ORIGINAL

Jonathan E. Singer, SBN 187908
Email: singer@fr.com
Fish & Richardson P.C.
Regent Business Centers LA LLC
555 West Fifth Street, 31st floor
Los Angeles, CA 90013
Tel: (213) 533-4240

Todd G. Miller, SBN 163200
Email: miller@fr.com
Fish & Richardson P.C.
12390 El Camino Real
San Diego, CA 92130
Tel: (858) 678-5070
Fax: (858) 678-5099

Attorneys for Plaintiffs
Eurand, Inc. and *Anesta AG*

IN THE UNITED STATES DISTRICT COURT
FOR THE CENTRAL DISTRICT OF CALIFORNIA
WESTERN DIVISION

SACV09-01098 CJC MLGx

EURAND, INC. and ANESTA AG,

Plaintiffs,

v.

ANCHEN PHARMACEUTICALS, INC. and ANCHEN, INC.,

Defendants.

Civil Action No. _____

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Eurand, Inc. and Anesta AG (collectively, "Plaintiffs") bring this Complaint against Defendants Anchen Pharmaceuticals, Inc. and Anchen, Inc. (collectively "Anchen" or "Anchen Defendants"), and in support state and allege 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, Titles 21 and 35, respectively, arising from the Anchen Defendants filing an Abbreviated New Drug Application ("ANDA") and an amendment thereto with the United States Food and Drug Administration ("FDA"). The Anchen Defendants' ANDA and amendment to the ANDA seek approval from the FDA to commercially market generic versions of the drug product AMRIX® (Cyclobenzaprine HCl extended release capsules) prior to the expiration of United States Patent Nos. 7,387,793 ("the '793 Patent") and 7,544,372 ("the '372 Patent"), which cover the AMRIX® product and a method of using the AMRIX® product, respectively. Plaintiffs have already filed an action against the Anchen Defendants in this district for infringement of the '793 Patent: Civil Action No. 09-4931 CBM (MLGx).

THE PARTIES

2. Plaintiff Eurand, Inc. ("Eurand") is a corporation, organized, existing and doing business under and by virtue of the laws of the State of Nevada, with its office and principal place of business located at 845 Center Drive, Vandalia, Ohio 45377.

3. Plaintiff Anesta AG ("Anesta") is a Swiss corporation having a principal place of business at Baarerstrasse 23CH-6300 Zug, Switzerland.

4. On information and belief, Defendant Anchen Pharmaceuticals, Inc. is a corporation organized and existing under the laws of the State of California, with a principal place of business at 9601 Jeronimo Road, Irvine, CA 92618-2025.

5. On information and belief, Defendant Anchen, Inc. is a corporation organized and existing under the laws of the State of Delaware, with a principal place of business at 9601 Jeronimo Road, Irvine, CA 92618-2025.

6. On information and belief, Defendants Anchen Pharmaceuticals, Inc. and Anchen, Inc. closely coordinate their commercial activities and hold themselves

out to the marketplace as one company. For example, during prosecution of Anchen Pharmaceuticals, Inc.'s trademark application for the word mark ANCHEN with respect to pharmaceutical products (serial no. 77051871), representatives for Anchen Pharmaceuticals, Inc. stated that Anchen Pharmaceuticals, Inc. is a "related entity" to Anchen, Inc. In addition, Anchen Pharmaceuticals, Inc.'s representatives stated that "Anchen Pharmaceuticals, Inc. and Anchen Incorporated, though separate legal entities, constitute a single source to the relevant public, and there is unity of control with respect to the nature and quality of the goods." On information and belief, Anchen Pharmaceuticals, Inc. and Anchen, Inc. have also simultaneously shared senior corporate officers with the same titles, including Margaret Choy, Senior Vice President of Regulatory Affairs. Ms. Choy is also the contact person listed in Anchen's Paragraph IV Notice Letters to Plaintiffs, which are discussed below.

7. On information and belief, Defendant Anchen Pharmaceuticals, Inc. is in the business of preparing generic pharmaceuticals that it distributes in the State of California and throughout the United States. On information and belief, Defendant Anchen Pharmaceuticals, Inc. conducts its North American operations, in part, through Anchen, Inc. On information and belief, together, they collaborate in the manufacture, marketing, and sale of many pharmaceutical products (including generic drug products manufactured and sold pursuant to approved abbreviated new drug applications) within the United States generally, and the State of California specifically. For example, the Anchen Defendants have sold millions of dollars worth of Bupropion and Divalproex pharmaceutical products within the United States generally, and the State of California specifically, under a stylized "Anchen" trademark (Anchen) that is owned by Anchen, Inc. (serial no. 77037779) (see drug labels attached as Exhibits E and F).

8. Although the Anchen Defendants' Divalproex product label lists Anchen Pharmaceuticals, Inc. as the source, it identifies the manufacturer as Anchen

Pharmaceuticals (Taiwan), Inc. (See Exhibit F). According to Anchen's website, Anchen Pharmaceuticals (Taiwan), Inc. is a wholly-owned subsidiary of Anchen, Inc. (see Exhibit G [screen printout of http://www.anchen.com/anchentaiwan.php]).

JURISDICTION AND VENUE

9. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a), 35 U.S.C. § 271, and the Declaratory Judgment Act, 28 U.S.C. §§ 2201-02.

10. Based on the facts and causes alleged herein, and for additional reasons to be further developed through discovery, this Court has personal jurisdiction over the Anchen Defendants.

11. On information and belief, this Court has personal jurisdiction over Anchen, Inc. by virtue of its systematic and continuous contacts with the State of California.

12. On information and belief, Anchen, Inc. plans to continue to maintain continuous and systematic contacts with the State of California, including but not limited to, its aforementioned business of preparing generic pharmaceuticals that it distributes in the State of California in collaboration with Anchen Pharmaceuticals, Inc.

13. This Court has personal jurisdiction over Anchen Pharmaceuticals, Inc. by virtue, *inter alia*, of its incorporation in California.

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

BACKGROUND

Genesis of the Delaware and California Actions

15. As discussed in further detail below, the Anchen Defendants filed ANDA No. 91-281 and an amendment thereto seeking to market generic versions of the drug product AMRIX® (Cyclobenzaprine HCl extended release capsules).

16. Plaintiffs market and distribute AMRIX® nationwide, including in California. The filing of ANDA 91-281 and the amendment thereto evidences an

intent by the Anchen Defendants to compete with Plaintiffs and place their product into every market where AMRIX® is currently found, including California.

17. In May 2009, as required by applicable federal law, the Anchen Defendants sent Plaintiffs a Paragraph IV letter (defined below) stating that they had filed ANDA 91-281 with the FDA seeking approval to engage in the commercial manufacture, use or sale throughout the United States, including California, of a generic version of Plaintiffs' patented drug product, AMRIX®. 21 U.S.C. § 355(j)(2)(B)(i)(iii).

18. In August 2009, the Anchen Defendants sent Plaintiffs a second Paragraph IV letter (defined below) stating that they had filed an amendment to ANDA 91-281 with the FDA seeking approval to engage in the commercial manufacture, use or sale throughout the United States, including California, of a generic version of Plaintiffs' patented drug product, AMRIX®.

19. Under the Hatch-Waxman Act of 1984, an owner of a patented drug must file an action in federal court within 45 days of receiving a Paragraph IV letter ("45-day window") in order to receive certain benefits under the Act, including a stay of approval of the generic drug for up to 30 months during the pendency of litigation, as appropriate. 21 U.S.C. § 355 (c)(3)(c).

20. On July 7, 2009, within 45 days of receiving the Anchen Defendants' first Paragraph IV Letter, Plaintiffs filed and served an action against Anchen Pharmaceuticals, Inc. and Anchen, Inc. for infringement of the '793 Patent in the United States District Court for the District of Delaware, Civil Action No. 09-492 (the "Delaware I Action"). A copy of the Complaint in the Delaware I Action is attached hereto as Exhibit A.

21. On September 23, 2009, within 45 days of receiving the Anchen Defendants' second Paragraph IV Letter, Plaintiffs filed and served an action against Anchen Pharmaceuticals, Inc. and Anchen, Inc. for infringement of the '372 Patent in the United States District Court for the District of Delaware, Civil Action No.

09-715 (the "Delaware II Action"). A copy of the Complaint in the Delaware II Action is attached hereto as Exhibit B.

22. Defendants Anchen Pharmaceuticals, Inc. and Anchen, Inc. are properly subject to personal jurisdiction in the District of Delaware and judicial economy would be promoted by addressing all of Plaintiffs' claims for infringement of the '793 and '372 Patents in the Delaware Action. Plaintiffs have filed two other lawsuits in the District of Delaware against three other generic drug companies relating to AMRIX® and the '793 Patent: *Eurand, et al v. Mylan, Inc., et al*, Civ. No. 08-889 (filed November 26, 2008); and *Eurand, et al v. Impax Labs.*, Civ. No. 09-018 (filed January 7, 2009). The assigned Judge in these lawsuits and the Delaware I Action is the Honorable Sue Robinson of the District of Delaware.

23. In the Delaware I Action, Anchen Pharmaceuticals, Inc. has nonetheless contested personal jurisdiction in Delaware. Upon information and belief, Plaintiffs understand that Anchen Pharmaceuticals, Inc. may also contest personal jurisdiction in the Delaware II Action. The Hatch-Waxman Act does not address squarely the consequences of the grant of a motion to dismiss for lack of personal jurisdiction in a plaintiff's chosen forum. It is possible that such a dismissal could result in a plaintiff losing the benefit of the 30-month stay of ANDA approval even if the plaintiff refiled the action in another jurisdiction, since the refiling would occur after the 45-day window. Therefore, district courts have countenanced the filing of additional "protective suits" within the 45-day window to ensure a plaintiff will not lose the benefits of the 30-month stay should the court in the chosen forum dismiss the action for lack of personal jurisdiction. *See e.g., Adams Respiratory Therapeutics, Inc. v. Perrigo Co.*, 2007 WL 4284877 (W.D. Mich. Dec. 3, 2007); *PDL Biopharma, Inc. v. Sun Pharmaceutical Industries, Ltd.*, 2007 WL 2261386 (E.D. Mich. Aug. 6, 2007); *Celgene Corp. v. Abrika Pharmaceuticals, Inc.*, 2007 WL 1456156 (D.N.J. May 17, 2007).

24. Accordingly, although Plaintiffs believe the District of Delaware has personal jurisdiction over both Anchen Defendants, and Delaware is their preferred choice of forum to litigate the claims for relief set forth in this Complaint, Plaintiffs beg the Court's indulgence and file this Complaint for infringement of the '372 Patent as a "protective suit" to protect Plaintiffs' rights under the Hatch-Waxman Act in the event the District of Delaware were to determine that there is no personal jurisdiction over the Anchen Defendants in Delaware.

25. On July 9, 2009, Plaintiffs similarly filed a "protective suit" in this District for infringement of the '793 Patent by the Anchen Defendants. *See* CV09-4931 CBM (MLGx).

FACTS RELEVANT TO ALL CAUSES

26. On June 17, 2008, the United States Patent and Trademark Office ("PTO") duly and legally issued the '793 Patent to Plaintiff Eurand. A true and correct copy of the '793 Patent is attached hereto as Exhibit C.

27. Eurand is the lawful owner by assignment of the '793 Patent and owns all rights, title and interest in the '793 Patent, including all rights needed to bring this patent infringement action.

28. On or about August 23, 2007, Anesta obtained, via an Asset Purchase Agreement ("APA"), all right, title, and interest in approved New Drug Application ("NDA") No. 21-777 for cyclobenzaprine hydrochloride extended-release capsules, in 15mg and 30mg doses, both sold under the AMRIX® trademark. Under the APA, Anesta also obtained an exclusive license to the '793 Patent in the United States.

29. On June 9, 2009, the PTO duly and legally issued the '372 Patent to Plaintiff Eurand. A true and correct copy of the '372 Patent is attached hereto as Exhibit D.

30. Eurand is the lawful owner by assignment of the '372 Patent and owns all rights, title and interest in the '372 Patent, including all rights needed to bring this patent infringement action.

31. Under the APA, Anesta has an exclusive license to the '372 Patent in the United States.

32. The FDA approved AMRIX® for marketing in the United States under NDA No. 21-777, pursuant to section 505(b) of the Federal Food Drug and Cosmetics Act ("FFDCA"), 21 U.S.C. § 355(b).

33. In conjunction with NDA No. 21-777, Anesta listed both the '793 and '372 Patents in the Orange Book as patents "with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." 21 U.S.C. § 355(b)(1).

34. On or about June 3, 2009 and May 29, 2009, Eurand and Anesta respectively received a letter dated May 28, 2009, and signed by a representative of Anchen, purporting to be notice of Anchen's filing of ANDA No. 91-281 seeking to market 15 mg and 30 mg generic versions of AMRIX® Cyclobenzaprine HCl extended release capsules (the "Anchen Generic Products") and allegedly containing a Paragraph IV Certification required by 21 U.S.C. § 355(j)(2)(b)(i) and (ii), with respect to the '793 Patent. (Anchen's "First Paragraph IV Notice Letter").

35. On or about August 13, 2009, Plaintiffs received a letter dated August 13, 2009, and signed by a representative of Anchen, purporting to be notice of Anchen's filing of an amendment to ANDA No. 91-281 seeking to market the Anchen Generic Products in 15 mg and 30 mg dosages and allegedly containing a Paragraph IV Certification required by 21 U.S.C. § 355(j)(2)(b)(i) and (ii), with respect to the '372 Patent. (Anchen's "Second Paragraph IV Notice Letter").

36. Anchen's First Paragraph IV Notice Letter to Plaintiffs stated Anchen's intention to seek approval to market generic versions of AMRIX® Cyclobenzaprine HCl extended release capsules prior to the expiration of the '793 Patent.

37. Anchen's Second Paragraph IV Notice Letter to Plaintiffs states Anchen's intention to seek approval to market generic versions of AMRIX® Cyclobenzaprine HCl extended release capsules prior to the expiration of the '372 Patent.

38. Anchen's First and Second Paragraph IV Notice Letters both fail to comply with the requirements of 21 U.S.C. § 355 (j)(2)(B)(iv)(II) because, *inter alia*, they contain very limited information about the generic formulation for which Anchen filed ANDA No. 91-281. For example, Anchen's First and Second Paragraph IV Notice Letters do not list any of the ingredients in the proposed generic versions, or the amounts of those ingredients.

39. In Anchen's First and Second Paragraph IV Notice Letters, the Anchen Defendants offered confidential access to portions of ANDA No. 91-281 on terms and conditions set forth in paragraph VII of the Letters ("the Anchen Offers"). The Anchen Defendants requested that Plaintiffs accept the Anchen Offers before receiving access to Anchen's ANDA No. 91-281. The Anchen Offers contained unreasonable restrictions, above and beyond those that would apply under a protective order, on who could view the ANDA. For example, the Anchen Offers unreasonably limited the fields of practice and other activities of outside counsel and any other person who accepted access to the ANDA.

40. Under 21 U.S.C. § 355(j)(5)(C)(i)(III), an offer of confidential access "shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information."

41. Since receiving Anchen's First and Second Paragraph IV Notice Letters and the accompanying Anchen Offers, Plaintiffs have negotiated with the Anchen Defendants to procure a copy of ANDA No. 91-281 under restrictions "as would apply had a protective order been issued." These negotiations have been

unsuccessful. For example, the Anchen Defendants' most recent proposal continues to unreasonably limit the fields of practice and other activities of any person, including outside counsel, who accepts access to the ANDA. The Anchen Defendants have refused to modify these restrictions despite Judge Robinson's June 23, 2009 Order in two other AMRIX® cases pending in the District of Delaware, CIV-08-889 and CIV-09-018, rejecting similar proposals made by the defendants there. In addition, the Anchen Defendants have refused to provide their ANDA to Plaintiffs under Delaware Local Rule 26.2.

42. Plaintiffs are not aware of any other means of obtaining information regarding the Anchen Generic Products within the 45-day statutory period. In the absence of such information, Plaintiffs resort to the judicial process and the aid of discovery to obtain, under appropriate judicial safeguards, such information as is required to confirm its allegations of infringement and to present to the Court evidence that the Anchen Generic Products fall within the scope of one or more claims of the '793 and '372 Patents.

43. On July 7, 2009, within 45 days of receiving Anchen's First Paragraph IV Letter, Plaintiffs filed and served an action No. CIV-09-492 against the Anchen Defendants in the District of Delaware for infringement of the '793 Patent, which is currently pending. *See* Exhibit A. As noted above, on July 9, 2009, Plaintiffs also filed a "protective suit" in this District for infringement of the '793 patent by the Anchen Defendants. *See* CV09-4931 CBM (MLGx).

COUNT I

(Infringement of the '372 Patent Under 35 U.S.C. § 271(e)(2) against the Anchen Defendants)

44. Paragraphs 1 to 43 are incorporated herein as set forth above.

45. On information and belief, the Anchen Defendants, acting jointly, submitted ANDA No. 91-281 and the amendment thereto to the FDA to obtain approval under the FFDCA to engage in the commercial manufacture, use, or sale

throughout the United States, including California, of the Anchen Generic Products. By submitting this application and the amendment thereto, the Anchen Defendants, individually and collectively, committed an act of infringement with respect to the '372 Patent under 35 U.S.C. § 271(e)(2)(A).

46. On information and belief, any commercial manufacture, use, offer for sale, sale, and/or importation of the Anchen Generic Products prior to patent expiry will infringe the '372 Patent.

COUNT II

(Infringement of the '372 Patent Under 35 U.S.C. § 271 (b) against Anchen, Inc.)

47. Paragraphs 1 to 46 are incorporated herein as set forth above.

48. On information and belief, Anchen, Inc. actively induced Anchen Pharmaceuticals, Inc. to submit ANDA No. 91-281 and the amendment thereto to the FDA to obtain approval under the FFDCA to engage in the commercial manufacture, use, or sale throughout the United States including California of the Anchen Generic Products.

49. Upon information and belief, Anchen, Inc. will be actively involved in the manufacture, marketing, and sale of the Anchen Generic Products, should FDA approval be granted.

50. On information and belief, any such commercial manufacture, use, offer for sale, and/or importation of the Anchen Generic Products prior to patent expiry will infringe the '372 Patent. By engaging in a cooperative venture with Anchen Pharmaceuticals, Inc. to submit the ANDA and the amendment thereto to the FDA to obtain approval under the Food, Drug, and Cosmetic Act to engage in the commercial manufacture, use, or sale throughout the United States, including California, of the Anchen Generic Products, Anchen, Inc. committed an act of indirect infringement with respect to the '372 Patent under 35 U.S.C. § 271(b).

COUNT III

(Declaratory Judgment of Infringement of the '372 Patent Under 35 U.S.C. § 271 against the Anchen Defendants)

51. Paragraphs 1 to 50 are incorporated herein as set forth above.

52. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

53. There is an actual case or controversy such that the Court may entertain Plaintiffs' request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

54. The Anchen Defendants and/or their agents have made, and will continue to make, substantial preparation in the United States to manufacture, sell, offer to sell, and/or import generic versions of AMRIX® products.

55. The Anchen Defendants' actions indicate a refusal to change the course of their action in the face of acts by Plaintiffs.

56. On information and belief, any commercial manufacture, use, offer for sale, and/or importation of generic versions of AMRIX® by the Anchen Defendants prior to patent expiry will directly and/or indirectly infringe, contribute to the infringement of and/or induce infringement of the '372 Patent.

57. Plaintiffs are entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of the Anchen Generic Products, by the Anchen Defendants, prior to patent expiry, will infringe the '372 Patent.

INJUNCTIVE RELIEF

58. Plaintiffs will be irreparably harmed by the Anchen Defendants' infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

PRAYER FOR RELIEF

Plaintiffs respectfully pray for the following relief:

a. That judgment be entered that the Anchen Defendants, individually and/or collectively, have infringed the '372 Patent under 35 U.S.C. § 271(e)(2)(A) by submitting ANDA No. 91-281 and the amendment thereto under the Federal Food, Drug, and Cosmetic Act, and that the commercial manufacture, use, offer for sale, and/or importation of the Anchen Generic Products prior to patent expiry will constitute an act of infringement of the '372 Patent;

b. That judgment be entered that Anchen, Inc. has infringed the '372 Patent under 35 U.S.C. § 271(b) by inducing Anchen Pharmaceuticals, Inc. to submit ANDA No. 91-281 and amendment thereto under the Federal Food Drug, and Cosmetic Act, as a joint venture in which Anchen, Inc. will participate in the commercial manufacture, use, offer for sale, sale, and/or importation of the Anchen Generic Products prior to patent expiry, which will constitute an act of infringement of the '372 Patent;

c. That an order be issued under 35 U.S.C. § 271(e)(4)(A) that the effective date of any FDA approval of ANDA No. 91-281 shall be a date which is not earlier than the expiration date of the '372 Patent including any extensions;

d. That an injunction be issued under 35 U.S.C. § 271(e)(4)(B) permanently enjoining Anchen Pharmaceuticals, Inc., Anchen, Inc., their officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with any of them or acting on their behalf, from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of any drug product covered by the '372 Patent;

e. That damages or other monetary relief be awarded to Plaintiffs under 35 U.S.C. § 271(e)(4)(C) as appropriate;

f. That a declaration be issued under 28 U.S.C. § 2201 that if

Anchen Pharmaceuticals, Inc., Anchen, Inc., their officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with any of them or acting on their behalf, engage in the commercial manufacture, use, offer for sale, sale, and/or importation of the Anchen Generic Products prior to patent expiry, it will constitute an act of direct and/or indirect infringement of the '372 Patent;

g. That this is an exceptional case under 35 U.S.C. § 285, and that Plaintiffs be awarded reasonable attorneys' fees and costs; and

h. That this Court award such other and further relief as it may deem just and proper.

Dated: September 23, 2009

FISH & RICHARDSON P.C.

By: _____
Todd G. Miller (SBN 163200)
Attorneys for Plaintiffs
Eurand, Inc. and Anesta AG

30503410.doc

Exhibit A

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

EURAND, INC., CEPHALON, INC., and ANESTA AG,

Plaintiffs,

v.

ANCHEN PHARMACEUTICALS, INC. and ANCHEN, INC.,

Defendants.

Civil Action No. 09 - 492

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Eurand, Inc., Cephalon, Inc. and Anesta AG (collectively, "Plaintiffs") bring this Complaint against Defendants Anchen Pharmaceuticals, Inc. and Anchen, Inc. (collectively "Anchen" or "Anchen Defendants"), and in support state and allege 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, Titles 21 and 35, respectively, arising from Anchen filing an Abbreviated New Drug Application with the United States Food and Drug Administration ("FDA"), seeking approval to commercially market generic versions of the drug product AMRIX® (Cyclobenzaprine HCl extended release capsules) prior to the expiration of United States Patent No. 7,387,793 ("the '793 Patent"), which covers the AMRIX® product.

THE PARTIES

2. Plaintiff Eurand, Inc. ("Eurand") is a corporation, organized, existing and doing business under and by virtue of the laws of the State of Nevada, with its office and principal place of business located at 845 Center Drive, Vandalia, Ohio 45377.

3. Plaintiff Cephalon, Inc. ("Cephalon") is a corporation organized, existing and doing business under and by virtue of the laws of the State of Delaware, with its office and principal place of business located at 41 Moores Road, Frazer, Pennsylvania 19355.

4. Plaintiff Anesta AG ("Anesta") is a Swiss corporation having a principal place of business at Baarerstrasse 23CH-6300 Zug, Switzerland.

5. On information and belief, Defendant Anchen Pharmaceuticals, Inc. is a corporation organized and existing under the laws of the State of California, with a principal place of business at 9601 Jeronimo Road, Irvine, CA 92618-2025.

6. On information and belief, Defendant Anchen, Inc. is a corporation organized and existing under the laws of the State of Delaware, with a principal place of business at 9601 Jeronimo Road, Irvine, CA 92618-2025.

7. On information and belief, Defendants Anchen Pharmaceuticals, Inc. and Anchen, Inc. closely coordinate their commercial activities and hold themselves out to the marketplace as one company. For example, during prosecution of Anchen Pharmaceuticals, Inc.'s trademark application for the word mark ANCHEN with respect to pharmaceutical products (serial no. 77051871), representatives for Anchen Pharmaceuticals, Inc. stated that "Anchen Pharmaceuticals, Inc. and Anchen Incorporated, though separate legal entities, constitute a single source to the relevant public, and there is unity of control with respect to the nature and quality of the goods." On information and belief, Anchen Pharmaceuticals, Inc. and Anchen, Inc. have also simultaneously shared senior corporate officers with the same titles, including Margaret Choy, Senior Vice President of Regulatory Affairs. Ms. Choy is also the contact person listed in Anchen's Paragraph IV Notice Letter to Plaintiffs, which is discussed below.

8. On information and belief, Defendant Anchen Pharmaceuticals, Inc. is in the business of preparing generic pharmaceuticals that it distributes in the State of Delaware and throughout the United States. On information and belief, Defendant Anchen Pharmaceuticals, Inc. conducts its North American operations, in part, through Anchen, Inc. On information and belief, together, they collaborate in the manufacture, marketing, and sale of many pharmaceutical products (including generic drug products manufactured and sold pursuant to approved abbreviated new drug applications) within the United States generally, and the State of Delaware specifically. For example, Anchen has sold millions of dollars worth of Bupropion and Divalproex pharmaceutical products within the United States generally, and the State of Delaware specifically, under a stylized "Anchen" trademark (Anchen) that is owned by Anchen, Inc. (serial no. 77037779) (*see* drug labels attached as **Exhibits B and C**).

JURISDICTION AND VENUE

9. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a), 35 U.S.C. § 271, and the Declaratory Judgment Act, 28 U.S.C. §§ 2201-02.

10. Based on the facts and causes alleged herein, and for additional reasons to be further developed through discovery, this Court has personal jurisdiction over the Anchen Defendants.

11. This Court has personal jurisdiction over Anchen Pharmaceuticals, Inc. by virtue of the fact that, *inter alia*, it has committed—or aided, abetted, contributed to, or participated in the commission of—the tortious act of patent infringement that has led to foreseeable harm and injury to Cephalon, a Delaware corporation.

12. In addition, on information and belief, this court has personal jurisdiction over Anchen Pharmaceuticals, Inc. by virtue of its systematic and continuous contacts with the State of Delaware.

13. On information and belief, Anchen Pharmaceuticals, Inc. plans to continue to maintain continuous and systematic contacts with the State of Delaware, including but not limited to, its aforementioned business of preparing generic pharmaceuticals that it distributes in the State of Delaware.

14. This Court has personal jurisdiction over Anchen, Inc. by virtue, *inter alia*, of its incorporation in Delaware.

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

FACTS RELEVANT TO ALL CAUSES

16. On July 17, 2008, the United States Patent and Trademark Office ("PTO") duly and legally issued U.S. Patent No. 7,387,793 ("the '793 Patent") to Plaintiff Eurand. A true and correct copy of the '793 Patent is attached hereto as **Exhibit A.**

17. Eurand is the lawful owner by assignment of the '793 Patent and owns all rights, title and interest in the '793 Patent, including all rights needed to bring this patent infringement action.

18. On or about August 23, 2007, Anesta obtained, via an Asset Purchase Agreement ("APA"), all right, title, and interest in approved New Drug Application ("NDA") No. 21-777 for cyclobenzaprine hydrochloride extended-release capsules, in 15mg and 30mg doses, both sold under the AMRIX® trademark. Under the APA, Anesta also obtained an exclusive license to the '793 patent in the United States.

19. Anesta is a wholly-owned subsidiary of Cephalon and was, at all times relevant to this complaint, acting as an agent of Cephalon.

20. The FDA approved AMRIX® for marketing in the United States under NDA No. 21-777, pursuant to section 505(b) of the Federal Food Drug and Cosmetics Act ("FFDCA"), 21 U.S.C. § 355(b).

21. In conjunction with NDA No. 21-777, Anesta listed the '793 Patent in the Orange Book as a patent "with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." 21 U.S.C. § 355(b)(1)).

22. On or about June 3, 2009, Eurand received a letter dated May 28, 2009, and signed by a representative of Anchen, purporting to be notice of Anchen's filing of ANDA No. 91-281 seeking to market 15 mg and 30 mg generic versions of AMRIX® Cyclobenzaprine HCl extended release capsules (the "Anchen Generic Products") and allegedly containing a Paragraph IV Certification required by 21 U.S.C. § 355(j)(2)(b)(i) and (ii), with respect to the '793 Patent. (Anchen's "Paragraph IV Notice Letter").

23. On or about May 29, 2009, Cephalon (on behalf of itself and Anesta) received the same Anchen Paragraph IV Notice Letter dated May 28, 2009, and signed by a representative of Anchen, purporting to be notice of Anchen's filing of an ANDA seeking to market 15 mg and 30 mg generic versions of AMRIX® Cyclobenzaprine HCl extended release capsules and allegedly containing a Paragraph IV Certification required by 21 U.S.C. § 355(j)(2)(b)(i) and (ii), with respect to the '793 Patent.

24. Anchen's Paragraph IV Notice Letters to both Eurand and Cephalon state Anchen's intention to seek approval to market generic versions of AMRIX® Cyclobenzaprine HCl extended release capsules prior to the expiration of the '793 Patent.

25. The Anchen Paragraph IV Notice Letters sent to both Eurand and Cephalon fail to comply with the requirements of 21 U.S.C. § 355 (j)(2)(B)(iv)(II) because, *inter alia*, they contain very limited information about the generic formulation for which Anchen filed ANDA No. 91-281. For example, the Anchen Paragraph IV Notice Letters do not list any of the ingredients in the proposed generic versions, or the amounts of those ingredients.

26. In the Anchen Paragraph IV Notice Letters, Anchen offered confidential access to portions of ANDA No. 91-281 on terms and conditions set forth in paragraph VII of the Letters ("the Anchen Offer"). Anchen requested that Plaintiffs accept the Anchen Offer before receiving access to Anchen's ANDA No. 91-281. The Anchen Offer contained unreasonable restrictions, above and beyond those that would apply under a protective order, on who could view the ANDA. For example, the Anchen Offer unreasonably limited the fields of practice and other activities of outside counsel and any other person who accepted access to the ANDA.

27. Under 21 U.S.C. § 355(j)(5)(C)(i)(III), an offer of confidential access "shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information."

28. Since receiving the Anchen Paragraph IV Notice Letters and the accompanying Anchen Offer, Plaintiffs have negotiated with Anchen to procure a copy of ANDA No. 91-281 under restrictions "as would apply had a protective order been issued." These negotiations have been unsuccessful. For example, Anchen's most recent proposal continues to unreasonably limit the fields of practice and other activities of any person, including outside counsel, who accepts access to the ANDA. Anchen has refused to modify these restrictions despite Judge Robinson's

June 23, 2009 Order in the AMRIX® cases pending in this District, CIV-08-889 and CIV-09-018, rejecting similar proposals made by the defendants there.

29. Plaintiffs are not aware of any other means of obtaining information regarding the Anchen Generic Products within the 45-day statutory period. In the absence of such information, Plaintiffs resort to the judicial process and the aid of discovery to obtain, under appropriate judicial safeguards, such information as is required to confirm its allegations of infringement and to present to the Court evidence that the Anchen Generic Products fall within the scope of one or more claims of the '793 patent.

COUNT I
(Infringement of the '793 Patent Under 35 U.S.C. § 271(e)(2) against the Anchen Defendants)

30. Paragraphs 1 to 29 are incorporated herein as set forth above.

31. On information and belief, the Anchen Defendants, acting jointly, submitted ANDA No. 91-281 to the FDA to obtain approval under the FFDCA to engage in the commercial manufacture, use, or sale throughout the United States, including Delaware, of the Anchen Generic Products. By submitting this application, the Anchen Defendants, individually and collectively, committed an act of infringement with respect to the '793 patent under 35 U.S.C. § 271(e)(2)(A).

32. On information and belief, any commercial manufacture, use, offer for sale, sale, and/or importation of the Anchen Generic Products prior to patent expiry will infringe the '793 patent.

COUNT II
(Infringement of the '793 Patent Under 35 U.S.C. § 271 (b) against Anchen, Inc.)

33. Paragraphs 1 to 32 are incorporated herein as set forth above.

34. On information and belief, Anchen, Inc. actively induced Anchen Pharmaceuticals, Inc. to submit ANDA No. 91-281 to the FDA to obtain approval under the FFDCA to engage in the commercial manufacture, use, or sale throughout the United States including Delaware of the Anchen Generic Products. By actively inducing submission of ANDA No. 91-281, Anchen Inc. has committed an act of indirect infringement with respect to the '793 patent under 35 U.S.C. § 271(b).

35. On information and belief, any commercial manufacture, use, offer for sale, and/or importation of the Anchen Generic Products prior to patent expiry will infringe the '793 patent.

COUNT III
(Declaratory Judgment of Infringement of the '793 Patent Under 35 U.S.C. § 271 against the Anchen Defendants)

36. Paragraphs 1 to 35 are incorporated herein as set forth above.

37. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

38. There is an actual case or controversy such that the Court may entertain Plaintiffs' request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

39. The Anchen Defendants and/or their agents have made, and will continue to make, substantial preparation in the United States to manufacture, sell, offer to sell, and/or import generic versions of AMRIX® products.

40. The Anchen Defendants' actions indicate a refusal to change the course of their action in the face of acts by Plaintiffs.

41. On information and belief, any commercial manufacture, use, offer for sale, and/or importation of generic versions of AMRIX® by the Anchen Defendants prior to patent

expiry will directly and/or indirectly infringe, contribute to the infringement of and/or induce infringement of the '793 patent.

42. Plaintiffs are entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of the Anchen Generic Products, by the Anchen Defendants, prior to patent expiry, will infringe the '793 patent.

INJUNCTIVE RELIEF

43. Plaintiffs will be irreparably harmed by the Anchen Defendants' infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

PRAYER FOR RELIEF

Plaintiffs respectfully pray for the following relief:

a. That judgment be entered that the Anchen Defendants, individually and/or collectively, have infringed the '793 patent under 35 U.S.C. § 271(e)(2)(A) by submitting ANDA No. 91-281 under the Federal Food, Drug, and Cosmetic Act, and that the commercial manufacture, use, offer for sale, and/or importation of the Anchen Generic Products prior to patent expiry will constitute an act of infringement of the '793 patent;

b. That judgment be entered that Anchen, Inc. has infringed the '793 patent under 35 U.S.C. § 271(b) by inducing Anchen Pharmaceuticals, Inc. to submit ANDA No. 91-281 under the Federal Food Drug, and Cosmetic Act, and that the commercial manufacture, use, offer for sale, sale, and/or importation of the Anchen Generic Products prior to patent expiry will constitute an act of infringement of the '793 patent;

c. That an order be issued under 35 U.S.C. § 271(e)(4)(A) that the effective date of any FDA approval of ANDA No. 91-281 shall be a date which is not earlier than the expiration date of the '793 patent including any extensions;

d. That an injunction be issued under 35 U.S.C. § 271(e)(4)(B) permanently enjoining Anchen Pharmaceuticals, Inc., Anchen, Inc., their officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with any of them or acting on their behalf, from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of any drug product covered by the '793 patent;

e. That damages or other monetary relief be awarded to Plaintiffs under 35 U.S.C. § 271(e)(4)(C) as appropriate;

f. That a declaration be issued under 28 U.S.C. § 2201 that if Anchen Pharmaceuticals, Inc., Anchen, Inc., their officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with any of them or acting on their behalf, engage in the commercial manufacture, use, offer for sale, sale, and/or importation of the Anchen Generic Products prior to patent expiry, it will constitute an act of direct and/or indirect infringement of the '793 patent;

g. That this is an exceptional case under 35 U.S.C. § 285, and that Plaintiffs be awarded reasonable attorneys' fees and costs; and

h. That this Court award such other and further relief as it may deem just and proper.

FISH & RICHARDSON P.C.

By: _____

William J. Marsden, Jr. (#2247)
Susan M. Coletti (#4690)
Jennifer Hall (#5122)
222 Delaware Avenue, 17th Floor
P.O. Box 1114
Wilmington, DE 19899-1114
Tel: 302-652-5070
Fax: 302-652-0607
Email: marsden@fr.com
coletti@fr.com
jhall@fr.com

John D. Garretson
John S. Goetz
Wing H. Liang
FISH & RICHARDSON P.C.
601 Lexington Avenue
52nd Floor
New York, NY 10022-4611
(212) 765-5070

Jonathan E. Singer
FISH & RICHARDSON P.C.
60 South Sixth Street
3200 RBC Plaza
Minneapolis, MN 55402
(612) 335-5070

Attorneys for Plaintiffs
Eurand, Inc., Cephalon, Inc., and Anesta AG

OF COUNSEL:

Tryn T. Stimart
COOLEY GODWARD KRONISH LLP
777 6th Street N.W. Suite 1100
Washington, DC 20001
(202) 842-7800

Richard S. Sanders
COOLEY GODWARD KRONISH LLP
The Prudential Tower
800 Boylston St., 46th Floor
Boston, MA 02199
(617) 937-2317

Attorneys for Eurand, Inc.

Dated: July 7, 2009

Exhibit A

US007387793B2

(12) **United States Patent**
Venkatesh et al.

(10) **Patent No.: US 7,387,793 B2**
(45) **Date of Patent: Jun. 17, 2008**

(54) **MODIFIED RELEASE DOSAGE FORMS OF SKELETAL MUSCLE RELAXANTS**

(75) Inventors: **Gopi Venkatesh**, Vandalia, OH (US); **James M. Clevenger**, Vandalia, OH (US)

(73) Assignee: **Eurand, Inc.**, Vandalia, OH (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 470 days.

(21) Appl. No.: **10/713,929**

(22) Filed: **Nov. 14, 2003**

(65) **Prior Publication Data**

US 2005/0106247 A1 May 19, 2005

(51) **Int. Cl.**
A61K 9/14 (2006.01)

(52) **U.S. Cl.** **424/489**

(58) **Field of Classification Search** 424/489
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,590,062	A		5/1986	Jang
4,728,513	A		3/1988	Ventouras
4,743,248	A		5/1988	Bartoo et al.
4,780,319	A		10/1988	Zentner et al.
4,789,549	A		12/1988	Khan et al.
4,795,644	A		1/1989	Zentner
4,814,183	A		3/1989	Zentner
4,839,177	A	*	6/1989	Colombo et al. 424/482
4,851,228	A		7/1989	Zentner et al.
4,851,229	A		7/1989	Magruder et al.
4,882,167	A		11/1989	Jang
4,996,047	A		2/1991	Kelleher et al.
5,008,114	A		4/1991	Loverecich
5,120,548	A		6/1992	McClelland et al.
5,260,069	A		11/1993	Chen
5,350,584	A		9/1994	McClelland et al.
5,366,738	A		11/1994	Rork et al.
5,407,686	A	*	4/1995	Patel et al. 424/468
5,422,122	A		6/1995	Powell
5,582,838	A		12/1996	Rork et al.
5,874,418	A		2/1999	Stella et al.
5,882,682	A		3/1999	Rork et al.
5,952,451	A		9/1999	Zhao
6,004,582	A		12/1999	Faour et al.
6,020,000	A		2/2000	Wong et al.
6,451,345	B1		9/2002	Percel et al.
6,500,454	B1		12/2002	Percel et al.
6,627,223	B2		9/2003	Percel et al.
6,663,888	B2		12/2003	Percel et al.
2003/0099711	A1	*	5/2003	Meadows et al. 424/474
2003/0215496	A1	*	11/2003	Patel et al. 424/452
2004/0166160	A1		8/2004	Subramanian et al.
2004/0197407	A1		10/2004	Subramanian et al.

FOREIGN PATENT DOCUMENTS

WO	98/06439		2/1998
WO	98/18610		5/1998
WO	98/53802		12/1998
WO	99/12524		3/1999
WO	WO99/12524	*	3/1999
WO	99/18937		4/1999
WO	99/30671		6/1999
WO	WO99/30671	*	6/1999
WO	01/15668		3/2001
WO	03/020242		3/2003

OTHER PUBLICATIONS

U.S. Appl. No. 10/335,295, filed Dec. 2002, Venkatesh et al.
U.S. Appl. No. 10/619,924, filed Jul. 2003, Venkatesh et al.
Akimoto, M. et al., "Evaluation of sustained-release granules of chlorphenesin carbamate in dogs and humans," *International Journal of Pharmaceutics*, 100, pp. 133-142 (1993).

* cited by examiner

Primary Examiner—MP Woodward
Assistant Examiner—Bethany Barham
(74) *Attorney, Agent, or Firm*—Cooley Godward Kronish LLP

(57) **ABSTRACT**

A unit dosage form, such as a capsule or the like, for delivering a skeletal muscle relaxant, such as cyclobenzaprine hydrochloride, into the body in an extended or sustained release fashion comprising one or more populations of drug-containing particles (beads, pellets, granules, etc.) is disclosed. At least one bead population exhibits a predesigned sustained release profile. Such a drug delivery system is designed for once-daily oral administration to maintain an adequate plasma concentration—time profile, thereby providing relief of muscle spasm associated with painful musculoskeletal conditions over a 24 hour period.

20 Claims, 4 Drawing Sheets

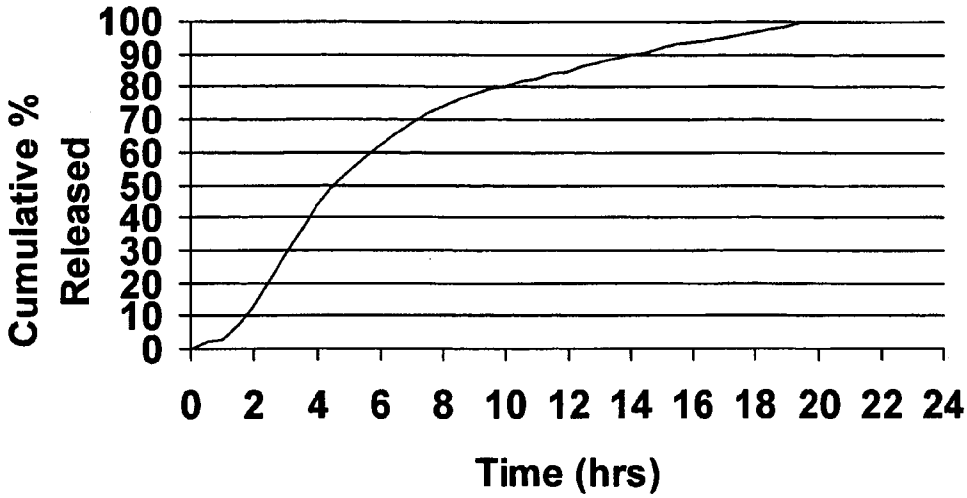

Cumulative % Released
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hrs)

FIG. 1

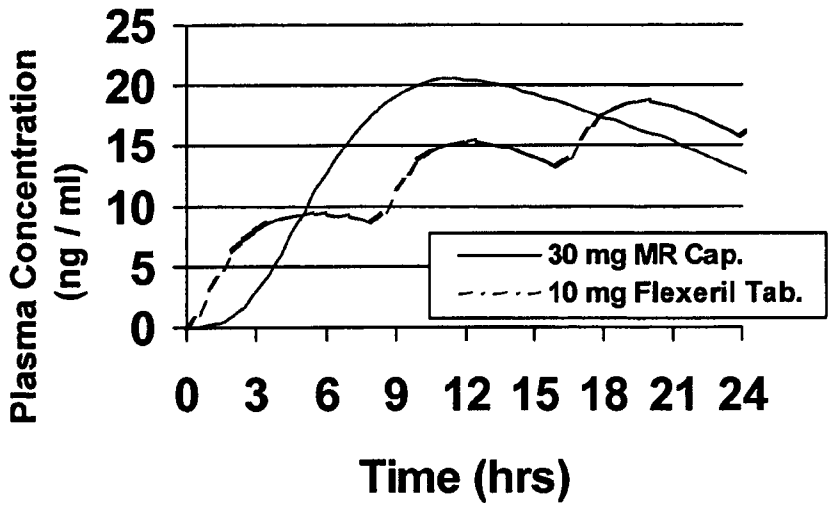

Plasma Concentration (ng / ml)
25
20
15
10
5
0
0 3 6 9 12 15 18 21 24
Time (hrs)
30 mg MR Cap.
10 mg Flexeril Tab.

FIG. 2

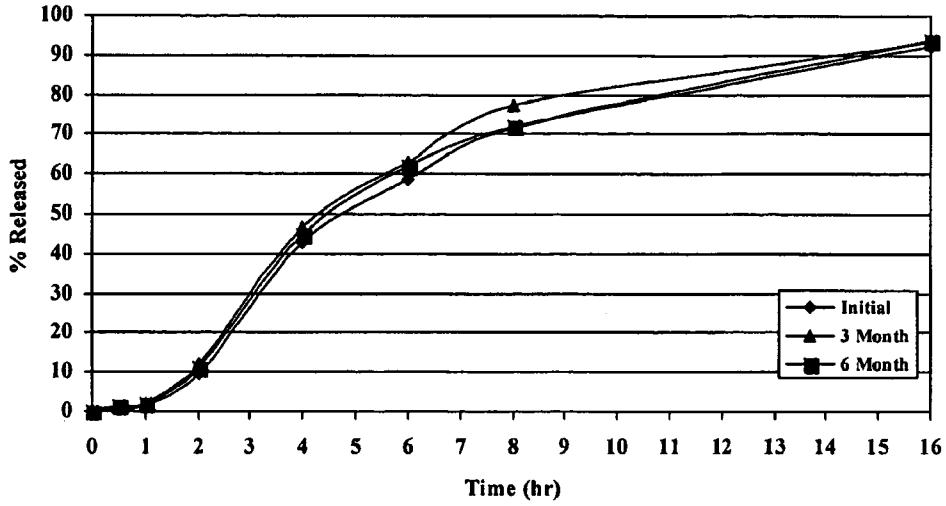

% Released
Time (hr)
Initial
3 Month
6 Month

FIG. 3

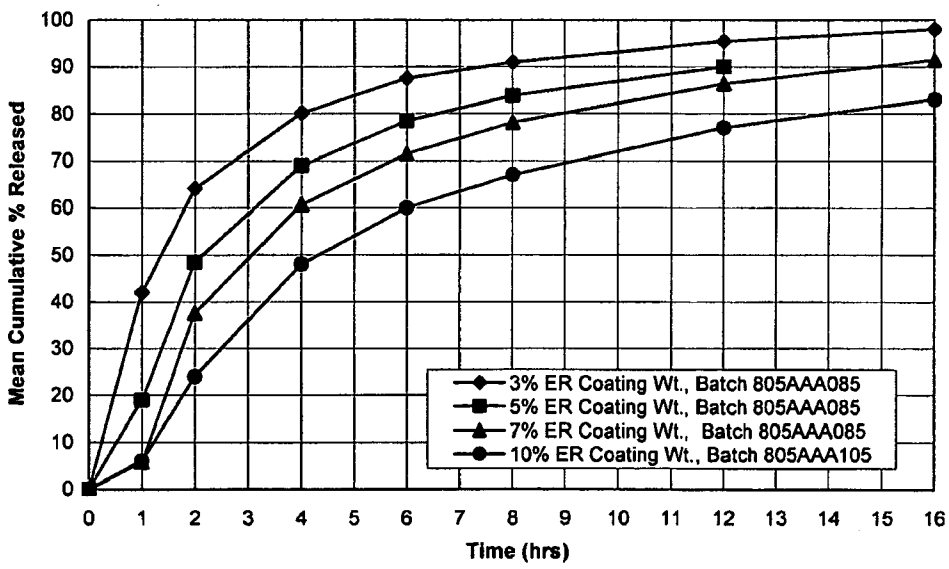

Mean Cumulative % Released
Time (hrs)
3% ER Coating Wt., Batch 805AAA085
5% ER Coating Wt., Batch 805AAA085
7% ER Coating Wt., Batch 805AAA085
10% ER Coating Wt., Batch 805AAA105

FIG. 4

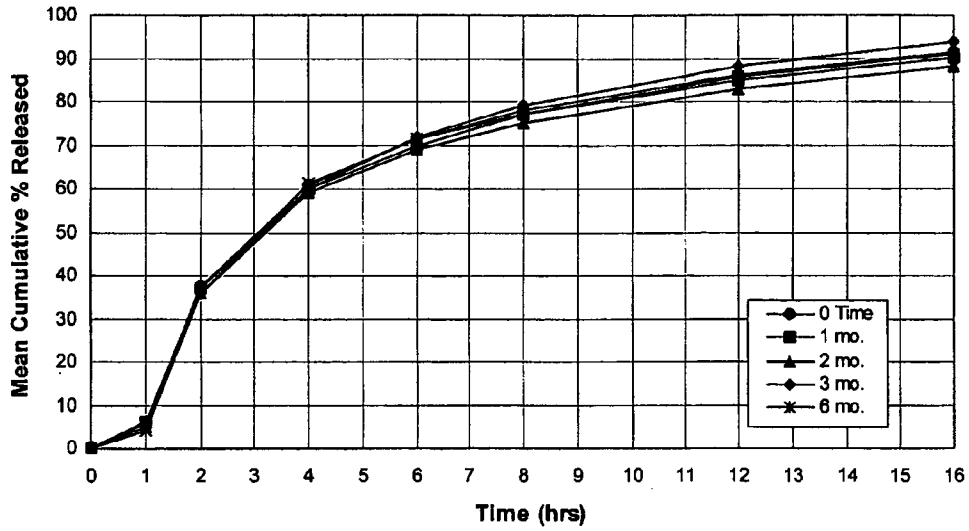

Mean Cumulative % Released
Time (hrs)
0 Time
1 mo.
2 mo.
3 mo.
6 mo.

FIG. 5

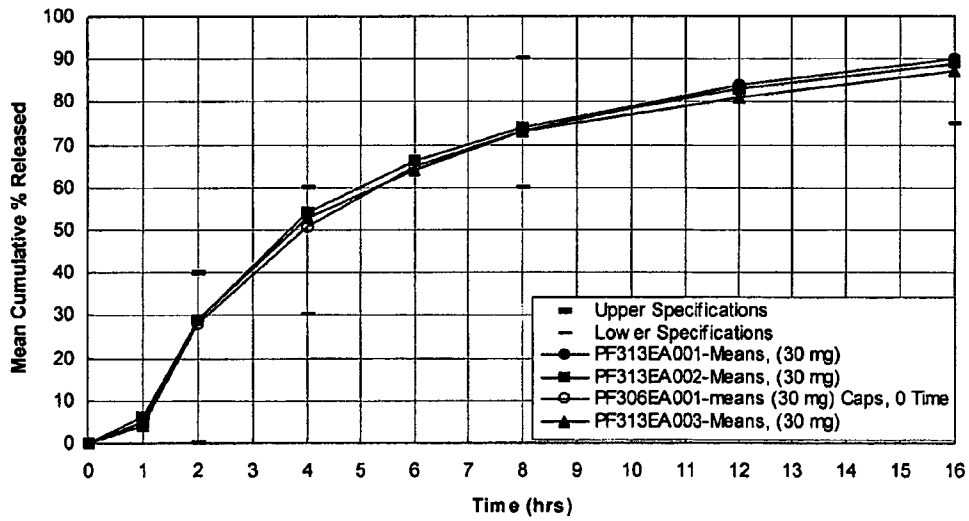

Mean Cumulative % Released
Time (hrs)
Upper Specifications
Lower Specifications
PF313EA001-Means, (30 mg)
PF313EA002-Means, (30 mg)
PF306EA001-means (30 mg) Caps, 0 Time
PF313EA003-Means, (30 mg)

FIG. 6

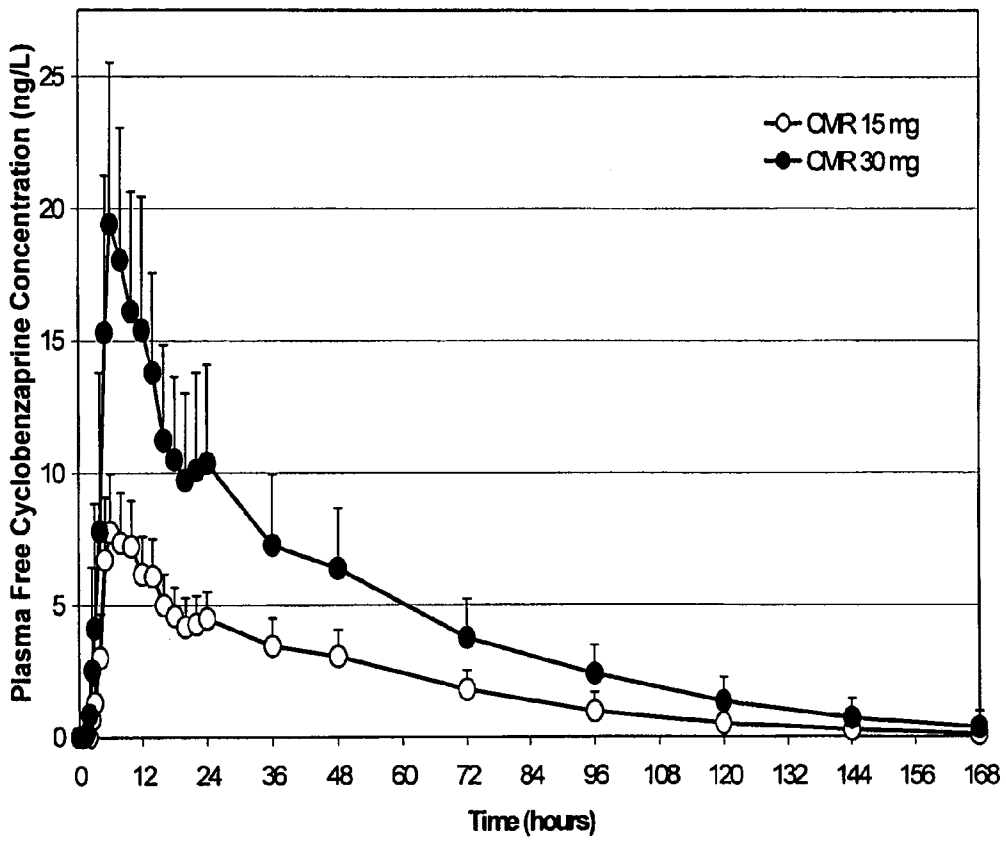

Plasma Free Cyclobenzaprine Concentration (ng/L)
0
5
10
15
20
25
0
12
24
36
48
60
72
84
96
108
120
132
144
156
168
Time (hours)
CMR 15 mg
CMR 30 mg

FIG. 7

MODIFIED RELEASE DOSAGE FORMS OF SKELETAL MUSCLE RELAXANTS

TECHNICAL FIELD

A major objective of developing and commercializing controlled release dosage forms for indications such as cardiovascular diseases, chronic pain, relief of muscle spasm and associated symptoms especially in the elderly is to deliver the drug so as to maintain the drug at therapeutically effective concentrations over an extended period of time, thereby enhancing patient compliance and therapeutic efficacy, thereby reducing both cost of treatment and side effects.

BACKGROUND OF THE INVENTION

Many therapeutic agents are most effective when made available at a constant rate at or near the absorption site. The absorption of therapeutic agents thus made available generally results in desired plasma concentrations leading to maximum efficacy and minimum toxic side effects. Much effort has been devoted to developing matrix tablet based and multi-particulate capsule based drug delivery systems for oral applications.

U.S. Pat. No. 4,839,177 to Colombo, et al, assigned to Jagotec AG, refers broadly to controlled release of active substances including medicaments and any type of substance which is to be released at a controlled rate into an aqueous fluid. The patent is directed to a system for the controlled-rate release of active substances consisting of a deposit core comprising an active substance and at least one of (a) a polymeric material having a high degree of swelling on contact with water and a gellable polymeric material or (b) a single polymeric material having both swelling and gelling properties, and a support platform applied to the deposit core wherein the support platform consists of a water insoluble polymeric material.

U.S. Pat. Nos. 4,851,228 and No. 4,968,507, both to Zentner et al., assigned to Merck & Company, refer to a multi-particulate osmotic pump for the controlled release of a pharmaceutically active agent, each osmotic pump element consisting essentially of a core containing an active agent and a rate controlling water insoluble wall comprising a semi-permeable polymer and at least one pH insensitive pore forming additive dispersed throughout the wall. U.S. Pat. No. 4,590,062 to Jang assigned to Tech Trade Corporation and U.S. Pat. No. 4,882,167 to Jang, are directed to a compressed product containing an active produced by dry blending with a matrix combination of a hydrophobic polymer (e.g. ethylcellulose) and a wax, fatty acid, neutral lipid or combination thereof.

U.S. Pat. No. 4,996,047 to Kelleher, assigned to Richardson-Vicks, is directed to an oral pharmaceutical composition in unit dosage form of ion-exchange resin particles having a pharmacologically active drug bound thereto wherein the drug-resin complex particles have been coated with a water-impermeable diffusion barrier to provide controlled release of the active drug. U.S. Pat. No. 5,120,548 to McClelland et al., assigned to Merck & Company, is directed to a controlled release drug delivery device comprising a composition of a polymer which swells upon exposure to an aqueous environment, a plurality of controlled release swelling modulators, at least one active agent and either a water insoluble polymer coating surrounding the composition or a microporous wall surrounding the composition. U.S. Pat. No. 5,350,584 to McClelland et al., assigned to Merck &

Company, relates to a process for the production of microcrystalline cellulose-free multiparticulates comprising a medicament and a charged resin. The resulting spheronized beads can be used in certain controlled release dosage forms.

U.S. Pat. No. 5,366,738 to Rork et al., assigned to Merck & Company, is directed to a drug delivery device for controlled release of an active agent. The drug delivery device includes a compressed core with an active agent and a polymer which forms gelatinous microscopic particles upon hydration and a water insoluble, water impermeable polymeric coating comprising a polymer and plasticizer which surrounds and adheres to the core.

U.S. Pat. No. 5,582,838 to Rork et al., assigned to Merck & Company, is related to a drug delivery device for the controlled release of a beneficial agent. The drug delivery device includes a compressed core having at least two layers: at least one layer is a mixture of a beneficial agent and a polymer which forms microscopic polymer gel beads upon hydration and at least one outer layer comprises a polymer which forms microscopic polymer gel beads upon hydration. A water insoluble, water impermeable coating is applied to the core and the coating has apertures exposing between about 5-75% of the core surface.

U.S. Pat. No. 5,874,418 to Stella et al., assigned to Cydex, is directed to a pharmaceutical composition comprising a carrier and a mixture of a sulfoalkyl ether-cyclodextrin and a therapeutic agent wherein a major portion of the therapeutic agent is not complexed to the sulfoalkyl ether-cyclodextrin derivative. Delayed, sustained or controlled release formulations are also described wherein the pharmaceutical core is coated with a film coating comprising a file forming agent and a pore forming agent. U.S. Pat. No. 5,882,682 to Rork et al., assigned to Merck & Company, is directed to a drug delivery process including the steps of preparing a uniform mixture of a polymer which forms gelatinous microscopic particles upon hydration, the beneficial agent and other excipients used in the preparation of the core; compressing the mixture into cores; coating the entire core with a water insoluble, water impermeable polymeric coating including a polymer and a plasticizer; and forming apertures through the coating.

U.S. Pat. No. 5,952,451 to Zhao, assigned to Guilford Pharmaceuticals is directed to a process for preparing high molecular weight poly(phosphoester) compositions comprising a biologically active substance and a poly(phosphoester) and the high molecular weight compositions produced thereby. The polymers so produced are useful in prolonged released drug delivery systems. U.S. Pat. No. 6,004,582 to Faour et al., assigned to Laboratorios Phoenix U.S.A., is directed to a multi-layered osmotic device comprising a compressed core including a first active agent and an osmotic agent, a semi-permeable membrane surrounding the core and having a preformed passageway therein wherein the membrane is permeable to a fluid in the environment of use and substantially impermeable to the first active agent. The semi-permeable membrane preferably consists essentially of cellulose acetate and poly(ethylene glycol). The external coat can includes poly(vinylpyrrolidone) and poly (ethylene glycol) and can further includes materials such as HPMC, ethylcellulose, hydroxyl ethylcellulose, CMC, dimethylaminoethyl methacrylate-methacrylic acid ester copolymer, ethyl acrylate-methyl methacrylate copolymer, and combinations thereof.

WO 99/18937 to Kleinbart et al., (Merck & Company), is directed to a composition comprising a pharmaceutically effective amount of cyclobenzaprine and calcium phosphate dibasic hydrous, wherein the tablet releases most of the

active component within an hour. WO 99/30671 to Ron, is directed to an oral delivery vehicle including an aspected particle comprising a pharmaceutically active component and excipients wherein the vehicle is formulated to provide controlled delivery of the pharmaceutically active component. The vehicle may further contain a coating to provide sustained drug delivery to the particle. WO 98/53802 to Faour et al., (Laboratorios Phoenix USA), is directed to a multi-layered osmotic device that is capable of delivering a first active agent in an outer lamina to one environment of use and a second active agent in the core to another environment of use. An erodible polymer coat between an internal semipermeable membrane and a second active agent-containing external coat comprises poly(vinylpyrrolidone)-vinyl acetate) copolymer. The active agent in the core is delivered through a pore containing an erodible plug.

WO 98/18610 to Van Lengerich, is directed to particles containing an active agent, which provide controlled release of the active ingredient without substantial destruction of the matrix material. A release-rate controlling component is incorporated in a matrix to control the rate-release of the encapsulant from the particles. A hydrophobic component or a high water binding capacity component may be used for extending the release time. Release properties may also be controlled by precoating the encapsulant and/or coating the particles with a film-forming component. WO 98/06439 to Oedemoed, (Osteotech), is directed to a composition comprising a biologically active agent encapsulated in a matrix comprising a polyether ester copolymer, such as polyethylene glycol terephthalate/polybutylene-terephthalate copolymer. The polyether ester copolymer protects the active agent from degradation and thereby facilitates the drug delivery.

Cyclobenzaprine hydrochloride, a skeletal muscle relaxant, is a centrally acting drug which reduces or abolishes excessive tonic muscle activity in hypertonic as opposed to hyperphasic disorders. Flexeril IR (immediate release) tablets containing 10 mg of cyclobenzaprine HCl are administered three times a day to relieve skeletal muscle spasm of local origin without interfering with muscle function. The oral administration thrice daily is an issue of patient compliance, especially with the elderly. Hence, there is a need for modified release skeletal muscle relaxant suitable for a single administration. More particularly, there is a need for modified release (MR) cyclobenzaprine hydrochloride capsules, 15 and 30 mg, which would substantially minimize intersubject variability and improve the quality of life, especially in the elderly population.

SUMMARY OF THE INVENTION

The present invention provides a modified release, multiparticulate dosage form of a skeletal muscle relaxant comprising one or more bead populations which provides an extended release profile of the active under in vitro conditions closely mimicking the profile simulated from pharmaco-kinetic modeling. One of the bead populations is an ER (extended release) Bead population typically comprising a coating of a water insoluble polymer alone, or in combination with a water soluble polymer, applied onto active containing cores. The active core of the dosage form of the present invention may comprise an inert particle such as a sugar sphere, or an acidic or alkaline buffer crystal, which is coated with a skeletal muscle relaxant such as cyclobenzaprine hydrochloride-containing film-forming formulation, preferably a water-soluble film forming composition. The first coating formulation may contain, in addition to the active, a binder such as hydroxypropyl cellulose. The drug layered beads may be coated with a protective seal coating of OPADRY® Clear to produce IR Beads. Alternatively, the core particle may be formed by granulating and dry milling and/or by extrusion and spheronization of a pharmaceutical composition containing the active. The amount of drug in the core will depend on the dose required and typically varies from about 5 to about 60% by weight.

ER Beads can be produced by applying a functional membrane comprising a water insoluble polymer alone or in combination with a water soluble polymer onto IR Beads. The capsule formulation for once a day, oral administration of a skeletal muscle relaxant prepared in accordance with the present invention comprises ER Beads containing the active substance and optionally IR Beads. IR (immediate release) Beads allow immediate release of the active while ER Beads allow an extended release profile of the active over several hours. Upon oral administration, such a capsule formulation provides for therapeutically effective plasma profiles over an extended period of time, thereby resulting in improved patient compliance.

In accordance with one embodiment of the invention a pharmaceutical dosage form of a skeletal muscle relaxant is provided. The dosage form includes one or more bead populations and provides a modified release profile. At least one of the bead populations includes extended release (ER) beads wherein the ER beads include a core particle (IR (immediate release) bead) containing a skeletal muscle relaxant and an ER (extended release) coating comprising a water insoluble polymer surrounding the core. The dosage form, in accordance with certain embodiments, when dissolution tested using United States Pharmacopoeia Apparatus 2 (paddles @ 50 rpm) in 900 mL of 0.1N HCl (or a suitable dissolution medium) at 37° C. exhibits a drug release profile substantially corresponding to the following pattern:

- after 2 hours, no more than about 40% of the total active is released;
- after 4 hours, from about 40-65% of the total active is released;
- after 8 hours, from about 60-85% of the total active is released; and
- after 12 hours, from about 75-85% of the total active is released.

The dosage form thereby provides a therapeutically effective plasma concentration over an extended period of time, typically over a period of 24 hours to treat muscle spasm associated with painful musculoskeletal conditions in humans.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be described in further detail with reference to the accompanying Figures wherein:

FIG. **1** shows the proposed target release profile for cyclobenzaprine hydrochloride MR (modified release) capsules, 15 and 30 mg.

FIG. **2** shows the simulated Day **1** plasma level following dosing of 1×10 mg Flexeril® given 3 times a day and 1×10 mg cyclobenzaprine HCl MR capsule given once-daily.

FIG. **3** shows the drug release profiles for cyclobenzaprine HCl ER (extended release) beads of Example 2.

FIG. **4** compares the drug release profiles as a function of membrane coating of Example 3.

FIG. **5** shows the drug release profiles for cyclobenzaprine HCl ER beads of Example 3 stored in induction sealed HDPE bottles on accelerated stability.

FIG. **6** shows the drug release profiles for 30 mg cyclobenzaprine HCl MR capsules of Example 4.

FIG. **7** shows the plasma levels for cyclobenzaprine HCl MR capsules, 15 and 30 mg of Example 5.

DETAILED DESCRIPTION OF THE INVENTION

All documents cited are, in relevant part, incorporated herein by reference; the citation of any document is not to be construed as an admission that it is prior art with respect to the present invention.

The active core of the dosage form of the present invention may be comprised of an inert particle or an acidic or alkaline buffer crystal, which is coated with a drug-containing film-forming formulation and preferably a water-soluble film forming composition to form a water-soluble/dispersible particle. Alternatively, the active may be prepared by granulating and milling and/or by extrusion and spheronization of a polymer composition containing the drug substance. The amount of drug in the core will depend on the dose that is required, and typically varies from about 5 to 60 weight %. Generally, the polymeric coating on the active core will be from about 4 to 20% based on the weight of the coated particle, depending on the type of release profile required and/or the polymers and coating solvents chosen. Those skilled in the art will be able to select an appropriate amount of drug for coating onto or incorporating into the core to achieve the desired dosage. In one embodiment, the inactive core may be a sugar sphere or a buffer crystal or an encapsulated buffer crystal such as calcium carbonate, sodium bicarbonate, fumaric acid, tartaric acid, etc. which alters the microenvironment of the drug to facilitate its release.

The drug-containing particle may be coated with an extended release (ER) coating comprising a water insoluble polymer or a combination of a water insoluble polymer and a water soluble polymer to provide ER beads. In accordance with certain embodiments, the water insoluble polymer and the water soluble polymer may be present at a weight ratio of from 100/0 to 65/35, more particularly from about 95/5 to 70/30, and still more particularly at a ratio of from about 85/15 to 75/25. The extended release coating is applied in an amount necessary to provide the desired release profile. The extended release coating typically comprises from about 1% to 15%, more particularly from about 7% to 12%, by weight of the coated beads.

The present invention also provides a method of making a modified release dosage form including a mixture of two bead populations. In accordance with one embodiment, the method includes the steps of:

1. preparing a drug-containing core by coating an inert particle such as a non-pareil seed, an acidic buffer crystal or an alkaline buffer crystal with a drug and a polymeric binder or by granulation and milling or by extrusion/spheronization to form an immediate release (IR) bead;
2. coating the IR bead with a plasticized water-insoluble polymer alone such as ethylcellulose or in combination with a water soluble polymer such as hydroxypropylmethylcellulose to form an Extended Release (ER) bead;
3. filling into hard gelatin capsules ER Beads alone or in combination with IR Beads at a proper ratio to produce MR (modified release) capsules providing the desired release profile.

IR beads when tested in accordance with the following procedure release at least about 70%, more specifically at least about 90% of the active within 30 minutes.

Dissolution Procedure:

Dissolution Apparatus: USP Apparatus 2 (Paddles at 50 rpm), dissolution medium: 900 mL 0.1N HCl (or a suitable dissolution medium) at 37° C. and Drug Release determination by HPLC).

An aqueous or a pharmaceutically acceptable solvent medium may be used for preparing drug-containing core particles. The type of film forming binder that is used to bind the drug to the inert sugar sphere is not critical but usually water soluble, alcohol soluble or acetone/water soluble binders are used. Binders such as polyvinylpyrrolidone (PVP), polyethylene oxide, hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC), polysaccharides such as dextran, corn starch may be used at concentrations from about 0.5 to 5 weight %, although other concentrations may be useful. The drug substance may be present in this coating formulation in the solution form or may be dispersed at a solid content up to about 35 weight % depending on the viscosity of the coating formulation.

In accordance with certain embodiments, the drug substance, optionally a binder such as PVP, a dissolution rate controlling polymer (if used), and optionally other pharmaceutically acceptable excipients are blended together in a planetary mixer or a high shear granulator such as Fielder and granulated by adding/spraying a granulating fluid such as water or alcohol. The wet mass can be extruded and spheronized to produce spherical particles (beads) using an extruder/marumerizer. In these embodiments, the drug load could be as high as 90% by weight based on the total weight of the extruded/spheronized core.

Representative muscle relaxants include cyclobenzaprine, dantrolene sodium, methocarbamol, metaxalone, carisoprodol, diazepam and pharmaceutically acceptable salts or derivatives thereof. Cyclobenzaprine hydrochloride is a particularly useful muscle relaxant. As used herein, the useful muscle relaxants include the base, pharmaceutically acceptable salts thereof such as hydrochloride, stereoisomers thereof and mixtures thereof.

Representative examples of water insoluble polymers useful in the ER coating include ethylcellulose powder or an aqueous dispersion (such as AQUACOAT® ECD-30), cellulose acetate, polyvinyl acetate (Kollicoat SR#30D from BASF), neutral copolymers based on ethyl acrylate and methylmethacrylate, copolymers of acrylic and methacrylic acid esters with quaternary ammonium groups such as Eudragit NE, RS and RS30D, RL or RL30D and the like. Representative examples of water soluble polymers useful herein include low molecular weight hydroxypropyl methylcellulose (HPMC), methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, polyethylene glycol (PEG of molecular weight>3000) and mixtures thereof. The extended release coating will typically be applied at a thickness ranging from about 1 weight % up to 15 weight % depending on the solubility of the active in water and the solvent or latex suspension based coating formulation used.

The coating compositions used in forming the membranes are usually plasticized. Representative examples of plasticizers that may be used to plasticize the membranes include triacetin, tributyl citrate, triethyl citrate, acetyl tri-n-butyl citrate diethyl phthalate, polyethylene glycol, polypropylene glycol, castor oil, dibutyl sebacate, acetylated monoglycerides and the like or mixtures thereof. The plasticizer may comprise about 3 to 30 wt. % and more typically about 10 to 25 wt. % based on the polymer. The type of plasticizer and

its content depends on the polymer or polymers, nature of the coating system (e.g., aqueous or solvent based, solution or dispersion based and the total solids).

In general, it is desirable to prime the surface of the particle before applying an extended release membrane coating or to separate the different membrane layers by applying a thin hydroxypropyl methylcellulose (HPMC)(OPADRY® Clear) film. While HPMC is typically used, other primers such as hydroxypropylcellulose (HPC) can also be used.

The membrane coatings can be applied to the core using any of the coating techniques commonly used in the pharmaceutical industry, but fluid bed coating is particularly useful.

The present invention is applied to multi-dose forms, i.e., drug products in the form of multi-particulate dosage forms (pellets, beads, granules or mini-tablets) or in other forms suitable for oral administration. As used herein, these terms are used interchangeably to refer to multi-particulate dosage forms.

The invention also provides a method of making an extended release dosage form which includes a mixture of two or more bead populations. In accordance with one aspect of the present invention, the method includes the steps of:

(a) coating an inert particle such as a non-pareil seed, an acidic buffer crystal or an alkaline buffer crystal with a drug and polymeric binder to form an active drug particle (IR beads), which may be present in the unit dosage form to act as a bolus dose;

(b) coating the active drug particle with a solution or suspension of a water insoluble polymer or a mixture of water soluble and water insoluble polymers to form an extended release coated drug particle (ER beads);

(c) filling into a hard gelatin capsule ER beads alone and optionally, in combination with IR beads at a proper ratio ranging from 95/5 to 70/30 (ER beads/IR beads) to produce a MR (modified release) capsule exhibiting a target drug release profile.

The following non-limiting examples illustrate the capsule dosage forms manufactured in accordance with the invention using cyclobenzaprine hydrochloride as a test case, which exhibit in vitro drug release profiles, similar to that predicted by performing modeling exercises. Such dosage forms when orally administered, would enable maintaining drug plasma concentrations at therapeutically effective levels over extended periods of time, thereby significantly improving patient compliance.

EXAMPLE 1

Cyclobenzaprine is well absorbed after oral administration, but there is a large intersubject variation in plasma levels. It is eliminated quite slowly with a half-life as long as one to three days. The present treatment regimen of 10 mg three times daily is an issue of patient compliance, especially the elderly. Hence, a modified release dosage form (capsule) was designed with a release profile shown in FIG. **1**. To determine if this is the proper release profile, the pharmacokinetics data of cyclobenzaprine following a single dose of 10 mg Flexeril® tablets administered 3 times a day was taken from the literature. A pharmacokinetic model was developed from this data using WinNonlin™ Version 1.5.

The resulting model parameters are listed below:

Model Parameter	Value
Volume of Distribution/F	429 L
K01	0.2031 hr^{-1}
K10	0.1004 hr^{-1}
K12	0.0828 hr^{-1}
K21	0.0398 hr^{-1}
Tlag	0 hr
Dose	2 x 10 mg Tablets

Theoretical plasma levels were simulated using the pharmacokinetic model given above and the target release rate given in FIG. **1**. FIG. 2 shows the simulated plasma levels for day one following dosing of 1x10 mg Flexeril® Tablet given 3 times a day and the proposed Cyclobenzaprine HCl MR Capsule, 30 mg given once a day.

EXAMPLE 2

Cyclobenzaprine Hydrochloride (1,200 g) was slowly added to an aqueous solution of polyvinylpyrrolidone such as Povidone USP (K-29/32, 80 g) and mixed well. # 25-30 mesh sugar spheres (2,640 g) were coated with the drug solution in a Glatt fluid bed coater, equipped with a 9" bottom spray Wurster insert to provide IR beads with a coating weight of about 9%. The drug containing particles were dried, and a seal coat of OPADRY® Clear (2% w/w) was first applied and dried in the Glatt fluid bed unit as a precautionary measure to drive off excessive surface moisture. The composition and batch quantities of the IR Beads were given in 5 to 10 kg. Following the second coating process the IR Beads were passed through 14 and 25 mesh screens. Beads remaining on the 14-mesh screen were discarded as oversized beads and beads passing through the 25-mesh screen were discarded as undersized beads.

The next step in the process was to apply an extended release polymer membrane by spraying AQUACOAT® ECD **30**, an aqueous dispersion of ethylcellulose with dibutyl sebacate (76:24), onto the IR Beads for a weight gain of approximately 10%. The same fluid bed equipment was used to produce ER (extended release) Beads by further coating the AQUACOAT® coated beads with OPADRY® Clear for a weight gain of 2% w/w prior to curing at 60° C. in a conventional oven for a period of 24 hours. The batch size was 5 to 10 kg. The drug release profiles are shown in FIG. **3**. The figure also shows the drug release profiles from ER Beads stored in induction sealed HDPE bottles at 25° C./60% RH for 6 months.

EXAMPLE 3

Cyclobenzaprine Hydrochloride (2.5 kg) was dissolved in 50/50 acetone/purified water. 25-30 mesh Sugar spheres, (7.3 kg) were coated with the drug solution in a Glatt fluid bed coater, equipped with a 9" bottom spray Wurster insert. The drug containing particles were dried, and a seal coat of OPADRY® Clear (2% w/w) was first applied and dried in the Glatt fluid bed unit as a precautionary measure to drive off excessive surface moisture. 910 g of ethylcellulose (Ethocel Premium Standard 10 cps) and 90 g of diethyl phthalate were dissolved in 98/02 acetone/purified water and applied onto the IR Beads (9 kg) in the Glatt GPCG 5 in accordance with the present invention. The release rates of the ER Beads will vary depending upon the film weight of the ER coating. One

batch of IR Beads was coated for a final weight gain of 7% based on the weight of coated beads wherein samples of the ER Beads were removed during the ER coating process to yield beads with increasing coating weights. Another batch was coated for 10% weight gain and all the coated bead batches were cured at 60° C. for 4 hours in a conventional oven. FIG. **4** shows the relationship between the ER coating weights and the release rate of the finished ER coated Beads.

A batch was coated with a 7% ER coating and cured at 60° C. for 4 hours. No changes were noted in the release rates, assay values or impurity levels after storage in HDPE bottles at 40° C./75% RH for a period of 6 months. The release rates for the samples are shown in FIG. **5**.

EXAMPLE 4

The drug layering, seal coating, and ER Coating processes were scaled-up to Glatt GPCG 120 equipped with an 18" bottom spray Wurster insert (batch size: 80 kg for IR Beads and 85 kg for ER Beads). The process parameters of each of the processes were optimized. The drug layering solution (9% weight gain), seal coating solution, and the ER coating solution (9% weight gain) were sprayed onto the sugar spheres or IR Beads while maintaining the product temperature between narrow limits. Following the seal or ER coating the beads were passed through 14 and 25 mesh screens discarding any beads remaining on the 14 mesh screen. The ER Beads were also cured at 60° C. for a period of 4 hours. The Extended Release Beads were then filled into size 4 capsules to produce Cyclobenzaprine HCl MR Capsules, 15 and 30 mg. The drug release profiles of 30 mg capsules of one pivotal clinical and three registration stability batches are presented in FIG. **6**.

EXAMPLE 5

A Randomized double-blind two-period crossover study to assess the safety and bioavailability of Cyclobenzaprine HCl Modified-release (CMR) 15 mg and 30 mg in healthy male and female volunteers (N=14 or 15) was performed. Each subject received one 15 mg or 30 mg capsule of CMR in the morning, separated by a 14-day washout period between doses. The results are presented in Table 1 and FIG. **7** wherein AUC_{0-168} refers to the area under the plasma concentration-time curve to the last measurable time point (168 hrs) calculated by the linear trapezoidal rule, $AUC_{0-\infty}$ refers to area under the concentration-time curve to infinity, C_{max} refers to the maximum blood plasma concentration and T_{max} refers to the time to maximum plasma levels of cyclobenzaprine.

TABLE 1

Pharmacokinetic Results: Mean (±SD) pharmacokinetic parameters are presented for subjects in the Safety population in the following table

	CMR 15 mg N = 15	CMR 30 mg N = 14
AUC_{0-168} (ng · hr/mL)	318.30 ± 114.657	736.60 ± 259.414
$AUC_{0-\infty}$ (ng · hr/mL)	354.075 ± 119.8037	779.889 ± 277.6349
C_{max} (ng/mL)	8.315 ± 2.1635	19.851 ± 5.8765
Time to Peak, T_{max} (hr)	8.1 ± 2.94	7.1 ± 1.59
Elimination Half-life, $t_{1/2}$ (hr)	33.401 ± 10.2882	31.977 ± 10.1310

The treatments were significantly different from each other as values for AUCs and C_{max} were higher for CMR 30 mg than those for CMR 15 mg. The bioavailability of CMR 30 mg was approximately twice that of CMR 15 mg as shown by the AUCs. The adjusted mean ratio of CMR 30 mg to CMR 15 mg was greater than about 2 for each of the AUCs and C_{max}, specifically the calculated values were 2.42 for AUC_{0-168} ($p<0.001$), 2.286 for $AUC_{0-\infty}$ ($p<0.001$), and 2.424 for C_{max} ($p<0.001$). Overall, both CMR 15 mg and 30 mg were well tolerated during the study.

Accordingly, one aspect of the invention relates to a dosage form containing cyclobenzaprine hydrochloride as a skeletal muscle relaxant wherein the pharmaceutical dosage form provides a maximum blood plasma concentration (C_{max}) within the range of about 80% to 125% of about 20 ng/mL of cyclobenzaprine HCl, an AUC_{0-168} within the range of about 80% to 125% of about 740 ng·hr/mL and a T_{max} within the range of about 80% to 125% of about 7 hours following oral administration of a single 30 mg cyclobenzaprine HCl MR Capsule.

While the invention has been described in detail and with reference to specific examples thereof, it will be apparent to one skilled in the art that various changes and modifications can be made without departing from the spirit and scope thereof.

What is claimed is:

1. A multi-particulate pharmaceutical dosage form of a skeletal muscle relaxant providing a modified release profile comprising a population of extended release beads,

wherein said extended release beads comprise

an active-containing core particle comprising a skeletal muscle relaxant selected from the group consisting of cyclobenzaprine, pharmaceutically acceptable salts or derivatives thereof and mixtures thereof; and

an extended release coating comprising a water insoluble polymer membrane surrounding said core,

wherein said dosage form when dissolution tested using United States Pharmacopoeia Apparatus 2 (paddles @ 50 rpm) in 900 mL of 0.1N HCl at 37° C. exhibits a drug release profile substantially corresponding to the following pattern:

after 2 hours, no more than about 40% of the total active is released;

after 4 hours, from about 40-65% of the total active is released

after 8 hours, from about 60-85% of the total active is released;

wherein said dosage form provides therapeutically effective plasma concentration over a period of 24 hours to treat muscle spasm associated with painful musculoskeletal conditions when administered to a patient in need thereof; and

wherein said water insoluble polymer membrane comprises a water insoluble polymer selected from the group consisting of ethers of cellulose, esters of cellulose, cellulose acetate, ethyl cellulose, polyvinyl acetate, neutral copolymers based on ethylacrylate and methylmethacrylate, copolymers of acrylic and methacrylic acid esters with quaternary ammonium groups, pH-insensitive ammonio methacrylic acid copolymers, and mixtures thereof; and a plasticizer selected from the group consisting of triacetin, tributyl citrate, tri-ethyl citrate, acetyl tri-n-butyl citrate, diethyl phthalate, dibutyl sebacate, polyethylene glycol, polypropylene glycol, castor oil, acetylated mono- and di-glycerides and mixtures thereof.

2. The pharmaceutical dosage form of claim **1**, wherein said skeletal muscle relaxant comprises cyclobenzaprine hydrochloride.

3. The pharmaceutical dosage form of claim **2** wherein said pharmaceutical dosage form provides a maximum blood plasma concentration (C_{max}) within the range of about 80% to

125% of about 20 ng/mL of cyclobenzapnine HCl and an AUC_{0-168} within the range of about 80% to 125% of about 740 ng·hr/mL and a T_{max} within the range of 80% to 125% of about 7 hours following oral administration of a single 30 mg cyclobenzapnine HCl MR Capsule.

4. The pharmaceutical dosage form of claim **3** wherein the adjusted mean ratio of CMR 30 mg/CMR 15 mg is greater than about 2 for each of AUC_{0-168} ($p<0.001$), $AUC_{0-\infty}$ ($p<0.001$), and C_{max} ($p<0.001$).

5. The pharmaceutical dosage form of claim **1**, wherein said dosage form comprises only one extended release bead population.

6. The pharmaceutical dosage form of claim **1**, wherein said water insoluble polymer membrane on the drug cores comprises from about 7% to 12% by weight of the extended release beads.

7. The pharmaceutical dosage form of claim **1**, wherein said extended release coating further comprises a water soluble polymer selected from the group consisting of methylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, polyethylene glycol polyvinylpyrrolidone and mixtures thereof.

8. The pharmaceutical dosage form of claim **1**, wherein said skeletal muscle relaxant comprises cyclobeuzaprine.

9. The pharmaceutical dosage form of claim **1**, wherein said drug release profile substantially corresponds to the following pattern:

after 2 hours, no more than about 40% of the total active is released;

after 4 hours, from about 40-65% of the total active is released;

after 8 hours, from about 60-85% of the total active is released; and

after 12 hours, from about 75-85% of the total active is released.

10. The pharmaceutical dosage form of claim **1**, wherein said extended release coating further comprises a water soluble polymer selected from the group consisting of methylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, polyethylene glycol polyvinylpyrrolidone and mixtures thereof.

11. The pharmaceutical dosage form of claim **1**, wherein the water insoluble polymer membrane comprises ethyl cellulose.

12. The pharmaceutical dosage form of claim **11**, wherein said plasticizer is diethyl phthalate.

13. The pharmaceutical dosage form of claim **11**, wherein the extended release coating further comprises a water soluble polymer selected from the group consisting of methylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, polyethylene glycol polyvinylpyrrolidone and mixtures thereof.

14. The pharmaceutical dosage form of claim **12**, wherein the extended release coating further comprises a water soluble polymer selected from the group consisting of methylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, polyethylene glycol polyvinylpyrrolidone and mixtures thereof.

15. The pharmaceutical dosage form of claim **14**, wherein the water soluble polymer is hydroxypropyl methylcellulose.

16. The pharmaceutical dosage form of claim **15**, wherein the skeletal muscle relaxant is cyclobenzaprine hydrochloride.

17. The pharmaceutical dosage form of claim **16**, wherein the water insoluble polymer membrane comprises from about 7% to 12% by weight of the extended release beads.

18. The pharmaceutical dosage form of claim **17**, wherein the drug release profile substantially corresponds to the following pattern:

after 2 hours, no more than about 40% of the total active is released;

after 4 hours, from about 40-65% of the total active is released;

after 8 hours, from about 60-85% of the total active is released; and

after 12 hours, from about 75-85% of the total active is released.

19. The pharmaceutical dosage form of claim **1**, wherein said water insoluble polymer membrane comprises a water insoluble polymer selected from the group consisting of ethers of cellulose, esters of cellulose, pH-insensitive ammonio methacrylic acid copolymers, and mixtures thereof.

20. The pharmaceutical dosage form of claim **19**, wherein said extended release coating further comprises a water soluble polymer selected from the group consisting of methylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, polyethylene glycol polyvinylpyrrolidone and mixtures thereof.

* * * * *

Exhibit B

BUPROPION HYDROCHLORIDE EXTENDED-RELEASE - bupropion hydrochloride tablet, film coated, extended release

Anchen Pharmaceuticals, Inc.

BOXED WARNING

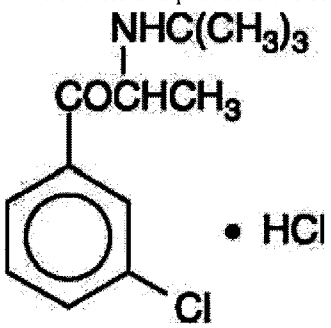
Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of bupropion hydrochloride extended-release tablets (XL) or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Bupropion hydrochloride extended-release tablets (XL) are not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use)

DESCRIPTION

Bupropion hydrochloride extended-release tablets (XL), an antidepressant of the aminoketone class, are chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines.

It is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The molecular formula is $C_{13}H_{18}ClNO \cdot HCl$. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. The structural formula is:



Bupropion hydrochloride extended-release tablets (XL) are supplied for oral administration as 150-mg and 300-mg, round white to off-white extended-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: ethyl alcohol, ethylcellulose, hydrochloric acid, hydroxypropylcellulose, methacrylic acid copolymer, povidone, silicon dioxide and hydrogenated vegetable oil. The tablets are printed with edible black ink. The insoluble shell of the extended-release tablet may remain intact during gastrointestinal transit and is eliminated in the feces. USP drug release testing is pending.

CLINICAL PHARMACOLOGY

Pharmacodynamics: Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine, and dopamine, and does not inhibit monoamine oxidase or the re-uptake of serotonin. While the mechanism of action of bupropion, as with other antidepressants, is unknown, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms.

Pharmacokinetics: Bupropion is a racemic mixture. The pharmacologic activity and pharmacokinetics of the individual enantiomers have not been studied. The mean elimination half-life (±SD) of bupropion after chronic dosing is 21 (±9) hours, and steady-state plasma concentrations of bupropion are reached within 8 days.

In a study comparing 14-day dosing with bupropion hydrochloride extended-release tablets (XL) 300 mg once daily to the immediate-release formulation of bupropion at 100 mg 3 times daily, equivalence was demonstrated for peak plasma concentration and area under the curve for bupropion and the 3 metabolites (hydroxybupropion, threohydrobupropion, and erythrohydrobupropion). Additionally, in a study comparing 14-day dosing with bupropion hydrochloride extended-release tablets (XL) 300 mg once daily to the sustained-release formulation of bupropion at 150 mg 2 times daily, equivalence was demonstrated for peak plasma concentration and area under the curve for bupropion and the 3 metabolites.

Absorption: Following oral administration of bupropion hydrochloride extended-release tablets (XL) to healthy volunteers, time to peak plasma concentrations for bupropion was approximately 5 hours and food did not affect the C_{max} or AUC of bupropion.

Distribution: In vitro tests show that bupropion is 84% bound to human plasma proteins at concentrations up to 200 mcg/mL. The extent of protein binding of the hydroxybupropion metabolite is similar to that for bupropion, whereas the extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion.

Metabolism: Bupropion is extensively metabolized in humans. Three metabolites have been shown to be active: hydroxybupropion, which is formed via hydroxylation of the *tert*-butyl group of bupropion, and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, which are formed via reduction of the carbonyl group. In vitro findings suggest that cytochrome P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion. Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency and toxicity of the metabolites relative to bupropion have not been fully characterized. However, it has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is one half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are 5-fold less potent than bupropion. This may be of clinical importance because the plasma concentrations of the metabolites are as high or higher than those of bupropion.

Because bupropion is extensively metabolized, there is the potential for drug-drug interactions, particularly with those agents that are metabolized by the cytochrome P450IIB6 (CYP2B6) isoenzyme. Although bupropion is not metabolized by cytochrome P450IID6 (CYP2D6), there is the potential for drug-drug interactions when bupropion is co-administered with drugs metabolized by this isoenzyme (see PRECAUTIONS: Drug Interactions).

In humans, peak plasma concentrations of hydroxybupropion occur approximately 7 hours after administration of bupropion hydrochloride extended-release tablets (XL). Following administration of bupropion hydrochloride extended-release tablets (XL), peak plasma concentrations of hydroxybupropion are approximately 7 times the peak level of the parent drug at steady state. The elimination half-life of hydroxybupropion is approximately 20 (±5) hours, and its AUC at steady state is about 13 times that of bupropion. The times to peak concentrations for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the hydroxybupropion metabolite. However, their elimination half-lives are longer, approximately 33 (±10) and 37 (±13) hours, respectively, and steady-state AUCs are 1.4 and 7 times that of bupropion, respectively.

Bupropion and its metabolites exhibit linear kinetics following chronic administration of 300 to 450 mg/day.

Elimination: Following oral administration of 200 mg of ^{14}C-bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. However, the fraction of the oral dose of bupropion excreted unchanged was only 0.5%, a finding consistent with the extensive metabolism of bupropion.

Population Subgroups: Factors or conditions altering metabolic capacity (e.g., liver disease, congestive heart failure [CHF], age, concomitant medications, etc.) or elimination may be expected to influence the degree and extent of accumulation of the active metabolites of bupropion. The elimination of the major metabolites of bupropion may be affected by reduced renal or hepatic function because they are moderately polar compounds and are likely to undergo further metabolism or conjugation in the liver prior to urinary excretion.

Hepatic: The effect of hepatic impairment on the pharmacokinetics of bupropion was characterized in 2 single-dose studies, one in patients with alcoholic liver disease and one in patients with mild to severe cirrhosis. The first study showed that the half-life of hydroxybupropion was significantly longer in 8 patients with alcoholic liver disease than in 8 healthy volunteers (32±14 hours versus 21±5 hours, respectively). Although not statistically significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be greater (by 53% to 57%) in patients with alcoholic liver disease. The differences in half-life for bupropion and the other metabolites in the 2 patient groups were minimal.

The second study showed no statistically significant differences in the pharmacokinetics of bupropion and its active metabolites in 9 patients with mild to moderate hepatic cirrhosis compared to 8 healthy volunteers. However, more variability was observed in some of the pharmacokinetic parameters for bupropion (AUC, C_{max}, and T_{max}) and its active metabolites ($t_{½}$) in patients with mild to moderate hepatic cirrhosis. In addition, in patients with severe hepatic cirrhosis, the bupropion C_{max} and AUC were substantially increased (mean difference: by approximately 70% and 3-fold, respectively) and more variable when compared to values in healthy volunteers; the mean bupropion half-life was also longer (29 hours in patients with severe hepatic cirrhosis vs 19 hours in healthy subjects). For the metabolite hydroxybupropion, the mean C_{max} was approximately 69% lower. For the combined amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, the mean C_{max} was approximately 31% lower. The mean AUC increased by about 1½-fold for hydroxybupropion and about 2½-fold for threo/erythrohydrobupropion. The median T_{max} was observed 19 hours later for hydroxybupropion and 31 hours later for threo/erythrohydrobupropion. The mean half-lives for hydroxybupropion and threo/erythrohydrobupropion were increased 5- and 2-fold, respectively, in patients with severe hepatic cirrhosis compared to healthy volunteers (see WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Renal: There is limited information on the pharmacokinetics of bupropion in patients with renal impairment. An inter-study comparison between normal subjects and patients with end-stage renal failure demonstrated that the parent drug C_{max} and AUC values were comparable in the 2 groups, whereas the hydroxybupropion and threohydrobupropion metabolites had a 2.3 and 2.8-fold increase, respectively, in AUC for patients with end-stage renal failure. The elimination of the major metabolites of bupropion may be reduced by impaired renal function (see PRECAUTIONS: Renal Impairment).

Left Ventricular Dysfunction: During a chronic dosing study with bupropion in 14 depressed patients with left ventricular dysfunction (history of CHF or an enlarged heart on x-ray), no apparent effect on the pharmacokinetics of bupropion or its metabolites was revealed, compared to healthy volunteers.

Age: The effects of age on the pharmacokinetics of bupropion and its metabolites have not been fully characterized, but an exploration of steady-state bupropion concentrations from several depression efficacy studies involving patients dosed in a range of 300 to 750 mg/day, on a 3 times daily schedule, revealed no relationship between age (18 to 83 years) and plasma concentration of bupropion. A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects. These data suggest there is no prominent effect of age on bupropion concentration; however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (see PRECAUTIONS: Geriatric Use).

Gender: A single-dose study involving 12 healthy male and 12 healthy female volunteers revealed no sex-related differences in the pharmacokinetic parameters of bupropion.

Smokers: The effects of cigarette smoking on the pharmacokinetics of bupropion were studied in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and 17 were nonsmokers. Following oral administration of a single 150-mg dose of bupropion, there was no statistically significant difference in C_{max}, half-life, T_{max}, AUC, or clearance of bupropion or its active metabolites between smokers and nonsmokers.

CLINICAL TRIALS

Major Depressive Disorder: The efficacy of bupropion as a treatment for major depressive disorder was established with the immediate-release formulation of bupropion in two 4-week, placebo-controlled trials in adult inpatients and in one 6-week, placebo-controlled trial in adult outpatients. In the first study, patients were titrated in a bupropion dose range of 300 to 600 mg/day of the immediate-release formulation on a 3 times daily schedule; 78% of patients received maximum doses of 450 mg/day or less. This trial demonstrated the effectiveness of bupropion on the Hamilton Depression Rating Scale (HDRS) total score, the depressed mood item (item 1) from that scale, and the Clinical Global Impressions (CGI) severity score. A second study included 2 fixed doses of the immediate-release formulation of bupropion (300 and 450 mg/day) and placebo. This trial demonstrated the effectiveness of bupropion, but only at the 450-mg/day dose of the immediate-release formulation; the results were positive for the HDRS total score and the CGI severity score, but not for HDRS item 1. In the third study, outpatients received 300 mg/day of the immediate-release formulation of bupropion. This study demonstrated the effectiveness of bupropion on the HDRS total score, HDRS item 1, the Montgomery-Asberg Depression Rating Scale, the CGI severity score, and the CGI improvement score.

In a longer-term study, outpatients meeting DSM-IV criteria for major depressive disorder, recurrent type, who had responded during an 8-week open trial on bupropion (150 mg twice daily of the sustained-release formulation) were randomized to continuation of their same dose of bupropion or placebo, for up to 44 weeks of observation for relapse. Response during the open phase was defined as CGI Improvement score of 1 (very much improved) or 2 (much improved) for each of the final 3 weeks. Relapse during the double-blinded phase was defined as the investigator's judgment that drug treatment was needed for worsening depressive symptoms. Patients receiving continued bupropion treatment experienced significantly lower relapse rates over the subsequent 44 weeks compared to those receiving placebo.

Although there are no independent trials demonstrating the antidepressant effectiveness of bupropion hydrochloride extended-release tablets (XL), studies have demonstrated similar bioavailability of bupropion hydrochloride extended-release tablets (XL) to both the immediate-release formulation and to the sustained-release formulations of bupropion under steady-state conditions, i.e., bupropion hydrochloride extended-release tablets (XL) 300 mg once daily was shown to have bioavailability that was similar to that of 100 mg 3 times daily of the immediate-release formulation of bupropion and to that of 150 mg 2 times daily of the sustained-release formulation of bupropion, with regard to both peak plasma concentration and extent of absorption, for parent drug and metabolites.

INDICATIONS AND USAGE

Major Depressive Disorder: Bupropion hydrochloride extended-release tablets (XL) are indicated for the treatment of major depressive disorder.

The efficacy of bupropion in the treatment of a major depressive episode was established in two 4-week controlled trials of inpatients and in one 6-week controlled trial of outpatients whose diagnoses corresponded most closely to the Major Depression category of the APA Diagnostic and Statistical Manual (DSM) (see CLINICAL TRIALS).

A major depressive episode (DSM-IV) implies the presence of 1) depressed mood or 2) loss of interest or pleasure; in addition, at least 5 of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt, or suicidal ideation.

The efficacy of bupropion in maintaining an antidepressant response for up to 44 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial with the sustained-release formulation of bupropion (see CLINICAL TRIALS). Nevertheless, the physician who elects to use bupropion hydrochloride extended-release tablets (XL) for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Bupropion hydrochloride extended-release tablets (XL) are contraindicated in patients with a seizure disorder.

Bupropion hydrochloride extended-release tablets (XL) are contraindicated in patients treated with ZYBAN® (bupropion hydrochloride extended-release tablets (SR), Wellbutrin® (bupropion hydrochloride tablets), the immediate-release formulation, Wellbutrin® SR (bupropion hydrochloride extended-release tablets (SR)), the sustained-release formulation, or any other medications that contain bupropion because the incidence of seizure is dose dependent.

Bupropion hydrochloride extended-release tablets (XL) are contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures noted in patients treated for bulimia with the immediate-release formulation of bupropion.

Bupropion hydrochloride extended-release tablets (XL) are contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines).

The concurrent administration of bupropion hydrochloride extended-release tablets (XL) and a monoamine oxidase (MAO) inhibitor is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with bupropion hydrochloride extended-release tablets (XL).

Bupropion hydrochloride extended-release tablets (XL) are contraindicated in patients who have shown an allergic response to bupropion or the other ingredients that make up bupropion hydrochloride extended-release tablets (XL).

WARNINGS

Clinical Worsening and Suicide Risk:

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1.

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Drug-Related Increases
<18	14 additional cases
18-24	5 additional cases
	Drug-Related Diseases
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal

link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.
Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.
Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for bupropion hydrochloride extended-release tablets (XL) should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.
Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that bupropion hydrochloride extended-release tablets (XL) are not approved for use in treating bipolar depression.
Patients should be made aware that bupropion hydrochloride extended-release tablets (XL) contain the same active ingredient found in ZYBAN®, used as an aid to smoking cessation treatment, and that bupropion hydrochloride extended-release tablets (XL) should not be used in combination with ZYBAN®, or any other medications that contain bupropion, such as Wellbutrin® SR (bupropion hydrochloride extended-release tablets (SR)), the sustained-release formulation or Wellbutrin® (bupropion hydrochloride tablets), the immediate-release formulation.
Seizures: Bupropion is associated with a dose-related risk of seizures. The risk of seizures is also related to patient factors, clinical situations, and concomitant medications, which must be considered in selection of patients for therapy with bupropion hydrochloride extended-release tablets (XL). Bupropion hydrochloride extended-release tablets (XL) should be discontinued and not restarted in patients who experience a seizure while on treatment.
As bupropion hydrochloride extended-release tablets (XL) are bioequivalent to both the immediate-release formulation of bupropion and to the sustained-release formulation of bupropion, the seizure incidence with bupropion hydrochloride extended-release tablets (XL), while not formally evaluated in clinical trials, may be similar to that presented below for the immediate-release and sustained-release formulations of bupropion.
- **Dose: At doses up to 300 mg/day of the sustained-release formulation of bupropion, the incidence of seizure is approximately 0.1% (1/1,000).**

Data for the immediate-release formulation of bupropion revealed a seizure incidence of approximately 0.4% (i.e., 13 of 3,200 patients followed prospectively) in patients treated at doses in a range of 300 to 450 mg/day. This seizure incidence (0.4%) may exceed that of some other marketed antidepressants.
Additional data accumulated for the immediate-release formulation of bupropion suggested that the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day. The 600 mg dose is twice the usual adult dose and one and one-third the maximum recommended daily dose (450 mg) of bupropion hydrochloride extended-release tablets (XL). Thisdisproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.
- **Patient factors: Predisposing factors that may increase the risk of seizure with bupropion use include history of head trauma or prior seizure, central nervous system (CNS) tumor, the presence of severe hepatic cirrhosis, and concomitant medications that lower seizure threshold.**

- **Clinical situations: Circumstances associated with an increased seizure risk include, among others, excessive use of alcohol or sedatives (including benzodiazepines); addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and anorectics; and diabetes treated with oral hypoglycemics or insulin.**

- **Concomitant medications: Many medications (e.g., antipsychotics, antidepressants, theophylline, systemic steroids) are known to lower seizure threshold.**

Recommendations for Reducing the Risk of Seizure: **Retrospective analysis of clinical experience gained during the development of bupropion suggests that the risk of seizure may be minimized if**
- **the total daily dose of bupropion hydrochloride extended-release tablets (XL) does *not* exceed 450 mg,**

- **the rate of incrementation of dose is gradual.**

Bupropion hydrochloride extended-release tablets (XL) should be administered with extreme caution to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or patients treated with other agents (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold.

Hepatic Impairment: Bupropion hydrochloride extended-release tablets (XL) should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients a reduced frequency and/or dose is required, as peak bupropion, as well as AUC, levels are substantially increased and accumulation is likely to occur in such patients to a greater extent than usual. The dose should not exceed 150 mg every other day in these patients (see CLINICAL PHARMACOLOGY, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Potential for Hepatotoxicity: In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted.

PRECAUTIONS

General: ***Agitation and Insomnia:*** Increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment, have been associated with treatment with bupropion. Patients in placebo-controlled trials of major depressive disorder with the sustained-release formulation of bupropion, experienced agitation, anxiety, and insomnia as shown in Table 2.

Table 2. Incidence of Agitation, Anxiety, and Insomnia in Placebo-Controlled Trials of Sustained-release Formulation of Bupropion for Major Depressive Disorder

Adverse Event Team	Sustained-release formulation of bupropion 300 mg/day (n=376)	Sustained-release formulation of bupropion 400 mg/day (n=114)	Placebo (n=385)
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Insomnia	11%	16%	6%

In clinical studies of major depressive disorder, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs.

Symptoms in these studies were sufficiently severe to require discontinuation of treatment in 1% and 2.6% of patients treated with 300 and 400 mg/day, respectively, of bupropion sustained-release tablets and 0.8% of patients treated with placebo.

Psychosis, Confusion, and Other Neuropsychiatric Phenomena: Depressed patients treated with bupropion have been reported to show a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment.

Activation of Psychosis and/or Mania: Antidepressants can precipitate manic episodes in bipolar disorder patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Bupropion hydrochloride extended-release tablet (XL) is expected to pose similar risks.

Altered Appetite and Weight: In placebo-controlled studies of major depressive disorder using the sustained-release formulation of bupropion, patients experienced weight gain or weight loss as shown in Table 3.

Table 3. Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials of Sustained-release Formulation of Bupropion for Major Depressive Disorder

Weight Change	Sustained-release formulation of bupropion 300 mg/day (n=339)	Sustained-release formulation of bupropion 400 mg/day (n=112)	Placebo (n=347)
Gained >5lbs	3%	2%	4%
Lost >5lbs	14%	19%	6%

In studies conducted with the immediate-release formulation of bupropion, 35% of patients receiving tricyclic antidepressants gained weight, compared to 9% of patients treated with the immediate-release formulation of bupropion. If weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight-reducing potential of bupropion hydrochloride extended-release tablets (XL) should be considered.

Allergic Reactions: Anaphylactoid/anaphylactic reactions characterized by symptoms such as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have been reported in clinical trials with bupropion. In addition, there have been rare spontaneous post-marketing reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with bupropion. A patient should stop taking bupropion hydrochloride extended-release tablets (XL) and consult a doctor if experiencing allergic or anaphylactoid/anaphylactic reactions (e.g., skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during treatment. Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity have been reported in association with bupropion. These symptoms may resemble serum sickness.

***Cardiovascular Effects*:** In clinical practice, hypertension, in some cases severe, requiring acute treatment, has been reported in patients receiving bupropion alone and in combination with nicotine replacement therapy. These events have been observed in both patients with and without evidence of preexisting hypertension.

Data from a comparative study of the sustained-release formulation of bupropion, nicotine transdermal system (NTS), the combination of sustained-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the combination of sustained-release bupropion and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of patients treated with sustained-release bupropion, NTS, and placebo, respectively. The majority of these patients had evidence of preexisting hypertension. Three patients (1.2%) treated with the combination of a ZYBAN® and NTS and 1 patient (0.4%) treated with NTS had study medication discontinued due to hypertension compared to none of the patients treated with a sustained-release formulation of bupropion or placebo. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement.

There is no clinical experience establishing the safety of bupropion hydrochloride extended-release tablets (XL) in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups.

Bupropion was well tolerated in depressed patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants, and was also generally well tolerated in a group of 36 depressed inpatients with stable congestive heart failure (CHF). However, bupropion was associated with a rise in supine blood pressure in the study of patients with CHF, resulting in discontinuation of treatment in 2 patients for exacerbation of baseline hypertension.

Hepatic Impairment: Bupropion hydrochloride extended-release tablets (XL) should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients, a reduced frequency and/or dose is required. Bupropion hydrochloride extended-release tablets (XL) should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and reduced frequency and/or dose should be considered in patients with mild to moderate hepatic cirrhosis.

All patients with hepatic impairment should be closely monitored for possible adverse effects that could indicate high drug and metabolite levels (see CLINICAL PHARMACOLOGY, WARNINGS, and DOSAGE AND ADMINISTRATION).

Renal Impairment: There is limited information on the pharmacokinetics of bupropion in patients with renal impairment. An inter-study comparison between normal subjects and patients with end-stage renal failure demonstrated that the parent drug C_{max} and AUC values were comparable in the 2 groups, whereas the hydroxybupropion and threohydrobupropion metabolites had a 2.3 and 2.8-fold increase, respectively, in AUC for patients with end-stage renal failure. Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and subsequently excreted by the kidneys. Bupropion hydrochloride extended-release tablets (XL) should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered as bupropion and the metabolites of bupropion may accumulate in such patients to a greater extent than usual. The patient should be closely monitored for possible adverse effects that could indicate high drug or metabolite levels.

Information for Patients: Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with bupropion hydrochloride extended-release tablets (XL) and should counsel them in its appropriate use. A patient Medication Guide About "Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions" and other important information about using bupropion hydrochloride extended-release tablets (XL) is available for bupropion hydrochloride extended-release tablets (XL). The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents.

Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guides is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking bupropion hydrochloride extended-release tablets (XL).

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Patients should be made aware that bupropion hydrochloride extended-release tablets (XL) contain the same active ingredient found in ZYBAN®, used as an aid to smoking cessation treatment, and that bupropion hydrochloride extended-release tablets (XL) should not be used in combination with ZYBAN®, or any other medications that contain bupropion, such as Wellbutrin® SR (bupropion hydrochloride extended-release tablets (SR)), the sustained-release formulation or Wellbutrin® (bupropion hydrochloride tablets), the immediate-release formulation.

Patients should be told that bupropion hydrochloride extended-release tablets (XL) should be discontinued and not restarted if they experience a seizure while on treatment.

Patients should be told that any CNS-active drug like bupropion hydrochloride extended-release tablets (XL) may impair their ability to perform tasks requiring judgment or motor and cognitive skills. Consequently, until they are reasonably certain that bupropion hydrochloride extended-release tablets (XL) do not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery.

Patients should be told that the excessive use or abrupt discontinuation of alcohol or sedatives (including benzodiazepines) may alter the seizure threshold. Some patients have reported lower alcohol tolerance during treatment with bupropion hydrochloride extended-release tablets (XL). Patients should be advised that the consumption of alcohol should be minimized or avoided.

Patients should be advised to inform their physicians if they are taking or plan to take any prescription or over-the-counter drugs. Concern is warranted because bupropion hydrochloride extended-release tablets (XL) and other drugs may affect each other's metabolism.

Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to swallow bupropion hydrochloride extended-release tablets (XL) whole so that the release rate is not altered. Do not chew, divide, or crush tablets.

Patients should be advised that they may notice in their stool something that looks like a tablet. This is normal. The medication in bupropion hydrochloride extended-release tablets (XL) is contained in a non-absorbable shell that has been specially designed to slowly release drug in the body. When this process is completed, the empty shell is eliminated from the body.

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

Few systemic data have been collected on the metabolism of bupropion following concomitant administration with other drugs or, alternatively, the effect of concomitant administration of bupropion on the metabolism of other drugs.

Because bupropion is extensively metabolized, the coadministration of other drugs may affect its clinical activity. *In vitro* studies indicate that bupropion is primarily metabolized to hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug interaction between bupropion hydrochloride extended-release tablets (XL) and drugs that are substrates or inhibitors of the CYP2B6 isoenzyme (e.g., orphenadrine, thiotepa, and cyclophosphamide). In addition, *in vitro* studies suggest that paroxetine, sertraline, norfluoxetine, and fluvoxamine as well as nelfinavir, ritonavir, and efavirenz inhibit the hydroxylation of bupropion. No clinical studies have been performed to evaluate this finding. The threohydrobupropion metabolite of bupropion does not appear to be produced by the cytochrome P450 isoenzymes. The effects of concomitant administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites were studied in 24 healthy young male volunteers. Following oral administration of two 150-mg tablets of the sustained-release formulation of bupropion with and without 800 mg of cimetidine, the pharmacokinetics of bupropion and hydroxybupropion were unaffected. However, there were 16% and 32% increases in the AUC and Cmax, respectively, of the combined moieties of threohydrobupropion and erythrohydrobupropion.

While not systematically studied, certain drugs may induce the metabolism of bupropion (e.g., carbamazepine, phenobarbital, phenytoin).

Multiple oral doses of bupropion had no statistically significant effects on the single dose pharmacokinetics of lamotrigine in 12 healthy volunteers.

Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in humans. In one study, following chronic administration of bupropion, 100 mg 3 times daily to 8 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism. Nevertheless, there may be the potential for clinically important alterations of blood levels of coadministered drugs.

Drugs Metabolized By Cytochrome P450IID6 (CYP2D6): Many drugs, including most antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics are metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this isoenzyme, bupropion and hydroxybupropion are inhibitors of CYP2D6 isoenzyme *in vitro*. In a study of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of the CYP2D6 isoenzyme, daily doses of bupropion given as 150 mg twice daily followed by a single dose of 50 mg desipramine increased the C_{max}, AUC, and $t_{1/2}$ of desipramine by an average of approximately 2-, 5-, and 2-fold, respectively. The effect was present for at least 7 days after the last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6 has not been formally studied.

Therefore, co-administration of bupropion with drugs that are metabolized by CYP2D6 isoenzyme including certain antidepressants (e.g., nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medication. If bupropion is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original medication should be considered, particularly for those concomitant medications with a narrow therapeutic index.

MAO Inhibitors: Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

Levodopa and Amantadine: Limited clinical data suggest a higher incidence of adverse experiences in patients receiving bupropion concurrently with either levodopa or amantadine. Administration of bupropion hydrochloride extended-release tablets (XL) to patients receiving either levodopa or amantadine concurrently should be undertaken with caution, using small initial doses and gradual dose increases.

Drugs That Lower Seizure Threshold: Concurrent administration of bupropion hydrochloride extended-release tablets (XL) and agents (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold should be undertaken only with extreme caution (see WARNINGS). Low initial dosing and gradual dose increases should be employed.
Nicotine Transdermal System: (see PRECAUTIONS: Cardiovascular Effects).
Alcohol: In postmarketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with bupropion. The consumption of alcohol during treatment with bupropion hydrochloride extended-release tablets (XL) should be minimized or avoided (also see CONTRAINDICATIONS).

Carcinogenesis, Mutagenesis, Impairment of Fertility
Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. These doses are approximately 7 and 2 times the maximum recommended human dose (MRHD), respectively, on a mg/m^2 basis. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day (approximately 2 to 7 times the MRHD on a mg/m^2 basis); lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.
Bupropion produced a positive response (2 to 3 times control mutation rate) in 2 of 5 strains in the Ames bacterial mutagenicity test and an increase in chromosomal aberrations in 1 of 3 *in vivo* rat bone marrow cytogenetic studies.
A fertility study in rats at doses up to 300 mg/kg/day revealed no evidence of impaired fertility.

Pregnancy

Teratogenic Effects
Pregnancy Category C. In studies conducted in rats and rabbits, bupropion was administered orally at doses up to 450 and 150 mg/kg/day, respectively (approximately 11 and 7 times the maximum recommended human dose [MRHD], respectively, on a mg/m^2 basis), during the period of organogenesis. No clear evidence of teratogenic activity was found in either species; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day, approximately equal to the MRHD on a mg/m^2 basis) and greater. Decreased fetal weights were seen at 50 mg/kg and greater.

When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately 7 times the MRHD on a mg/m^2 basis) prior to mating and throughout pregnancy and lactation, there were no apparent adverse effects on offspring development.

One study has been conducted in pregnant women. This retrospective, managed-care database study assessed the risk of congenital malformations overall, and cardiovascular malformations specifically, following exposure to bupropion in the first trimester compared to the risk of these malformations following exposure to other antidepressants in the first trimester and bupropion outside of the first trimester. This study included 7,005 infants with antidepressant exposure during pregnancy, 1,213 of whom were exposed to bupropion in the first trimester. The study showed no greater risk for congenial malformations overall, or cardiovascular malformations specifically, following first trimester bupropion exposure compared to exposure to all other antidepressants in the first trimester, or bupropion outside of the first trimester. The results of this study have not been corroborated. Bupropion hydrochloride extended-release tablets (XL) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery
The effect of bupropion hydrochloride extended-release tablets (XL) on labor and delivery in humans is unknown.

Nursing Mothers
Like many other drugs, bupropion and its metabolites are secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from bupropion hydrochloride extended-release tablets (XL), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS: Clinical Worsening and Suicide Risk). Anyone considering the use of bupropion hydrochloride extended-release tablets (XL) in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use
Of the approximately 6,000 patients who participated in clinical trials with bupropion sustained-release tablets (depression and smoking cessation studies), 275 were ≥65 years old and 47 were ≥75 years old. In addition, several hundred patients 65 and over participated in clinical trials using the immediate-release formulation of bupropion (depression studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects; however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (see CLINICAL PHARMACOLOGY).
Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. The risk of toxic reaction to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see PRECAUTIONS: Renal Impairment and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS
(See also WARNINGS and PRECAUTIONS.)
Major Depressive Disorder: Bupropion hydrochloride extended-release tablets (XL) have been demonstrated to have similar bioavailability both to the immediate-release formulation of bupropion and to the sustained-release formulation of bupropion (see CLINICAL PHARMACOLOGY). The information included under this subsection is based primarily on data from controlled clinical trials with the sustained-release formulation of bupropion.
Adverse Events Leading to Discontinuation of Treatment With the Immediate-Release or Sustained-Release Formulations of Bupropion: In placebo-controlled clinical trials, 9% and 11% of patients treated with 300 and 400 mg/day, respectively, of the sustained-release formulation of bupropion and 4% of patients treated with placebo discontinued treatment due to adverse events. The specific adverse events in these trials that led to discontinuation in at least 1% of patients treated with either 300 mg/day or 400 mg/day of the sustained-release formulation of bupropion, and at a rate at least twice the placebo rate are listed in Table 4.
Table 4. Treatment Discontinuations Due to Adverse Events in Placebo-Controlled Trials

Adverse Event Team	Sustained-release formulation of bupropion 300 mg/day (n=376)	Sustained-release formulation of bupropion 400 mg/day (n=114)	Placebo (n=385)
Rash	2.4%	0.9%	0.0%
Nausea	0.8%	1.8%	0.3%
Agitation	0.3%	1.8%	0.3%
Migraine	0.0%	1.8%	0.3%

In clinical trials with the immediate-release formulation of bupropion, 10% of patients and volunteers discontinued due to an adverse event. Events resulting in discontinuation, in addition to those listed above for the sustained-release formulation of bupropion, include vomiting, seizures, and sleep disturbances.
Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated With the Immediate-Release or Sustained-Release Formulations of Bupropion: Table 5 enumerates treatment-emergent adverse events that occurred among patients treated with 300 and 400 mg/day of the sustained-release formulation of bupropion and with placebo in controlled trials. Events that occurred in either the 300- or 400-mg/day group at an incidence of 1% or more and were more frequent than in the placebo group are included. Reported adverse events were classified using a COSTART-based Dictionary.
Accurate estimates of the incidence of adverse events associated with the use of any drug are difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician judgments, etc. The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.
Finally, it is important to emphasize that the tabulation does not reflect the relative severity and/or clinical importance of the events. A better perspective on the serious adverse events associated with the use of bupropion is provided in the WARNINGS and PRECAUTIONS sections.
Table 5. Treatment-Emergent Adverse Events in Placebo-Controlled Trials*

Body System/ Adverse Event	Sustained-release formulation of bupropion 300 mg/day (n=376)	Sustained-release formulation of bupropion 400 mg/day (n=114)	Placebo (n=385)
Body (General)			
Headache	26%	25%	23%
Infection	8%	9%	6%
Abdominal pain	3%	9%	2%
Asthenia	2%	4%	2%
Chest pain	3%	4%	1%
Pain	2%	3%	2%

Fever	1%	2%	----
Cardiovascular			
Palpitation	2%	6%	2%
Flushing	1%	4%	----
Migraine	1%	4%	1%
Hot flashes	1%	3%	1%
Digestive			
Dry mouth	17%	24%	7%
Nausea	13%	18%	8%
Constipation	10%	5%	7%
Diarrhea	5%	7%	6%
Anorexia	5%	3%	2%
Vomiting	4%	2%	2%
Dysphagia	0%	2%	0%
Musculoskeletal			
Myalgia	2%	6%	3%
Arthralgia	1%	4%	1%
Arthritis	0%	2%	0%
Twitch	1%	2%	----
Nervous System			
Insomia	11%	16%	6%
Dizziness	7%	11%	5%
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Tremor	6%	3%	1%
Nervousness	5%	3%	3%
Somnolence	2%	3%	2%
Irritability	3%	2%	2%
Memory decreased	----	3%	1%
Paresthesia	1%	2%	1%
Central nervous System stimulation	2%	1%	1%
Respiratory			
Pharyngitis	3%	11%	2%
Sinusitis	3%	1%	2%
Increased cough	1%	2%	1%
Skin			
Sweating	6%	5%	2%
Rash	5%	4%	1%
Pruritus	2%	4%	2%
Urticaria	2%	1%	0%
Special senses			
Tinnitus	6%	6%	2%
Taste Perversion	2%	4%	--
Amblyopia	3%	2%	2%
Urogenital			
Urinary frequency	2%	5%	2%
Urinary Urgency	--	2%	0%
Vaginal Hemorrhage†	0%	2%	--
Urinary tract Infection	1%	0%	--