for the primary efficacy variable, will be compared using the Mantel-Haenszel chi-square test stratified on study site. The comparison of the standard-dose colchicine and placebo groups of the ITT population is the primary comparison of interest. The sensitivity to alternate definitions of response (based both on magnitude of reduction from baseline as well as time point) will be evaluated as secondary endpoints. As additional sensitivity analyses, these tests will also be repeated for the PP and Evaluable populations if the sample sizes differ from the overall ITT population by more than 10%.

For secondary efficacy analysis, the number of responders in the low-dose colchicine group will be compared to placebo and also to standard-dose colchicine using the Mantel-Haenszel chi-square test stratified on study site. Change in pain intensity, interference with sleep, time to 50% reduction in pain, and time to complete pain relief will be analyzed as continuous variables using analysis of covariance with study site, treatment group, and site by treatment interaction as independent variables for change in pain intensity and interference with sleep, with baseline score as a covariate. For the Investigator's clinical assessment of inflammation (erythema, swelling, and tenderness to touch) and Investiga-

36

will be conducted at the final clinic visit (Visit 4 or Visit 5). Vital signs and body weight will be measured at each Post Flare visit (Visit 3 and 4 or 5). For those patients in whom there is an unresolved AE or clinically significant treatment emergent laboratory abnormality, there will be one additional follow up visit 14 days post flare onset (Visit 6).

Safety analysis will be performed by coding adverse events using a standardized medical dictionary and the incidence summarized by treatment group; tabulations will be prepared of all AEs as well as by relationship and by severity. Adverse events resulting in termination and events meeting regulatory criteria for seriousness will also be tabulated separately. Descriptive statistics (mean, median, standard deviation, and range) of clinical laboratory testing results and vital sign measurements will be generated for each treatment group and change from the most recent value prior to onset of the acute gout flare calculated; no inferential testing will be performed. Treatment emergent abnormalities on physical examination will be tabulated and listed by treatment group. By patient listings of all safety data and concomitant medication use will be generated.

Study Results

The following data were obtained in general accordance with the above protocol.

Out of 813 patients screened, 575 were randomized to treatment with 185 patients having a gouty flare and receiving study drug. The intent-to-treat population consisted of 184 patients (52 received standard dose, 74 received low dose and 58 received placebo).

| Number of Responders Based on Target Joint Pain Score at 24 Hours Post First Dose | | | | | | |
|-----------------------------------------------------------------------------------|------------------------|-------------------|---------------------------------------|---------------------------------|---------------------------------|--|
| Colchicine Dose | | Placebo | Odds Ratio (95% Confidence Intervals) | | | |
| Low (N = 74) N (%) | High (N = 52) N (%) | (N = 58) N (%) | Low vs. Placebo | High vs. Placebo | High vs. Low | |
| 28 (37.8) | 17 (32.7) | 9 (15.5) | 3.31 (1.41, 7.77) P = 0.0046 | 2.64 (1.06, 6.62) P = 0.0343 | 0.80 (0.38, 1.68) P = 0.5529 | |

tor's global assessment of response to treatment, the treatment groups will be compared using the Mantel-Haenszel chi-square test stratified on study site.

Safety assessments will be made based on patient and Investigator inputs. Patients will be initially screened in the clinic for inclusion by review of medical history and concomitant medication use, physical examination, measurement of vital signs (oral temperature, sitting radial or brachial pulse rate, respiratory rate, and sitting blood pressure), body weight, and clinical laboratory testing (serum biochemistry, complete blood count, and urinalysis). After randomization, clinical laboratory tests, concomitant medication use, medical history and current complaints (AE) will be reviewed every 3 months until an acute gout flare occurs in order to ensure continued eligibility. Compliance with key inclusion/exclusion criteria (based on intervening medical history and concomitant medication use) will be reconfirmed by the Gout Flare Call Center prior to authorizing the start of study drug. Following the start of study drug, patients will record any severe gastrointestinal AEs on their diaries and these will be recorded in the Case Report Form (CRF) at each clinic visit. Full physical examinations and clinical laboratory testing

| Cumulative Distribution of Degree of Percent Improvement for Target Joint Pain Score at 24 Hours Post First Dose | | | | |
|---------------------------------------------------------------------------------------------------------------------|---------------|--------------|------------------|--|
| Colchicine Dose | | | | |
| % Improvement | High (N = 52) | Low (N = 74) | Placebo (N = 58) | |
| >=0% | 52 (100.0%) | 74 (100.0%) | 58 (100.0%) | |
| >=10% | 32 (61.5%) | 47 (63.5%) | 24 (41.4%) | |
| >=20% | 29 (55.8%) | 45 (60.8%) | 21 (36.2%) | |
| >=30% | 21 (40.4%) | 39 (52.7%) | 17 (29.3%) | |
| >=40% | 21 (40.4%) | 36 (48.6%) | 14 (24.1%) | |
| >=50% | 19 (36.5%) | 30 (40.5%) | 10 (17.2%) | |
| >=60% | 15 (28.8%) | 24 (32.4%) | 7 (12.1%) | |
| >=70% | 10 (19.2%) | 20 (27.0%) | 4 (6.9%) | |
| >=80% | 9 (17.3%) | 15 (20.3%) | 3 (5.2%) | |
| >=90% | 6 (11.5%) | 9 (12.2%) | 2 (3.4%) | |
| >=100% | 6 (11.5%) | 8 (10.8%) | 2 (3.4%) | |

US 7,964,647 B2

37

38

| Treatment Response Based on at Least a 2-Unit Reduction in Target Joint Pain Score at 24 Hours and 32 Hours Post First Dose | | | | | | |
|-----------------------------------------------------------------------------------------------------------------------------|--------------------------|--------------|------------------|--------------------------------------|---------------------------------|---------------------------------|
| Hours Post First Dose | Number (%) of Responders | | | Treatment Comparisons | | |
| | Colchicine Dose | | | (Odds Ratio and 95% CI) ¹ | | |
| | High (N = 52) | Low (N = 74) | Placebo (N = 58) | High vs. Placebo | Low vs. Placebo | High vs. Low |
| 24 | 18 (34.6) | 32 (43.2) | 10 (17.2) | 2.54 (1.04, 6.18) p = 0.0368 | 3.66 (1.61, 8.32) p = 0.0015 | 0.69 (0.33, 1.45) p = 0.3298 |
| 32 | 20 (38.5) | 34 (45.9) | 10 (17.2) | 3.00 (1.24, 7.24) p = 0.0126 | 4.08 (1.80, 9.27) p = 0.0005 | 0.74 (0.36, 1.51) p = 0.4033 |

¹The p-value is from the unstratified Pearson chi-square test.

| Target Joint Pain at Baseline, 24 Hours and 32 Hours Post First Dose, and Change from Baseline (LOCF) - ITT Population | | | | | | | |
|------------------------------------------------------------------------------------------------------------------------|------------|------------------|-----------------|---------------------|------------------------------------|--------------------|--------------|
| Time Point | Statistic | Colchicine Dose | | | Treatment Comparisons ¹ | | |
| | | High (N = 52) | Low (N = 74) | Placebo (N = 58) | High vs. Placebo | Low vs. Placebo | High vs. Low |
| 24 Hours Post First Dose | | | | | | | |
| Baseline | Mean (SD) | 6.9 (1.59) | 6.9 (1.72) | 6.8 (1.44) | -1.3 | -1.5 | 0.2 |
| | Median | 7.0 (4, 10) | 7.0 (4, 10) | 7.0 (4, 10) | p = 0.0145 | p = 0.0055 | p = 0.7540 |
| | (Mix, Max) | | | | | | |
| Change | Mean (SD) | -2.0 (2.93) | -2.2 (3.46) | -0.7 (2.77) | | | |
| | Median | -2.0 (-9, 4) | -2.0 (-9, 5) | -0.0 (-8, 4) | | | |
| | (Mix, Max) | | | | | | |
| 32 Hours Post First Dose | | | | | | | |
| Baseline | Mean (SD) | 6.9 (1.59) | 6.9 (1.72) | 6.8 (1.44) | -1.6 | -1.6 | 0.1 |
| | Median | 7.0 (4, 10) | 7.0 (4, 10) | 7.0 (4, 10) | p = 0.0057 | p = 0.0038 | p = 0.9238 |
| | (Mix, Max) | | | | | | |
| Change | Mean (SD) | -2.3 (3.05) | -2.4 (3.59) | -0.7 (2.95) | | | |
| | Median | -2.0 (-9, 3) | -2.5 (-9, 5) | 0.0 (-8, 4) | | | |
| | (Mix, Max) | | | | | | |

²Tabled values are the difference between treatment groups mean change from baseline and p-value from ANCOVA with treatment group as the independent variable and baseline score as the covariate.

| Total Pain Relief (TOTPAR) Based on All Target Joint Pain Scores | | | | |
|------------------------------------------------------------------|-------------------|------------------|------------------|------------------|
| Time Point | Statistic | Colchicine Dose | | |
| | | High (N = 52) | Low (N = 74) | Placebo (N = 58) |
| Hour 24 | n | 51 ¹ | 74 | 58 |
| | Mean (SD) | 20.9 (48.42) | 30.5 (61.44) | 9.5 (45.87) |
| | Median (Mix, Max) | 11.5 (-102, 135) | 23.0 (-112, 185) | 7.3 (-90, 142) |
| Hour 32 | n | 51 | 74 | 58 |
| | Mean (SD) | 31.9 (63.83) | 45.5 (82.05) | 12.2 (59.88) |
| | Median (Mix, Max) | 27.5 (-102, 185) | 34.1 (-128, 257) | 7.3 (-114, 142) |

¹Patient 1026-1005 did not have a diary and the 24-hour call to the Call Center was 27 hours after the initial call. As indicated in the SAP, the Call Center pain score was not eligible for substitution for the missing diary. This patient has been excluded from the TOTPAR summary.

US 7,964,647 B2

39

40

| Number (%) of Patients Using Rescue Medication Up to and Including the 24-Hour Post First Dose Assessment | | | | | |
|-----------------------------------------------------------------------------------------------------------|-----------------|---------------------|-------------------------------------------------|---------------------------------|---------------------------------|
| Colchicine Dose | | | | | |
| High (N = 52) | Low (N = 74) | Placebo (N = 58) | Treatment Comparison (Odds Ratio and 95% CI) | | |
| n (%) | n (%) | n (%) | High vs. Placebo | Low vs. Placebo | High vs. Low |
| 18 (34.6) | 23 (31.1) | 29 (50.0%) | 0.53 (0.25, 1.14) p = 0.1034 | 0.45 (0.22, 0.92) p = 0.0273 | 1.17 (0.55, 2.50) p = 0.6768 |

| Change from Baseline in Target Joint Pain Scores at 24 Hours Post First Dose with Interval of Time of Dose Relative to Flare Onset as Covariate (LOCF) - ITT Population | | | | | | | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|------------------|-----------------|---------------------|------------------------------------|--------------------|--------------|
| | | Colchicine Dose | | | Treatment Comparisons ¹ | | |
| Statistic | | High (N = 52) | Low (N = 74) | Placebo (N = 58) | High vs. Placebo | Low vs. Placebo | High vs. Low |
| Early Treatment Start (within 4 hours) | | | | | | | |
| Baseline | Mean (SD) | 6.9 (1.59) | 6.9 (1.72) | 6.8 (1.44) | -1.3 | -1.5 | 0.2 |
| | Median (Mix, Max) | 7.0 (4, 10) | 7.0 (4, 10) | 7.0 (4, 10) | p = 0.0145 | p = 0.0055 | p = 0.7540 |
| Change | Mean (SD) | -2.0 (2.93) | -2.2 (3.46) | -0.7 (2.77) | | | |
| | Median (Mix, Max) | -2.0 (-9, 4) | -2.0 (-9, 5) | -0.0 (-8, 4) | | | |
| Late Treatment Start (after 4 hours) | | | | | | | |
| Baseline | Mean (SD) | 6.9 (1.59) | 6.9 (1.72) | 6.8 (1.44) | -1.6 | -1.6 | 0.1 |
| | Median (Mix, Max) | 7.0 (4, 10) | 7.0 (4, 10) | 7.0 (4, 10) | p = 0.0057 | p = 0.0038 | p = 0.9238 |
| Change | Mean (SD) | -2.3 (3.05) | -2.4 (3.59) | -0.7 (2.95) | | | |
| | Median (Mix, Max) | -2.0 (-9, 3) | -2.5 (-9, 5) | 0.0 (-8, 4) | | | |

¹Patient 1016-1013 was missing a flare onset time and Patients 1002-1007, 1018-1008, 1006-1013, 1009-1011, 1010-1005, 1010-1010, 1026-1002, 1026-1007, 1064-1007, and 1068-1022 appear to have taken the first dose of study medication prior to flare onset.

²Tabled values are the difference between treatment groups mean change from baseline and p-value from ANCOVA with treatment group as the independent variable and baseline score as the covariate.

50

-continued

| Overall Summary of Treatment Emergent Adverse Events - Safety Population | | | |
|--------------------------------------------------------------------------|---------------------------|--------------------------|------------------------------|
| Colchicine Dose | | | |
| | High (N = 52) n (%) | Low (N = 74) n (%) | Placebo (N = 59) n (%) |
| Total Number of TEAEs ¹ | 85 | 34 | 27 |
| Number (%) of Patients with at Least One TEAE | 40 (76.9) | 27 (36.5) | 16 (27.1) |
| Number (%) of Patients with at Least One Mild TEAE | 15 (28.8) | 19 (25.7) | 9 (15.3) |
| Number (%) of Patients with at Least One Moderate TEAE | 15 (28.8) | 8 (10.8) | 6 (10.2) |
| Number (%) of Patients with at Least One Severe TEAE | 10 (19.2) | 0 | 1 (1.7) |

55

60

65

| Overall Summary of Treatment Emergent Adverse Events - Safety Population | | | |
|--------------------------------------------------------------------------|---------------------------|--------------------------|------------------------------|
| Colchicine Dose | | | |
| | High (N = 52) n (%) | Low (N = 74) n (%) | Placebo (N = 59) n (%) |
| Number (%) of Patients with a TEAE | 0 | 0 | 0 |
| Discontinuing Study | | | |
| Number (%) of Patients with a Treatment Emergent SAE | 0 | 0 | 0 |

¹Patients reporting more than one adverse event are only counted once for a given event.

US 7,964,647 B2

41

42

| Number (%) of Patients with at Least One Treatment-Emergent Gastrointestinal Adverse Event Recorded on the Diary or the CRF- Safety Population | | | | | | |
|------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|-----------|------------------------|---------|------------------|---------|
| Method of Capture | Colchicine Dose | | | | | |
| | Standard (N = 52) | | Low (N = 74) | | Placebo (N = 59) | |
| | All | Severe | All | Severe | All | Severe |
| Captured on Adverse Event CRF ¹ | 40 (76.9) ² | 10 (19.2) | 19 (25.7) | 0 | 12 (20.3) | 0 |
| Captured on Patient Diary | 48 (92.3) ² | 13 (25.0) | 32 (43.2) ³ | 3 (4.1) | 15 (25.4) | 2 (3.4) |
| Captured on Patient Diary or Adverse Event CRF | 49 (94.2) ² | 18 (34.6) | 33 (44.6) | 3 (4.1) | 16 (27.1) | 2 (3.4) |

¹Gastrointestinal adverse events captured on the AE CRF include the MedDRA preferred terms of "diarrhoea", "nausea", "vomiting", "abdominal pain", or "abdominal pain lower", "abdominal pain upper", "abdominal discomfort", or "dyspepsia".

²Statistically significantly different from placebo and from Low-dose colchicine (95% CI of odds ratio does not include "1").

³Statistically significantly different from placebo (95% CI of odds ratio does not include "1").

| Number (%) of Patients with at Least One Severe TEAE in Any Treatment Group- Safety Population | | | | | | | |
|------------------------------------------------------------------------------------------------|---------------------------|-------------------|----------------------------------|-------------------|------------------------|-----------------------|--------------------|
| MedDRA System Organ Class MedDRA Preferred Term | Colchicine Dose | | | | Odds Ratio | | |
| | | Low | All | Placebo | (95% Confidence) | | |
| | High (N = 52) n (%) | (N = 74) n (%) | Colchicine (N = 126) n (%) | (N = 59) n (%) | High vs. Placebo | Low vs. Placebo | High vs. Low |
| Number of Patients with at Least One Severe TEAE | 10 (19.2) | 0 | 10 (7.9) | 1 (1.7) | 13.8 (1.7, 112) | — | — |
| Gastrointestinal Disorders | 10 (19.2) | 0 | 10 (7.9) | 0 | — | — | — |
| Diarrhea | 10 (19.2) | 0 | 10 (7.9) | 0 | — | — | — |
| Melaena | 1 (1.9) | 0 | 1 (0.8) | 0 | — | — | — |
| Nausea | 1 (1.9) | 0 | 1 (0.8) | 0 | — | — | — |
| Metabolism and Nutrition Disorders | 0 | 0 | 0 | 1 (1.7) | — | — | — |
| Gout | 0 | 0 | 0 | 1 (1.7) | — | — | — |
| Musculoskeletal and Connective Tissue Disorders | 1 (1.9) | 0 | 1 (0.8) | 0 | — | — | — |
| Pain in Extremity | 1 (1.9) | 0 | 1 (0.8) | 0 | — | — | — |

| Number (%) of Patients with at Least One Drug-Related Treatment Emergent Adverse Events with an Incidence of $\geq 2\%$ of Patients in Any Treatment Group | | | | | | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|-----------------------|------------------------------|------------------------------------------|-----------------|-----------------|
| MedDRA System Organ Class MedDRA Preferred Term | Colchicine Dose | | Placebo (N = 59) n (%) | Odds Ratio (95% Confidence Intervals) | | |
| | High (N = 52) n (%) | Low (N = 74) n (%) | | High vs. Placebo | Low vs. Placebo | High vs. Low |
| Number of Patients with at Least One Drug-Related TEAE | 38 (73.1) | 21 (28.4) | 14 (23.7) | 8.7 (3.7, 20.6) | 1.3 (0.6, 2.8) | 6.9 (3.1, 15.2) |
| Gastro-intestinal Disorders | 38 (73.1) | 18 (24.3) | 11 (18.6) | 11.8 (4.8, 29.0) | 1.4 (0.6, 3.3) | 8.4 (3.8, 19.0) |
| Diarrhea | 38 (73.1) | 16 (21.6) | 8 (13.6) | 17.3 (6.6, 45.4) | 1.8 (0.7, 4.4) | 9.8 (4.3, 22.5) |
| Nausea | 7 (13.5) | 3 (4.1) | 3 (5.1) | 2.9 (0.7, 11.9) | 0.8 (0.2, 4.1) | 3.7 (0.9, 15.0) |
| Vomiting | 8 (15.4) | 0 | 0 | — | — | — |

As shown in the above tables, standard dose colchicine produced $\geq 50\%$ pain reduction at 24 hrs without pain rescue in a greater proportion of patients than did placebo (32.7% vs. 15.5%, $p=0.0343$; odds ratio 2.64 (95% CI, 1.06, 6.62), and more gastrointestinal side effects than placebo (73.1% vs.

18.6%, odds ratio 11.8 {95% CI, 4.8, 29.0}), in particular more diarrhea than placebo (73.1% vs. 13.6%, odds ratio 17.3 {95% CI, 6.6, 45.4}). Low dose colchicine also produced $\geq 50\%$ pain reduction at 24 hrs without pain rescue in a greater proportion of patients than did placebo (37.8% vs.

15.5%, $p=0.0046$; odds ratio 3.31 (95% CI, 1.41, 7.77)), and more gastrointestinal side effects than placebo (24.3% vs. 18.6%, odds ratio 1.4 {95% CI, 0.7 to 11.9}), but did not significantly differ from placebo with respect to diarrhea (21.6% vs. 13.6%, odds ratio 1.8 {95% CI, 0.7 to 4.4}). Severe diarrhea occurred in 19.2% of patients taking high-dose colchicine while not occurring in the low-dose colchicine group. Vomiting occurred in 15.4% of patients taking high-dose colchicine while not occurring in the low-dose colchicine group.

Based on the primary efficacy variable of $\geq 50\%$ pain reduction at 24 hrs without pain rescue, the proportion of responders to the standard dose and the low dose colchicine regimens was not significantly different ($p=0.5529$). The odds ratio for being a responder to standard dose colchicine vs. being a responder to low dose colchicine was 0.80 (95% CI, 0.38, 1.68). The proportion of patients rescued prior to 24 hours for the standard dose, low dose and placebo were 34.6%, 28.4% and 48.3%, respectively.

FIG. 1 summarizes efficacy data from the trial. FIG. 1 shows the fraction of all patients improved at 24 hrs post-first dose, regardless of pain rescue, as a function of the percent improvement in pain for each of the three treatment methods (standard dose, low dose, placebo). For example, 49% of patients taking the low dose achieved at least 40% relief compared to 24% of the patients on placebo.

Standard dose oral colchicine was established to be effective, but burdened by significant diarrhea. In contrast, although low dose colchicine was not significantly different from standard dose colchicine in efficacy, low dose colchicine was not significantly different from placebo with respect to diarrhea. This trial provides a new evidence basis for acute gout treatment, specifically supporting the unexpected superiority of a low dose colchicine dosing regimen of 2 tablets of 0.6 mg followed in 1 hour by 1 tablet. The higher standard dose colchicine dosing regimen did not improve patient outcome, but did increase adverse events.

Example 4

Pharmacokinetic Study in Healthy Adults of Single vs. Multiple Oral Doses of Colchicine Tablets

This study was a single-center, open-label, single-sequence, two-period study to evaluate the pharmacokinetic profile of colchicine following single and multiple oral doses of colchicine tablets, 0.6 mg, in healthy volunteers.

In Period 1, study subjects received a 0.6-mg dose of colchicine after an overnight fast of at least 10 hours. In Period 2, subjects received a 0.6-mg dose of colchicine in the morning and the evening (approximately 12 hours later) for 10 days (steady state regimen). Subjects received a light breakfast served 60 minutes following dose administration in the morning and the evening dose was administered 90 minutes after an evening meal on Days 15 through 24 only. On Day 25, the colchicine dose was administered after an overnight fast of at least 10 hours and lunch was served 4 hours post-dose. Study periods were separated by a 14-day wash-out. Following the single dose and the last dose of the multiple dose regimen (beginning on the mornings of Day 1 and Day 25, respectively), blood samples were collected (6 mL each) from each subject within 1 hour prior to dosing and after dose administration at study hours 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 (while confined) and 36, 48, 72, and 96 (on an outpatient basis). Plasma concentrations of colchicine and its metabolites were determined using validated LC/MS-MS methods.

Thirteen healthy, non-smoking subjects with a mean age of 25.5 years (range 19 to 38 years) and within 15% of ideal body weight were enrolled in this study. All subjects completed both dosing periods according to protocol.

After a single dose, plasma concentrations are no longer quantifiable 24 hours post-dose in all but 1 subject. After the last dose of the steady state regimen, concentrations remained quantifiable for 48 to 72 hours. Review of individual subject data shows that no subject experienced a secondary colchicine peak, either following a single dose or upon multiple dosing.

All 2-O-demethylcolchicine (2-DMC) concentrations were below the level of quantitation (LOQ, 0.2 ng/mL) and only one sample from 1 subject (of 13 subjects) had a detectable 3-O-demethylcolchicine (3-DMC) concentration which was near the level of quantitation. Therefore, metabolites are not discussed further.

In healthy adults, colchicine appears to be readily absorbed when given orally, reaching a mean maximum plasma concentration of 2.5 ng/mL in 1.5 hours after a single dose. The drug is distributed widely, with an apparent volume of distribution of 540 L, greatly exceeding total body water. The elimination half-life as calculated following a single oral dose is approximately 5 hours. Levels were not detectable by 24 hours post-dose and this is therefore not an accurate estimate. Pharmacokinetic parameter values are summarized in the table below.

Review of trough plasma concentrations indicates that steady state was attained by approximately the eighth day of dosing for most subjects. Colchicine may have a diurnal variation reflected in the observed Cmin concentrations at steady state. Cmin concentrations prior to the morning dose are approximately 12% higher than the Cmin concentrations prior to the evening dose (Day 23 and Day 24). The mean Cmin concentration observed on Day 25 was 0.907 ng/mL.

Colchicine accumulated following administration of multiple doses to an extent greater than expected. Exposure was nearly two-fold higher (approximately 1.7 based on AUC [Day 25 AUC_{0- ∞]/Day 1 AUC_{0- ∞]) and approximately 1.5 based on C_{max} [Day 25 C_{max}/Day 1 C_{max}]). This observation could be attributable to an underestimation of AUC _{∞} following a single dose. With the higher plasma levels that occur with repeated dosing, a longer terminal elimination half life is apparent, 26.6 hours. Pharmacokinetic parameter values are summarized in the tables below.}}

TABLE 10

| Colchicine Pharmacokinetic Parameter Values Following Administration of A Single Oral Dose of Colchicine 0.6 mg in Healthy Adults | | | | | | |
|-----------------------------------------------------------------------------------------------------------------------------------|----------------------------------|----------------------------------------------------|-----------------------------|--------------------------|---------------|--------------------------|
| | AUC _{0-t} (pg-hr/mL) | AUC _{0-∞} (pg-hr/mL) | C _{max} (pg/mL) | T _{max} (hr) | Kel (1/hr) | T _{1/2} (hr) |
| N | 13 | 13 | 13 | 13 | 13 | 13 |
| MEAN | 10508.54 | 12281.90 | 2470.77 | 1.50 | 0.1829 | 4.95 |
| STDEV | 3544.82 | 4423.34 | 706.98 | 0.54 | 0.0592 | 4.43 |
| % CV | 33.73 | 36.02 | 28.61 | 36.00 | 32.39 | 89.54 |
| MEDIAN | 10560.90 | 11451.45 | 2714.00 | 1.50 | 0.1992 | 3.48 |
| MIN | 4812.88 | 7252.66 | 1584.00 | 1.00 | 0.0359 | 2.84 |
| MAX | 18128.65 | 23838.48 | 3977.00 | 3.00 | 0.2443 | 19.29 |

TABLE 11

| Colchicine Pharmacokinetic Parameter Values Following Administration of Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults | | | | | | | | | |
|---------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|----------------------------------|------------------------------------|-----------------------------|-----------------------------|-----------------------------|--------------------------|---------------|--------------------------|
| | AUC _{0-τ} (pg-hr/mL) | AUC _{0-τ} (pg-hr/mL) | AUC _{0-inf} (pg-hr/mL) | C _{max} (pg/mL) | C _{min} (pg/mL) | C _{ave} (pg/mL) | T _{max} (hr) | Kel (1/hr) | T _{1/2} (hr) |
| N | 13 | 13 | 13 | 13 | 13 | 13 | 13 | 13 | 13 |
| MEAN | 43576.96 | 29056.23 | 54198.77 | 3553.15 | 906.51 | 1210.68 | 1.31 | 0.03 | 26.60 |
| STDEV | 9333.26 | 4531.30 | 9214.54 | 843.45 | 152.19 | 188.80 | 0.60 | 0.00 | 4.33 |
| % CV | 21.42 | 15.59 | 17.00 | 23.74 | 16.79 | 15.59 | 45.61 | 16.34 | 16.26 |
| MEDIAN | 41925.10 | 28452.15 | 54113.43 | 3734.00 | 903.50 | 1185.51 | 1.00 | 0.03 | 26.51 |
| MIN | 29328.78 | 20791.98 | 37599.76 | 1977.00 | 636.23 | 866.33 | 0.50 | 0.02 | 20.82 |
| MAX | 58265.35 | 36083.95 | 67944.65 | 4957.00 | 1149.67 | 1503.50 | 3.00 | 0.03 | 33.65 |

TABLE 12

| Mean (% CV) Colchicine Pharmacokinetic Parameter Values Following Administration of Single and Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|-------------|
| | Vd/F (L) | CL/F (L/hr) |
| Colchicine 0.6-mg Single Dose (N = 13) | | |
| Day 1 | 341 (54.4) | 54.1 (31.0) |
| Colchicine 0.6 mg b.i.d. × 10 days | | |
| Day 25 | 1150 (18.73) | 30.3 (19.0) |

CL = Dose/AUC_{0-τ} (Calculated from mean values)
Vd = CL/K_e (Calculated from mean values)

In the above table, the parameter CL/F denotes the apparent total body clearance after administration, calculated as Total Dose/Total AUC_{0-τ}; and V_d/F denotes the apparent total volume of distribution after administration, calculated as Total Dose/(Total AUC_∞ × K_e).

Example 5

Pharmacokinetic Study in Healthy Adults of Low Dose Acute Gout Regimen: 1.8 mg Over 2 Hours

This study was a single-center, single-period, open-label pharmacokinetic study conducted in healthy subjects under

later. Blood samples for measurement of colchicine plasma concentrations and metabolites were collected (relative to the first dose of study drug) at pre-dose; 0.5 and 1 hour post-dose (prior to second dose); and 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 36, and 48 hours post-dose. Subjects were confined until 48 hours post-dose and then returned 72 and 96 hours after the first dose for additional blood sampling on an outpatient basis. Plasma concentrations of colchicine and its metabolites were determined using validated LC/MS-MS methods.

2-DMC concentrations were below the LOQ for all subjects. Eight of 13 subjects had at least one measurable 3-DMC concentration (29 total 3-DMC measurable concentrations). 3-DMC concentrations ranged from 0.20 ng/mL (near the LOQ) to 0.45 ng/mL and were observed 1 to 4 hours post-dose. Given these low levels, metabolites are not discussed further herein.

When colchicine was administered in this low-dose regimen, concentrations increased to a maximum of 6.2 ng/mL, occurring 1.81 hours after the initial dose (0.81 hours after the second dose). Most of the subjects (10 of 13 subjects or 77%) experienced a secondary peak within 6 hours after the first of the two doses, attributed to intestinal secretion and re-absorption and/or biliary recirculation.

The terminal elimination half-life was 23.6 hours. A summary of the pharmacokinetic parameter values is provided in the table below.

TABLE 12

| COLCHICINE PHARMACOKINETIC PARAMETER VALUES AFTER LOW-DOSE COLCHICINE (1.8 MG OVER 2 HOURS) ADMINISTRATION IN HEALTHY ADULTS | | | | | | | | |
|------------------------------------------------------------------------------------------------------------------------------|-----------------------------|--------------------------|----------------------------------------|--------------------------------------|--------------------------|-----------------|-----------------------------|--------------------------|
| | C _{max} (pg/mL) | T _{max} (hr) | Total AUC _{0-τ} (pg-hr/mL) | Total AUC _∞ (pg-hr/mL) | K _e (1/hr) | CL/F (mL/hr) | V _{area} /F (L) | t _{1/2} (hr) |
| N | 13 | 13 | 13 | 13 | 13 | 13 | 13 | 13 |
| MEAN | 6192.77 | 1.81 | 43787.55 | 52070.06 | 0.0326 | 36950.93 | 1188.72 | 23.63 |
| STDEV | 2433.70 | 0.38 | 11437.48 | 13689.27 | 0.0100 | 9993.17 | 319.56 | 9.24 |
| % CV | 39.30 | 21.24 | 26.12 | 26.29 | 30.80 | 27.04 | 26.88 | 39.10 |
| MEDIAN | 5684.00 | 2.00 | 43942.15 | 50783.77 | 0.0322 | 35444.40 | 1149.35 | 21.56 |
| MIN | 3160.00 | 1.00 | 28821.45 | 34171.00 | 0.0141 | 24295.73 | 774.19 | 13.80 |
| MAX | 11370.00 | 2.50 | 58931.99 | 74087.08 | 0.0502 | 52676.24 | 1724.36 | 49.20 |

fasting conditions. It was designed to characterize the pharmacokinetic profile of a low-dose regimen of colchicine (1.8 mg over 2 hours) used as one of the treatment arms in the randomized, controlled trial in patients with an acute gout flare discussed above.

Thirteen healthy, non-smoking subjects with a mean age of 29.3 years (range 20 to 49 years) and within 15% of ideal body weight were enrolled in this study. Subjects received 2×0.6 mg tablets initially followed by 1×0.6 mg tablet 1 hour

Example 6

Pharmacokinetic Study in Healthy Adults of a Standard-Dose Acute Gout Regimen: 4.8 mg Colchicine Over 6 Hours.

This study was a single center, randomized, double-blind, double-dummy pharmacokinetic and exploratory ECG safety study.

US 7,964,647 B2

47

With respect to the pharmacokinetic aspect of the study, on Day 1, following a minimum of 10 hours overnight fast, subjects received the appropriate randomized study drug (combination of over-encapsulated active drug or placebo capsules such that the blind was preserved). Those randomized to colchicine received 4.8 mg over 6 hours (initially 2x0.6 mg tablets followed by 1x0.6 mg tablet every hour for six additional doses). Those randomized to moxifloxacin received 1x400 mg tablet. Both dosing regimens were followed by a 4-hour post-dose fast (post-dose fast for colchicine arm started after the first dose of colchicine administered). Blood samples were obtained on Day 1 at the following time points (relative to the first dose of study drug): pre-dose and 1 (prior to second dose), 3 (prior to fourth dose), 6 (prior to final dose), 6.17, 6.33, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 10, 12, 23, 36, 48, 72 and 96 hours post-dose. Subjects were confined until 48 hours post-dose and then returned 72 and 96 hours after the first dose for additional blood sampling on an outpatient basis. Plasma concentrations of colchicine and its metabolites were determined using validated LC/MS-MS methods.

48

Eighteen healthy, non-smoking subjects with a mean age of 28.7 years (range 18 to 50 years) and within 15% of ideal body weight were enrolled in this study. Fifteen subjects were randomized to receive colchicine and 3 subjects were randomized to receive moxifloxacin as a positive control for QTc prolongation. All subjects completed the study according to protocol.

When colchicine was administered as the standard-dose regimen used in the treatment of patients experiencing an acute gout flare, colchicine concentrations increased to a maximum of 6.8 ng/mL (similar to the reported C_{max} in the low-dose regimen) and absorbed approximately 4.5 hours after the initial dose (3.5 hours after the second dose). Most of the subjects (13 of 15 subjects receiving colchicine or 87%) experienced a secondary peak within 6 hours after a single oral dose, attributed to intestinal secretion and re-absorption and/or biliary recirculation. The terminal elimination half-life was 31.38 hours. A summary of the pharmacokinetic parameter values is provided in the table below.

TABLE 13

| MEAN (% CV) COLCHICINE PHARMACOKINETIC PARAMETER VALUES AFTER STANDARD-DOSE COLCHICINE (4.8 MG OVER 6 HOURS) ADMINISTRATION IN HEALTHY ADULTS | | | | | | | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|--------------------------|----------------------------------------|--------------------------------------|---------------------------------------|-----------------|-----------------------------|--------------------------|
| | C _{max} (ng/mL) | T _{max} (hr) | Total AUC _{0-t} (ng·hr/mL) | Total AUC _∞ (ng·hr/mL) | K _{el} (h ⁻¹) | CL/F (mL/hr) | V _{area} /F (L) | t _{1/2} (hr) |
| N | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| MEAN | 6.84 | 4.47 | 104.95 | 118.20 | 0.0242 | 43168.87 | 1876.09 | 31.38 |
| STDEV | 1.30 | 1.99 | 24.61 | 26.01 | 0.0088 | 12862.03 | 456.19 | 8.36 |
| % CV | 18.94 | 44.65 | 23.45 | 22.01 | 36.59 | 29.79 | 24.32 | 26.65 |
| MEDIAN | 6.69 | 3.12 | 113.12 | 126.47 | 0.0212 | 37954.71 | 1902.14 | 32.76 |
| MIN | 4.95 | 3.12 | 53.74 | 61.31 | 0.0147 | 31386.01 | 805.92 | 15.03 |
| MAX | 8.60 | 7.50 | 138.24 | 152.93 | 0.0461 | 78287.41 | 2639.21 | 47.22 |

2-DMC concentrations were below LOQ for all subjects. Fourteen of 15 subjects had at least one measurable 3-DMC concentration; the 3-DMC concentrations ranged from 0.25 ng/mL (near the LOQ) to 0.42 ng/mL and were observed 1.12 to 12.12 hours post-dose. Summary mean 3-DMC pharmacokinetic parameter values can be found in the table below. The observed mean 3-DMC C_{max}, AUC_{0-t}, and AUC_∞ concentrations were approximately 4.7%, 2%, and 4.1% of the observed mean colchicine C_{max}, AUC_{0-t}, AUC_∞ concentrations, respectively.

TABLE 14

| Mean (% CV) 3-DMC Pharmacokinetic Parameter Values after Standard-Dose Colchicine (4.8 mg over 6 hours) Administration in Healthy Adults | | | | | | |
|---------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|--------------------------------------|---------------------------------|-------------------------------|--------------------------|-------------------------|
| | C _{max} (ng/mL) | T _{max} ¹ (h) | AUC _{0-t} (ng·h/mL) | AUC _∞ (ng·h/mL) | Ke (h ⁻¹) | t _{1/2} (h) |
| | N = 15 | N = 14 | N = 13 | N = 8 | N = 8 | N = 8 |
| Standard Dose | 0.32 | 5.06 | 2.09 | 4.84 | 0.1418 | 6.93 |
| N = 15 | (16.35) | (3.12-8.12) | (40.29) | (42.73) | (60.15) | (64.35) |

¹T_{max} reported mean (range)

US 7,964,647 B2

49

Example 7

Food Effect Study Single Dose Vs.
COL-Probenecid® (0.5 MG Colchicine/500 MG
Probenecid)

The clinical study of this example was a randomized, single-dose, three-way crossover study testing the bioequivalence of two formulations of colchicine administered under standard fasting conditions, one the 0.6 mgA colchicine formulation of Example 2 (test product) and one a marketed combination product, 0.5 mg colchicine/500 mg probenecid tablets (COL-PROBENECID®, Watson Laboratories, Inc.) (reference product), and the effect of food on the test product by dosing following a high-fat breakfast.

Twenty-eight healthy non-smoking adult volunteers (male and female) and no alternates initiated the study. Subjects received three single doses, in a randomized sequence of three treatment periods. On each occasion, subjects received either one colchicine tablet USP, 0.6 mg (test product) given either with food or in a standard fasting condition or one colchicine 0.5 mg/probenecid 500 mg tablet (reference product) given in a standard fasting condition. Each treatment period was separated by a 14-day washout.

The two dosing conditions were (1) Standard Fasting Conditions (either colchicine tablets USP, 0.6 mg (test A) or reference product, COL-PROBENECID®): 1 tablet of test product (Test A) or reference product with 240 mL of room temperature water after an overnight fast of at least 10 hours; subjects will continue to fast for 4 hours post-dose; and (2)

50

dard meal) depending on the randomization, was allowed from 1 hour prior to dose administration until 2 hours after dosing. When fluids were restricted, they will be allowed ad libitum but will generally be controlled.

5 Dinner was served approximately 13.5 hours prior to dose administration. At 30 minutes before dose administration, those subjects to be dosed after eating (depending on randomization) were served the standardized, high-fat and high-calorie breakfast (FDA standard meal). All subjects fasted for at least 4 hours after dosing. Clear fluids, such as water, were allowed during fasting.

Subjects were served standardized meals and beverages, controlled by the clinic during periods of confinement. Meals were the same in content and quantity during each confinement period. No grapefruit and/or grapefruit containing products or caffeine and/or xanthine containing products were allowed during the confinement portions of the study.

During confinement, only non-strenuous activity was permitted. Following dose administration, subjects remained in a seated or upright position for at least 4 hours to ensure proper gastric emptying and subject safety.

Blood (6 mL) was collected in K2 EDTA vacutainers with samples taken within 1 hour prior to dosing (0 hour) and after dose administration at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours (while confined) and 36, 48, 72, and 96 hours (on an outpatient basis). 1. Colchicine and metabolite plasma concentrations (colchicine, 2-DMC, 3-DMC, and 10 demethylcolchicine) were measured using a validated bioanalytical method.

Pharmacokinetic results comparing the test product under fed and fasting conditions are shown below.

TABLE 15

| Pharmacokinetic results of colchicine test product under fed and fasting | | | | | | |
|----------------------------------------------------------------------------|--------------------|----------|----------------|----------|----------------------------|----------------------------|
| Ln-Transformed Data | | | | | | |
| PK Variable | Least Squares Mean | | Geometric Mean | | 90% Confidence Interval | |
| | Test B | Test A | Test B | Test A | % Ratio | (Lower Limit, Upper Limit) |
| C_{max} (ng/mL) | 7.784 | 7.781 | 2402.55 | 2393.60 | 100.37 | (89.84, 112.14) |
| AUC_{0-t} (ng/mL-hr) | 9.201 | 9.334 | 9906.40 | 11310.90 | 87.58 | (78.07, 98.26) |
| AUC_{0-inf} (ng/mL-hr) | 9.300 | 9.468 | 10939.73 | 12939.64 | 84.54 | (76.73, 93.15) |
| Geometric means are based on least squares means of ln-transformed values. | | | | | | |
| Non-Transformed Data | | | | | | |
| PK Variable | Least Squares Mean | | | | 90% Confidence Interval | |
| | Test B | Test A | % Ratio | | (Lower Limit, Upper Limit) | |
| C_{max} (pg/mL) | 2486.99 | 2493.15 | 99.75 | | (90.43, 109.07) | |
| AUC_{0-t} (pg/mL-hr) | 10438.89 | 12536.56 | 83.27 | | (72.79, 93.74) | |
| AUC_{0-inf} (pg/mL-hr) | 11345.62 | 13907.83 | 81.58 | | (71.53, 91.63) | |
| T_{max} (hr) | 1.85 | 1.35 | 137.14 | | (111.11, 163.17) | |
| K_{el} (hr ⁻¹) | 0.1902 | 0.1520 | 125.13 | | (107.67, 142.58) | |
| $T_{1/2}$ (hr) | 4.34 | 6.27 | 69.17 | | (45.2, 93.14) | |

55

High-fat Breakfast (colchicine tablets USP, 0.6 mg): 1 tablet of test product (Test B) with 240 mL of room temperature water 30 minutes after initiation of a standardized, high-fat and high-calorie breakfast (FDA standard meal) preceded by an overnight fast.

Subjects were confined for at least 15 hours prior to and until at least 24 hours after dosing each period. During each period, subjects returned on four separate occasions for outpatient blood sampling.

No fluid, except that given with drug administration and the standardized high-fat and high-calorie breakfast (FDA stan-

TABLE 16

| Descriptive statistics for Pharmacokinetic Parameters for Test Product A (0.6 mg) - Fasting conditions | | | |
|-----------------------------------------------------------------------------------------------------------|----------------------|---------------------|--------------|
| | AUC0-t (pg-hr/mL) | AUC0-inf (pg-hr/mL) | Cmax (pg/mL) |
| N | 25 | 24 | 25 |
| Arithmetic Mean | 12589 | 14113 | 2503 |
| STDev | 6210.729 | 5595.398 | 722.049 |
| % CV | 48.621 | 39.648 | 28.847 |

65

US 7,964,647 B2

51

TABLE 16-continued

| Descriptive statistics for Pharmacokinetic Parameters for Test Product A (0.6 mg) - Fasting conditions | | | |
|-----------------------------------------------------------------------------------------------------------|----------------------------------|---------------------------------|--------------------------|
| | AUC _{0-t} (pg-hr/mL) | AUC _{0-inf} (pg-hr/mL) | C _{max} (pg/mL) |
| Median | 11412.80 | 12756.02 | 2473.00 |
| Min | 4430.73 | 6674.96 | 1291.00 |
| Max | 30787.30 | 27789.51 | 3989.00 |

TABLE 17

| Descriptive statistics for Pharmacokinetic Parameters for Test Product A (0.6 mg) - Fed conditions | | | |
|-------------------------------------------------------------------------------------------------------|----------------------------------|---------------------------------|--------------------------|
| | AUC _{0-t} (pg-hr/mL) | AUC _{0-inf} (pg-hr/mL) | C _{max} (pg/mL) |
| N | 25 | 22 | 25 |
| Arithmetic Mean | 10491 | 11404 | 2497 |
| STDev | 4024.804 | 2895.681 | 695.091 |
| % CV | 38.374 | 25.392 | 27.838 |
| Median | 9556.25 | 10964.17 | 2293.00 |
| Min | 6168.53 | 7128.50 | 1256.00 |
| Max | 26031.15 | 20101.33 | 3930.00 |

Food was observed to have negligible effect on rate of absorption, as indicated by the percent ratio of ln-transformed C_{max} data of 100.37, but decreased the extent of absorption by about 15%, as indicated by the percent ratio of ln-transformed AUC_{0-t} and AUC_{0-inf} values of 87.56 and 84.54, respectively. Under fasted and fed conditions, the mean C_{max} was 2.5 ng/mL. T_{max} was 1.35 hrs under fasted conditions and 1.85 hrs under fed conditions.

Pharmacokinetic results comparing the test product to the reference product are shown in the tables below. The difference in colchicine potency of the test and reference products was corrected by calculating dose-normalized values in the pharmacokinetic parameters.

TABLE 18

| Summary of Statistical Analysis Colchicine Test Product A (0.6 mg) - Fasting vs Reference Product C (0.5 mg) - Fasting (Dose Normalized to 0.5 mg) N = 25 | | | | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-------------|----------------|----------------------------|-------------------------|----------------------------|
| Ln-Transformed Data | | | | | | |
| PK Variable | Least Squares Mean | | Geometric Mean | | 90% Confidence Interval | |
| | Test A | Reference C | Test A | Reference C | % Ratio | (Lower Limit, Upper Limit) |
| C _{max} (ng/mL) | 7.598 | 7.374 | 1994.67 | 1594.51 | 125.10 | (111.97, 139.76) |
| AUC _{0-t} (ng/mL-hr) | 9.151 | 8.833 | 9425.75 | 6858.61 | 137.43 | (122.5, 154.18) |
| AUC _{0-inf} (ng/mL-hr) | 9.286 | 8.970 | 10783.03 | 7863.34 | 137.13 | (124.46, 151.09) |
| Geometric means are based on least squares means of ln-transformed values. | | | | | | |
| Non-Transformed Data | | | | | | |
| PK Variable | Least Squares Mean | | | 90% Confidence Interval | | |
| | Test A | Reference C | % Ratio | (Lower Limit, Upper Limit) | | |
| C _{max} (pg/mL) | 2076.08 | 1688.54 | 122.95 | (110.07, 135.83) | | |
| AUC _{0-t} (pg/mL-hr) | 10435.91 | 8016.44 | 130.18 | (115.25, 145.11) | | |
| AUC _{0-inf} (pg/mL-hr) | 11565.28 | 8230.68 | 140.51 | (126.04, 154.99) | | |
| T _{max} (hr) | 1.35 | 1.34 | 100.11 | (74.05, 126.17) | | |
| Kel (hr ⁻¹) | 0.1520 | 0.1970 | 77.16 | (63.69, 90.63) | | |
| T _{1/2} (hr) | 6.27 | 3.78 | 165.89 | (126.13, 205.65) | | |

52

The 0.6 mgA colchicine tablet, formulated as in Example 2, showed enhanced bioavailability over COL-PROBENECID®. The formulation disclosed herein showed a greater rate and extent of absorption than did the COL-PROBENECID®.

Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges directed to the same component or property are inclusive and independently combinable.

All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention as used herein. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. The terms wt %, weight percent, percent by weight, etc. are equivalent and interchangeable.

Embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is

US 7,964,647 B2

53

encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

I claim:

1. A method of treating a patient having an acute gouty arthritis attack with colchicine consisting of

54

administering 1.2 mg oral colchicine to a human patient having an acute gouty arthritis attack at the onset of the acute gouty arthritis attack, followed by 0.6 mg oral colchicine one hour later.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 7,964,647 B2
APPLICATION NO. : 12/407980
DATED : June 21, 2011
INVENTOR(S) : Matthew W. Davis

Page 1 of 2

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 5, line 41, delete “mitotis,” and insert -- mitosis, --, therefor.

In column 10, line 4, delete “and HPLC” and insert -- and UPLC --, therefor.

In column 10, line 41, delete “(HPLC)” and insert -- (UPLC) --, therefor.

In column 12, line 42, delete “calorimetric” and insert -- colorimetric --, therefor.

In column 13, line 44, after “manufacture” insert -- . --.

In column 13, line 66, delete “N-formyldeactylcholchicine,” and insert
-- N-formyldeacetylcolchicine, --, therefor.

In column 15, line 42, delete “AVICELL®” and insert -- AVICEL® --, therefor.

In column 15, line 55, after “composition” insert -- . --.

In column 15, line 61, delete “alignates,” and insert -- alginates, --, therefor.

In column 16, line 14-15, delete “crosscarmelose” and insert -- croscarmellose --, therefor.

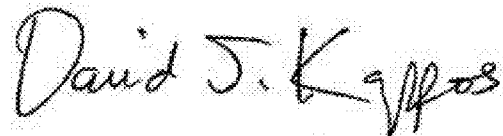
In column 18, line 5, delete “or HPLC” and insert -- or UPLC --, therefor.

In column 20, line 32, after “0.5%” insert -- . --.

In column 21, line 59, delete “methanl” and insert -- methanol --, therefor.

In column 22, line 29, delete “Volumetric” and insert -- Volumetric --, therefor.

Signed and Sealed this
Fifteenth Day of November, 2011

A handwritten signature in black ink, reading "David J. Kappos". The signature is written in a cursive, slightly slanted style. The "D" is large and loops around the "a". The "K" is prominent, and the "os" at the end is written with a flourish.

David J. Kappos
Director of the United States Patent and Trademark Office

CERTIFICATE OF CORRECTION (continued)

Page 2 of 2

U.S. Pat. No. 7,964,647 B2

In column 22, line 33, delete “Volumetric” and insert -- Volumetric --, therefor.

In column 28, line 49, delete “probenicid.” and insert -- probenacid. --, therefor.

In column 37-38, line 31, delete “goup” and insert -- group --, therefor.

In column 41, line 66, delete “CT,” and insert -- CI, --, therefor.

In column 44, line 16, delete “demethylcolchicine” and insert -- demethylcolchicine --, therefor.

In column 52, line 26, after “interchangeable” insert -- . --.

EXHIBIT F

US007964648B2

(12) **United States Patent**
Davis

(10) **Patent No.:** **US 7,964,648 B2**
(45) **Date of Patent:** ***Jun. 21, 2011**

(54) **METHODS FOR CONCOMITANT
ADMINISTRATION OF COLCHICINE AND A
SECOND ACTIVE AGENT**

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C07C 239/00 (2006.01)
C07C 211/00 (2006.01)
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(52) **U.S. Cl.** **514/629; 564/123; 564/308; 564/427;
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568/306**

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ABSTRACT

Methods for concomitant administration of colchicine
together with one or more second active agents, e.g., keto-
conazole and ritonavir, are disclosed. Such methods reduce
the dangers commonly associated with such concomitant
administration and provide additional benefits. Methods of
notifying health care practitioners and patients regarding
appropriate dosing for concomitant administration of colchi-
cine together with second active agents are also provided.

8 Claims, 5 Drawing Sheets

US 7,964,648 B2

Page 2

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FIG. 1

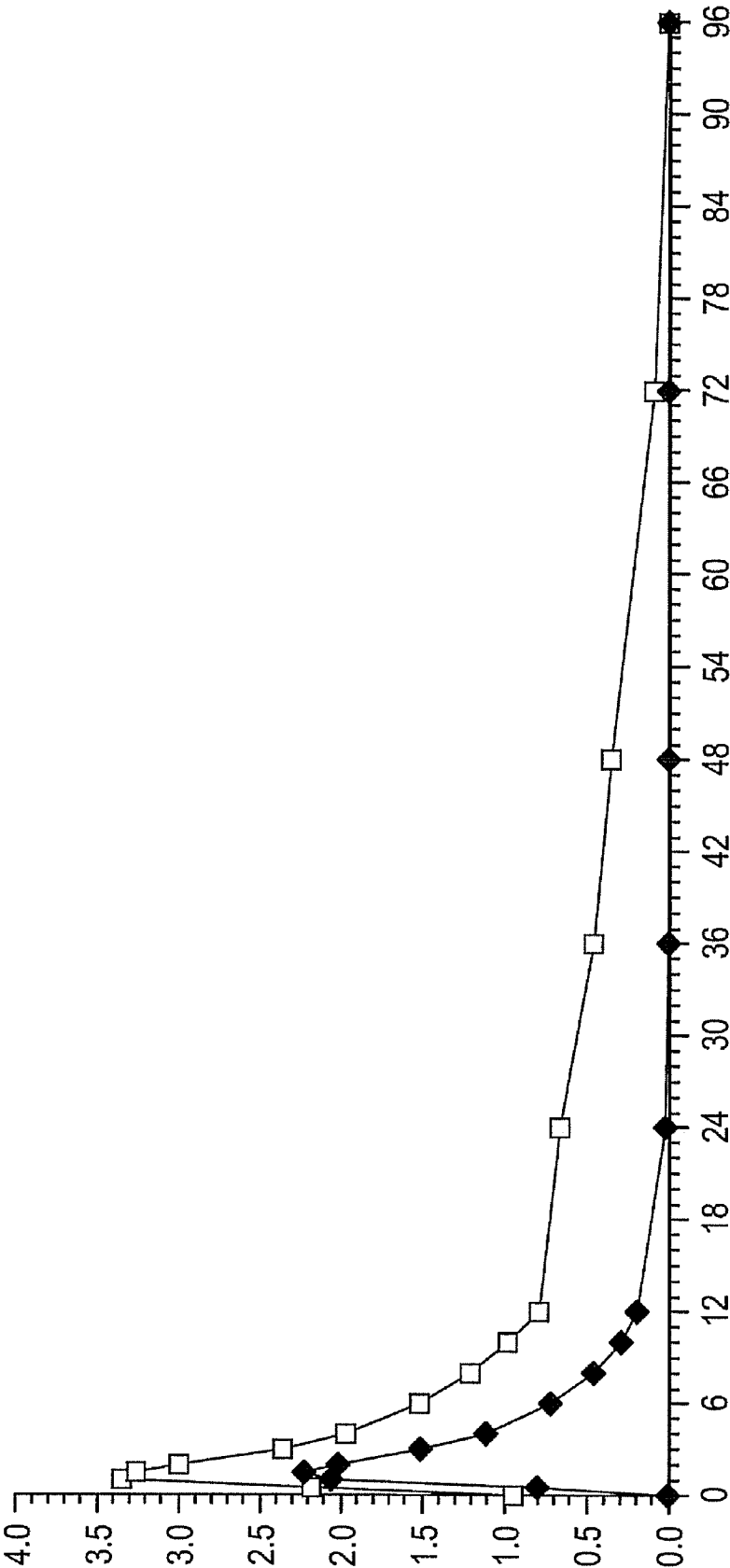


FIG. 2

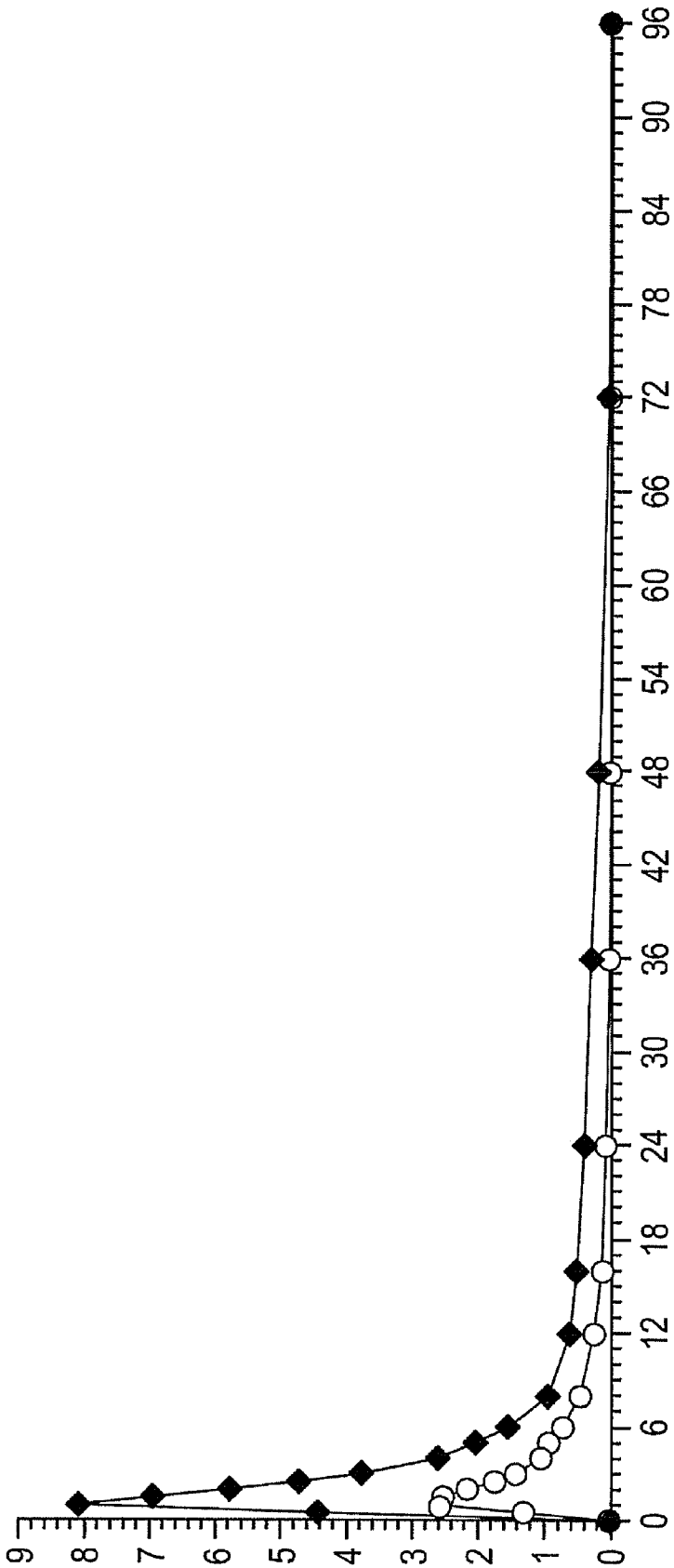


FIG. 3

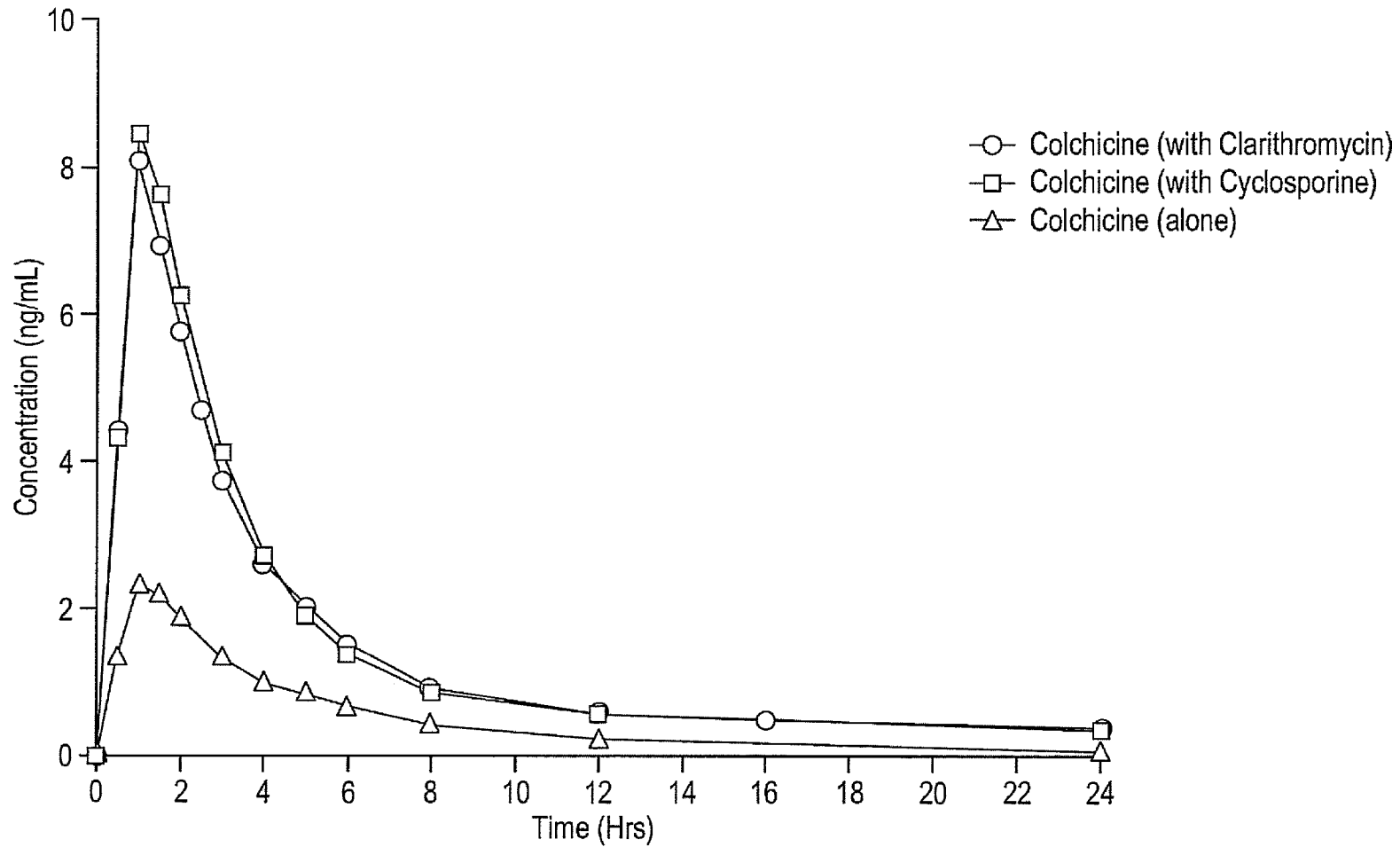


FIG. 4

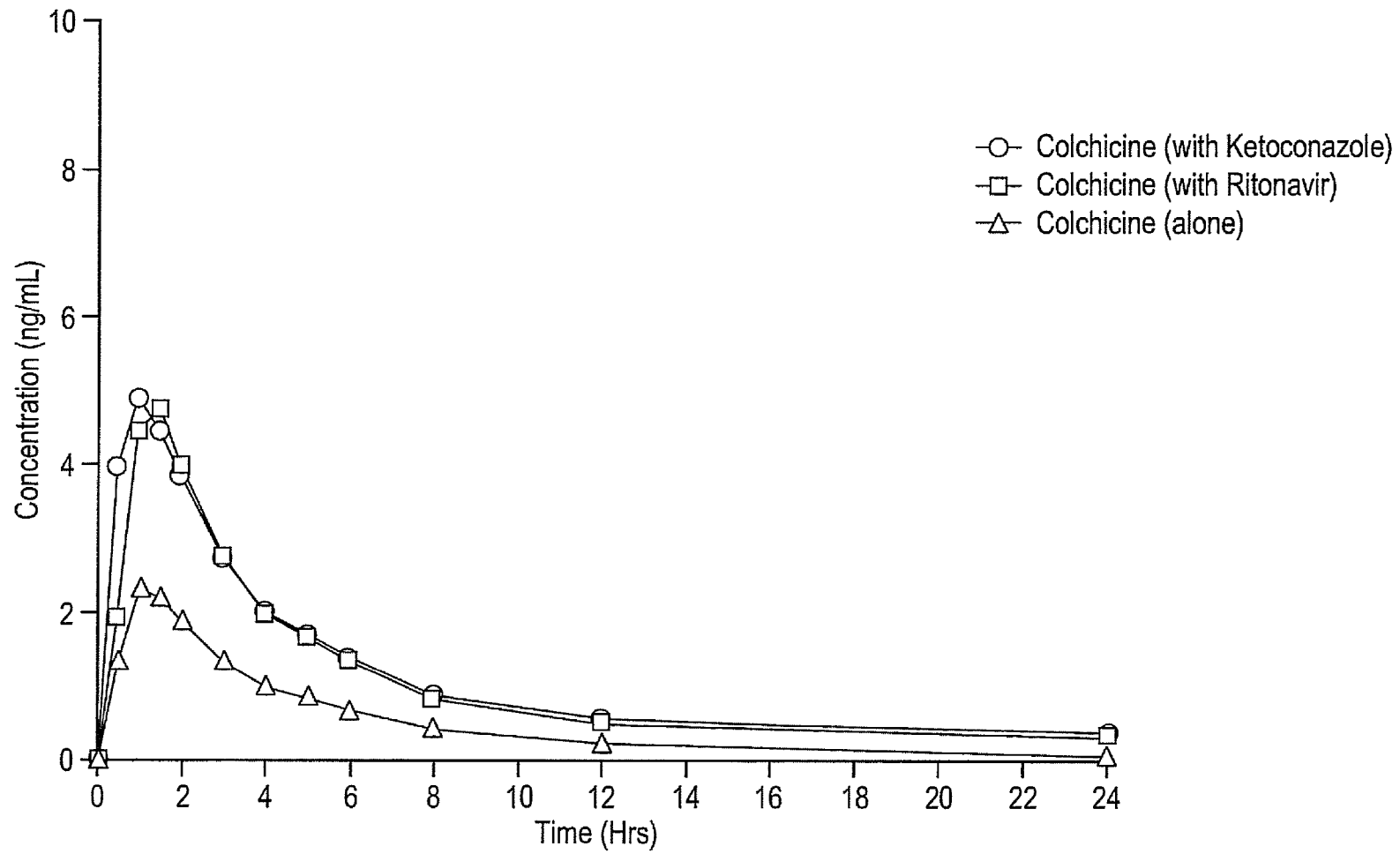
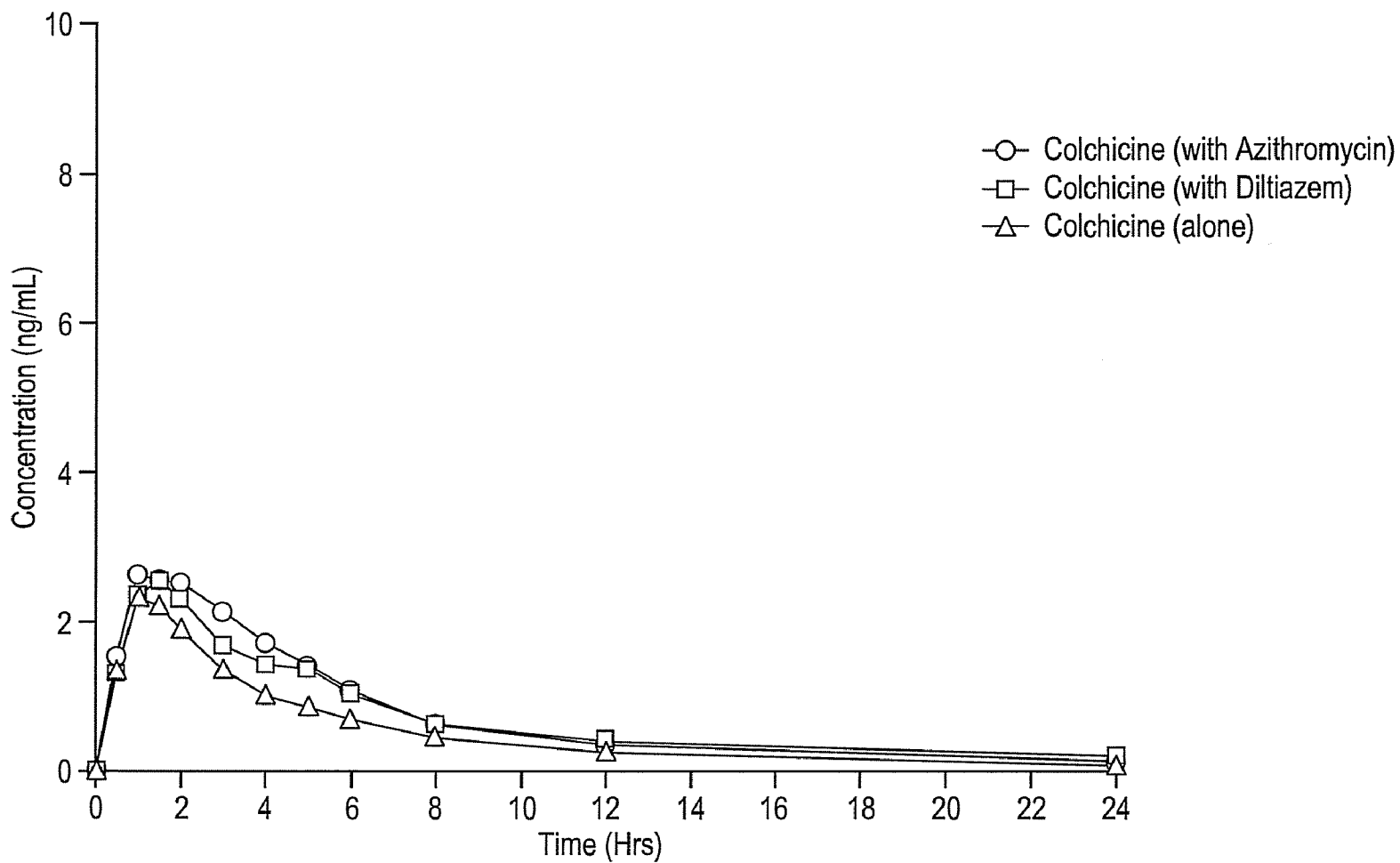


FIG. 5



US 7,964,648 B2

1

METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND A SECOND ACTIVE AGENT

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a Continuation of U.S. patent application Ser. No. 12/372,046, filed Feb. 17, 2009, which is a Nonprovisional of U.S. Provisional Application Ser. Nos. 61/138,141 filed Dec. 17, 2008 and 61/152,067 filed Feb. 12, 2009, all of which are hereby incorporated by reference in their entirety.

FIELD OF THE DISCLOSURE

This disclosure relates to methods allowing for the co-administration of colchicine together with one or more second active agents for therapeutic purposes with improved safety compared to prior methods of administration.

BACKGROUND

Colchicine, chemical name (–)-N-[(7S, 12aS)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide, is an alkaloid found in extracts of *Colchicum autumnale*, *Gloriosa superba*, and other plants. It is a microtubule-disrupting agent used in the treatment of gout and other conditions that may be treated, relieved or prevented with anti-inflammatory treatment. Colchicine impairs the motility of granulocytes and can prevent the inflammatory phenomena that initiate an attack (or flare) of gout. Colchicine also inhibits mitosis, resulting in effects in cells with high turnover rates such as those in the gastrointestinal tract and bone marrow. The primary adverse side effects of colchicine therapy include gastrointestinal upset such as diarrhea and nausea.

Colchicine has a narrow therapeutic index. The margin between an effective dose and a toxic dose of colchicine is much narrower than that of many other widely used drugs. Consequently, actions that result in increased colchicine levels in patients receiving colchicine therapy are particularly dangerous. Co-administration of colchicine to patients along with certain other drugs can have the effect of increasing colchicine levels. Such drug-drug interactions with colchicine have been reported to result in serious morbid complications and, in some cases, death.

Colchicine is rapidly absorbed from the gastrointestinal tract. Peak concentrations occur in 0.5 to 2 hours. The drug and its metabolites are distributed in leukocytes, kidneys, liver, spleen and the intestinal tract. Colchicine is metabolized in the liver and excreted primarily in the feces with 10 to 20% eliminated unchanged in the urine.

Gout (or gouty arthritis) is a disease caused by a build up of uric acid in the joints. Such a build up is typically due to an overproduction of uric acid, or to a reduced ability of the kidney to excrete uric acid. Gout is characterized by excruciating, sudden, unexpected, burning pain, as well as by swelling, redness, warmth, and stiffness in the affected joint. Low-grade fever may also be present. A gout flare is a sudden attack of pain in affected joints, especially in the lower extremities, and most commonly in the big toe. In afflicted individuals, the frequency of gout flares typically increases over time. In this manner, gout progresses from acute gout to chronic gout, which involves repeated episodes of joint pain.

Colchicine can reduce pain in attacks of acute gout flares and also can be used beneficially for treating adults for pro-

2

phylaxis of gout flares. Although its exact mode of action in the relief of gout is not completely understood, colchicine is known to decrease the inflammatory response to urate crystal deposition by inhibiting migration of leukocytes, to interfere with urate deposition by decreasing lactic acid production by leukocytes, to interfere with kinin formation and to diminish phagocytosis and subsequent inflammatory responses.

Cytochrome p450 (CYP) enzymes are agents of drug metabolism that are found in the liver, the gastrointestinal tract and other locations in the body. CYP enzymes occur in a variety of closely related proteins referred to as isozymes and different CYP isozymes may preferentially metabolize different drugs. The 3A family of CYP isozymes, particularly CYP3A4, is also known to be involved in many clinically significant drug-drug interactions, including those involving colchicine and second active agents. While drugs are often targets of CYP-mediated metabolism, some may also alter the expression and activity of such enzymes, thus impacting the metabolism of other drugs. The biotransformation of colchicine in human liver microsomes involves formation of 3-demethylcolchicine and 2-demethylcolchicine. As shown by experiments using antibodies against CYP3A4 and experiments using chemical inhibition of CYP3A4, this transformation is correlated with (and thus apparently mediated by) CYP3A4 activity.

P-glycoprotein (P-gp) is an ATP-dependent cell surface transporter molecule that acts as an ATPase efflux pump for multiple cytotoxic agents, including colchicine. P-gp actively pumps certain compounds, including drugs such as colchicine, out of cells. P-gp is encoded by the Adenosine triphosphate-binding cassette subfamily B member 1 (ABCB1) gene, also referred to as the multiple drug resistance 1 gene (MDR1).

Since colchicine acts intracellularly, the combined effects of CYP3A4 inhibition and P-gp inhibition by second active agents that also interact with CYP3A4 and P-gp can cause colchicine toxicity in patients taking what would be a safe dose of colchicine in the absence of concomitant second agent administration. Various studies of adverse reactions from exposure to multiple drugs have found that 6.5-23% of the adverse reactions result from drug-drug interactions. Unfortunately, each year a number of deaths occur as the direct result of patients adding a concomitant prescription pharmaceutical product to their existing medication regimen.

There accordingly remains a need for improved methods for administering colchicine to individuals who are concomitantly being treated with second active agents so as to reduce the possibility of colchicine toxicity while maintaining the sometimes life-saving advantages of being able to administer the two (or more) agents concomitantly. The present disclosure addresses this need and provides further advantages.

SUMMARY

In one embodiment, a method of treating an individual in need of treatment with colchicine comprises concomitantly administering to the individual colchicine and another drug, for example, ketoconazole or ritonavir or cyclosporine, wherein the colchicine is administered as a dosing regimen with a starting colchicine dose of no more than about 0.6 mg colchicine, followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours and no more frequently than once every hour wherein each additional colchicine dose is no greater than about 0.6 mg. According to another embodiment, the other drug is, for example, verapamil or diltiazem, and the starting colchicine dose during coadministration with

US 7,964,648 B2

3

the other drug is no more than about 1.2 mg colchicine, followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours.

In another aspect, a method of using colchicine comprises increasing the blood plasma levels of colchicine in a individual being administered doses of about 0.6 mg or less of colchicine to treat a colchicine-treatable condition, said method comprising the concomitant dosing of the individual with a sufficient amount of ketoconazole to increase the C_{max} of colchicine by about 90%, or to increase the AUC_{0-8} of colchicine in the individual by about 190%, or to increase the AUC_{0-inf} of colchicine in the individual by about 205%, or to decrease the clearance of colchicine by about 70%, compared to the C_{max} , AUC_{0-8} , AUC_{0-inf} or clearance in a matched individual not administered concomitant ketoconazole.

In yet another aspect, a method of using colchicine comprises increasing the blood plasma levels of colchicine in an individual being administered doses of about 0.6 mg or less of colchicine to treat a colchicine-treatable condition, said method comprising the concomitant dosing of the individual with a sufficient amount of ritonavir to increase the C_{max} of colchicine by about 170%, or to increase the AUC_{0-8} of colchicine in the individual by about 245%, or to decrease the clearance of colchicine by about 70%, compared to the C_{max} , AUC_{0-8} , or clearance in a matched individual not administered concomitant ritonavir.

In another embodiment, a method for using colchicine comprises a pharmacy receiving a prescription for colchicine for a patient who is concomitantly being treated with ketoconazole or ritonavir or verapamil, and the pharmacy dispensing colchicine in response to receipt of the prescription, wherein the dispensing is preceded by: entering, into a first computer readable storage medium in functional communication with a computer, of a unique patient identifier for said patient and at least one drug identifier for colchicine linked to the patient identifier so as to indicate that colchicine is to be administered to the patient, wherein the computer has been programmed to issue a drug-drug interaction alert when the at least one drug identifier for colchicine is entered linked to the patient identifier so as to indicate that colchicine is to be administered to the patient and when the patient identifier is also linked to an identifier indicating that ketoconazole or ritonavir or verapamil is being concomitantly administered to the patient, wherein, upon entry of the at least one drug identifier for colchicine linked to the patient identifier, a drug-drug interaction alert is issued to one or more of a pharmacy technician, a pharmacist, or a pharmacy customer obtaining the colchicine, said alert indicating that that ketoconazole or ritonavir is being concomitantly administered to the patient and that prior to the colchicine being dispensed, the colchicine dosing regimen must be reviewed and, if necessary adjusted, so that when the colchicine is delivered to the pharmacy customer obtaining the colchicine it is delivered along with instructions for the colchicine to be taken in accordance with a dosing regimen of no more than about 0.6 mg colchicine, followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours and no more frequently than once every hour wherein each additional colchicine dose is no greater than about 0.6 mg.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ritonavir, wherein the adjusted daily dosage amount of colchicine is about 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount

4

of colchicine is a dose suitable for the patient if the patient were not receiving concomitant ritonavir.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ketoconazole, wherein the adjusted daily dosage amount of colchicine is about 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant ketoconazole.

A method of treating an individual in need of treatment for gout flares, comprises concomitantly administering colchicine and azithromycin, and carefully monitoring the individual for potential toxicity. The method further comprises adjusting the dose of colchicine or azithromycin as necessary to avoid adverse side effects.

A method of treating an individual with colchicine comprises concomitantly administering colchicine and verapamil, and carefully monitoring the individual for signs and symptoms of adverse side effects. The method further comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of verapamil, wherein the adjusted daily dosage amount of colchicine is about 50% to 75% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for a patient if the patient were not receiving concomitant verapamil.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows mean colchicine plasma concentrations following administration of single and multiple oral doses of colchicine 0.6 mg in healthy adults, N=13, Y axis=colchicine concentration, ng/mL, X axis=time in hours, ◆=day 1, ■=day 25. See Example 1.

FIG. 2 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin in healthy adults, Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=23, ●=colchicine alone, ◆=colchicine plus clarithromycin. See Example 2.

FIG. 3 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin and steady-state cyclosporine in healthy adults, Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=18, ▲=colchicine alone, ●=colchicine plus clarithromycin, ■=colchicine plus cyclosporine.

FIG. 4 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state ketoconazole and steady-state ritonavir in healthy adults, Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=18, ▲=colchicine alone, ●=colchicine plus ketoconazole, ■=colchicine plus ritonavir.

FIG. 5 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state azithromycin and steady-state diltiazem in healthy adults, Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=18, ▲=colchicine alone, ●=colchicine plus azithromycin, ■=colchicine plus diltiazem.

These and other embodiments, advantages and features of the present invention become clear when detailed description is provided in subsequent sections.

DETAILED DESCRIPTION

Disclosed herein are methods for safely administering colchicine concomitantly with a second active agent, wherein the second active agent is a CYP3A4 inhibitor, a P-gp inhibitor, or both. Exemplary second active agents that are CYP3A4 and P-gp inhibitors are azithromycin, ketoconazole, ritonavir, diltiazem, verapamil and cyclosporine. It has now been discovered that certain reduced or limited colchicine dosage amounts, when administered with concomitantly administered recommended dosage amounts of second active agents that are CYP3A4 inhibitors, P-gp inhibitors, or both, achieve plasma colchicine levels that are therapeutically effective, but are not significantly higher, and therefore not significantly more toxic, than plasma levels achieved by administration of manufacturers' recommended colchicine dosages in the absence of concomitant administration with the second active agent. Thus, colchicine and second active agents that are CYP3A4 inhibitors, P-gp inhibitors, or both, can be administered concomitantly with improved safety when colchicine is administered as disclosed herein.

Without being held to theory, it has been hypothesized by the inventors herein that P-gp inhibition is more important in the elimination of colchicine than CYP3A4 inhibition. The CYP3A4 and P-gp inhibition potential of clarithromycin, azithromycin, ketoconazole, ritonavir, diltiazem and cyclosporine are given in Table 1. Based on their level of P-gp inhibition, it was predicted that clarithromycin and cyclosporine will increase colchicine concentrations more than ketoconazole or ritonavir, which will increase colchicine levels more than verapamil, azithromycin or diltiazem. The results presented herein confirm this hypothesis.

TABLE 1

| CYP3A4 and P-gp inhibition potential of second active agents | | |
|--------------------------------------------------------------|----------------------------|---------------------------|
| Drug | CYP3A Inhibition potential | P-gp Inhibition potential |
| Clarithromycin | +++++ | +++++ |
| Cyclosporine | +++++ | +++++ |
| Ketoconazole | +++++ | +++ |
| Ritonavir | +++++ | +++ |
| Verapamil | ++ | ++ |
| Diltiazem | + | + |
| Azithromycin | + | + |

Ritonavir (Norvir®, Abbott Laboratories) is an inhibitor of Human Immunodeficiency Virus (HIV) protease and is approved for the treatment of HIV-infection when used as part of a highly active antiretroviral therapy (HAART) regimen at the recommended dose of 600 mg twice daily. Although a very potent and effective protease inhibitor at the recommended dose, ritonavir is not well tolerated by HIV-infected patients at the approved dose and therefore, is generally not used clinically as a sole, therapeutic protease inhibitor within a HAART regimen. Rather, ritonavir is used more often as a pharmacokinetic enhancer or 'boosting agent' when combined with other approved protease inhibitors that are CYP3A4 and P-gp substrates and also have inherent bioavailability issues, such as poor bioavailability due to first pass effect. Improving the pharmacokinetic disposition of other protease inhibitors is possible due to the potent CYP3A4 and P-gp inhibitory activity ritonavir possesses. Sub-therapeutic ritonavir doses are used to achieve pharmacokinetic enhance-

ment of the co-administered protease inhibitors; typically 100 mg of ritonavir administered twice daily is the ritonavir dose used in combination with the primary protease inhibitor. This low-dose ritonavir regimen boosts the bioavailability of the second protease inhibitor without contributing significantly to the adverse event profile of the HAART regimen.

Cyclosporine (Neoral®, Novartis Pharmaceuticals Corporation) is the active principle in Neoral® an oral formulation that immediately forms a microemulsion in an aqueous environment. Cyclosporine is indicated for kidney, liver, and heart transplantation; rheumatoid arthritis and psoriasis. Cyclosporine is extensively metabolized by the CYP3A4 enzyme system in the liver, and to a lesser degree in the gastrointestinal tract, and the kidney. The metabolism of cyclosporine can be altered by the co-administration of a variety of agents.

Ketoconazole is a synthetic broad-spectrum antifungal agent available in scored white tablets, each containing 200 mg ketoconazole base for oral administration. Ketoconazole tablets are indicated for the treatment of the following systemic fungal infections: candidiasis, chronic mucocutaneous candidiasis, oral thrush, candiduria, blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. Ketoconazole is a potent inhibitor of the CYP3A4 enzyme system. Co-administration of ketoconazole and drugs primarily metabolized by the CYP3A4 enzyme may result in increased plasma concentrations of the drugs that could increase or prolong both therapeutic and adverse side effects.

Azithromycin is a macrolide antibiotic indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in specific conditions. Azithromycin remains the sole agent developed and marketed within the azalide macrolide subclass. Due to its dibasic structure, azithromycin has demonstrated unique pharmacokinetic properties that differ significantly from those of classic macrolide agents. Azithromycin's pharmacokinetics are characterized by low concentrations in serum, secondary to rapid and significant uptake by fibroblasts and acute reactant cells such as polymorphonuclear leukocytes (PMNs), monocytes, and lymphocytes. Azithromycin is a weak to moderate CYP3A4 inhibitor.

Diltiazem (Cardizem® CD, Biovail Pharmaceuticals, Inc. [Biovail]) is an extended-release (ER) calcium ion influx inhibitor available in blue capsules, each containing 240 mg diltiazem hydrochloride for oral administration. Diltiazem ER capsules are indicated for the treatment of hypertension and the management of chronic stable angina and angina due to coronary artery spasm. Diltiazem is a CYP3A4 and P-gp inhibitor.

Verapamil HCl ER (Mylan Pharmaceuticals, Inc.) is a calcium ion influx inhibitor available in a pale green, capsule shaped, film-coated tablets, each containing 240 mg verapamil hydrochloride for oral administration. Verapamil HCl ER tablets are indicated for the management of hypertension. Verapamil HCl ER is a potent CYP3A4 and P-gp inhibitor.

In one embodiment, colchicine is administered to an individual suffering from a condition treatable with colchicine, and the concomitant second active agent (e.g., ketoconazole, ritonavir, cyclosporine, verapamil, or diltiazem or any other CYP3A4 or P-gp inhibitor) is administered concurrently while the colchicine administration is reduced, or the individual has recently completed a dosing regimen of the second active agent, in which case the colchicine administration may still be reduced for a period of time.

In one embodiment, disclosed herein is a method of administering colchicine and a second active agent (e.g., ketoconazole).

US 7,964,648 B2

7

zole, ritonavir, or cyclosporine) wherein an individual is administered the colchicine according to a colchicine dosing regimen of a single starting colchicine dose of no more than about 0.6 mg colchicine, followed by either no additional colchicine doses within about 12, 24, 48, or 72 hours, or followed by at least one additional colchicine dose within 12 hours and no more frequently than once every hour (e.g., every 3, 4, 6, 8, or 12 hours). In this embodiment, each additional colchicine dose is specifically no greater than about 0.3 mg and the individual is an adult individual or a pediatric individual. Specifically, the starting colchicine dose is about 0.6 mg or about 0.3 mg, and each additional colchicine dose is about 0.3 mg. In one embodiment, when additional doses are administered, only two, three, or four additional colchicine doses are administered within about 24 hours. Specifically, the individual is an adult individual and the starting colchicine dose is about 0.6 mg, and each additional colchicine dose, if any, is about 0.3 mg. In one embodiment, only three additional colchicine doses are administered within about 24 hours.

In one embodiment, disclosed herein is a method of administering colchicine and a second active agent (e.g., verapamil or diltiazem) wherein an individual is administered the colchicine according to a colchicine dosing regimen of a single starting colchicine dose of no more than about 1.2 mg colchicine, followed by either no additional colchicine doses within about 12, 24, 48, or 72 hours, or followed by at least one additional colchicine dose within 12 hours and no more frequently than once every hour (e.g., every 3, 4, 6, 8, or 12 hours). In this embodiment, each additional colchicine dose is specifically no greater than about 0.3 mg or 0.6mg and the individual is an adult individual or a pediatric individual. Specifically, the starting colchicine dose is about 0.6mg or 1.2 mg, and each additional colchicine dose is about 0.3 mg or 0.6mg. In one embodiment, when additional doses are administered, only two, three, or four additional colchicine doses are administered within about 24 hours. Specifically, the individual is an adult individual and the starting colchicine dose is about 1.2 mg, and each additional colchicine dose, if any, is about 0.3 mg or 0.6 mg. In one embodiment, only three additional colchicine doses are administered within about 24 hours.

In one embodiment, the second active agent is ketoconazole or ritonavir. In one embodiment, the ketoconazole is administered to the individual at a dosage of about 200 mg daily and the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by 0, 1, 2, 3, or 4 additional colchicine doses of about 0.6 mg every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In another embodiment, the ritonavir is administered to the individual at a dosage of about 200 to 1200 mg daily (e.g., in 2x100 mg doses or 2x600 mg doses) and the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by 0, 1, 2, 3, or 4 additional colchicine doses of about 0.6 mg every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In an exemplary regimen for treatment of acute gout flares, ingestion of colchicine is continued until a total of no more than about 1.2, 1.4, 1.6, 1.8, 2, or 2.4 mg of colchicine has been ingested, after which ingestion of colchicine is stopped until a subsequent acute gout flare occurs. More preferably, the colchicine is administered as a dosage form of 0.6 mg (e.g., one 0.6 mg colchicine tablet), or 0.3 mg (e.g., one half of a 0.6 mg tablet) of colchicine and administration of the dosage form is not repeated within a period of at least about two days, preferably at least about three days.

8

In one embodiment, the second active agent (e.g., ketoconazole or ritonavir or cyclosporine) is administered to the individual before the colchicine is administered to the individual, and wherein the administration of second active agent is terminated no more than about fourteen days prior to the initiation of colchicine administration. For example, the method comprises administering colchicine to an individual also taking a second active agent (e.g., ketoconazole or ritonavir or cyclosporine), or having completed treatment with the second active agent within the prior 14 days, the individual being administered a single dose of about 0.6 mg or about 0.3 mg of colchicine to treat a gout flare, which administration is not repeated within any 3-day period. According to this embodiment if the second active agent is instead verapamil or diltiazem, if the second active agent is terminated no more than about fourteen days prior to the initiation of the colchicine administration to treat a gout flare, the single dose of colchicine is about 1.2mg not to be repeated within a 3-day period.

In another aspect, herein disclosed is a method for increasing the blood plasma levels of colchicine in an individual to whom colchicine is being administered to treat or prevent a colchicine-responsive condition. This method comprises the concomitant dosing of the individual with a sufficient amount of ketoconazole to increase the C_{max} of colchicine by about 90%, or to increase the AUC_{0-t} of colchicine in the individual by about 190%, or to increase the AUC_{0-inf} of colchicine in the individual by about 205%, or to decrease the clearance of colchicine by about 70%, compared to the C_{max} , AUC_{0-t} , or clearance in the same or a matched individual when not being administered a concomitant ketoconazole. In a specific embodiment, the individual is being administered no more than hourly doses of about 0.6 mg of colchicine or less, and the amount of ketoconazole is about 200 mg. In one embodiment, the single dose is one 0.6 mg colchicine tablet.

In yet another aspect, herein disclosed is a method for increasing the blood plasma levels of colchicine in an individual to whom colchicine is being administered to treat or prevent a colchicine-responsive condition. This method comprises the concomitant dosing of the individual with a sufficient amount of ritonavir to increase the C_{max} of colchicine by about 170%, or to increase the AUC_{0-t} of colchicine in the individual by about 245%, or to decrease the clearance of colchicine by about 70%, compared to the C_{max} , AUC_{0-t} , or clearance in the same or a matched individual when not being administered concomitant ritonavir. In a specific embodiment, the individual is being administered no more than hourly doses of about 0.6 mg of colchicine or less, and the amount of ritonavir is about 200 to about 1200 mg. In one embodiment, the single dose is one 0.6 mg colchicine tablet.

In one embodiment, a method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ritonavir, wherein the adjusted daily dosage amount of colchicine is 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant ritonavir. Treating is, for example, to prevent gout flares, to treat acute gout, or to treat familial Mediterranean fever. When the colchicine is administered to prevent gout flares, the adjusted daily dosage amount of colchicine may be reduced from a 0.6 mg twice daily intended dose to a 0.6 mg once daily adjusted dose. Alternatively, when the colchicine is administered to prevent gout flares, wherein the adjusted daily dosage amount of colchicine is reduced from a 0.6 mg once daily intended dose to a 0.3 mg once daily adjusted dose.

US 7,964,648 B2

9

In one embodiment, when treating is for acute gout, the intended daily dosage amount is 1.8 to 2.4 mg, and the maximum adjusted daily dosage amount is 0.6 mg, not to be repeated within 3 days. In another embodiment, treating is for acute gout, the intended daily dosage amount is 2.4 to 4.8 mg and the maximum adjusted daily dosage amount is 0.6 to 1.2 mg, not to be repeated within 3 days. In yet another embodiment, treating is for familial Mediterranean fever and the daily dosage amount 1.2 to 2.4 mg for adults, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. In another embodiment, treating is for familial Mediterranean fever and the intended daily dosage amount is 0.9 to 1.8 mg for children 6-12 years or 4-6 years, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. The concomitantly administered dose of ritonavir is, for example, 200 mg per day. In one embodiment, the ritonavir is administered to the patient before the colchicine is administered to the patient, and wherein the administration of ritonavir is terminated no more than about fourteen days prior to the initiation of colchicine administration. The method optionally further comprises carefully monitoring the individual for potential toxicity. Any 0.3 mg dose contemplated in this method can be a single 0.3 mg dosage form or one-half a 0.6 mg dosage form, e.g. one-half a 0.6 mg colchicine tablet.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ketoconazole, wherein the adjusted daily dosage amount of colchicine is 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant ketoconazole. Treating is, for example, to prevent gout flares, to treat acute gout, or to treat familial Mediterranean fever. When the colchicine is administered to prevent gout flares, the adjusted daily dosage amount of colchicine may reduced from a 0.6 mg twice daily intended dose to a 0.6 mg once daily adjusted dose. Alternatively, when the colchicine is administered to prevent gout flares, wherein the adjusted daily dosage amount of colchicine is reduced from a 0.6 mg once daily intended dose to a 0.3 mg once daily adjusted dose. In one embodiment, when treating is for acute gout, the intended daily dosage amount is 1.8 to 2.4 mg, and the maximum adjusted daily dosage amount is 0.6 mg, not to be repeated within 3 days. In another embodiment, treating is for acute gout, the intended daily dosage amount is 2.4 to 4.8 mg and the maximum adjusted daily dosage amount is 0.6 to 1.2 mg, not to be repeated within 3 days. In yet another embodiment, treating is for familial Mediterranean fever and the daily dosage amount 1.2 to 2.4 mg for adults, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. In another embodiment, treating is for familial Mediterranean fever and the intended daily dosage amount is 0.9 to 1.8 mg for children 6-12 years or 4-6 years, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. The concomitantly administered dose of ketoconazole is, for example, 250 mg per day. In one embodiment, the ketoconazole is administered to the patient before the colchicine is administered to the patient, and wherein the administration of ketoconazole is terminated no more than about fourteen days prior to the initiation of colchicine administration. The method optionally further comprises carefully monitoring the individual for potential toxicity. Any 0.3 mg dose contemplated in this method can be a single 0.3 mg dosage form or one-half a 0.6 mg dosage form, e.g. one-half a 0.6 mg colchicine tablet.

10

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of cyclosporine, wherein the adjusted daily dosage amount of colchicine is 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant cyclosporine. Treating is, for example, to prevent gout flares, to treat acute gout, or to treat familial Mediterranean fever. When the colchicine is administered to prevent gout flares, the adjusted daily dosage amount of colchicine may reduced from a 0.6 mg twice daily intended dose to a 0.3 mg once daily adjusted dose. Alternatively, when the colchicine is administered to prevent gout flares, wherein the adjusted daily dosage amount of colchicine is reduced from a 0.6 mg once daily intended dose to a 0.3 mg once every other day adjusted dose. In one embodiment, when treating is for acute gout, the intended daily dosage amount is 1.8 to 2.4 mg, and the maximum adjusted daily dosage amount is 0.6 mg, not to be repeated within 3 days. In another embodiment, treating is for acute gout, the intended daily dosage amount is 2.4 to 4.8 mg and the maximum adjusted daily dosage amount is 0.6 to 1.2 mg, not to be repeated within 3 days. In yet another embodiment, treating is for familial Mediterranean fever and the daily dosage amount 1.2 to 2.4 mg for adults, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. In another embodiment, treating is for familial Mediterranean fever and the intended daily dosage amount is 0.9 to 1.8 mg for children 6-12 years or 4-6 years, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. The concomitantly administered dose of cyclosporine can be various dosage strengths administered per day, and can be administered as an oral preparation, topically, or intravenously. In one embodiment, the cyclosporine is administered to the patient before the colchicine is administered to the patient, and wherein the administration of cyclosporine is terminated no more than about fourteen days prior to the initiation of colchicine administration. The method optionally further comprises carefully monitoring the individual for potential toxicity. Any 0.3 mg dose contemplated in this method can be a single 0.3 mg dosage form or one-half a 0.6 mg dosage form, e.g. one-half a 0.6 mg colchicine tablet.

In another embodiment, colchicine is concomitantly administered with azithromycin. Concomitant administration of azithromycin with colchicine increases exposure to colchicine approximately 46% and thus has the potential to produce colchicine toxicity. During concomitant use of azithromycin and colchicine, the physician should carefully monitor individuals for any signs or symptoms of colchicine toxicity. Additionally, dosing adjustments to either the colchicine and/or the azithromycin may be necessary to avoid adverse side effects.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of verapamil, wherein the adjusted daily dosage amount of colchicine is 50% to 75% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant verapamil. Treating is, for example, to prevent gout flares, to treat acute gout, or to treat familial Mediterranean fever. When the colchicine is administered to prevent gout flares, the adjusted daily dosage amount of colchicine may reduced from a 0.6 mg twice daily intended dose to a 0.3 mg once daily adjusted

dose. In one embodiment, when treating is for acute gout, the intended daily dosage amount is 1.8 to 2.4 mg, and the maximum adjusted daily dosage amount is 1.2 mg. In another embodiment, treating is for acute gout, the intended daily dosage amount is 2.4 to 4.8 mg and the maximum adjusted daily dosage amount is about one-third the intended daily dosage amount. In yet another embodiment, treating is for familial Mediterranean fever and the daily dosage amount 1.2 to 2.4 mg for adults, and the maximum adjusted daily dosage amount is 1.2 mg, given, for example, in two 0.6 mg doses. In one embodiment, the verapamil is administered to the patient

Acute Gout
Acute gout, or gout flares, can be treated according to the following treatment schedule. This table indicates the original, or intended, dose, i.e., the dose of colchicine recommended absent concomitant administration of the drugs listed below. This table also presents the dose adjustment of the present invention, or the recommended colchicine dose to be administered when the strong and moderate CYP3A4 and P-gp inhibitors are administered concomitantly with colchicine when the patient is being treated for acute gout, or an acute gout flare.

| Drug | Colchicine Dose Recommendation | |
|-------------------------------|-------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| | Original Intended Dose (Total Dose) | Dose Adjustment |
| Strong CYP3A4 Inhibitors | | |
| Regimen Reduced by Two Thirds | | |
| Erythromycin | 1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 tablet) one hour later. | 0.6 mg (1 tablet) × 1 dose. Dose to be repeated no earlier than 3 days. |
| Ketoconazole | | |
| Ritonavir | Dose to be repeated no earlier than 3 days. | |
| Moderate CYP3A4 Inhibitors | | |
| Regimen Reduced by One Third | | |
| Diltiazem | 1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 tablet) one hour later. | 1.2 mg (2 tablets) × 1 dose. Dose to be repeated no earlier than 3 days. |
| Verapamil | Dose to be repeated no earlier than 3 days. | |
| Strong P-gp Inhibitors | | |
| Regimen Reduced by Two Thirds | | |
| Cyclosporine | 1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 tablet) one hour later. | 0.6 mg (1 tablet) × 1 dose. Dose to be repeated no earlier than 3 days. |
| | Dose to be repeated no earlier than 3 days. | |

before the colchicine is administered to the patient, and wherein the administration of verapamil is terminated no more than about fourteen days prior to the initiation of colchicine administration. The method optionally further comprises carefully monitoring the individual for potential toxicity. Any 0.3 mg dose contemplated in this method can be a single 0.3 mg dosage form or one-half a 0.6 mg dosage form, e.g. one-half a 0.6 mg colchicine tablet.

Disclosed herein are specific dosage reductions of colchicine that improve safety when colchicine is co-administered with certain active agents. The dose of colchicine recommended for administration without co-administration of certain other active agents, such as CYP3A4 or P-gp inhibitors, is referred to as an intended daily dosage amount. The reduced or modified daily dosage amount determined from the experiments presented herein is referred to as an adjusted daily dosage amount. An adjusted daily dosage amount is thus a daily dosage amount that can be safely co-administered with a second active agent as disclosed herein. A dose adjustment is thus a dose of colchicine and does not include cessation of colchicine, that is, a dose of 0 mg of colchicine.

In these and other embodiments, the colchicine-responsive condition is gout (e.g., a gout flare in a chronic gout sufferer), familial Mediterranean fever (FMF), thrombocytopenic purpura, pericarditis, scleroderma, or Behçet's disease. In some embodiments, the treatment with colchicine is either palliative or prophylactic. The gout may be acute gout, e.g. a gout flare, or chronic gout.

Chronic Gout
For chronic gout, an original intended daily dosage amount is 1.2 mg or 6 mg. Alternatively, an intended daily dosage amount of chronic gout can be as much as 2.4 mg per day. The daily dosage amount for chronic gout can be administered at one time or dosed at intervals throughout the day, e.g. twice daily, three times daily, or four times daily.
Chronic gout, with and without a concomitant dose of another drug, can be treated according to the following treatment schedule:

Colchicine Dose Adjustment for Co-administration with Interacting Drugs If No Alternative Available

| Drug | Colchicine Dose Recommendation | |
|----------------|--------------------------------|-----------------------------|
| | Original Intended Dose | Dose Adjustment |
| Clarithromycin | 0.6 mg twice daily | 0.3 mg once daily |
| | 0.6 mg once daily | 0.3 mg once every other day |
| Cyclosporine | 0.6 mg twice daily | 0.3 mg once daily |
| | 0.6 mg once daily | 0.3 mg once every other day |
| Erythromycin | 0.6 mg twice daily | 0.3 mg once daily |
| | 0.6 mg once daily | 0.3 mg once every other day |
| Ritonavir | 0.6 mg twice daily | 0.6 mg once daily |
| | 0.6 mg once daily | 0.3 mg once daily |

Familial Mediterranean Fever
Familial Mediterranean Fever (FMF) can be treated according to the following intended daily dosing schedule:

US 7,964,648 B2

13

| Age | Daily dosage amount | |
|-------------------------------|---------------------|---------|
| | Usual | Maximum |
| Adults and children >12 years | 1.2 mg | 2.4 mg |
| Children >6 to 12 years | 0.9 mg | 1.8 mg |
| Children 4 to 6 years | 0.3 mg | 1.8 mg |

When colchicine is given to patients with FMF concomitantly with other drugs, the adjusted (reduced) dosage amount of colchicine, according to this embodiment, is provided in the table below:

| Concomitant Drug Class or Food | Noted or Anticipated Outcome | Clinical Comment |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Strong CYP3A4 Inhibitors: atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin | Significant increase in colchicine plasma levels ¹ ; fatal colchicine toxicity has been reported with clarithromycin, a strong CYP3A4 inhibitor. Similarly, significant increase in colchicine plasma levels is anticipated with other strong CYP3A4 inhibitors. | Use colchicine with caution at reduced maximum dose of 0.3 mg twice daily with increased monitoring for adverse effects. In patients with renal or hepatic impairment, use of colchicine in conjunction with these drugs is contraindicated. |
| Moderate CYP3A4 inhibitors: amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, verapamil | Significant increase in colchicine plasma concentration is anticipated. Neuromuscular toxicity has been reported with diltiazem and verapamil interactions. | Use colchicine with caution at reduced maximum dose of 0.6 mg twice daily with increased monitoring for adverse effects. In patients with renal or hepatic impairment, use a maximum dose of 0.3 mg twice daily. |
| Strong P-gp Inhibitors e.g. Cyclosporine, ranolazine. | Significant increase in colchicine plasma levels ¹ ; fatal colchicine toxicity has been reported with cyclosporine, a strong P-gp inhibitor. Similarly, significant increase in colchicine plasma levels is anticipated with other strong P-gp inhibitors. | Use colchicine with caution at reduced maximum dose of 0.3 mg twice daily with increased monitoring for adverse effects. In patients with renal or hepatic impairment, use of colchicine in conjunction with these drugs is contraindicated. |

Pharmacy management systems are computer-based systems that are widely used by commercial pharmacies to manage prescriptions and to provide pharmacy and medical personnel with warnings and guidance regarding drugs being administered to individuals. Such systems typically provide alerts warning either or both of health care providers and patients when a drug that may be harmful to the particular patient is prescribed. For example, such systems can provide alerts warning that a patient has an allergy to a prescribed drug, or is receiving concomitant administration of a drug that can have a dangerous interaction with a prescribed drug. U.S. Pat. Nos. 5,758,095, 5,833,599, 5,845,255, 6,014,631, 6,067, 524, 6,112,182, 6,317,719, 6,356,873, and 7,072,840, each of which is incorporated herein by reference, disclose various pharmacy management systems and aspects thereof. Many pharmacy management systems are now commercially available, e.g., CENTRICITY Pharmacy from BDM Information Systems Ltd., General Electric Healthcare, Waukesha, Wis., Rx30 Pharmacy Systems from Transaction Data Systems, Inc., Ocoee, Fla., SPEED SCRIPT from Digital Simplistics,

14

Inc., Lenexa, Ky., and various pharmacy management systems from OPUS-ISM, Hauppauge, N.Y.

In another aspect, herein disclosed are methods for using colchicine which methods involve the use of pharmacy management systems.

In one aspect, one such method comprises a pharmacy receiving a prescription for colchicine for a patient who is suffering from gout (e.g., acute gout flares or chronic gout) and who is concomitantly being treated with a second active agent (e.g., ketoconazole or ritonavir) that is an inhibitor of CYP3A and P-glycoprotein, followed by the pharmacy dispensing colchicine in response to receipt of the prescription, wherein the dispensing is preceded by entry into a first computer readable storage medium, in functional communication

with a computer, of a unique patient identifier for said patient and at least one drug identifier for colchicine linked to the patient identifier so as to indicate that colchicine is to be administered to the patient. The computer is programmed to issue a drug-drug interaction alert when the at least one drug identifier for colchicine is entered linked to the patient identifier so as to indicate that colchicine is to be administered to the patient and when the patient identifier is also linked to an identifier indicating that a second active agent (e.g., ketoconazole or ritonavir) that is an inhibitor of CYP3A4 or P-glycoprotein is being concomitantly administered to the patient. Upon entry of the at least one drug identifier for colchicine linked to the patient identifier, a drug-drug interaction alert is issued to one or more of a pharmacy technician, a pharmacist, or a pharmacy customer obtaining the colchicine, said alert indicating that a second active agent (e.g., ketoconazole or ritonavir) is being concomitantly administered to the patient and that prior to the colchicine being dispensed, the colchicine dosing regimen must be reviewed and, if necessary adjusted, so that when the colchicine is delivered to the phar-

US 7,964,648 B2

15

macy customer obtaining the colchicine it is delivered along with instructions for the colchicine to be taken in accordance with a dosing regimen of no more than one about 0.6 mg colchicine dose to start (e.g., following the onset of the acute gout attack or the first sign of a gout flare) followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours and no more frequently than once every hour and wherein each additional colchicine dose is no greater than about 0.6 mg, and wherein the patient ingests the colchicine as instructed.

The drug-drug interaction alert is preferably issued as one or both of a written warning on a display screen of the pharmacy management computer system, and a printed warning. The printed warning may be attached to or packaged with the dispensed prescription.

In one aspect, the identifier indicating that ketoconazole is being concomitantly administered to the patient is an identifier indicating that the second active agent is ketoconazole and is linked to at least one further identifier indicating that the ketoconazole is prescribed so that 200 mg of ketoconazole is to be ingested by the patient daily, in which case the dosing regimen for colchicine is preferably one about 0.6 mg colchicine dose to start, optionally followed by additional colchicine doses, e.g., 0, 1, 2, 3, or 4 additional colchicine doses within 24 hours of about 0.3 mg ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In another embodiment, the identifier indicating that ketoconazole is being concomitantly administered to the patient is an identifier indicating that the second active agent is ketoconazole is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the ketoconazole is prescribed so that about 200 mg of ketoconazole is to be ingested by the patient daily, in which case the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every six to eight hours) after the preceding colchicine dose. In one embodiment, the dosing regimen calls for the about 0.3 mg colchicine dose every six to eight hours. In another embodiment, the dosing regimen calls for one dose of the colchicine every eight to twelve hours.

In yet another preferred aspect, the identifier indicating that ketoconazole is being concomitantly administered to the patient is an identifier indicating that the second active agent is ketoconazole and is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the ketoconazole is prescribed so that about 200 mg of ketoconazole is to be ingested by the patient daily and the dosing regimen is one about 0.3 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 2, 3, 4, 5, 6, 7, or 8 hours (e.g., every eight to twelve hours) after the preceding colchicine dose.

A preferred dosing regimen calls for ingestion of colchicine to be continued until a total of no more than 1.2 mg or 2.4 mg of colchicine has been ingested, after which ingestion of colchicine is to be stopped, e.g., for at least 2, 3, 4, 5, 6, or 7 days, or until a subsequent acute gout flare, or the first sign of a subsequent gout flare, occurs.

16

In another aspect, the identifier indicating that ritonavir is being concomitantly administered to the patient is an identifier indicating that the second active agent is ritonavir and is linked to at least one further identifier indicating that the ritonavir is prescribed so that 200 or 1200 mg of ritonavir is to be ingested by the patient daily, in which case the dosing regimen for colchicine is preferably one about 0.6 mg colchicine dose to start, optionally followed by additional colchicine doses, e.g., 0, 1, 2, 3, or 4 additional colchicine doses within 24 hours of about 0.3 mg ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In another embodiment, the identifier indicating that ritonavir is being concomitantly administered to the patient is an identifier indicating that the second active agent is ritonavir is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the ritonavir is prescribed so that about 1200 mg of ritonavir is to be ingested by the patient daily, in which case the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every six to eight hours) after the preceding colchicine dose. In one embodiment, the dosing regimen calls for the about 0.3 mg colchicine dose every six to eight hours. In another embodiment, the dosing regimen calls for one dose of the colchicine every eight to twelve hours.

In yet another aspect, the identifier indicating that ritonavir is being concomitantly administered to the patient is an identifier indicating that the second active agent is ritonavir and is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the ritonavir is prescribed so that about 1200 mg of ritonavir is to be ingested by the patient daily and the dosing regimen is one about 0.3 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 2, 3, 4, 5, 6, 7, or 8 hours (e.g., every eight to twelve hours) after the preceding colchicine dose.

Also disclosed herein is a dosage adjustment method for administering colchicine to a patient to treat a medical condition, the patient concomitantly treated with a second active agent. The second active agent may be, for example, ritonavir, ketoconazole, cyclosporine, verapamil, or diltiazem. The method comprises determining a first colchicine dosing regimen (the colchicine dosing regimen suitable for administration in the absence of co-administration with a second active agent, which dosing regimen may consist of one or more doses of colchicine); and determining a second active agent dosing regimen; and administering the second active agent to the patient at the second active agent dosing regimen while concomitantly administering colchicine to the patient according to a second colchicine dosing regimen, which may consist of one or more reduced colchicine doses. The second colchicine dosing regimen is a fraction of the first colchicine dosing regimen, where the fraction is obtained by administering reduced colchicine doses or by reducing the frequency of colchicine doses, and wherein the fraction is less than or equal to about $\frac{2}{3}$ or less than or equal to about $\frac{1}{2}$ or less than or equal to about $\frac{1}{3}$.

According to this embodiment, upon the administering the second active agent to the patient at the second active agent dosing regimen while concomitantly administering colchicine to the patient at the second colchicine dosing regimen,

US 7,964,648 B2

17

the therapeutic circulating level of colchicine is achieved in the patient. Preferably, the fraction is selected from $\frac{1}{12}$, $\frac{1}{6}$, $\frac{1}{4}$, $\frac{1}{3}$, $\frac{5}{12}$, and $\frac{1}{2}$, more preferably, the fraction is $\frac{1}{3}$ or $\frac{1}{2}$. In one embodiment, if the second colchicine dosing regimen comprises a "first" colchicine dose, and one or more "subsequent" colchicine doses, each subsequent colchicine dose may be the same as the first dose, or a fraction of the first dose. The fraction is selected from about $\frac{1}{12}$, about $\frac{1}{6}$, about $\frac{1}{4}$, about $\frac{1}{3}$, about $\frac{5}{12}$, about $\frac{1}{2}$, and about $\frac{7}{12}$, e.g., about $\frac{1}{2}$ or about $\frac{2}{3}$. In one example, the second colchicine dosing regimen is once-a-day, twice-a-day, three-times-a-day or four-times-a-day. In a variation of this example, the initial treatment day in, a second colchicine dosing regimen that lasts for more than one day, has one more dose administered than are administered each subsequent day.

Preferably the second active agent is selected from ketoconazole, cyclosporine, ritonavir, verapamil, or diltiazem. The specific conditions are selected from gout, FMF, thrombocytopenic purpura, and Behçet's disease. In one embodiment, the gout is an acute gout flare and the colchicine treatment schedule is an acute treatment schedule adapted for treatment of acute gout flares, or the gout is chronic gout, and the colchicine treatment schedule is a chronic treatment schedule adapted for prophylaxis, or prevention, of flares. In another embodiment, the fraction of colchicine administered to the patient concomitantly with a second active agent that is a CYP3A4 or P-gp inhibitor is $\frac{1}{3}$ or $\frac{1}{2}$ the original intended amount of colchicine and treatment with colchicine is initiated subsequent to or at the same time as initiation of treatment with the second active agent.

Colchicine is one of the most widely used drugs for treating familial Mediterranean fever (FMF). It has been reported that 5-10% of FMF patients do not show a beneficial response to colchicine administration. A polymorphism in the ABCB1 gene, the "ABCB1 3435 C to T polymorphism" has been reported to correlate with this lack of response to colchicine treatment, with patients with the homozygous TT genotype exhibiting the most pronounced "non-responder" phenotypes.

Accordingly, in another aspect, provided herein is a method for treating a patient suffering from FMF, which patient is a colchicine non-responder. Preferably, the patient is homozygous for the TT genotype of the ABCB1 3435 C to T polymorphism. The method entails the concomitant administration of a P-gp inhibitor and colchicine to the patient. Exemplary P-gp inhibitors include ketoconazole and ritonavir. Preferred dosages of the P-gp inhibitor for this purpose correspond to those called for in the prescribing information for the drug in question. For ketoconazole, an exemplary dosage is 200 mg per day. For ritonavir, an exemplary dosage is 200 or 1200 mg per day. Specific colchicine dosing regimens for this purpose are the same as used for treatment of FMF in responders, though the doses of colchicine administered may be increased as tolerated, e.g., up to two to three times the typical doses.

The following examples further illustrate aspects of this disclosure but should not be construed as in any way limiting its scope. In particular, the conditions are merely exemplary and can be readily varied by one of ordinary skill in the art.

EXAMPLES

Example 1

Pharmacokinetic Study in Healthy Adults of Single vs. Multiple Oral Doses of Colchicine Tablets

This study was a single-center, open-label, single-sequence, two-period study to evaluate the pharmacokinetic

18

profile of colchicine following single and multiple oral doses of colchicine tablets, 0.6 mg, in healthy volunteers.

In Period 1, study subjects received a 0.6-mg dose of colchicine after an overnight fast of at least 10 hours. In Period 2, subjects received a 0.6 mg dose of colchicine in the morning and the evening (approximately 12 hours later) for 10 days (steady state regimen). Subjects received a light breakfast served 60 minutes following dose administration in the morning and the evening dose was administered 90 minutes after an evening meal on Days 15 through 24 only. On Day 25, the colchicine dose was administered after an overnight fast of at least 10 hours and lunch was served 4 hours post-dose. Study periods were separated by a 14-day wash-out. Following the single dose and the last dose of the multiple dose regimen (beginning on the mornings of Day 1 and Day 25, respectively), blood samples were collected (6 mL each) from each subject within 1 hour prior to dosing and after dose administration at study hours 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 (while confined) and 36, 48, 72, and 96 (on an outpatient basis). Plasma concentrations of colchicine and its metabolites were determined using validated LC/MS-MS methods.

Thirteen healthy, non-smoking subjects with a mean age of 25.5 years (range 19 to 38 years) and within 15% of ideal body weight were enrolled in this study. All subjects completed both dosing periods according to protocol.

After a single dose, plasma concentrations are no longer quantifiable 24 hours post-dose in all but 1 subject. After the last dose of the steady state regimen, concentrations remained quantifiable for 48 to 72 hours. Review of individual subject data shows that no subject experienced a secondary colchicine peak, either following a single dose or upon multiple dosing.

All 2-O-demethylcolchicine (2-DMC) concentrations were below the level of quantitation (LOQ, 0.2 ng/mL) and only one sample from 1 subject (of 13 subjects) had a detectable 3-O-demethylcolchicine (3-DMC) concentration, which was near the level of quantitation. Therefore, metabolites are not discussed further.

In healthy adults, colchicine appears to be readily absorbed when given orally, reaching a mean maximum plasma concentration of 2.5 ng/mL in 1.5 hours after a single dose. The drug is distributed widely, with an apparent volume of distribution of 540 L, greatly exceeding total body water. The elimination half-life as calculated following a single oral dose is approximately 5 hours. Levels were not detectable by 24 hours post-dose and this is therefore not an accurate estimate. Pharmacokinetic parameter values are summarized in the table below.

Review of trough plasma concentrations indicates that steady state was attained by approximately the eighth day of dosing for most subjects. Colchicine may have a diurnal variation reflected in the observed C_{min} concentrations at steady state. C_{min} concentrations prior to the morning dose are approximately 12% higher than the C_{min} concentrations prior to the evening dose (Day 23 and Day 24). The mean C_{min} concentration observed on Day 25 was 0.907 ng/mL.

Colchicine accumulated following administration of multiple doses to an extent greater than expected. Exposure was nearly two-fold higher (approximately 1.7 based on AUC [Day 25 AUC_{0-∞}/Day 1 AUC_{0-∞}] and approximately 1.5 based on C_{max} [Day 25 C_{max}/Day 1 C_{max}]). This observation could be attributable to an underestimation of AUC_∞ following a single dose. With the higher plasma levels that occur with repeated dosing, a longer terminal elimination half life is apparent, 26.6 hours. Pharmacokinetic parameter values are summarized in Tables 3-5.

TABLE 3

| Colchicine Pharmacokinetic Parameter Values Following Administration of A Single Oral Dose of Colchicine 0.6 mg in Healthy Adults (N = 13) | | | | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------|----------|---------|-------|----------|---------|----------|
| | MEAN | STDEV | % CV | MEDIAN | MIN | MAX |
| AUC _{0-t} (pg-hr/mL) | 10494.66 | 3544.08 | 33.77 | 10560.90 | 4812.88 | 18091.85 |
| AUC _{0-inf} (pg-hr/mL) | 12268.18 | 4422.08 | 36.05 | 11451.45 | 7252.66 | 23801.68 |
| C _{max} (pg/mL) | 2450.15 | 702.11 | 28.66 | 2480.00 | 1584.00 | 3977.00 |
| T _{max} (hr) | 1.50 | 0.54 | 36.00 | 1.50 | 1.00 | 3.00 |
| K _{el} (1/hr) | 0.1829 | 0.0592 | 32.38 | 0.1992 | 0.0359 | 0.2443 |
| T _{1/2} (hr) | 4.95 | 4.43 | 89.54 | 3.48 | 2.84 | 19.29 |

TABLE 4

| Colchicine Pharmacokinetic Parameter Values Following Administration of Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults (N = 13) | | | | | | |
|------------------------------------------------------------------------------------------------------------------------------------------------------|----------|---------|-------|----------|----------|----------|
| | MEAN | STDEV | % CV | MEDIAN | MIN | MAX |
| AUC _{0-t} (pg-hr/mL) | 43576.96 | 9333.26 | 21.42 | 41925.10 | 29328.78 | 58265.35 |
| AUC _{0-τ} (pg-hr/mL) | 20366.61 | 3322.12 | 16.31 | 20423.08 | 13719.18 | 25495.25 |
| AUC _{0-inf} (pg-hr/mL) | 54198.77 | 9214.54 | 17.00 | 54113.43 | 37599.76 | 67944.65 |
| C _{max} (pg/mL) | 3553.15 | 843.45 | 23.74 | 3734.00 | 1977.00 | 4957.00 |
| C _{min} (pg/mL) | 906.51 | 152.19 | 16.79 | 903.50 | 636.23 | 1149.67 |
| C _{ave} (pg/mL) | 1697.22 | 276.84 | 16.31 | 1701.92 | 1143.26 | 2124.60 |
| T _{max} (hr) | 1.31 | 0.60 | 45.61 | 1.00 | 0.50 | 3.00 |
| K _{el} (1/hr) | 0.0267 | 0.0044 | 16.34 | 0.0261 | 0.0206 | 0.0333 |
| T _{1/2} (hr) | 26.60 | 4.33 | 16.26 | 26.51 | 20.82 | 33.65 |

TABLE 5

| Mean (% CV) Colchicine Pharmacokinetic Parameter Values Following Administration of Single and Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|-------------|
| | Vd/F (L) | CL/F (L/hr) |
| Colchicine 0.6-mg Single Dose (N = 13) | | |
| Day 1 | 341 (54.4) | 54.1 (31.0) |
| Colchicine 0.6 mg b.i.d. × 10 days | | |
| Day 25 | 1150 (18.73) | 30.3 (19.0) |

CL = Dose/AUC_{0-t} (Calculated from mean values)
Vd = CL/K_{el} (Calculated from mean values)

In tables, the parameter CL/F denotes the apparent total body clearance after administration, calculated as Total Dose/ Total AUC_{0-τ}; and V_d/F denotes the apparent total volume of distribution after administration, calculated as Total Dose/ (Total AUC_∞ × K_{el}). FIG. 1 shows mean colchicine plasma concentrations following administration of single and multiple oral doses of colchicine 0.6 mg in healthy adults.

Example 2

Clinical Drug-Drug Interaction Study of Colchicine and Clarithromycin

A single-center, open-label, one sequence, two-period study was carried out in 23 healthy subjects. On Day 1, a single 0.6-mg dose of colchicine was administered. After completing a 21-day washout period, all subjects received 250 mg of clarithromycin administered twice daily for 7 days (Days 22 through 29), a sufficient dose and duration to inhibit CYP3A4 and Pgp. On the final day (Day 29), a single dose of colchicine was co-administered with the clarithromycin dose. When combined with steady-state clarithromycin, there is a significant increase in exposure to colchicine as compared to when colchicine is given alone: the mean C_{max} and AUC_{0-t} concentrations increased 167% and 250%, respectively. In addition, co-administration of clarithromycin and colchicine resulted in an increase of 233% in the plasma elimination half-life (t_{1/2}) of colchicine and a 75% decrease in apparent clearance (CL/F). A summary of the mean (% CV) colchicine pharmacokinetic parameters for Day 1 (colchicine administered alone) and Day 29 (colchicine co-administered with steady-state clarithromycin) are given in the table below and illustrated in Table 5.

21
TABLE 6

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Clarithromycin in Healthy Adults | | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|--------------------------------------|
| Arithmetic Mean (% CV) | | |
| Parameter (units) | Colchicine (N = 23) | Colchicine + Clarithromycin (N = 23) |
| AUC ₀₋₄ (ng · hr/mL) | 12.37 (37.64) | 41.95 (23.31) |
| AUC _{0-inf} (ng · hr/mL) | 15.53 (49.6) | 52.62 (22.84) |
| C _{max} (ng/mL) | 2.84 (30.97) | 8.44 (17.63) |
| T _{max} (hr)* | 1.50 (0.50-2.00) | 1.00 (0.50-2.00) |
| CL/F (L/hr) | 46.8 (43.68) | 12.0 (23.75) |

FIG. 2 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin in healthy adults. Based on the foregoing data, it is concluded that the dose of colchicine co-administered with clarithromycin should be reduced by 2/3.

Example 3

Clinical Drug-Drug Interaction Study of Colchicine and Cyclosporine

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

A single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with cyclosporine on Day 15. Cyclosporine was administered as a single-dose (1×100 mg capsule) on the morning of Day 15. A 14 day washout period was completed after the first colchicine dose on Day 1 and prior to the co-administration of colchicine and cyclosporine doses on Day 15.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 15. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on a confined basis. Subjects were then return to the clinic on a non-confined basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration on Days 2-5 (Period 1) and Days 16-19 (Period 2). Cyclosporine plasma concentrations were not measured.

TABLE 7

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Cyclosporine in Healthy Adults | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|------------------------------------|
| Arithmetic Mean (% CV) | | |
| Parameter (units) | Colchicine (N = 23) | Colchicine + Cyclosporine (N = 23) |
| AUC ₀₋₄ (ng · hr/mL) | 12.55 | 39.83 |
| AUC _{0-inf} (ng · hr/mL) | 15.00 | 47.31 |
| C _{max} (ng/mL) | 2.72 | 8.82 |

22
TABLE 7-continued

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Cyclosporine in Healthy Adults | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|------------------------------------|
| Arithmetic Mean (% CV) | | |
| Parameter (units) | Colchicine (N = 23) | Colchicine + Cyclosporine (N = 23) |
| T _{max} (hr)* | 1.15 | 1.13 |
| CL/F (L/hr) | 48.24 | 13.42 |

FIG. 3 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin and steady-state cyclosporine in healthy adults. Based on the foregoing data, the dose of colchicine co-administered with cyclosporine should be reduced by approximately 1/2 to 3/4.

Example 4

Clinical Drug-Drug Interaction Study of Colchicine and Ritonavir

An open-label, non-randomized, single-center, one-sequence, two-period drug interaction study was conducted in healthy male and female volunteers; there will be a 14-day washout between the two periods. Twenty-four (24) non-smoking non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

All subjects received a single 0.6-mg dose of colchicine on Day 1 administered under standard fasting conditions, followed by a 14-day washout period completed on an outpatient basis. At discharge on Day 2, study subjects were instructed to return to the clinical site on the mornings and evenings of Days 15 through 18 to receive two daily dosage amounts of ritonavir (1×100 mg ritonavir capsule twice daily (every 12 hours) on Days 15-18) in a 'directly-observed' fashion; after taking the first dose of ritonavir, subjects remained in the clinic for observation for 1 hour post-dose administration on Day 15. On the evening of Day 18, study participants remained at the clinic for their final study confinement period. In the morning on Day 19, study subjects received a single 0.6 mg colchicine dose with a single 100 mg ritonavir dose and study subjects received the final 100 mg ritonavir dose 12 hours later in the evening on Day 19 under standard fasting conditions.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 19. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on an inpatient basis. Subjects returned to the clinic on an outpatient basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration. Ritonavir plasma concentrations were not measured.

23

TABLE 8

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Ritonovir in Healthy Adults: ln-transformed data | | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|------------------------|---------|
| | Colchicine Alone | Colchicine + Ritonovir | % Ratio |
| C_{max} (pg/mL), geometric mean | 1798.37 | 4835.39 | 268.88 |
| AUC_{0-t} (pg · h/mL), geometric mean | 7642.71 | 27793.08 | 363.65 |
| AUC_{∞} (pg · h/mL), geometric mean | 9551.74 | 33771.36 | 353.56 |

TABLE 9

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Ritonavir in Healthy Adults | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|---------------------------|--|
| Parameter (units) | Arithmetic Mean (% CV) Median (Range) for T_{max} | | |
| | Colchicine + Ritonavir (N = 18) | Colchicine Alone (N = 18) | |
| AUC_{0-t} (ng · hr/mL) | 29.05 (30.76) | 8.41 (47.46) | |
| $AUC_{0-\infty}$ (ng · hr/mL) | 35.28 (29.79) | 10.41 (45.48) | |
| C_{max} (ng/mL) | 4.99 (25.18) | 1.87 (28.19) | |
| T_{max} (hr) | 1.5 (1-1.5) | 1 (0.5-1.5) | |
| CL/F (L/hr) | 18.59 (31.58) | 67.93 (39.47) | |

Following exposure to 100 mg b.i.d. x5 days, there was a significant increase in exposure to a single 0.6-mg colchicine (approximately 245%). Mean peak colchicine concentration increased by approximately 170%. Total apparent oral clearance was decreased by 70% with co-administration. T_{max} is not affected. Elimination half-life could not be estimated accurately as plasma concentrations were not quantifiable after 24 hours.

FIG. 4 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state ritonavir and steady-state ketoconazole in healthy adults. Based on the foregoing data, the dose of colchicine co-administered with ritonavir should be reduced by approximately 1/2.

Example 5

Clinical Drug-Drug Interaction Study of Colchicine and Ketoconazole

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers; there will be a 14-day washout between the two periods. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled.

A single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with ketoconazole on Day 19 (AM dose). Ketoconazole was administered for 5 consecutive days [200 mg twice daily (every 12 hours)] beginning on the morning of Day 15, with the last 200 mg ketoconazole dose administered on the evening of Day 19. Total study participation, exclusive of up to 28 days of screening, was approximately 24 days, during which subjects will be confined on two occasions for a total confinement of approximately 3 days.

24

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 19. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on an inpatient basis. Subjects then returnee to the clinic on an outpatient basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration. Ketoconazole plasma concentrations were not measured.

TABLE 10

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Ketoconazole in Healthy Adults: ln-transformed data | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|---------------------------|---------|
| | Colchicine Alone | Colchicine + Ketoconazole | % Ratio |
| C_{max} (pg/mL), geometric mean | 2598.28 | 5078.50 | 195.46 |
| AUC_{0-t} (pg · h/mL), geometric mean | 11087.99 | 33223.80 | 299.64 |
| AUC_{∞} (pg · h/mL), geometric mean | 13185.92 | 42143.00 | 319.61 |

TABLE 11

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Ketoconazole in Healthy Adults | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|------------------------------------|
| Parameter (units) | Arithmetic Mean (% CV) | |
| | Colchicine (N = 23) | Colchicine + Ketoconazole (N = 23) |
| AUC_{0-t} (pg · hr/mL) | 11988.61 | 34382.82 |
| $AUC_{0-\infty}$ (pg · hr/mL) | 14314.09 | 43688.90 |
| C_{max} (pg/mL) | 2779.08 | 5266.92 |
| T_{max} (hr)* | 1.00 | 1.02 |
| CL/F (L/hr) | 49301.09 | 14797.94 |

*Median (Range) for T_{max}

Following administration of ketoconazole 200 mg b.i.d. x5 days, there was a significant increase in exposure to a single oral dose of colchicine 0.6 mg (C_{max} and AUC_{0-t} increased by 90% and 190%, respectively, and $AUC_{0-\infty}$ increased by about 205%). Total apparent oral clearance decreased by 70% with co-administration. Elimination half-life could not be estimated accurately as plasma concentrations were not quantifiable after 24 hours.

FIG. 4 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state ritonavir and steady-state ketoconazole in healthy adults. Based on the foregoing data, the dose of colchicine co-administered with ketoconazole should be reduced by approximately 1/2.

Example 6

Clinical Drug-Drug Interaction Study of Colchicine and Azithromycin

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers; there was a

14-day washout between the two periods. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

A single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with the azithromycin on Day 19. Azithromycin was administered for 5 consecutive days (2x250 mg once daily [Day 15 only] and then 1x250 mg once daily Days 16-19) beginning on the morning of Day 15, with the last 250 mg azithromycin dose administered on the morning on Day 19. Total study participation, exclusive of up to 28 days of screening, was approximately 24 days, during which subjects were confined on two occasions for a total confinement of approximately 3 days.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 19. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on an inpatient basis. Subjects returned to the clinic on an outpatient basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration. Azithromycin plasma concentrations were not measured.

TABLE 12

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Azithromycin in Healthy Adults | | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|---------------------------|---------|
| | Colchicine Alone | Colchicine + Azithromycin | % Ratio |
| C _{max} (pg/mL), geometric mean | 2535.94 | 2856.22 | 112.63 |
| AUC _{0-∞} (pg · hr/mL), geometric mean | 10971.51 | 16090.52 | 146.66 |
| AUC _∞ (pg · hr/mL), geometric mean | 12931.80 | 18312.83 | 141.61 |

TABLE 13

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Azithromycin in Healthy Adults | | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|---------------------------|--|
| Parameter (units) | Arithmetic Mean (% CV) Median (Range) for T _{max} | | |
| | Colchicine + Azithromycin (N = 21) | Colchicine Alone (N = 21) | |
| AUC _{0-∞} (ng · hr/mL) | 17.16 (37.78) | 11.98 (45.81) | |
| AUC _{0-∞} (ng · hr/mL) | 19.61 (39.15) | 14.13 (46.73) | |
| C _{max} (ng/mL) | 3.05 (39.54) | 2.74 (41.52) | |
| T _{max} (hr) | 1.5 (0.5-3) | 1.0 (0.5-3) | |
| t _{1/2} (hr) | 6.71 (68.34) ¹ | 6.07 (66.15) ¹ | |
| CL/F (L/hr) | 35.01 (37.26) | 50.24 (40.31) | |

Following administration of azithromycin 500 mg on Day 1 followed by 250 mgx4 days, exposure to colchicine is increased (approximately 46% for AUC_{0-∞} and approximately 40% for AUC_∞). Mean peak colchicine concentration increased by approximately 12% and total apparent oral clearance decreased approximately 30% with co-administration. T_{max} was not affected.

FIG. 5 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose

colchicine (0.6 mg) co-administered with steady-state azithromycin and steady-state diltiazem in healthy adults.

Example 7

Clinical Drug-Drug Interaction study of Colchicine and Diltiazem

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

As single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with diltiazem ER on Day 21. Diltiazem ER was administered for 7 consecutive days (1x240 mg capsule once daily on Days 15-21) beginning on the morning of Day 15, with the last 240 mg diltiazem ER dose administered on the morning on Day 21. A 14-day washout period was completed after the first colchicine dose on Day 1 and prior to the administration of the first diltiazem ER dose on Day 15.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 21. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on an inpatient basis. Subjects returned to the clinic on an outpatient basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration. Diltiazem plasma concentrations were not measured.

TABLE 14

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Diltiazem in Healthy Adults | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|------------------------|---------|
| | Colchicine Alone | Colchicine + Diltiazem | % Ratio |
| C _{max} (pg/mL), geometric mean | 2006.42 | 2583.22 | 128.75 |
| AUC _{0-∞} (pg · h/mL), geometric mean | 9154.55 | 15740.37 | 171.94 |
| AUC _∞ (pg · h/mL), geometric mean | 11022.30 | 19902.98 | 180.57 |

TABLE 15

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Diltiazem in Healthy Adults | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|---------------------------|
| Parameter (units) | Arithmetic Mean (% CV) Median (Range) for T _{max} | |
| | Colchicine + Diltiazem (N = 20) | Colchicine Alone (N = 20) |
| AUC _{0-∞} (ng · hr/mL) | 17.73 | 10.04 |
| AUC _{0-∞} (ng · hr/mL) | 22.49 | 12.03 |
| C _{max} (ng/mL) | 2.80 | 2.17 |
| T _{max} (hr) | 1.48 | 1.15 |
| t _{1/2} (hr) | 12.50 | 5.51 |
| CL/F (L/hr) | 463.49 | 395.83 |

US 7,964,648 B2

27

FIG. 5 shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state azithromycin and steady-state diltiazem in healthy adults.

Example 8

Clinical Drug-Drug Interaction Study of Colchicine and Verapamil

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

A single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with verapamil HCl ER on Day 19. Verapamil HCl ER was administered for 5 consecutive days (1x240 mg tablet once daily on Days 15-19) beginning on the morning of Day 15, with the last 240 mg verapamil HCl ER dose administered on the morning on Day 19. A 14-day washout period was completed after the first colchicine dose on Day 1 and prior to the administration of the first verapamil HCl ER dose on Day 15.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 19. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on a confined basis. Subjects returned to the clinic on a non-confined basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration on Days 2-5 (Period 1) and Days 20-23 (Period 2). Verapamil plasma concentrations were not measured.

TABLE 16

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Verapamil in Healthy Adults | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|------------------------|---------|
| | Colchicine Alone | Colchicine + Verapamil | % Ratio |
| C _{max} (pg/mL), geometric mean | 2768.77 | 3639.68 | 131.45 |
| AUC ₀₋₄ (pg · h/mL), geometric mean | 12256.40 | 23889.21 | 194.94 |
| AUC _∞ (pg · h/mL), geometric mean | 14415.79 | 29556.75 | 205.03 |

TABLE 17

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Verapamil in Healthy Adults | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|---------------------------|--|
| Parameter (units) | Arithmetic Mean (% CV) Median (Range) for T _{max} | | |
| | Colchicine + Verapamil (N = 24) | Colchicine Alone (N = 24) | |
| AUC ₀₋₄ (ng · hr/mL) | 24.64 | 13.09 | |
| AUC _{0-∞} (ng · hr/mL) | 30.59 | 15.37 | |
| C _{max} (ng/mL) | 3.85 | 2.97 | |
| T _{max} (hr) | 1.15 | 1.22 | |

28

TABLE 17-continued

| Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Verapamil in Healthy Adults | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|---------------------------|
| Parameter (units) | Arithmetic Mean (% CV) Median (Range) for T _{max} | |
| | Colchicine + Verapamil (N = 24) | Colchicine Alone (N = 24) |
| t _{1/2} (hr) | 17.17 | 6.24 |
| CL/F (L/hr) | 21.01 | 43.93 |

Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges directed to the same component or property are inclusive and independently combinable.

All methods described herein can be performed in a suitable order unless otherwise indicated or clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., “such as”) herein is intended to better illuminate the disclosure and is non-limiting unless otherwise specified. No language in the specification should be construed as indicating that any non-claimed element as essential to the practice of the claimed embodiments. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this disclosure belongs. The terms wt %, weight percent, percent by weight, etc. are equivalent and interchangeable.

In the specification and claims that follow, references will be made to a number of terms which shall be defined to have the following meaning.

The terms “a” and “an” do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The term “or” means “and/or”. The terms “comprising”, “having”, “including”, and “containing” are to be construed as open-ended terms (i.e., meaning “including, but not limited to”).

“Concomitant” and “concomitantly” as used herein refer to the administration of at least two drugs to a patient either simultaneously or within a time period during which the effects of the first administered drug are still operative in the patient. Thus, if the first drug is, e.g., clarithromycin and the second drug is colchicine, the concomitant administration of the second drug can occur as much as one to two weeks, preferably within one to seven days, after the administration of the first drug. This is because clarithromycin can exert a long-lasting inhibition of CYP3A isozymes so that CYP3A activity in the patient may not return to pre-clarithromycin-administration levels for as much as two weeks after the cessation of clarithromycin administration. If colchicine is the first drug, administration of a second drug would be concomitant if done within 1 to 2 days, preferably 12 to 24 hours.

A “dose” means the measured quantity of a drug to be taken at one time by a patient.

A “dosage amount” means an amount of a drug suitable to be taken during a fixed period, usually during one day (i.e. daily). A “daily dosage amount” is the total dosage amount taken in one day, that is, a 24 hour period.

“Dosing regimen” means the dose of a drug taken at a first time by a patient and the interval (time or symptomatic) and

US 7,964,648 B2

29

dosage amounts at which any subsequent doses of the drug are taken by the patient. Each dose may be of the same or different.

A "patient" means a human or non-human animal in need of medical treatment. Medical treatment can include treatment of an existing condition, such as a disease or disorder, prophylactic or preventative treatment, or diagnostic treatment. In preferred embodiments the patient is human.

"Providing" means giving, administering, selling, distributing, transferring (for profit or not), manufacturing, compounding, or dispensing.

"Risk" means the probability or chance of adverse reaction, injury, or other undesirable outcome arising from a medical treatment. An "acceptable risk" means a measure of the risk of harm, injury, or disease arising from a medical treatment that will be tolerated by an individual or group. Whether a risk is "acceptable" will depend upon the advantages that the individual or group perceives to be obtainable in return for taking the risk, whether they accept whatever scientific and other advice is offered about the magnitude of the risk, and numerous other factors, both political and social. An "acceptable risk" of an adverse reaction means that an individual or a group in society is willing to take or be subjected to the risk that the adverse reaction might occur since the adverse reaction is one whose probability of occurrence is small, or whose consequences are so slight, or the benefits (perceived or real) of the active agent are so great. An "unacceptable risk" of an adverse reaction means that an individual or a group in society is unwilling to take or be subjected to the risk that the adverse reaction might occur upon weighing the probability of occurrence of the adverse reaction, the consequences of the adverse reaction, and the benefits (perceived or real) of the active agent. "At risk" means in a state or condition marked by a high level of risk or susceptibility.

Pharmacokinetic parameters referred to herein describe the in vivo characteristics of drug (or a metabolite or a surrogate marker for the drug) over time. These include plasma concentration (C), as well as C_{max} , C_n , C_{24} , T_{max} , and AUC. " C_{max} " is the measured plasma concentration of the active agent at the point of maximum, or peak, concentration. " C_{min} " is the measured plasma concentration of the active agent at the point of minimum concentration. " C_n " is the measured plasma concentration of the active agent at about n hours after administration. " C_{24} " is the measured plasma concentration of the active agent at about 24 hours after administration. The term " T_{max} " refers to the time from drug administration until C_{max} is reached. "AUC" is the area under the curve of a graph of the measured plasma concentration of an active agent vs. time, measured from one time point to another time point. For example AUC_{0-t} is the area under the curve of plasma concentration versus time from time 0 to time t, where time 0 is the time of initial administration of the drug. Time t can be the last time point with measurable plasma concentration for an individual formulation. The $AUC_{0-\infty}$, AUC_{∞} or AUC_{0-inf} is the calculated area under the curve of plasma concentration versus time from time 0 to time infinity. In steady-state studies, $AUC_{0-\tau}$ is the area under the curve of plasma concentration over the dosing interval (i.e., from time 0 to time τ (tau), where tau is the length of the dosing interval. Other pharmacokinetic parameters are the parameter K_e or K_d , the terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve; $t_{1/2}$ the terminal elimination half-life, calculated as $0.693/K_{el}$. CL/F denotes the apparent total body clearance after administration, calculated as $Total\ Dose/Total\ AUC_{\infty}$; and V_{area}/F denotes the apparent total volume of distribution after administration, calculated as $Total\ Dose/(Total\ AUC_{\infty} \times K_{el})$.

30

"Side effect" means a secondary effect resulting from taking a drug. The secondary effect can be a negative (unfavorable) effect (i.e., an adverse side effect) or a positive (favorable) effect.

The most frequently reported adverse side effects to colchicine therapy are gastrointestinal, specifically abdominal pain with cramps, diarrhea, nausea, and vomiting. Less frequently or rarely reported adverse side effects associated with colchicine therapy include anorexia, agranulocytosis, allergic dermatitis, allergic reactions, alopecia, angioedema, aplastic anemia, bone marrow depression, myopathy, neuropathy, skin rash, thrombocytopenic disorder, and urticaria.

Whether a patient experiences an adverse side effect can be determined by obtaining information from the patient regarding onset of certain symptoms which may be indicative of the adverse side effect, results of diagnostic tests indicative of the adverse side effect, and the like.

Embodiments are described herein, including the best modes known to the inventors. Variations of such embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The skilled artisan is expected to employ such variations as appropriate, and the disclosed methods are expected to be practiced otherwise than as specifically described herein. Accordingly, all modifications and equivalents of the subject matter recited in the claims appended hereto are included to the extent permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed unless otherwise indicated herein or otherwise clearly contradicted by context.

What is claimed is:

1. A method of treating a patient with colchicine, comprising

orally administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ketoconazole,

wherein the adjusted daily dosage amount of colchicine is 25% to 50% of an intended daily dosage amount of colchicine, and

wherein the intended daily dosage amount of colchicine is a dosage amount suitable for the patient if the patient were not receiving concomitant ketoconazole.

2. The method of claim 1, wherein the treating is for the prophylaxis of gout flares, and wherein the intended daily dosage amount of colchicine suitable for the patient if the patient were not receiving concomitant ketoconazole is 0.6 mg twice daily or 0.6 mg once daily.

3. The method of claim 1, wherein the treating is for acute gout flares, and wherein the intended daily dosage amount of colchicine suitable for the patient if the patient were not receiving concomitant ketoconazole is 1.2 mg at the first sign of flare, followed by 0.6 mg one hour later, dose to be repeated no earlier than 3 days.

4. The method of claim 1, wherein the treating is for familial Mediterranean fever

wherein the adjusted daily dosage amount of colchicine is a maximum colchicine dosage amount of 0.6 mg of colchicine per day which is a reduction from the intended daily dosage amount of colchicine in the absence of concomitant ketoconazole wherein the intended daily dosage amount is a maximum daily dosage amount as follows:

US 7,964,648 B2

31

| Age | Daily dosage amount | |
|-------------------------------|---------------------|---------|
| | Usual | Maximum |
| Adults and children >12 years | 1.2 mg | 2.4 mg |
| Children >6 to 12 years | 0.9 mg | 1.8 mg |
| Children 4 to 6 years | 0.3 mg | 1.8 mg. |

5. The method of claim 2, wherein the adjusted daily dosage amount of colchicine is 25% of a 0.6 mg twice daily intended dose. 10

32

6. The method of claim 2, wherein the adjusted daily dosage amount of colchicine is 25% of a 0.6 mg once daily intended dose.

7. The method of claim 1, wherein the concomitantly administered dose of ketoconazole is 200 mg twice per day.

8. The method of claim 3, wherein the adjusted daily dosage amount is about 50% of the intended daily dosage amount.

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