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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

VIVUS, INC., **Plaintiff,** **v.** **TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICAL INDUSTRIES LTD.,** **Defendants.**	**Civil Action No. _____** **COMPLAINT FOR PATENT INFRINGEMENT** **(Filed Electronically)**

Plaintiff VIVUS, Inc. ("VIVUS"), by its undersigned attorneys, for its Complaint against defendants Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd. (collectively, "Teva") alleges as follows:

Nature of the Action

1. This is an action for patent infringement under the patent laws of the United States, 35 U.S.C. §100, *et seq.*, arising from Teva's filing of an Abbreviated New Drug Application ("ANDA") with the United States Food and Drug Administration ("FDA") seeking approval to commercially market generic versions of VIVUS' QSYMIA® drug products prior to the expiration of United States Patent Nos. 7,056,890 (the "'890 patent"), 7,553,818 (the "'818 patent"), 7,659,256 (the "'256 patent"), 7,674,776 (the "'776 patent"), 8,580,298 (the "'298

patent"), 8,580,299 (the "'299 patent"), 8,895,057 (the "'057 patent"), and 8,895,058 (the "'058 patent") owned by VIVUS (collectively, "the patents-in-suit").

The Parties

2. Plaintiff VIVUS is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 351 E. Evelyn Avenue, Mountain View, California 94041.

3. On information and belief, defendant Teva Pharmaceuticals USA, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 1090 Horsham Road, North Wales, Pennsylvania 19454.

4. On information and belief, defendant Teva Pharmaceutical Industries Ltd. is an Israeli corporation having a principal place of business at 5 Basel Street, Petah Tikva 49131, Israel.

5. On information and belief, defendant Teva Pharmaceuticals USA, Inc. is a wholly-owned subsidiary of defendant Teva Pharmaceutical Industries Ltd.

6. On information and belief, defendants Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd. manufacture and/or distribute generic drugs for sale and use throughout the United States, including in this Judicial District. On information and belief, defendants Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd. also prepare and/or aid in the preparation and submission of ANDAs to the FDA.

7. On information and belief, the acts of Teva Pharmaceuticals USA, Inc. complained of herein were done at the direction of, with the authorization of, or with the cooperation, participation, or assistance of, or at least in part for the benefit of, Teva Pharmaceutical Industries Ltd.

Jurisdiction and Venue

8. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

9. This Court has personal jurisdiction over Teva Pharmaceuticals USA, Inc. by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey. On information and belief, Teva Pharmaceuticals USA, Inc. is registered to do business in the State of New Jersey under entity ID No. 0100250184. In addition, on information and belief, Teva Pharmaceuticals USA, Inc. has appointed a registered agent for service of process in New Jersey (Corporate Creations Network Inc., 811 Church Road #105, Cherry Hill, NJ 08002).

10. On information and belief, Teva Pharmaceuticals USA, Inc. holds licenses in the State of New Jersey as a "wholesaler" and "manufacturer and wholesaler" of drugs, with License Nos. 5003436 and 5000583, respectively. On information and belief, Teva Pharmaceuticals USA, Inc. employs people throughout the State of New Jersey, including at least the following two locations: 8 Gloria Ln, Fairfield, NJ 07004 and 400 Chestnut Ridge Rd, Woodcliff Lake, NJ 07677. On information and belief, Teva Pharmaceuticals USA, Inc. conducts business in this District and purposefully avails itself of this forum by, among other things, making, shipping, using, offering to sell or selling, or causing others to use, offer to sell, or sell, pharmaceutical products in the State of New Jersey and deriving revenue from such activities. Also, on information and belief, Teva Pharmaceuticals USA, Inc. has customers in the State of New Jersey.

11. On information and belief, Teva Pharmaceuticals USA, Inc. has been sued for patent infringement in this District and did not contest personal jurisdiction in this District in at least the following cases: *Amarin Pharma, Inc., et al. v. Teva Pharmaceuticals USA, Inc.*, No. 14-3558, *Boehringer Ingelheim Pharma GmBH & Co. KG, et al. v. Teva Pharmaceuticals USA,*

Inc., et al., No. 14-7811, *Helsinn Healthcare S.A., et al., v. Teva Pharmaceuticals USA, Inc., et al.*, No. 14-6341, *Novo Nordisk Inc., et al., v. Teva Pharmaceuticals USA, Inc.*, No. 14-4248, *Otsuka Pharmaceutical Co., Ltd. v. Teva Pharmaceuticals USA, Inc., et al.*, No. 14-5878, *United Therapeutics Corp. v. Teva Pharmaceuticals USA, Inc.*, No. 14-5498. Further, on information and belief, Teva Pharmaceuticals USA, Inc. has purposefully availed itself of the benefits of this forum by filing counterclaims in each of those actions. Additionally, on information and belief, Teva Pharmaceuticals USA, Inc. has availed itself of this forum by bringing civil actions for patent infringement in this forum in at least the following cases: *Teva Pharmaceuticals USA, Inc., et al. v. Doctor Reddy's Laboratories, Ltd., et al.*, No. 14-5672, *Teva Pharmaceuticals USA, Inc., et al. v. Synthon Pharmaceuticals, Inc., et al.*, No. 15-472.

12. This Court has personal jurisdiction over Teva Pharmaceutical Industries Ltd. by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey. On information and belief, Teva Pharmaceutical Industries Ltd. conducts business in this District, and purposefully avails itself of this forum by, among other things, making, shipping, using, offering to sell or selling, or causing others to use, offer to sell, or sell, pharmaceutical products in the State of New Jersey and deriving revenue from such activities. Also, on information and belief, Teva Pharmaceutical Industries Ltd. has customers in the State of New Jersey.

13. On information and belief, Teva Pharmaceutical Industries Ltd. has been sued for patent infringement in this District and did not contest personal jurisdiction in this District in at least the following case: *Boehringer Ingelheim Pharma GmBH & Co. KG, et al. v. Teva Pharmaceuticals USA, Inc., et al.*, No. 14-7811. Further, on information and belief, Teva Pharmaceutical Industries Ltd. has purposefully availed itself of the benefits of this forum by filing counterclaims in that action. Additionally, on information and belief, Teva Pharmaceutical

Industries Ltd. has availed itself of the benefits of this forum by bringing civil actions for patent infringement in this forum. *See, e.g., Teva Pharmaceuticals USA, Inc., et al. v. Doctor Reddy's Laboratories, Ltd., et al.*, No. 14-5672, *Teva Pharmaceuticals USA, Inc., et al. v. Synthon Pharmaceuticals, Inc., et al.*, No. 15-472.

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

The Patent-In-Suit

15. On June 6, 2006, the United States Patent and Trademark Office ("USPTO") duly and lawfully issued the '890 patent, entitled "Combination therapy for effecting weight loss and treating obesity" to VIVUS as assignee of the inventor Thomas Najarian. A copy of the '890 patent is attached hereto as Exhibit A.

16. On June 30, 2009, the USPTO duly and lawfully issued the '818 patent, entitled "Combination therapy for effecting weight loss and treating obesity" to VIVUS as assignee of the inventor Thomas Najarian. A copy of the '818 patent is attached hereto as Exhibit B.

17. On February 9, 2010, the USPTO duly and lawfully issued the '256 patent, entitled "Combination therapy for effecting weight loss and treating obesity" to VIVUS as assignee of the inventor Thomas Najarian. A copy of the '256 patent is attached hereto as Exhibit C.

18. On March 9, 2010, the USPTO duly and lawfully issued the '776 patent, entitled "Combination therapy for effecting weight loss and treating obesity" to VIVUS as assignee of the inventor Thomas Najarian. A copy of the '776 patent is attached hereto as Exhibit D.

19. On November 12, 2013, the USPTO duly and lawfully issued the '298 patent, entitled "Low dose topiramate/phentermine composition and methods of use thereof" to VIVUS as assignee of the inventors Thomas Najarian, Peter Y. Tam and Leland F. Wilson. A copy of the '298 patent is attached hereto as Exhibit E.

20. On November 12, 2013, the USPTO duly and lawfully issued the '299 patent, entitled "Escalating dosing regimen for effecting weight loss and treating obesity" to VIVUS as assignee of the inventors Thomas Najarian, Peter Y. Tam and Leland F. Wilson. A copy of the '299 patent is attached hereto as Exhibit F.

21. On November 25, 2014, the USPTO duly and lawfully issued the '057 patent, entitled "Escalating dosing regimen for effecting weight loss and treating obesity" to VIVUS as assignee of the inventors Thomas Najarian, Peter Y. Tam, and Leland F. Wilson. A copy of the '057 patent is attached hereto as Exhibit G.

22. On November 25, 2014, the USPTO duly and lawfully issued the '058 patent, entitled "Low dose topiramate/phentermine composition and methods of use thereof" to VIVUS as assignee of the inventors Thomas Najarian, Peter Y. Tam, and Leland F. Wilson. A copy of the '058 patent is attached hereto as Exhibit H.

The QSYMIA® Drug Products

23. VIVUS holds an approved New Drug Application ("NDA") under Section 505(a) of the Federal Food Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for phentermine and topiramate extended-release capsules (NDA No. 022580), which it sells under the trade name QSYMIA®. The claims of the patents-in-suit cover, *inter alia*, pharmaceutical compositions containing combinations of phentermine and topiramate, and methods of use and administration of combinations of phentermine and topiramate. VIVUS owns the patents-in-suit.

24. Pursuant to 21 U.S.C. § 355(b)(1) and attendant FDA regulations, the patents-in-suit are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to QSYMIA®.

Acts Giving Rise to This Suit

25. Pursuant to Section 505 of the FFDCA, Teva filed ANDA No. 208175 ("Teva's ANDA") seeking approval to engage in the commercial use, manufacture, sale, offer for sale or importation of 15/92 mg, 11.25/69 mg, 7.5/46 mg, and 3.75/23 mg capsules containing as the active pharmaceutical ingredients, phentermine and topiramate extended-release ("Teva's Proposed Product"), before the patents-in-suit expire.

26. On information and belief, in connection with the filing of its ANDA as described in the preceding paragraph, Teva has provided a written certification to the FDA, as called for by Section 505 of the FFDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Teva's Paragraph IV Certification"), alleging that the claims of the patents-in-suit are invalid, unenforceable, and/or will not be infringed by the activities described in Teva's ANDA.

27. No earlier than March 4, 2015, Teva sent written notice of its Paragraph IV Certification to VIVUS ("Teva's Notice Letter") pursuant to 21 U.S.C. § 355(j)(2)(B). Teva's Notice Letter alleged that the claims of the patents-in-suit are invalid, unenforceable, and/or will not be infringed by the activities described in Teva's ANDA. Teva's Notice Letter also informed VIVUS that Teva seeks approval to market Teva's Proposed Product before the patents-in-suit expire.

Count I: Infringement of the '890 Patent

28. Plaintiff repeats and realleges the allegations of paragraphs 1-27 as though fully set forth herein.

29. Teva's submission of its ANDA to obtain approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of phentermine and topiramate extended-release capsules, prior to the expiration of the '890 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

30. There is a justiciable controversy between the parties hereto as to the infringement of the ’890 patent.

31. Unless enjoined by this Court, upon FDA approval of Teva’s ANDA, Teva will infringe the ’890 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Teva’s Proposed Product in the United States.

32. Unless enjoined by this Court, upon FDA approval of Teva’s ANDA, Teva will induce infringement of the ’890 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Teva’s Proposed Product in the United States. On information and belief, upon FDA approval of Teva’s ANDA, Teva will intentionally encourage acts of direct infringement with knowledge of the ’890 patent and knowledge that its acts are encouraging infringement.

33. Unless enjoined by this Court, upon FDA approval of Teva’s ANDA, Teva will contributorily infringe the ’890 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Teva’s Proposed Product in the United States. On information and belief, Teva has had and continues to have knowledge that Teva’s Proposed Product is especially adapted for a use that infringes the ’890 patent and that there is no substantial non-infringing use for Teva’s Proposed Product.

34. VIVUS will be substantially and irreparably damaged and harmed if Teva’s infringement of the ’890 patent is not enjoined.

35. VIVUS does not have an adequate remedy at law.

36. This case is an exceptional one, and VIVUS is entitled to an award of its reasonable attorneys’ fees under 35 U.S.C. § 285.

Count II: Infringement of the ’818 Patent

37. Plaintiff repeats and realleges the allegations of paragraphs 1-36 as though fully set forth herein.

38. Teva’s submission of its ANDA to obtain approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of phentermine and topiramate extended-release capsules, prior to the expiration of the ’818 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

39. There is a justiciable controversy between the parties hereto as to the infringement of the ’818 patent.

40. Unless enjoined by this Court, upon FDA approval of Teva’s ANDA, Teva will infringe the ’818 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Teva’s Proposed Product in the United States.

41. Unless enjoined by this Court, upon FDA approval of Teva’s ANDA, Teva will induce infringement of the ’818 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Teva’s Proposed Product in the United States. On information and belief, upon FDA approval of Teva’s ANDA, Teva will intentionally encourage acts of direct infringement with knowledge of the ’818 patent and knowledge that its acts are encouraging infringement.

42. Unless enjoined by this Court, upon FDA approval of Teva’s ANDA, Teva will contributorily infringe the ’818 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Teva’s Proposed Product in the United States. On information and belief, Teva has had and continues to have knowledge that Teva’s Proposed Product is especially adapted for a use that infringes the ’818 patent and that there is no substantial non-infringing use for Teva’s Proposed Product.

43. VIVUS will be substantially and irreparably damaged and harmed if Teva's infringement of the '818 patent is not enjoined.

44. VIVUS does not have an adequate remedy at law.

45. This case is an exceptional one, and VIVUS is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count III: Infringement of the '256 Patent

46. Plaintiff repeats and realleges the allegations of paragraphs 1-45 as though fully set forth herein.

47. Teva's submission of its ANDA to obtain approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of phentermine and topiramate extended-release capsules, prior to the expiration of the '256 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

48. There is a justiciable controversy between the parties hereto as to the infringement of the '256 patent.

49. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will infringe the '256 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Teva's Proposed Product in the United States.

50. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will induce infringement of the '256 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Teva's Proposed Product in the United States. On information and belief, upon FDA approval of Teva's ANDA, Teva will intentionally encourage acts of direct infringement with knowledge of the '256 patent and knowledge that its acts are encouraging infringement.

51. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will contributorily infringe the '256 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Teva's Proposed Product in the United States. On information and belief, Teva has had and continues to have knowledge that Teva's Proposed Product is especially adapted for a use that infringes the '256 patent and that there is no substantial non-infringing use for Teva's Proposed Product.

52. VIVUS will be substantially and irreparably damaged and harmed if Teva's infringement of the '256 patent is not enjoined.

53. VIVUS does not have an adequate remedy at law.

54. This case is an exceptional one, and VIVUS is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count IV: Infringement of the '776 Patent

55. Plaintiff repeats and realleges the allegations of paragraphs 1-54 as though fully set forth herein.

56. Teva's submission of its ANDA to obtain approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of phentermine and topiramate extended-release capsules, prior to the expiration of the '776 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

57. There is a justiciable controversy between the parties hereto as to the infringement of the '776 patent.

58. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will infringe the '776 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Teva's Proposed Product in the United States.

59. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will induce infringement of the '776 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Teva's Proposed Product in the United States. On information and belief, upon FDA approval of Teva's ANDA, Teva will intentionally encourage acts of direct infringement with knowledge of the '776 patent and knowledge that its acts are encouraging infringement.

60. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will contributorily infringe the '776 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Teva's Proposed Product in the United States. On information and belief, Teva has had and continues to have knowledge that Teva's Proposed Product is especially adapted for a use that infringes the '776 patent and that there is no substantial non-infringing use for Teva's Proposed Product.

61. VIVUS will be substantially and irreparably damaged and harmed if Teva's infringement of the '776 patent is not enjoined.

62. VIVUS does not have an adequate remedy at law.

63. This case is an exceptional one, and VIVUS is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count V: Infringement of the '298 Patent

64. Plaintiff repeats and realleges the allegations of paragraphs 1-63 as though fully set forth herein.

65. Teva's submission of its ANDA to obtain approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of phentermine and topiramate extended-release capsules, prior to the expiration of the '298 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

66. There is a justiciable controversy between the parties hereto as to the infringement of the ’298 patent.

67. Unless enjoined by this Court, upon FDA approval of Teva’s ANDA, Teva will infringe the ’298 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Teva’s Proposed Product in the United States.

68. Unless enjoined by this Court, upon FDA approval of Teva’s ANDA, Teva will induce infringement of the ’298 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Teva’s Proposed Product in the United States. On information and belief, upon FDA approval of Teva’s ANDA, Teva will intentionally encourage acts of direct infringement with knowledge of the ’298 patent and knowledge that its acts are encouraging infringement.

69. Unless enjoined by this Court, upon FDA approval of Teva’s ANDA, Teva will contributorily infringe the ’298 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Teva’s Proposed Product in the United States. On information and belief, Teva has had and continues to have knowledge that Teva’s Proposed Product is especially adapted for a use that infringes the ’298 patent and that there is no substantial non-infringing use for Teva’s Proposed Product.

70. VIVUS will be substantially and irreparably damaged and harmed if Teva’s infringement of the ’298 patent is not enjoined.

71. VIVUS does not have an adequate remedy at law.

72. This case is an exceptional one, and VIVUS is entitled to an award of its reasonable attorneys’ fees under 35 U.S.C. § 285.

Count VI: Infringement of the ’299 Patent

73. Plaintiff repeats and realleges the allegations of paragraphs 1-72 as though fully set forth herein.

74. Teva’s submission of its ANDA to obtain approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of phentermine and topiramate extended-release capsules, prior to the expiration of the ’299 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

75. There is a justiciable controversy between the parties hereto as to the infringement of the ’299 patent.

76. Unless enjoined by this Court, upon FDA approval of Teva’s ANDA, Teva will infringe the ’299 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Teva’s Proposed Product in the United States.

77. Unless enjoined by this Court, upon FDA approval of Teva’s ANDA, Teva will induce infringement of the ’299 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Teva’s Proposed Product in the United States. On information and belief, upon FDA approval of Teva’s ANDA, Teva will intentionally encourage acts of direct infringement with knowledge of the ’299 patent and knowledge that its acts are encouraging infringement.

78. Unless enjoined by this Court, upon FDA approval of Teva’s ANDA, Teva will contributorily infringe the ’299 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Teva’s Proposed Product in the United States. On information and belief, Teva has had and continues to have knowledge that Teva’s Proposed Product is especially adapted for a use that infringes the ’299 patent and that there is no substantial non-infringing use for Teva’s Proposed Product.

79. VIVUS will be substantially and irreparably damaged and harmed if Teva's infringement of the '299 patent is not enjoined.

80. VIVUS does not have an adequate remedy at law.

81. This case is an exceptional one, and VIVUS is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count VII: Infringement of the '057 Patent

82. Plaintiff repeats and realleges the allegations of paragraphs 1-81 as though fully set forth herein.

83. Teva's submission of its ANDA to obtain approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of phentermine and topiramate extended-release capsules, prior to the expiration of the '057 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

84. There is a justiciable controversy between the parties hereto as to the infringement of the '299 patent.

85. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will infringe the '057 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Teva's Proposed Product in the United States.

86. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will induce infringement of the '057 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Teva's Proposed Product in the United States. On information and belief, upon FDA approval of Teva's ANDA, Teva will intentionally encourage acts of direct infringement with knowledge of the '057 patent and knowledge that its acts are encouraging infringement.

87. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will contributorily infringe the '057 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Teva's Proposed Product in the United States. On information and belief, Teva has had and continues to have knowledge that Teva's Proposed Product is especially adapted for a use that infringes the '057 patent and that there is no substantial non-infringing use for Teva's Proposed Product.

88. VIVUS will be substantially and irreparably damaged and harmed if Teva's infringement of the '057 patent is not enjoined.

89. VIVUS does not have an adequate remedy at law.

90. This case is an exceptional one, and VIVUS is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count VIII: Infringement of the '058 Patent

91. Plaintiff repeats and realleges the allegations of paragraphs 1-90 as though fully set forth herein.

92. Teva's submission of its ANDA to obtain approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of phentermine and topiramate extended-release capsules, prior to the expiration of the '058 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

93. There is a justiciable controversy between the parties hereto as to the infringement of the '058 patent.

94. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will infringe the '058 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Teva's Proposed Product in the United States.

95. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will induce infringement of the '058 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Teva's Proposed Product in the United States. On information and belief, upon FDA approval of Teva's ANDA, Teva will intentionally encourage acts of direct infringement with knowledge of the '058 patent and knowledge that its acts are encouraging infringement.

96. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will contributorily infringe the '058 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Teva's Proposed Product in the United States. On information and belief, Teva has had and continues to have knowledge that Teva's Proposed Product is especially adapted for a use that infringes the '058 patent and that there is no substantial non-infringing use for Teva's Proposed Product.

97. VIVUS will be substantially and irreparably damaged and harmed if Teva's infringement of the '058 patent is not enjoined.

98. VIVUS does not have an adequate remedy at law.

99. This case is an exceptional one, and VIVUS is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff VIVUS respectfully requests the following relief:

(A) A Judgment that Teva has infringed the patents-in-suit by submitting ANDA No. 208175;

(B) A Judgment that Teva has infringed, and that Teva's making, using, selling, offering to sell, or importing Teva's Proposed Product will infringe one or more claims of the patents-in-suit;

(C) An Order that the effective date of FDA approval of ANDA No. 208175 be a date which is not earlier than the later of the expiration of the patents-in-suit, or any later expiration of exclusivity to which Plaintiff is or becomes entitled;

(D) Preliminary and permanent injunctions enjoining Teva and its officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using, selling, offering to sell, or importing Teva's Proposed Product until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which Plaintiff is or becomes entitled;

(E) A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Teva, its officers, agents, attorneys and employees, and those acting in privity or concert with them, from practicing any methods as claimed in the patents-in-suit, or from actively inducing or contributing to the infringement of any claim of the patents-in-suit, until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which Plaintiff is or becomes entitled;

(F) A Declaration that the commercial manufacture, use, importation into the United States, sale, or offer for sale of Teva's Proposed Product will directly infringe, induce and/or contribute to infringement of the patents-in-suit;

(G) To the extent that Teva has committed any acts of infringement with respect to the compositions and methods claimed in the patents-in-suit, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), a judgment awarding Plaintiff VIVUS damages for such acts, together with interest;

(H) If Teva engages in the commercial manufacture, use, importation into the United States, sale, or offer for sale of Teva's Proposed Product prior to the expiration of the patents-in-

suit, a Judgment awarding damages to Plaintiff VIVUS resulting from such infringement, together with interest;

(I) Attorneys' fees in this action as an exceptional case pursuant to 35 U.S.C. § 285;

(J) Costs and expenses in this action; and

(K) Such further and other relief as this Court may deem just and proper.

Dated: April 15, 2015

By: s/ Charles M. Lizza

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CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1

I hereby certify that the matters captioned, *VIVUS, Inc. v. Actavis Laboratories FL, Inc.*, Civil Action No. 14-3786 (SRC)(CLW) and *VIVUS, Inc. v. Actavis Laboratories FL, Inc.*, Civil Action No. 15-1636 (SRC)(CLW), are related to the matter in controversy because the matter in controversy involves the same plaintiff and, in both cases, the defendants are seeking FDA approval to market a generic version of the same phentermine and topiramate extended release drug product.

I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court or of any pending arbitration or administrative proceeding.

Dated: April 15, 2015

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EXHIBIT A

US007056890B2

(12) **United States Patent**
Najarian

(10) **Patent No.: US 7,056,890 B2**
(45) **Date of Patent: Jun. 6, 2006**

(54) **COMBINATION THERAPY FOR EFFECTING WEIGHT LOSS AND TREATING OBESITY**

(75) Inventor: **Thomas Najarian**, Belmont, MA (US)

(73) Assignee: **VIVUS, Inc.**, Mountain View, CA (US)

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

(21) Appl. No.: **10/454,368**

(22) Filed: **Jun. 3, 2003**

(65) **Prior Publication Data**

US 2004/0002462 A1 Jan. 1, 2004

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/593,555, filed on Jun. 14, 2000, now abandoned.

(60) Provisional application No. 60/181,265, filed on Feb. 9, 2000, provisional application No. 60/178,563, filed on Jan. 26, 2000, provisional application No. 60/139,022, filed on Jun. 14, 1999.

(51) **Int. Cl.**
A61K 31/135 (2006.01)
A61K 31/70 (2006.01)

(52) **U.S. Cl.** **514/23**; 514/646

(58) **Field of Classification Search** 514/23, 514/646

See application file for complete search history.

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(57) **ABSTRACT**

The present invention features a novel therapy for effecting weight loss which involves treating a subject with a sympathomimetic agent (e.g., phentermine or a phentermine-like drug) in combination with an anticonvulsant sulfamate derivative (e.g., topiramate) such that the subject experiences weight loss.

The combination methods of the present invention also are effective against symptoms associated with Syndrome X. The invention also features pharmaceutical compositions and kits for use in the practice of these novel therapies.

54 Claims, No Drawings

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COMBINATION THERAPY FOR EFFECTING WEIGHT LOSS AND TREATING OBESITY

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. patent application Ser. No. 09/593,555, filed Jun. 14, 2000, now abandoned which claims priority under 35 U.S.C. §119(e)(1) to provisional U.S. Patent Applications Ser. No. 60/139,022, filed Jun. 14, 1999, Ser. No. 60/178,563, filed Jan. 26, 2000, and Ser. No. 60/181,265, filed Feb. 9, 2000, the disclosures of which are incorporated herein by reference in their entireties.

BACKGROUND OF THE INVENTION

About 97 million adults in the United States are overweight or obese. The medical problems caused by overweight and obesity can be serious and often life-threatening, and include diabetes, shortness of breath, gallbladder disease, hypertension, elevated blood cholesterol levels, cancer, arthritis, other orthopedic problems, reflux esophagitis (heartburn), snoring, sleep apnea, menstrual irregularities, infertility and heart trouble. Moreover, obesity and overweight substantially increase the risk of morbidity from hypertension, dyslipidemia, type 2 diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis and endometrial, breast, prostate, and colon cancers. Higher body weights are also associated with increases in all-cause mortality. Most or all of these problems are relieved or improved by permanent significant weight loss. Longevity is likewise significantly increased by permanent significant weight loss.

Weight loss treatments vary depending, at least in part, on the degree of weight loss one is attempting to achieve in a subject as well as on the severity of overweight or obesity exhibited by the subject. For example, treatments such as low-fat diet and/or regular exercise are often adequate in cases where a subject is only mildly overweight. Such treatments can be enhanced by controlled use of over-the-counter appetite suppressants including caffeine, ephedrine and phenylpropanolamine (Acutrim®, Dexatrim®). Moreover, prescription medications including amphetamine, diethylpropion (Tenuate®), mazindol (Mazanor®, Sanorex®), phentermine (Fastin®, lonamin®), phenmetrazine (Preludin®), phendimetrazine (Bontrol®, Plegine®, Adipost®, Dital®, Dyrexan®, Melfiat®, Prelu-2®, Rexigen Forte®), benzphetamine (Didrex®) and fluoxetine (Prozac®) are often used in the treatment of seriously overweight and/or obese subjects or patients. However, such treatments, at best, result in only ~5–10% weight loss (when accompanied with diet and exercise). Moreover, most of these treatments ultimately prove inadequate because they are either dangerous, ineffective or quickly lose their anorexient effect.

At least one class of these prescription medications, the phentermines (Fastin®, lonamin®), have been used as monotherapy in the treatment of obesity for about 30 years. The phentermines are members of a class of drugs known as the sympathomimetics for their ability to mimic stimulation of the central nervous system. The phentermines act on the hypothalamus, an appetite control center of the brain. Phentermine monotherapy can increase weight loss when used in combination with diet and exercise, as compared to diet and exercise alone. However, the drug loses effectiveness after about two weeks and, in fact, is not approved by the FDA for use beyond six weeks. Moreover, weight loss may not be permanent, especially after the drug is discontinued. Phentermine treatment is also associated with side effects including nervousness, irritability, headache, sweating, dry-mouth, nausea, and constipation.

In general, available weight loss drugs have limited efficacy and some clinically significant side effects. Studies of the weight loss medications dexfenfluramine (Guy-Grand, B. et al. (1989) *Lancet* 2:1142–5), orlistat (Davidson, M. H. et al. (1999) *JAMA* 281:235–42), sibutramine (Bray, G. A. et al. (1999) *Obes. Res.* 7:189–98), and phentermine (Douglas, A. et al. (1983) *Int. J. Obes.* 7:591–5) have shown similar effectiveness. Studies for each demonstrated a weight loss of about 5% of body weight for drug compared with placebo. Other serious considerations limit the clinical use of these drugs. Dexfenfluramine was withdrawn from the market because of suspected heart valvulopathy, orlistat is limited by GI side effects, sibutramine can cause hypertension, and phentermine has limited efficacy.

Various combination therapies that include phentermine as one of the agents have been investigated and have met with mixed success. The phentermines were, up until around 1997, often prescribed along with fenfluramine (Pondimin®) or dexfenfluramine (Redux®), nicknamed "fen", as a combination therapy known as fen-phen. Fenfluramine is a potent releaser of serotonin from serotonergic neurons which acts on a cerebral appetite center. When combined with phentermine, fenfluramine had the effect of enhancing and extending the anorexient action of phentermine. However in 1997, the Food and Drug Administration ("FDA") asked manufacturers to withdraw Pondimin® and Redux® due to studies which strongly suggested that the drugs cause damage to the mitral valve of the heart and pulmonary hypertension.

More recently, it has been suggested that phentermine in combination with anti depressants is a potentially effective therapy for effecting weight loss, U.S. Pat. No. 5,795,895. In particular, the anti-depressants suggested for use in this new combination therapy are members of a class of compounds known as selective serotonin reuptake inhibitors (SSRIs) which include fluoxetine (Prozac®), sertraline (Zoloft®), fluvoxamine maleate (Luvox®) and trazodone hydrochloride (Desyrel®). The combination therapy is also suggested to treat coexisting depression and/or obsessive-compulsive disorder.

Phentermine has also recently been tested in combination with bupropion (Wellbutrin®) for the treatment of obesity. Bupropion is an antidepressant that inhibits dopamine reuptake, as compared to serotonin uptake. It is also used to treat Attention Deficit Disorder (ADHD), bipolar depression, chronic fatigue syndrome, cocaine addiction, nicotine addiction, and lower back pain. While bupropion alone had a modest effect as a weight loss agent (when prescribed to patients following a 1200 calorie per day diet), patients receiving phentermine in combination with bupropion experienced no greater weight loss than those receiving bupropion alone. Moreover, bupropion use has been associated with drug-induced seizures causing it to be removed from the market by the FDA for at least five years before its re-introduction in 1989.

Accordingly, there exists a need for new, more effective weight loss treatments which are accompanied by fewer adverse or undesirable side effects or less serious side effects. In particular, there exists a need for developing medical weight loss treatments which can potentially lower major endpoints such as death and/or myocardial infarction rates by directly treating obesity rather than treating the

consequences of obesity (e.g., diabetes, hypertension, hyperlipidemia), as is currently the practice.

SUMMARY OF THE INVENTION

The present invention features a novel therapy for effecting weight loss which involves treating a subject with a sympathomimetic agent in combination with an anticonvulsant sulfamate derivative such that the subject experiences weight loss. In one aspect, the sympathomimetic agent is a compound having anorectic activity (e.g., amphetamine, methamphetamine, benzphetamine, phentermine, chlorphentermine, diethylpropran, phenmetrazine, and phendimetrazine). Preferably, the sympathomimetic agent is the drug phentermine (nicknamed "phen"). In another aspect, the anticonvulsant sulfamate derivative is the drug topiramate.

The combination methods of the present invention also are effective against symptoms associated with Syndrome X. Accordingly, in another aspect the invention features methods for treating Syndrome X with a combination of a sympathomimetic agent and an anticonvulsant sulfamate derivative (e.g., phentermine and topiramate, respectively) such that at least one symptom associated with Syndrome X is beneficially affected. Moreover, the combination methods of the present invention have been shown to have beneficial side effects, such as ameliorating sleep apnea and lowering blood pressure, blood glucose, blood lipid, and Hgb A1C levels. Accordingly, in another aspect the invention features methods for treating at least one side effect associated with obesity. In a preferred embodiment, at least one side effect of obesity is treated with a combination of a sympathomimetic agent in combination with an anticonvulsant sulfamate derivative.

The invention also features pharmaceutical compositions including therapeutically effective amounts of a sympathomimetic agent in combination with an anticonvulsant sulfamate derivative. Kits including the pharmaceutical compositions of the present invention are also featured (e.g., kits including the compositions packaged in a daily dosing regimen).

Combination therapy according to the invention provides an effective and efficient treatment for bringing about weight loss while, quite unexpectedly, simultaneously enabling a reduction in the effective dosage of each drug administered and minimizing the potential side effects of each individual drug. Administering topiramate with phentermine according to the invention, for example, is very effective in bringing about weight loss using a daily dose of topiramate that, a particularly preferred embodiment, is at most about half of the recommended daily dose of the drug (400 mg, for Topamax®) and a daily dose of phentermine that is also significantly reduced relative to the recommended daily dose (from 37.5 mg daily to 5–15 mg daily). At the same time, weight loss is achieved efficiently and the common side effects of each drug are substantially reduced. Applicant is unaware of any teaching suggesting the combination therapy of the invention; in fact, the 1999 Physicians' Desk Reference pertaining to phentermine specifically states that the drug is useful only in the context of short-term monotherapy and recommends not co-administering the drug with any other active agents.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a novel combination therapy for effecting weight loss in a subject. In particular, the present invention provides methods which involve treating the subject with a therapeutically effective amount of a combination of a sympathomimetic agent (e.g., phentermine or a phentermine-like compound) and an anticonvulsant sulfamate derivative (e.g., topiramate). The methods are particularly useful for the treatment of overweight and/or obesity, as well as in the treatment of Syndrome X.

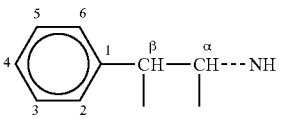
The phrase "therapeutically effective amount" as used herein refers to the amount of an agent, compound, drug, composition, or combination of the invention which is effective for producing some desired therapeutic effect upon administration to a subject or patient (e.g., a human subject or patient). The phrase "administering to a subject" or "administering to a patient" refers to the process of introducing an agent, compound, drug, composition or combination of the invention into the subject or patient's body via an art-recognized means of introduction (e.g., orally, transdermally, via injection, etc.).

The term "sympathomimetic agent" is a term of art and refers to agents or compounds which mimic or alter stimulation of the sympathetic nervous system (e.g., stimulates the peripheral nervous system) of an organism (e.g., mimic the stimulation naturally effected by physical activity, psychological stress, generalized allergic reaction and other situations in which the organism is provoked).

Preferred sympathomimetic agents for use in the present invention as well as there general clinical uses or effects are set forth in Table 1.

TABLE 1

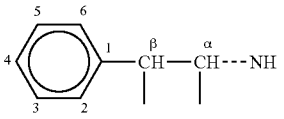
SYMPATHOMIMETIC AGENTS AND CLINICAL USES THEREOF†



					MAIN CLINICAL USES		
					αReceptor A N P V	βReceptor B C	CNS, 0
Phenylethylamine		H	H	H			
Epinephrine	3-OH, 4-OH	OH	H	CH_3	A, P, V	B, C	
Norepinephrine	3-OH, 4-OH	OH	H	H	P		
Epinine	3-OH, 4-OH	H	H	CH_3			
Dopamine	3-OH, 4-OH	H	H	H	P		
Dabutamine	3-OH, 4-OH	H	H	1 *		C	
Nordefrin	3-OH, 4-OH	OH	CH_3	H	V		

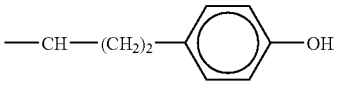
TABLE 1-continued

SYMPATHOMIMETIC AGENTS AND CLINICAL USES THEREOF†



					MAIN CLINICAL USES		
					αReceptor	βReceptor	
					A N P V	B C	CNS, 0
Ethylnorepinephrine	3-OH, 4-OH	OH	CH_2CH_3	H		B	
Isoproterenol	3-OH, 4-OH	OH	H	$CH(CH_3)_2$		B, C	
Protokylol	3-OH, 4-OH	OH	H	2 *		B	
Isoetharine	3-OH, 4-OH	OH	CH_2CH_3	$CH(CH_3)_2$		B	
Metaproterenol	3-OH, 5-OH	OH	H	$CH(CH_3)_2$		B	
Terbutaline	3-OH, 5-OH	OH	H	$C(CH_3)_3$		B	
Metaraminol	3-OH	OH	CH_3	H	P		
Phenylephrine	3-OH	OH	H	CH_3	N, P		
Tyramine	4-OH	H	H	H			
Hydroxyamphetamine	4-OH	H	CH_3	H	N, P	C	
Methoxyphenamine	2-OCH_3	H	CH_3	CH_3		B	
Methoxamine	2-OCH_3, 5-OCH_3	OH	CH_3	H	P		
Albuterol	3-CH_2OH, 4-OH	OH	H	$C(CH_3)_3$		B	
Amphetamine		H	CH_3	H			CNS, 0
Methamphetamine		H	CH_3	CH_3	P		CNS, 0
Benzphetamine		H	CH_3	CH_3			0
Ephedrine		OH	CH_3	CH_3	N, P	B, C	
Phenylpropanolamine		OH	CH_3	H	N		
Mephentermine		H	4 *	CH_3	N, P		
Phentermine		H	4 *	H			0
Chlorphentermine	4-Cl	H	4 *	H			0
Fenfluramine	3-CF_3	H	CH_3	C_2H_5			0
Tuaminoheptane	$CH_3(CH_2)_3$	H	CH_3	H	N		
Propylhexedrine	5 *	H	CH_3	CH_3	N		
Diethylpropran			6 *				
Phenmetrazine			7 *				0
Phendimetrazine			8 *				0

1



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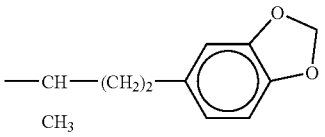

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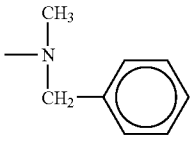

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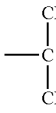

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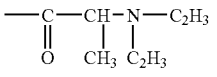
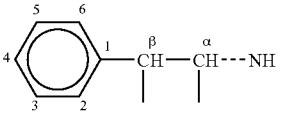
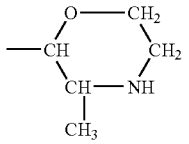
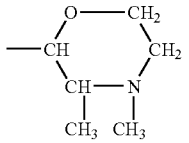


TABLE 1-continued

SYMPATHOMIMETIC AGENTS AND CLINICAL USES THEREOF†

		MAIN CLINICAL USES		
		αReceptor A N P V	βReceptor B C	CNS, 0
7				
8				

α Activity
A = Allergic reactions (includes β action)
N = Nasal decongestion
P = Pressor (may include β action)
V = Other local vasoconstriction
(e.g. in local anesthesia)
β Activity
B = Bronchodilator
C = Cardiac
CNS = Central nervous system
0 = Anorectic
* Numbers bearing an asterisk refer to the substituents numbered in the bottom rows of the table; substituent 5 replaces the phenyl rings, and 6, 7 and 8 are attached directly to the phenyl ring, replacing the ethylamine side chain.
†The α and β in the prototype formula refer to positions of the C atoms in the ethylamine side chain.

ln preferred embodiments, the sympathomimetic agent has anorexient properties (e.g., suppresses appetite) or is anorectic without significant toxicity to a subject or patient (e.g., a human) at therapeutically effective doses. ln a more preferred embodiment, the sympathomimetic agent has anorexient properties (e.g., suppresses appetite) or is anorectic without loss of efficacy or without adverse or undesirable side effects to a subject or patient (e.g., a human subject or patient) at therapeutically effective doses when prescribed in combination with topiramate. ln yet another embodiment, the sympathomimetic agent is phentermine or a phentermine-like compound. As defined herein, a phentermine-like compound is a compound structurally related to phentermine (e.g., an analog or derivative) which maintains an anorectic activity similar to that of phentermine. A preferred phentermine-like compound is chlorphentermine. ln yet another embodiment, the sympathomimetic agent is amphetamine or an amphetamine-like compound. As used herein, an "amphetamine-like compound" is a compound structurally related to amphetamine (e.g., an analog or derivative) which maintains an anorectic effect of amphetamine. ln yet another embodiment, the sympathomimetic agent is phenmetrazine or a phenmetrazine-like compound. As defined herein, a "phenmetrazine-like compound" is a compound structurally related to phenmetrazine (e.g., an analog or derivative) which maintains an anorectic effect of phenmetrazine. A preferred phenmetrazine-like compound is phendimetrazine. Analogs and/or derivatives of the compounds of the present invention can be tested for their ability to suppress appetite (e.g., suppress food intake) in a subject (e.g., a mammalian subject).

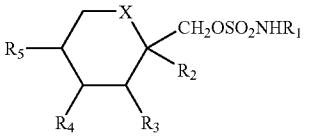
ln an exemplary preferred embodiment, the sympathomimetic agent is selected from the group consisting of amphetamine, methamphetamine, benzphetamine, phenylpropanolamine, phentermine, chlorphentermine, diethylpropion, phenmetrazine, and phendimetrazine (as set forth in Table 1. ln a particularly preferred embodiment, the sympathomimetic agent is phentermine. lt is also within the scope of the present invention to utilize other sympathomimetic agents including pseudo ephedrine (a stereoisomer of ephedrine, SUDAFED®), methylphenidate (RITALlN®) and other CNS stimulants including, for example, caffeine.

The terms "anticonvulsant sulfamate derivative" and "anticonvulsant sulfamate derivatives" are terms of art and refer to a class of sulfamate-derived compounds that possess anticonvulsant activity and have an art-recognized use in the treatment of epilepsy. ln particular, the anticonvulsant sulfamate derivatives are monosaccharide derivatives with sulfamate functionality. The anticonvulsant sulfamate derivatives for use in the present invention have one or more of the following modes of activity: modulation of voltage-dependent sodium conductance; potentiation of gamma-aminobutyric acid-evoked currents; inhibition of the kainate/alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) subtype of the glutamate receptor; and/or inhibition of carbonic anhydrase (e.g, a mechanism by which the anticonvulsant derivative of the present invention may

decrease the sensation of taste). The anticonvulsant sulfamate derivatives for use in the present invention are described further in U.S. Pat. Nos. 4,513,006, 5,384,327, 5,498,629, 5,753,693 and 5,753,694, as are methods of synthesizing such anticonvulsant sulfamate derivatives. The aforementioned patents are incorporated by reference herein in their entireties.

In preferred embodiments, the anticonvulsant sulfamate derivative is a compound having the following formula (I):

(I)



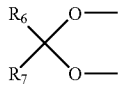
wherein:

X is CH_2 or O;

R_1 is H or alkyl; and

R_2, R_3, R_4 and R_5 are independently H or lower alkyl, with the proviso that when X is O, then R_2 and R_3 and/or R_4 and R_5 together may be a methylenedioxy group of the following formula (II):

(II)



in which R_6 and R_7 are the same or different and are H or lower alkyl, or are joined to form a cyclopentyl or cyclohexyl ring.

R_1 in particular is hydrogen or alkyl of about 1 to 4 carbons, such as methyl, ethyl, and isopropyl. Alkyl includes both straight and branched chain alkyl. Alkyl groups R_2, R_3, R_4, R_5, R_6 and R_7 are about 1 to 3 carbons and include methyl, ethyl, isopropyl and n-propyl.

A particular group of compounds of the formula (II) are those wherein X is oxygen and both R_2 and R_3, and R_4 and R_5 together are methylenedioxy groups of the formula (II), wherein R_6 and R_7 are both hydrogen, both alkyl, or combine to form a spiro cyclopentyl or cyclohexyl ring, in particular, where R_6 and R_7 are both alkyl such as methyl. A second group of compounds are those wherein X is CH_2 and R_4 and R_5 are joined to form a benzene ring. A third group of compounds of the formula (I) are those wherein both R_2 and R_3 are hydrogen.

In preferred embodiments, the anticonvulsant sulfamate derivatives have anorexient properties (e.g., suppress appetite) without significant toxicity to a subject or patient (e.g., a human) at therapeutically effective doses. In a more preferred embodiment, the anticonvulsant sulfamate derivatives have anorexient properties (e.g., suppress appetite) without significant adverse or undesirable side effects to a subject or patient (e.g., a human) at therapeutically effective doses when prescribed in combination with phentermine. In a particularly preferred embodiment the anticonvulsant sulfamate derivative is topiramate (Topamax®). Topiramate, also referred to in the art as 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate, has been demonstrated in clinical trials of human epilepsy to be effective as an adjunctive therapy or as monotherapy in treating simple and complex partial seizures and secondarily generalized seizures (E. Faught et al. (1995) *Epilepsia* 36(suppl 4):33; S. Sachdeo et al. (1995) *Epilepsia* 36(suppl 4):33) and is currently marketed for the treatment of simple and complex partial seizure epilepsy with or without secondary generalized seizures.

Dosages, Administration and Pharmaceutical Compositions:

The choice of appropriate dosages for the drugs used in combination therapy according to the present invention can be determined and optimized by the skilled artisan, e.g., by observation of the patient, including the patient's overall health, the response to the combination therapy, and the like. Optimization, for example, may be necessary if it is determined that a patient is not exhibiting the desired therapeutic effect or conversely, if the patient is experiencing undesirable or adverse side effects that are too many in number or are of a troublesome severity.

The sympathomimetic drug (e.g., a drug set forth in Table I) is prescribed at a dosage that is at most that which is routinely used by the skilled artisan (e.g., physician) to promote the desired therapeutic effect of the drug, when the drug is used as a monotherapy. Preferably, an anticonvulsant sulfamate derivative (e.g., a compound having formula (I) is prescribed at a lower dosage than routinely used by the skilled artisan (e.g., physician) to promote the desired therapeutic effect of the drug, when the drug is used as a monotherapy (e.g., in the treatment of epilepsy). A sympathomimetic drug or anticonvulsant sulfamate derivative may be prescribed, for example, at a dose of 5–1000, preferably 10–1500, more preferably 20–1000, and most preferably 25–50 mg daily In the preferred embodiment, wherein the anticonvulsant sulfamate derivative is topiramate, the maintenance dose given is at least 50 mg daily, and should be less than 400 mg daily; preferably, the maintenance dose should be in the range of about 50 mg to 250 mg daily, more preferably in the range of about 100 mg to 250 mg daily, and optimally in the range of about 100 mg to 200 mg daily. By "maintenance dose" is meant an ongoing daily dose given to a patient, typically after gradually increasing the daily dose from an initial, low dosage, over an extended time period, e.g., on the order of several weeks.

It is especially advantageous to formulate compositions of the invention in unit dosage form for ease of administration and uniformity of dosage. The term "unit dosage forms" as used herein refers to physically discrete units suited as unitary dosages for the individuals to be treated. That is, the compositions are formulated into discrete dosage units each containing a predetermined, "unit dosage" quantity of an active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specifications of the novel unit dosage forms of the invention are dependent on the unique characteristics of the composition containing the anticonvulsant or sympathomimetic agent and the particular therapeutic effect or effects to be achieved. Dosages can further be determined by reference to the usual dose and manner of administration of the ingredients. It is also within the scope of the present invention to formulate a single physically discrete dosage form having each of the active ingredients of the combination treatment (e.g., a single dosage form having anticonvulsant and sympathomimetic agent).

The method of administration of compositions or combinations of the invention will depend, in particular, on the type of sympathomimetic agent used and the chosen anticonvulsant sulfamate derivative. The sympathomimetic agent and the anticonvulsant sulfamate derivative may be

administered together in the same composition or simultaneously or sequentially in two separate compositions. Also, one or more sympathomimetic agents or one or more anticonvulsant sulfamate derivatives may be administered to a subject or patient either in the form of a therapeutic composition or in combination, e.g., in the form of one or more separate compositions administered simultaneously or sequentially. The schedule of administration will be dependent on the type of sympathomimetic agent(s) and anticonvulsant sulfamate derivative(s) chosen. For example, a sympathomimetic agent can have a stimulant effect and the degree of such stimulant effect may vary depending on the sympathomimetic agent chosen. Accordingly, a sympathomimetic agent having a significant stimulant effect might be administered earlier in the day than administration of a sympathomimetic agent having a lesser stimulant effect. Likewise, an anticonvulsant sulfamate derivative can have a sedative effect and the degree of such sedative effect may vary depending on the anticonvulsant sulfamate derivative chosen. Accordingly, an anticonvulsant sulfamate derivative having a significant sedative effect might be administered later in the day than administration of an anticonvulsant sulfamate derivative having a lesser sedative effect. Moreover, sympathomimetic agents and/or anticonvulsant agents having lesser stimulant or sedative effects, respectively, may be administered simultaneously.

Sympathomimetic agents and/or anticonvulsant sulfamate derivatives can also be administered along with a pharmaceutically acceptable carrier. As used herein "pharmaceutically acceptable carrier" includes any solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in compositions of the invention is contemplated.

A sympathomimetic agent alone, or in combination with an anticonvulsant sulfamate derivative in the form of a composition, is preferably administered orally. When the composition(s) are orally administered, an inert diluent or an assimilable edible carrier may be included. The composition and other ingredients may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the individual's diet. For oral therapeutic administration, the composition may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The percentage of the compositions and preparations may, of course, be varied. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. ln a particularly preferred embodiment, the present invention includes pharmaceutical composition comprising a therapeutically effective amount of a sympathomimetic agent and an anticonvulsant sulfamate derivative. ln one embodiment, the present invention includes a therapeutically-effective amount of a sympathomimetic agent and an anticonvulsant sulfamate derivative packaged in a daily dosing regimen (e.g., packaged on cards, packaged with dosing cards, packaged on blisters or blow-molded plastics, etc.). Such packaging promotes products and increases patient compliance with drug regimens. Such packaging can also reduce patient confusion. The present invention also features such kits further containing instructions for use.

The tablets, troches, pills, capsules and the like may also contain a binder, an excipient, a lubricant, or a sweetening agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar, or both. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed.

A sympathomimetic agent, alone or in combination with an anticonvulsant sulfamate derivative, can also be administered in a convenient manner such as by injection (subcutaneous, intravenous, etc.), inhalation, transdermal application, or rectal administration. Depending on the route of administration, the composition containing the sympathomimetic agent and/or anticonvulsant sulfamate derivative may be coated with a material to protect the compound from the action of acids and other natural conditions which may inactivate the compounds or compositions.

To administer the compositions, for example, transdermally or by injection, it may be necessary to coat the composition with, or co-administer the composition with, a material to prevent its inactivation. For example, the composition may be administered to an individual in an appropriate diluent or in an appropriate carrier such as liposomes. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Liposomes include water-in-oil-in-water CGF emulsions as well as conventional liposomes (Strejan et al. (1984) *J. Neuroimmunol*. 7:27). To administer the compositions containing the sympathomimetic agents and/or anticonvulsant sulfamate derivatives parenterally or intraperitoneally, dispersions can be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

Compositions suitable for injectable use include sterile aqueous solutions (where water-soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. ln all cases, the composition must be sterile and must be fluid to the extent that easy syringeability exists. lt must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents. ln many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

A preferred aspect of the present invention features prescribing phentermine in combination with topiramate to effect weight loss and/or to treat Syndrome X and/or a subset of symptoms thereof. Phentermine is administered at a daily dosage of about 5–60 mg, including but not limited to, doses of 8, 10, 15, 20, 25, 30, 35, 40, 45, 50, and 55 mg daily. lt is strongly preferred, however, that the amount of phentermine administered be in the range of about 5 to about 15 mg daily, since within that dosage range, therapeutic efficacy is

maintained within the context of the present combination therapy, and the side effects of the drug are minimized.

Preferably, the phentermine is taken by the patent in the morning and more preferably, is taken before breakfast. The phentermine is best taken in the morning because the drug is a stimulant as well as an appetite suppressant. When phentermine is prescribed (e.g., as part of the combination therapy described herein), physicians should be aware and may want to advise patients that the drug can be mildly habit forming. Phentermine can also cause increased nervousness, increased energy, irritability and, rarely, insomnia. Stopping phentermine may also cause tiredness lasting for up to 1–2 weeks. Phentermine can also raise blood pressure (e.g., during the early phases of treatment).

Administration of topiramate at dosages of ≧400 mg daily results is promotion of undesirable side effects (e.g., sedation, mental clouding). Accordingly, in the method of the invention, topiramate is prescribed at a maintenance dose of at least 50 mg to less than 400 mg daily, preferably about 50 mg to 250 mg daily, more preferably 100 mg to 250 mg daily, and optimally 100 mg to 200 mg daily, as noted above. In another preferred embodiment, the dosage of topiramate is increased gradually at the outset of the therapy in order to reduce the chance of undesirable side effects associated with higher doses of the drug. In an exemplary embodiment, the topiramate is administered at a dose of 25 mg daily for about the first 5–7 days (e.g., 6 days) of treatment, at a dose of about 50 mg daily for the next 5–7 days (e.g., 6 days), at a dose of 100 mg daily for about the next 6–8 days (e.g., 7 days) and about 100–150 mg daily for the next 20–26 days. From this point forward, the topiramate can be administered at a dose of 100–250 mg daily, preferably 100–200 mg daily. A particularly preferred dose for continued therapy is about 200 mg of topiramate daily. In another exemplary embodiment, the topiramate is of an immediate release form. In yet another exemplary embodiment, the topiramate is of a sustained release form.

In a preferred embodiment, topiramate is taken later in the day than the phentermine. Preferably, the patient takes the topiramate just before supper or later in the evening. Topiramate is best given later in the day because the drug can be sedating. In other embodiments, the topiramate is given BID (e.g., twice daily), TID (three times daily) or QID (four time daily). When prescribing topiramate, physicians should be aware and may want to advise patients that the drug can cause tiredness, fatigue, dizziness, difficulty with speech or finding words, difficulty concentrating, difficulty with balance, and/or numbness or tingling in the hands or feet. Less common side effects are nausea, coordination problems, abdominal pain, slowed thinking nervousness, depression, breast pain, painful periods, double or blurred vision, palpitations, low white blood count and kidney stones. A physician should also advise patients that the drug may not be taken if the patient is also taking Diamox (acetazolamide). No female patient should become pregnant while taking this drug as it may cause birth defects. If a female patient misses a period she should immediately discontinue taking the medication and inform the physician. Female patients should not be treated according to the methods of the present invention if breast-feeding a child. Patients should not drink alcohol or take sedating medications while taking topiramate since excess sedation can occur. Patients should also refrain from performing dangerous tasks (e.g. operating heavy machinery or driving) until they are comfortable with the side effects of the full dose (e.g., 200 mg daily). Patients should be advised not to increase the dosage beyond what is prescribed. Topiramate is not habit forming.

Yet another embodiment of the present invention features pharmaceutical compositions (e.g., for oral administration) comprising phentermine and topiramate in a single pharmaceutical formulation. Such compositions may be preferred, for example, to increase patient compliance (e.g., by reducing the number of administrations necessary to achieve the desired pharmacologic effect.)

In a preferred embodiment, the pharmaceutical composition includes phentermine in an immediate release form and further includes topiramate in a controlled release formulation. As defined herein, an "immediate release formulation" is one that has been formulated to allow, for example, the phentermine, to act as quickly as possible. Preferred immediate release formulations include, but are not limited to, readily dissolvable formulations. As defined herein, a "controlled release formulation" includes a pharmaceutical formulation that has been adapted such that drug release rates and drug release profiles can be matched to physiological and chronotherapeutic requirements or alternatively, has been formulated to effect release of a drug at a programmed rate. Preferred controlled release formulations include, but are not limited to, granules, delayed release granules, hydrogels (e.g., of synthetic or natural origin), other gelling agents (e.g., gel-forming dietary fibers), matrix-based formulations (e.g., formulations comprising a polymeric material having at least one active ingredient dispersed therethrough), granules within a matrix, polymeric mixtures, granular masses, and the like.

In one embodiment, a controlled release formulation is a delayed release form. As defined herein, a "delayed release form" is formulated in such a way as to delay, for example, topiramate's action for an extended period of time. A delayed release form can be formulated in such a way as to delay the release of an effective dose of topiramate for 4, 8, 12, 16 or 24 hours following the release of phentermine. In yet another preferred embodiment, a controlled release formulation is a sustained release form. As defined herein, a "sustained release form" is formulated in such a way as to sustain, for example, the topiramate's action over an extended period of time. A sustained release form can be formulated in such a way as to provide an effective dose of topiramate (e.g., provide a physiologically effective blood level) over a 4, 8, 12, 16 or 24 hour period.

Preferred compositions include a tablet core consisting essentially topiramate, said core being in association with a layer of phentermine. Preferably, the core has a delayed or sustained dissolution rate. In an exemplary embodiment, a tablet can comprise a first layer containing, for example, phentermine (e.g., in an immediate release formulation) and a core containing, for example, topiramate in a delayed release or sustained release formulation. Other exemplary embodiments can include, for example, a barrier between the first layer and core, said layer serving the purpose of limiting drug release from the surface of the core. Preferred barriers prevent dissolution of the core when the pharmaceutical formulation is first exposed to gastric fluid. For example, a barrier can comprise a disintegrant, a dissolution-retarding coating (e.g., a polymeric material, for example, an enteric polymer), or a hydrophobic coating or film, and/or can be selectively soluble in either the stomach or intestinal fluids. Such barriers permit the topiramate to leach out slowly and can cover substantially the whole surface of the core.

The above-described pharmaceutical compositions are designed to release the two effective agents of the combination therapy of the present invention sequentially, i.e., releasing topiramate after releasing phentermine, both

agents being contained in the same pharmaceutical composition. Preferred amounts of phentermine and topiramate are as described above with particularly preferred compositions comprising unit daily dosages of from about 5 mg to about 15 mg phentermine and from about 100 mg to 200 mg topiramate.

Pharmaceutical compositions so formulated may contain additional additives, suspending agents, diluents, binders or adjuvants, disintegrants, lubricants, glidants, stabilizers, coloring agents, flavoring agents, etc. These are conventional materials that may be incorporated in conventional amounts.

ln one embodiment, a method of the present invention is carried out, practiced, or performed such that weight loss in the subject or patient occurs. Accordingly, the methods of the present invention are particularly useful for the treatment of overweight or obese patients. As defined herein, "overweight" subjects or patients are between about 1 and 20 percent overweight (e.g., weighs 1–20% in excess of their ideal body weight). Also as defined herein, an "obese" subject or patient is greater than 20 percent overweight (e.g., weighs >20% in excess of his or her ideal body weight). Alternatively, the methods of the present invention are useful in the treatment of subjects or patients in need of losing weight, but who are not necessarily overweight or obese. For example, it may be desirable to achieve weight loss in subjects or patients having arthritis or prostheses such that the individual experiences fewer or less severe adverse effects resulting from bearing weight.

The combination therapies of the present invention will generally be administered until the patient has experienced the desired weight loss, and preferably has achieved an ideal body weight. Alternatively, the combination therapies of the present invention can be administered until the patient has achieved a weight loss of 5–10%, 10–15%, 15–20%, or 20–25% of their initial body mass (e.g. patient's starting weight).

The present inventor has also recognized that the combination therapy of the present invention ameliorates symptoms associated with Syndrome X. Syndrome X consists of a complex of medical problems that are largely associated with obesity, including, hypertension, diabetes or glucose intolerance and insulin resistance, hyperlipidemia, and often tiredness and sleepiness associated with sleep apnea. Patients are often treated with combinations of antihypertensives, lipid lowering agents, insulin or oral diabetic drugs, and various mechanical and surgical methods for treating sleep apnea. However, such treatments are often costly and do not treat the underlying problem of obesity. Moreover, some of the treatments for diabetes including insulin and oral diabetic agents actually aggravate Syndrome X by increasing insulin levels, increasing appetite, and increasing weight. This can lead to higher blood pressure and even higher cholesterol. Accordingly, one aspect of the present invention features a method of treating Syndrome X using the combination therapies described herein. ln one embodiment, the invention features a method of treating Syndrome X in a subject or patient which includes treating the subject with a therapeutically effective amount of a combination of an anticonvulsant sulfamate derivative (e.g., topiramate) and a sympathomimetic agent (e.g., phentermine or a phentermine-like compound), such that at least one symptom associated with Syndrome X is treated, i.e. beneficially affected. As defined herein, "treating or beneficially affecting a symptom" (e.g., a symptom associated with Syndrome X) refers to lessening, decreasing the severity of the symptom or reversing, ameliorating, or improving the symptom (e.g., decreasing hypertension, ameliorating diabetes, reversing glucose intolerance or insulin resistance, lessening hyperlipidemia, or decreasing tiredness and sleepiness associated with sleep apnea).

Treatment of Syndrome X according to the methods of the present invention includes treating, i.e., beneficially affecting, at least one, preferably two, more preferably three, more preferably four, five, or six symptoms associated with Syndrome X. ln a particularly preferred embodiment, all symptoms associated with Syndrome X are beneficially affected (e.g., lessened, reversed, ameliorated, etc.)

The present inventor has also recognized that the combination therapy of the present invention ameliorates some side effects associated with obesity, as described herein. Accordingly, one aspect of the present invention features a method of treating at least one side effect associated with obesity using the combination therapies described herein. ln one embodiment, the invention features a method of treating at least one obesity-related side effect in a subject or patient which includes treating the subject with a therapeutically effective amount of a combination of an anticonvulsant sulfamate derivative (e.g., topiramate) and a sympathomimetic agent (e.g., phentermine or a phentermine-like compound), such that at least one obesity-related side effect is effected. As defined herein, a "side effect associated with obesity" includes a symptom or disorder in a subject (e.g., a patient) which is secondary and/or results from (e.g., directly and/or indirectly results from) a medical condition for which the subject is obese and/or being treated. ln a preferred embodiment, the subject is obese and/or is being treated for obesity. ln another embodiment, the subject has at least one or more (e.g., two, three, four, five or more) side effect(s) selected from the group consisting of sleep apnea, high blood pressure and high blood sugar, high blood lipid, high Hgb A1C or other art-recognized side effects associated with obesity.

Whether in the treatment of Syndrome X or in the practicing of the methods of the present invention to effect weight loss (e.g., in the treatment of overweight and/or obesity) or in treatment of side effects associated with obesity, it will be apparent to the skilled artisan (e.g., physician) that monitoring of the patient is needed to determine the effectiveness of the treatments and to potentially modify the treatments (e.g., modify the dosing, time of drug administration, sequence of drug administration, as defined herein). Accordingly, in certain embodiments, the patient is monitored about every 2–6, preferably every 3–5 and more preferably every 4 weeks. Monitoring the effective of treatment to achieve weight loss includes, but is not limited to monitoring the subject or patient's body weight (e.g., comparing the patient's initial body weight to that at a follow-up visit, for example, four weeks after the initiation of treatment). Additional features of the subject or patient's health can also be monitored (i.e., monitoring the patient's overall health and/or monitoring the effectiveness of treatment of an undesired side effect of obesity) including, but not limited to the patient's blood pressure, blood sugar, serum lipid levels, etc. Likewise, monitoring a subject or patient for treatment of Syndrome X can include monitoring of at least one, preferably more than one symptom associated with Syndrome X.

This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patents, and published patent applications cited throughout this application are hereby incorporated by reference.

EXAMPLE 1

Patients as part of the following trial were treated according to the following dosage regimen. Patients took phentermine at a dose of 15 mg daily throughout the weight loss program, before breakfast. For the first 6 days, patients took one 25 mg tablet of topiramate before supper. For the next 6 days, patients took two 25 mg tablets of topiramate before supper. For the next 7 days (days 13–19), patients took 100 mg before supper daily using 4–25 mg tablets of topiramate daily. For days 20–26, patients took 150 mg of topiramate daily consisting of one-half of a 200 mg tablet and two 25-mg mg tablets of topiramate. From that point on, unless instructed otherwise by the physician, patients continued to take one 200 mg topiramate tablet daily before supper and continued the 15 mg phentermine daily in the morning. Patients were advised to drink at least eight (8) full glasses of water daily to reduce the risk of kidney stones which may result from taking topiramate.

Patients were advised that while the effect of phentermine is fairly rapid, the effect of topiramate is slower in onset. The weight reduction effect of topiramate will continue for as long as 18 months on the medication. That is, the patient can expect to continue gradual weight loss for up to 18 months on the medication. Of course, weight loss is maximal if the patient follows diet and/or exercise programs. The weight loss should exceed 15% of the patients starting weight. Thus, if the patient weighs about 200 pounds as of the start date, he/she might expect to lose at least 30 pounds in a period of 12–18 months. The following patient data has been collected.

TABLE 11

Patient's Initials	Age	Sex	Start Weight (lbs)	Start Blood Pressure	Follow-Up Date	Follow-Up Weight (lbs)	% Weight Loss	Follow-Up Blood Pressure
M.O.[1]	48	F	182	115/70	5 weeks	177	2.7%	120/80
					9 weeks	176	3.3%	110/70
T.M.	37	F	190	122/84	2 weeks, 5 days	178	6.3%	110/80
					6 weeks, 2 days	168	11.6%	125/80
D.M.(A)	28	M	286	138/90	4 weeks	279	2.4%	128/86
P.L.	55	F	144	132/84	4 weeks	141	2.1%	138/85
					9 weeks	137	4.9%	122/82
E.K.	52	F	181	130/100	5 weeks	175	3.3%	140/88
I.F.	41	F	196	95/60	6 weeks, 5 days			
D.M.(B)[2]	56	M	295	150/80	4 weeks, 2 days	297	(+0.7%)	148/82
					8 weeks, 2 days	287	2.7%	140/70

[1]Patient M.O. was being treated with Meridia ® at the onset of the study, which continued through the first 5 weeks of the study. At the 5-week follow up, M.O. was switched to the phentermine/topiramate regime described above.
[2]Patient D.M.(B) was being treated with phentermine alone at the onset of the study and was taking the full dose of topiramate by the fourth week of the study.

As is apparent from the above-described data, patients not previously treated with an anorexient at the outset of the study experienced an average of about 3.5% weight loss after only 2–6 weeks (e.g., patient T. M. lost 6.3% body weight, patient D. M.(A) lost 2.4% body weight, patient P. L. lost 2.1% body weight and patient E. K. lost 3.3% body weight). After only 6–9 weeks of treatment, patients (not previously treated with an anorexient at the outset of the study experienced an average of about 8.3% weight loss (e.g., patient T. M. lost 11.6% body weight and patient P. L. lost 4.9% body weight). The patient previously on Meridia® (patient M. O.) lost 3.3% body weight after being enrolled in the program for 9 weeks. Moreover, the patient previously on phentermine (patient D. M.(B)) lost a total of 2.7% body weight after being enrolled in the program for about 8 weeks. This particular patient reported that this is the most significant weight loss he has achieved to date, the patient having previously tried other conventional therapies.

In addition to the weight loss reported above, almost all patients enrolled in the study experienced decreased blood pressure. Moreover, patients involved in the study who had previously taken Redux, phen-fen, Meridia and/or other weight loss treatments report that they have not previously experienced the benefits of the combined phentermine/topiramate therapy. Patients report that they have no appetite, can resist food easily, can concentrate and function at work (even in attention-intensive jobs such as computer programming), have more energy and feel better. Patients also report experiencing fewer side effects than any previous weight loss treatments tried.

EXAMPLE 2

Extended results of the trial described in Example 1.

A total of thirteen patients were treated for 1–9 months with phentermine (15 mg daily) in the morning and up to 400 mg of topiramate (median dose 200 mg), in the evening. [Note: Patient D. M.(B) discussed above is not included in this data as he was on phentermine treatment prior to treatment with the combination therapy of the present invention.] Topiramate dose was gradually increased from 25 mg per day in increments of 25–50 mg weekly until either desirable weight loss took place or until side effects limited dose increases. [Note: A fourteenth patient discontinued treatment after 3 days due to nausea.] All thirteen patients tolerated treatment well with minimal side effects. Along with taking medication, patients were instructed to walk at least 30 minutes three times per week and to follow a low fat diet. No patients had taken diet medication for at least 3 months prior to treatment. Average baseline BMI was 32.5 (range 26–48).

Average weight loss for the thirteen patients was 11.8%. For seven patients who were on treatment the longest (range 5–9 months), the average weight loss was 14.4%. Patients reported that they had little or no appetite and that they actually felt better (Topiramate's usefulness is also being investigated as a mood stabilizer) than before therapy. Blood pressure, lipid, glucose, and Hgb A1C values were also favorably affected by this treatment.

Table lll sets forth patient data for the thirteen above-described patients treated with the combination therapy of the present invention.

TABLE lll

Patient Data: Combination Therapy*

Patient No.	% of Weight Loss	Baseline BMI	Current BMI	Weeks on Rx	Current Status
1	7.7	38	35	10	on Rx
2	10.3	25	23	4	Finished
3	6.8	48	44	5	d/c early - dropped out
4	16.8	30	24	35	on taper
5	23.2	30	23	41	on taper
6	8	41	38	40	on Rx
7	9.7	28	25	33	on taper
8	14.4	30	26	44	on Rx
9	15.9	27	21	32	on taper
10	9	33	31	7	d/c early - will restart
11	12.9	28	24	22	Finished
12	7	29	27	5	on Rx
13	12.1	34	31	6	on Rx

*data for thirteen patients
Average weight loss = 11.8% (13 patients)
Average weight loss ≧ 22 weeks on Rx = 14.4% (7 patients)
Average baseline BMI = 32.4

Table lV sets forth for the average blood pressure, blood glucose, Hgb A1C and blood lipid value for the thirteen patients.

TABLE lV

	BP mmHg	GLUCOSE mg/dL	HGBA1C %*	CHOL mg/dL	TRIG mg/dL
Average Pre-Treatment Value	131.3/85.9	107	6.48	212	189
Average On Treatment Value	122.6/78.4	102	5.05	210	172

*Numbers include 1 diabetic patient whose oral hypoglycemic was reduced by 50% while on the weight loss treatment.

One of the thirteen patients in the study also had severe sleep apnea with the usual complications of daytime sleepiness and fatigue. His symptoms have disappeared with the weight loss treatment.

Of the six patients (i.e., finished or on taper) who have completed the combination therapy of the present invention, five of the six achieved a body mass index (BMl) of 24 or better. The average pre-treatment or baseline BMl for these six patients was 28. The final average BMl was 23.3. The average weight loss was 17%.

EXAMPLE 3

The 56-year old male patient described previously (D. M.(B)) who was initially taking phentermine alone and had topiramate added to his regimen had a good effect from the combination. He once weighed as much as 395 pounds. When Redux was still on the mark in the United States, he was treated with a combination of diet, exercise, Redux and phentermine. His lowest weight attained was 285 pounds. When Redux was withdrawn from the market, he remained on phentermine but gained weight back to 295–300 pounds. When topiramate was added to his regimen, he managed to lose 25 pounds and is currently at 271 pounds, his lowest weight since he was in his 20s. He, along with most of the patients treated so far, reported that the treatment with topiramate and phentermine had fewer side effects and was more effective than any previous weight loss treatment using medications that he and others had tried. This 56-year old man exhibited lowered blood pressure (approx. 15 mm Hg systolic and 10 mm Hg diastolic).

EXAMPLE 4

Extended results of the trial described in Examples 1 and 2.

The cumulative data from a total of seventeen patients treated with the combination weight loss treatment of the present invention are set forth in Table V.

TABLE V

Patient Data: Combination Therapy*

PATIENT	% WEIGHT LOSS	BASE-LINE BMI	CURRENT BMI	WEEKS ON Rx	CURRENT STATUS
1	7.7	38	35	33	on Rx
2	10.3	25	23	4	Finished
3	6.8	48	44	5	d/c early - dropped out
4	16.8	30	24	58	on taper
5	23.2	30	23	64	on taper
6	17.5	41	33	63	on Rx
7	9.7	28	25	56	on taper
8	18.6	30	24	67	on Rx
9	15.9	27	21	55	on taper
10	9	33	31	7	d/c early-will restart
11	12.9	28	24	22	Finished
12	7	29	27	5	d/c early-will restart
13	12.1	34	31	6	d/c early-will restart
14	22.5	46	32	16	on Rx
15	10.1	50	45	12	on Rx
16	6.4	27	24	4	Finished
17	6.3	27	25	6	on Rx

*data for seventeen patients
AVERAGE WEIGHT LOSS = 12.5% (17 patients)
AVERAGE WEIGHT LOSS ≧ 22 WEEKS ON Rx = 15.3% (8 patients)
AVERAGE BASELINE BMI = 33.6

The present invention provides a novel combination therapy for the treatment of obese or overweight patients that can result in weight losses of greater than 5–10%, perhaps even as great as 15–20%. The therapy combines phentermine or a phentermine-like drug with drug previously recognized for the treatment of epileptic seizures, known as topiramate. The combination therapy results in greater initial weight loss than other recognized therapies, potential greater overall weight loss and can be continued for significant periods of time with fewer and less serious side effects than other recognized weight loss treatments. ln particular, the combination therapy far surpasses the modest anorexient effects of phentermine monotherapy and can be continued for significant periods of time without the loss of effectiveness experienced by patients being treated with phentermine alone. Moreover, the combination therapy has

been found to ameliorate symptoms associated with Syndrome X and accordingly, has potential use in the treatment of Syndrome X.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

I claim:

1. A pharmaceutical composition comprising about 50 mg to 250 mg topiramate and about 5 mg to about 15 mg phentermine.

2. The composition of claim **1**, comprising about 100 mg to 250 mg topiramate.

3. The composition of claim **2**, comprising about 100 mg to 200 mg topiramate.

4. The composition of claim **1**, comprising a dosage form that provides immediate release of the phentermine and controlled release of the topiramate.

5. The composition of claim **4**, wherein the dosage form comprises a core containing the topiramate and a coating containing the phentermine.

6. The composition of claim **4**, wherein the dosage form provides for delayed release of the topiramate.

7. The composition of claim **6**, wherein the dosage form additionally provides for sustained release of the topiramate.

8. A method for effecting weight loss in a subject comprising administering to the subject a maintenance dose of topiramate in the range of about 50 mg to 250 mg daily and a daily dose of phentermine in the range of about 5 mg to 15 mg.

9. The method of claim **8**, wherein the maintenance dose of topiramate is in the range of about 100 to 250 mg daily.

10. The method of claim **8**, wherein the maintenance dose of topiramate is in the range of about 100 to 200 mg daily.

11. The method of claim **8**, wherein the subject is overweight.

12. The method of claim **8**, wherein the subject is obese.

13. The method of claim **8**, wherein the subject is neither overweight nor obese.

14. The method of claim **8**, wherein the phentermine and the topiramate are administered separately.

15. The method of claim **14**, wherein the phentermine and the topiramate are administered at different times of the day.

16. The method of claim **15**, wherein the phentermine is administered in the morning and the topiramate is administered at least once later in the day.

17. The method of claim **8**, wherein the phentermine is contained in an immediate release dosage form.

18. The method of claim **17**, wherein the topiramate is contained in an immediate release dosage form or a controlled release dosage form.

19. The method of claim **18**, wherein the topiramate is contained in a controlled release dosage form.

20. The method of claim **19**, wherein the controlled release dosage form is a delayed release dosage form.

21. The method of claim **19**, wherein the controlled release dosage form is a sustained release dosage form.

22. The method of claim **8**, wherein the daily dose of phentermine is about 15 mg per day.

23. The method of claim **8**, wherein the phentermine and the topiramate are administered orally.

24. The method of claim **8**, wherein the phentermine and the topiramate are administered transdermally.

25. The method of claim **8**, wherein the phentermine and the topiramate are administered by injection.

26. The method of claim **8**, wherein the phentermine and the topiramate are administered simultaneously.

27. The method of claim **26**, wherein the phentermine and the topiramate are contained in a single pharmaceutical formulation.

28. The method of claim **27**, wherein the pharmaceutical formulation contains a unit dosage of phentermine and a unit dosage of topiramate.

29. The method of claim **28**, wherein the unit dosages are unit daily dosages, such that the formulation is administered once daily.

30. The method of claim **27**, wherein the formulation provides for immediate release of the phentermine and controlled release of the topiramate.

31. The method of claim **30**, wherein the formulation is composed of an oral dosage form that comprises a core containing the topiramate and a coating containing the phentermine.

32. The method of claim **30**, wherein the controlled release formulation provides for delayed release of the topiramate.

33. The method of claim **32**, wherein the controlled release formulation additionally provides for sustained release of the topiramate, such that a physiologically effective blood level of topiramate is sustained over an extended time period.

34. The method of claim **30**, wherein the controlled release formulation provides for sustained release of the topiramate, such that a physiologically effective blood level of topiramate is sustained over an extended time period.

35. The method of claim **30**, wherein the controlled release formulation is composed of granules, hydrogels, matrix formulations, and combinations thereof.

36. The method of claim **30**, wherein the controlled release formulation comprises about 5 mg to about 15 mg phentermine and about 100 mg to 200 mg topiramate.

37. The method of claim **30**, further including a barrier between the core and the coating to limit drug release from the core.

38. A method for effecting weight loss in a subject, comprising administering to the subject: (a) a daily dose of phentermine in the range of about 5 mg to 15 mg; and (b) a therapeutically effective amount of topiramate that is gradually increased, over an extended time period, from an initial daily dosage up to a final daily dosage suitable for continued maintenance therapy, wherein the final daily dosage is in the range of about 50 mg to 250 mg.

39. The method of claim **38**, wherein the initial daily dosage is about 25 mg.

40. The method of claim **38**, wherein the final daily dosage is in the range of about 100 mg to 250 mg.

41. The method of claim **40**, wherein the final daily dosage is in the range of about 100 mg to 200 mg.

42. The method of claim **39**, wherein the final daily dosage is in the range of about 100 mg to 250 mg.

43. The method of claim **42**, wherein the final daily dosage is in the range of about 100 mg to 200 mg.

44. The method of claim **38**, wherein the therapeutically effective amount of topiramate administered to the subject is increased on an approximately weekly basis over said extended time period.

45. The method of claim **44**, wherein the topiramate is administered at an initial daily dosage of 25 mg 5–7 days, at 50 mg daily for the next 5–7 days, at 100 mg daily for the

next 6–8 days, and about 100 mg to 150 mg daily for the next 20–26 days, and then at a maintenance dose of 100 mg to 200 mg daily.

46. A method of treating at least one side effect associated with obesity comprising administering to an obese subject a therapeutically effective daily dose of topiramate in the range of about 50 mg to 250 mg daily and a therapeutically effective daily dose of phentermine in the range of about 5 mg to 15 mg, such that at least one side effect associated with obesity is effectively treated.

47. The method of claim **46**, wherein the daily dose of topiramate is in the range of about 100 to 250 mg.

48. The method of claim **47**, wherein the daily dose of topiramate is in the range of about 100 mg to 200 mg.

49. A kit comprising a packaged combination of phentermine and topiramate, and instructions for a patient to carry out drug administration to achieve weight loss, wherein the phentermine and topiramate are present in separate and discrete dosage forms, and further wherein the topiramate dosage forms each contain about 50 mg to 250 mg topiramate and the phentermine dosage forms each contain about 5 mg to 15 mg phentermine.

50. The kit of claim **49**, wherein the topiramate dosage forms each contain about 100 mg to 250 mg topiramate.

51. The kit of claim **50**, wherein the topiramate dosage forms each contain about 100 mg to 200 mg topiramate.

52. A kit comprising a sealed package of controlled release dosage forms each containing about 50 mg to 250 mg topiramate and about 5 mg to 15 mg phentermine, wherein the dosage forms provide for immediate release of the phentermine and delayed release of the topiramate.

53. The kit of claim **52**, wherein the dosage forms each contain about 100 mg to 250 mg topiramate.

54. The kit of claim **53**, wherein the dosage forms each contain about 100 mg to 200 mg topiramate.

* * * * *

EXHIBIT B

US007553818B2

(12) **United States Patent**
Najarian

(10) **Patent No.: US 7,553,818 B2**
(45) **Date of Patent: *Jun. 30, 2009**

(54) **COMBINATION THERAPY FOR EFFECTING WEIGHT LOSS AND TREATING OBESITY**

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(63) Continuation-in-part of application No. 10/454,368, filed on Jun. 3, 2003, now Pat. No. 7,056,890, which is a continuation-in-part of application No. 09/593,555, filed on Jun. 14, 2000, now abandoned.

(60) Provisional application No. 60/181,265, filed on Feb. 9, 2000, provisional application No. 60/178,563, filed on Jan. 26, 2000, provisional application No. 60/139,022, filed on Jun. 14, 1999.

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A61K 31/135 (2006.01)
A61K 31/70 (2006.01)

(52) **U.S. Cl.** **514/23**; 514/646

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

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(57) **ABSTRACT**

The present invention features a novel therapy for effecting weight loss which involves treating a subject with a sympathomimetic agent (e.g., phentermine or a phentermine-like drug) in combination with an anticonvulsant sulfamate derivative (e.g., topiramate) such that the subject experiences weight loss.

The combination methods of the present invention also are effective against symptoms associated with Syndrome X. The invention also features pharmaceutical compositions and kits for use in the practice of these novel therapies.

24 Claims, No Drawings

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COMBINATION THERAPY FOR EFFECTING WEIGHT LOSS AND TREATING OBESITY

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. patent application Ser. No. 10/454,368, filed Jun. 3, 2003, which is a continuation-in-part of U.S. patent application Ser. No. 09/593,555, filed Jun. 14, 2000, now abandoned, which claims priority under 35 U.S.C. §119(e)(1) to provisional U.S. Patent Application Ser. No. 60/139,022, filed Jun. 14, 1999, Ser. No. 60/178,563, filed Jan. 26, 2000, and Ser. No. 60/181,265, filed Feb. 9, 2000. The aforementioned patent applications are incorporated herein by reference in their entireties.

BACKGROUND OF THE INVENTION

About 97 million adults in the United States are overweight or obese. The medical problems caused by overweight and obesity can be serious and often life-threatening, and include diabetes, shortness of breath, gallbladder disease, hypertension, elevated blood cholesterol levels, cancer, arthritis, other orthopedic problems, reflux esophagitis (heartburn), snoring, sleep apnea, menstrual irregularities, infertility and heart trouble. Moreover, obesity and overweight substantially increase the risk of morbidity from hypertension, dyslipidemia, type 2 diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis and endometrial, breast, prostate, and colon cancers. Higher body weights are also associated with increases in all-cause mortality. Most or all of these problems are relieved or improved by permanent significant weight loss. Longevity is likewise significantly increased by permanent significant weight loss.

Weight loss treatments vary depending, at least in part, on the degree of weight loss one is attempting to achieve in a subject as well as on the severity of overweight or obesity exhibited by the subject. For example, treatments such as low-fat diet and/or regular exercise are often adequate in cases where a subject is only mildly overweight. Such treatments can be enhanced by controlled use of over-the-counter appetite suppressants including caffeine, ephedrine and phenylpropanolamine (Acutrim®, Dexatrim®). Moreover, prescription medications including amphetamine, diethylpropion (Tenuate®), mazindol (Mazanor®, Sanorex®), phentermine (Fastin®, Ionamin®), phenmetrazine (Preludin®), phendimetrazine (Bontrol®, Plegine®, Adipost®, Dital®, Dyrexan®, Melfiat®, Prelu-2®, Rexigen Forte®), benzphetamine (Didrex®) and fluoxetine (Prozac®) are often used in the treatment of seriously overweight and/or obese subjects or patients. However, such treatments, at best, result in only ~5-10% weight loss (when accompanied with diet and exercise). Moreover, most of these treatments ultimately prove inadequate because they are either dangerous, ineffective or quickly lose their anorexient effect.

At least one class of these prescription medications, the phentermines (Fastin®, Ionamin®), have been used as monotherapy in the treatment of obesity for about 30 years. The phentermines are members of a class of drugs known as the sympathomimetics for their ability to mimic stimulation of the central nervous system. The phentermines act on the hypothalamus, an appetite control center of the brain. Phentermine monotherapy can increase weight loss when used in combination with diet and exercise, as compared to diet and exercise alone. However, the drug loses effectiveness after about two weeks and, in fact, is not approved by the FDA for use beyond six weeks. Moreover, weight loss may not be permanent, especially after the drug is discontinued. Phentermine treatment is also associated with side effects including nervousness, irritability, headache, sweating, dry-mouth, nausea, and constipation.

In general, available weight loss drugs have limited efficacy and some clinically significant side effects. Studies of the weight loss medications dexfenfluramine (Guy-Grand, B. et al. (1989) *Lancet* 2:1142-5), orlistat (Davidson, M. H. et al. (1999) *JAMA*281:235-42), sibutramine (Bray, G. A. et al. (1999) *Obes. Res.* 7:189-98), and phentermine (Douglas, A. et al. (1983) *Int. J. Obes.* 7:591-5) have shown similar effectiveness. Studies for each demonstrated a weight loss of about 5% of body weight for drug compared with placebo. Other serious considerations limit the clinical use of these drugs. Dexfenfluramine was withdrawn from the market because of suspected heart valvulopathy, orlistat is limited by GI side effects, sibutramine can cause hypertension, and phentermine has limited efficacy.

Various combination therapies that include phentermine as one of the agents have been investigated and have met with mixed success. The phentermines were, up until around 1997, often prescribed along with fenfluramine (Pondimin®) or dexfenfluramine (Redux®), nicknamed "fen", as a combination therapy known as fen-phen. Fenfluramine is a potent releaser of serotonin from serotonergic neurons which acts on a cerebral appetite center. When combined with phentermine, fenfluramine had the effect of enhancing and extending the anorexient action of phentermine. However in 1997, the Food and Drug Administration ("FDA") asked manufacturers to withdraw Pondimin® and Redux® due to studies which strongly suggested that the drugs cause damage to the mitral valve of the heart and pulmonary hypertension.

More recently, it has been suggested that phentermine in combination with anti depressants is a potentially effective therapy for effecting weight loss, U.S. Pat. No. 5,795,895. In particular, the anti-depressants suggested for use in this new combination therapy are members of a class of compounds known as selective serotonin reuptake inhibitors (SSRIs) which include fluoxetine (Prozac®), sertraline (Zoloft®), fluvoxamine maleate (Luvox®) and trazodone hydrochloride (Desyrel®). The combination therapy is also suggested to treat coexisting depression and/or obsessive-compulsive disorder.

Phentermine has also recently been tested in combination with bupropion (Wellbutrin®) for the treatment of obesity. Bupropion is an antidepressant that inhibits dopamine reuptake, as compared to serotonin uptake. It is also used to treat Attention Deficit Disorder (ADHD), bipolar depression, chronic fatigue syndrome, cocaine addiction, nicotine addiction, and lower back pain. While bupropion alone had a modest effect as a weight loss agent (when prescribed to patients following a 1200 calorie per day diet), patients receiving phentermine in combination with bupropion experienced no greater weight loss than those receiving bupropion alone. Moreover, bupropion use has been associated with drug-induced seizures causing it to be removed from the market by the FDA for at least five years before its re-introduction in 1989.

Accordingly, there exists a need for new, more effective weight loss treatments which are accompanied by fewer adverse or undesirable side effects or less serious side effects. In particular, there exists a need for developing medical weight loss treatments which can potentially lower major endpoints such as death and/or myocardial infarction rates by

directly treating obesity rather than treating the consequences of obesity (e.g., diabetes, hypertension, hyperlipidemia), as is currently the practice.

SUMMARY OF THE INVENTION

The present invention features a novel therapy for effecting weight loss which involves treating a subject with a sympathomimetic agent in combination with an anticonvulsant sulfamate derivative such that the subject experiences weight loss. In one aspect, the sympathomimetic agent is a compound having anorectic activity (e.g., amphetamine, methamphetamine, benzphetamine, phentermine, chlorphentermine, diethylpropran, phenmetrazine, and phendimetrazine). Preferably, the sympathomimetic agent is the drug phentermine (nicknamed "phen"). In another aspect, the anticonvulsant sulfamate derivative is the drug topiramate.

The combination methods of the present invention also are effective against symptoms associated with Syndrome X. Accordingly, in another aspect the invention features methods for treating Syndrome X with a combination of a sympathomimetic agent and an anticonvulsant sulfamate derivative (e.g., phentermine and topiramate, respectively) such that at least one symptom associated with Syndrome X is affected. Moreover, the combination methods of the present invention have been shown to have beneficial side effects, such as ameliorating sleep apnea and lowering blood pressure, blood glucose, blood lipid, and Hgb A1C levels. Accordingly, in another aspect the invention features methods for treating at least one side effect associated with obesity. In a preferred embodiment, at least one side effect of obesity is treated with a combination of a sympathomimetic agent in combination with an anticonvulsant sulfamate derivative.

The invention also features pharmaceutical compositions including therapeutically effective amounts of a sympathomimetic agent in combination with an anticonvulsant sulfamate derivative. Kits including the pharmaceutical compositions of the present invention are also featured (e.g., kits including the compositions packaged in a daily dosing regimen).

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a novel combination therapy for effecting weight loss in a subject. In particular, the present invention provides methods which involve treating the subject with a therapeutically effective amount of a combination of a sympathomimetic agent (e.g., phentermine or a phentermine-like compound) and an anticonvulsant sulfamate derivative (e.g., topiramate). The methods are particularly useful for the treatment of overweight and/or obesity, as well as in the treatment of Syndrome X.

The phrase "therapeutically effective amount" as used herein refers to the amount of an agent, compound, drug, composition, or combination of the invention which is effective for producing some desired therapeutic effect upon administration to a subject or patient (e.g., a human subject or patient). The phrase "administering to a subject" or "administering to a patient" refers to the process of introducing an agent, compound, drug, composition or combination of the invention into the subject or patient's body via an art-recognized means of introduction (e.g., orally, transdermally, via injection, etc.).

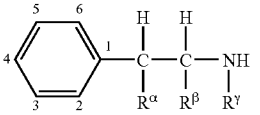
The term "sympathomimetic agent" is a term of art and refers to agents or compounds which "mimic" or alter stimulation of the sympathetic nervous system (e.g., stimulates the peripheral nervous system) of an organism (e.g., mimic the stimulation naturally effected by physical activity, psychological stress, generalized allergic reaction and other situations in which the organism is provoked).

Preferred sympathomimetic agents for use in the present invention as well as there general clinical uses or effects are set forth in Table 1.

TABLE 1

Sympathomimetic Agents and Clinical Uses Thereof

General structure:

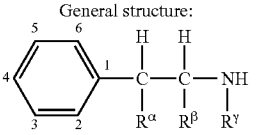


Agent name	Ring substituent(s)	R^{α}	R^{β}	R^{γ}	Main Clinical Uses: α Receptor A N P V	Main Clinical Uses: β Receptor B C	CNS, 0
Phenylethylamine		H	H	H			
Epinephrine	3-OH, 4-OH	OH	H	CH_3	A, P, V	B, C	
Norepinephrine	3-OH, 4-OH	OH	H	H	P		
Epinine	3-OH, 4-OH	H	H	CH_3			
Dopamine	3-OH, 4-OH	H	H	H	P		
Dobutamine	3-OH, 4-OH	H	H	1*		C	
Nordefrin	3-OH, 4-OH	OH	CH_3	H	V		
Ethylnorepinephrine	3-OH, 4-OH	OH	CH_2CH_3	H		B	
Isoproterenol	3-OH, 4-OH	OH	H	$CH(CH_3)_2$		B, C	
Protokylol	3-OH, 4-OH	OH	H	2*		B	
Isoetharine	3-OH, 4-OH	OH	CH_2CH_3	$CH(CH_3)_2$		B	
Metaproterenol	3-OH, 5-OH	OH	H	$CH(CH_3)_2$		B	
Terbutaline	3-OH, 5-OH	OH	H	$C(CH_3)_3$		B	
Metaraminol	3-OH	OH	CH_3	H	P		
Phenylephrine	3-OH	OH	H	CH_3	N, P		
Tyramine	4-OH	H	H	H			
Hydroxyamphetamine	4-OH	H	CH_3	H	N, P	C	
Methoxyphenamine	2-OCH_3	H	CH_3	CH_3		B	
Methoxamine	2-OCH_3, 5-OCH_3	OH	CH_3	H	P		

TABLE 1-continued

Sympathomimetic Agents and Clinical Uses Thereof

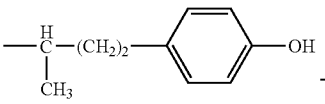
General structure:



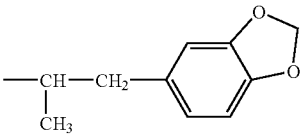
Main Clinical Uses

Agent name	Ring substituent(s)	R^{α}	R^{β}	R^{γ}	α Receptor A N P V	β Receptor B C	CNS, 0
Albuterol	3-CH_2OH, 4-OH	OH	H	$C(CH_3)_3$		B	
Amphetamine		H	CH_3	H			CNS, 0
Methamphetamine		H	CH_3	CH_3	P		CNS, 0
Benzphetamine		H	CH_3	—$NHR^{\gamma}$is replaced with 3*			0
Ephedrine		OH	CH_3	CH_3	N, P	B, C	
Phenylpropanolamine		OH	CH_3	H	N		
Mephentermine		H	—CHR^{β}— is replaced with 4*	CH_3	N, P		
Phentermine		H	—CHR^{β}— is replaced with 4*	H			0
Chlorphentermine	4-Cl	H	—CHR^{β}— is replaced with 4*	H			0
Fenfluramine	3-CF_3	H	CH_3	C_2H_5			0
Propylhexedrine	5*: phenyl ring is replaced with cyclohexyl	H	CH_3	CH_3	N		
Diethylpropion		6*: The substituent at the 1-position is replaced with 6, below.					0
Phenmetrazine		7*: The substituent at the 1-position is replaced with 7, below.					0
Phendimetrazine		8*: The substituent at the 1-position is replaced with 8, below.					0

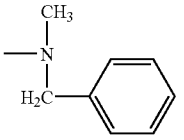
*1:



*2:



*3:



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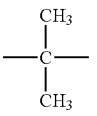
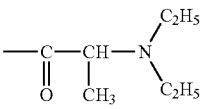
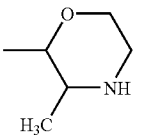


*5:

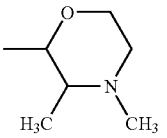
*6:



*7:



*8:



α Activity
A = Allergic reactions (includes β action)
N = Nasal decongestion
P = Pressor (may include β action)
V = Other local vasoconstriction (e.g. in local anesthesia)

β Activity
B = Bronchodilator
C = Cardiac

CNS = Central nervous system
0 = Anorectic

*Numbers bearing an asterisk refer to the substituents numbered in the bottom rows of the table; substituent 5 replaces the phenyl rings, and 6, 7 and 8 are attached directly to the phenyl ring, replacing the ethylamine side chain.
†The α and β in the prototype formula refer to positions of the C atoms in the ethylamine side chain.

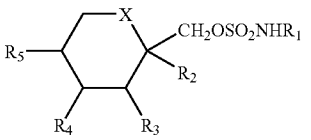
In preferred embodiments, the sympathomimetic agent has anorexient properties (e.g., suppresses appetite) or is anorectic without significant toxicity to a subject or patient (e.g., a human) at therapeutically effective doses. In a more preferred embodiment, the sympathomimetic agent has anorexient properties (e.g., suppresses appetite) or is anorectic without loss of efficacy or without adverse or undesirable side effects to a subject or patient (e.g., a human subject or patient) at therapeutically effective doses when prescribed in combination with topiramate. In yet another embodiment, the sympathomimetic agent is phentermine or a phentermine-like compound. As defined herein, a "phentermine-like compound" is a compound structurally related to phentermine (e.g., an analog or derivative) which maintains an anorectic

activity similar to that of phentermine. A preferred phentermine-like compound is chlorphentermine. In yet another embodiment, the sympathomimetic agent is amphetamine or an amphetamine-like compound. As used herein, an "amphetamine-like compound" is a compound structurally related to amphetamine (e.g., an analog or derivative) which maintains an anorectic effect of amphetamine. In yet another embodiment, the sympathomimetic agent is phenmetrazine or a phenmetrazine-like compound. As defined herein, a "phenmetrazine-like compound" is a compound structurally related to phenmetrazine (e.g., an analog or derivative) which maintains an anorectic effect of phenmetrazine. A preferred phenmetrazine-like compound is phendimetrazine. Analogs and/or derivatives of the compounds of the present invention can be tested for their ability to suppress appetite (e.g., suppress food intake) in a subject (e.g., a mammalian subject).

In an exemplary preferred embodiment, the sympathomimetic agent is selected from the group consisting of amphetamine, methamphetamine, benzphetamine, phenylpropanolamine, phentermine, chlorphentermine, diethylpropion, phenmetrazine, and phendimetrazine (as set forth in Table 1. In a particularly preferred embodiment, the sympathomimetic agent is phentermine. It is also within the scope of the present invention to utilize other sympathomimetic agents including pseudo ephedrine (a stereoisomer of ephedrine, SUDAFED®), methylphenidate (RITALIN®), tuaminoheptane, and other CNS stimulants including, for example, caffeine.

The terms "anticonvulsant sulfamate derivative" and "anticonvulsant sulfamate derivatives" are terms of art and refer to a class of sulfamate-derived compounds that possess anticonvulsant activity and have an art-recognized use in the treatment of epilepsy. In particular, the anticonvulsant sulfamate derivatives are monosaccharide derivatives with sulfamate functionality. The anticonvulsant sulfamate derivatives for use in the present invention have one or more of the following modes of activity: modulation of voltage-dependent sodium conductance; potentiation of gamma-aminobutyric acid-evoked currents; inhibition of the kainate/alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) subtype of the glutamate receptor; and/or inhibition of carbonic anhydrase (e.g, a mechanism by which the anticonvulsant derivative of the present invention may decrease the sensation of taste). The anticonvulsant sulfamate derivatives for use in the present invention are described further in U.S. Pat. Nos. 4,513,006, 5,384,327, 5,498,629, 5,753,693 and 5,753,694, as are methods of synthesizing such anticonvulsant sulfamate derivatives. The aforementioned patents are incorporated by reference herein in their entireties.

In preferred embodiments, the anticonvulsant sulfamate derivative is a compound having the following formula (I):



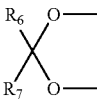
(I)

wherein:

X is CH_2 or O;

R_1 is H or alkyl; and

R_2, R_3, R_4 and R_5 are independently H or lower alkyl, with the proviso that when X is O, then R_2 and R_3 and/or R_4 and R_5 together may be a methylenedioxy group of the following formula (II):



(II)

in which R_6 and R_7 are the same or different and are H or lower alkyl, or are joined to form a cyclopentyl or cyclohexyl ring.

R_1 in particular is hydrogen or alkyl of about 1 to 4 carbons, such as methyl, ethyl, or isopropyl. Alkyl includes both straight and branched chain alkyl. Alkyl groups R_2, R_3, R_4, R_5, R_6 and R_7 are about 1 to 3 carbons and include methyl, ethyl, isopropyl and n-propyl.

A particular group of compounds of the formula (I) are those wherein X is oxygen and both R_2 and R_3, and R_4 and R_5 together are methylenedioxy groups of the formula (II), wherein R_6 and R_7 are both hydrogen, both alkyl, or combine to form a spiro cyclopentyl or cyclohexyl ring, in particular, where R_6 and R_7 are both alkyl such as methyl. A second group of compounds are those wherein X is CH_2 and R_4 and R_5 are joined to form a benzene ring. A third group of compounds of the formula (I) are those wherein both R_2 and R_3 are hydrogen.

In preferred embodiments, the anticonvulsant sulfamate derivatives have anorexient properties (e.g., suppress appetite) without significant toxicity to a subject or patient (e.g., a human) at therapeutically effective doses. In a more preferred embodiment, the anticonvulsant sulfamate derivatives have anorexient properties (e.g., suppress appetite) without significant adverse or undesirable side effects to a subject or patient (e.g., a human) at therapeutically effective doses when prescribed in combination with phentermine. In a particularly preferred embodiment the anticonvulsant sulfamate derivative is topiramate (Topamax®). Topiramate, also referred to in the art as 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate, has been demonstrated in clinical trials of human epilepsy to be effective as an adjunctive therapy or as monotherapy in treating simple and complex partial seizures and secondarily generalized seizures (E. Faught et al. (1995) *Epilepsia* 36(suppl 4):33; S. Sachdeo et al. (1995) *Epilepsia* 36(suppl 4):33) and is currently marketed for the treatment of simple and complex partial seizure epilepsy with or without secondary generalized seizures.

Dosages, Administration and Pharmaceutical Compositions:

The choice of appropriate dosages for the drugs used in combination therapy according to the present invention can be determined and optimized by the skilled artisan, e.g., by observation of the patient, including the patient's overall health, the response to the combination therapy, and the like. Optimization, for example, may be necessary if it is determined that a patient is not exhibiting the desired therapeutic effect or conversely, if the patient is experiencing undesirable or adverse side effects that are too many in number or are of a troublesome severity.

Preferably, a sympathomimetic drug (e.g., a drug set forth in Table 1) is prescribed at a dosage routinely used by the skilled artisan (e.g., physician) to promote the desired therapeutic effect of the drug, when the drug is used as a monotherapy. Preferably, an anticonvulsant sulfamate derivative

(e.g., a compound having formula 1) is prescribed at a lower dosage than routinely used by the skilled artisan (e.g., physician) to promote the desired therapeutic effect of the drug, when the drug is used as a monotherapy (e.g., in the treatment of epilepsy). In a preferred embodiment, a sympathomimetic drug or anticonvulsant sulfamate derivative is prescribed at a dose of between 5-1000, preferably between 10-1500, more preferably between 20-1000 and most preferably between 25-50 mg daily.

It is especially advantageous to formulate compositions of the invention in unit dosage form for ease of administration and uniformity of dosage. The term "unit dosage forms" as used herein refers to physically discrete units suited as unitary dosages for the individuals to be treated. That is, the compositions are formulated into discrete dosage units each containing a predetermined, "unit dosage" of an active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specifications of the novel dosage unit forms of the invention are dependent on the unique characteristics of the composition containing the anticonvulsant or sympathomimetic agent and the particular therapeutic effect to be achieved. Dosages can further be determined by reference to the usual dose and manner of administration of the ingredients. It is also within the scope of the present invention to formulate a single physically discrete dosage form having each of the active ingredients of the combination treatment (e.g., a single dosage form having an anticonvulsant agent and a sympathomimetic agent).

The method of administration of compositions or combinations of the invention will depend, in particular, on the type of sympathomimetic agent used and the chosen anticonvulsant sulfamate derivative. The sympathomimetic agent and the anticonvulsant sulfamate derivative may be administered together in the same composition or simultaneously or sequentially in two separate compositions. Also, one or more sympathomimetic agents or one or more anticonvulsant sulfamate derivatives may be administered to a subject or patient either in the form of a therapeutic composition or in combination, e.g., in the form of one or more separate compositions administered simultaneously or sequentially. The schedule of administration will be dependent on the type of sympathomimetic agent(s) and anticonvulsant sulfamate derivative(s) chosen. For example, a sympathomimetic agent can have a stimulant effect and the degree of such stimulant effect may vary depending on the sympathomimetic agent chosen. Accordingly, a sympathomimetic agent having a significant stimulant effect might be administered earlier in the day than administration of a sympathomimetic agent having a lesser stimulant effect. Likewise, an anticonvulsant sulfamate derivative can have a sedative effect and the degree of such sedative effect may vary depending on the anticonvulsant sulfamate derivative chosen. Accordingly, an anticonvulsant sulfamate derivative having a significant sedative effect might be administered later in the day than administration of an anticonvulsant sulfamate derivative having a lesser sedative effect. Moreover, sympathomimetic agents and/or anticonvulsant agents having lesser stimulant or sedative effects, respectively, may be administered simultaneously.

Sympathomimetic agents and/or anticonvulsant sulfamate derivatives can also be administered along with a pharmaceutically acceptable carrier. As used herein "pharmaceutically acceptable carrier" includes any solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in compositions of the invention is contemplated.

A sympathomimetic agent alone, or in combination with an anticonvulsant sulfamate derivative in the form of a composition, is preferably administered orally. When the composition(s) are orally administered, an inert diluent or an assimilable edible carrier may be included. The composition and other ingredients may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the individual's diet. For oral therapeutic administration, the composition may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The percentage of the compositions and preparations may, of course, be varied. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. In a particularly preferred embodiment, the present invention includes pharmaceutical composition comprising a therapeutically effective amount of a sympathomimetic agent and an anticonvulsant sulfamate derivative. In one embodiment, the present invention includes a therapeutically-effective amount of a sympathomimetic agent and an anticonvulsant sulfamate derivative packaged in a daily dosing regimen (e.g., packaged on cards, packaged with dosing cards, packaged on blisters or blow-molded plastics, etc.). Such packaging promotes products and increases patient compliance with drug regimens. Such packaging can also reduce patient confusion. The present invention also features such kits further containing instructions for use.

The tablets, troches, pills, capsules and the like may also contain a binder, an excipient, a lubricant, or a sweetening agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed.

A sympathomimetic agent, alone or in combination with an anticonvulsant sulfamate derivative, can also be administered in a convenient manner such as by injection (subcutaneous, intravenous, etc.), inhalation, transdermal application, or rectal administration. Depending on the route of administration, the composition containing the sympathomimetic agent and/or anticonvulsant sulfamate derivative may be coated with a material to protect the compound from the action of acids and other natural conditions which may inactivate the compounds or compositions.

To administer the compositions, for example, transdermally or by injection, it may be necessary to coat the composition with, or co-administer the composition with, a material to prevent its inactivation. For example, the composition may be administered to an individual in an appropriate diluent or in an appropriate carrier such as liposomes. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Liposomes include water-in-oil-in-water CGF emulsions as well as conventional liposomes (Strejan et al. (1984) *J. Neuroimmunol.* 7:27). To administer the compositions containing the sympathomimetic agents and/or anticonvulsant sulfamate derivatives parenterally or intraperitoneally, dispersions can be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

Compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. In all cases, the composi-

tion must be sterile and must be fluid to the extent that easy syringability exists. lt must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene gloycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents. ln many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol and sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

A preferred aspect of the present invention features prescribing phentermine in combination with topiramate to effect weight loss and/or to treat Syndrome X and/or a subset of symptoms thereof. A preferred dose for phentermine is between about 5-60 mg daily, including but not limited to doses of 8, 10, 15, 20, 25, 30, 35, 40, 45, 50 and 55 mg daily. A particularly preferred dose for phentermine is about 15 mg daily. ln an exemplary embodiment, the phentermine is of an immediate release form.

Preferably, the phentermine is taken by the patent in the morning and more preferably, is taken before breakfast. The phentermine is best taken in the morning because the drug is a stimulant as well as an appetite suppressant. When phentermine is prescribed (e.g., as part of the combination therapy described herein), physicians should be aware and may want to advise patients that the drug can be mildly habit forming. Phentermine can also cause increased nervousness, increased energy, irritability and, rarely, insomnia. Stopping phentermine may also cause tiredness lasting for up to 1-2 weeks. Phentermine can also raise blood pressure (e.g., during the early phases of treatment).

A preferred dose for topiramate is between about 50-1500 mg daily. As discussed previously, prescription of topiramate at dosages of ≧400 mg daily results is promotion of undesirable side effects (e.g., sedation, mental clouding). Accordingly, in a preferred embodiment, topiramate is prescribed at a dose of about 50-400 mg daily. ln another preferred embodiment, the dosage of topiramate is increased gradually at the outset of the therapy in order to reduce the chance of undesirable side effects associated with higher doses of the drug. ln an exemplary embodiment, the topiramate is administered at a dose of 25 mg daily for about the first 5-7 days (e.g., 6 days) of treatment, at a dose of about 50 mg daily for the next 5-7 days (e.g., 6 days), at a dose of 100 mg daily for about the next 6-8 days (e.g., 7 days) and about 150 mg daily for the next 20-26 days. From this point forward, the topiramate can be administered at a dose of 150-250 mg daily, including but not limited to doses of 175, 200, and 225 mg daily. A particularly preferred dose for continued therapy is about 200 mg of topiramate daily. ln another exemplary embodiment, the topiramate is of an immediate release form. ln yet another exemplary embodiment, the topiramate is of a sustained release form.

ln a preferred embodiment, topiramate is taken later in the day than the phentermine. Preferably, the patient takes the topiramate just before supper or later in the evening. Topiramate is best given later in the day because the drug can be sedating. ln other embodiments, the topiramate is given BlD (e.g., twice daily), TlD (three times daily) or QlD (four time daily). When prescribing topiramate, physicians should be aware and may want to advise patients that the drug can cause tiredness, fatigue, dizziness, difficulty with speech or finding words, difficulty concentrating, difficulty with balance, and/or numbness or tingling in the hands or feet. Less common side effects are nausea, coordination problems, abdominal pain, slowed thinking nervousness, depression, breast pain, painful periods, double or blurred vision, palpitations, low white blood count and kidney stones. A physician should also advise patients that the drug may not be taken if the patient is also taking Diamox (acetazolamide). No female patient should become pregnant while taking this drug as it may cause birth defects. lf a female patient misses a period she should immediately discontinue taking the medication and inform the physician. Female patients should not be treated according to the methods of the present invention if breast feeding a child. Patients should not drink alcohol or take sedating medications while taking topiramate since excess sedation can occur. Patients should also refrain from performing dangerous tasks (e.g. operating heavy machinery or driving) until they are comfortable with the side effects of the full dose (e.g., 200-400 mg daily). Patients should be advised not to increase the dosage beyond what is prescribed. Topiramate is not habit forming.

Yet another embodiment of the present invention features pharmaceutical compositions (e.g., for oral administration) comprising phentermine and topiramate in a single pharmaceutical formulation. Such compositions may be preferred, for example, to increase patient compliance (e.g., by reducing the number of administrations necessary to achieve the desired pharmacologic effect).

ln a preferred embodiment, the pharmaceutical composition includes phentermine in an immediate release form and further includes topiramate in a controlled release formulation. As defined herein, an "immediate release formulation" is one which has been formulated to allow, for example, the phentermine, to act as quickly as possible. Preferred immediate release formulations include, but are not limited to, readily dissolvable formulations. As defined herein, a "controlled release formulation" includes a pharmaceutical formulation that has been adapted such that drug release rates and drug release profiles can be matched to physiological and chronotherapeutic requirements or, alternatively, has been formulated to effect release of a drug at a programmed rate. Preferred controlled release formulations include, but are not limited to, granules, delayed release granules, hydrogels (e.g., of synthetic or natural origin), other gelling agents (e.g., gel-forming dietary fibers), matrix-based formulations (e.g., formulations comprising a polymeric material having at least one active ingredient dispersed therethrough), granules within a matrix, polymeric mixtures, granular masses, and the like.

ln one embodiment, a controlled release formulation is a delayed release form. As defined herein, a "delayed release form" is formulated in such a way as to delay, for example, topiramate's action for an extended period of time. A delayed release form can be formulated in such a way as to delay the release of an effective dose of topiramate for 4, 8, 12, 16 or 24 hours following the release of phentermine. ln yet another preferred embodiment, a controlled release formulation is a sustained release form. As defined herein, a "sustained release form" is formulated in such a way as to sustain, for example, the topiramate's action over an extended period of time. A sustained release form can be formulated in such a

way as to provide an effective dose of topiramate (e.g., provide a physiologically effective blood level) over a 4, 8, 12, 16 or 24 hour period.

Preferred compositions include a tablet core consisting essentially of topiramate, said core being in association with a layer of phentermine. Preferably, the core has a delayed or sustained dissolution rate. In an exemplary embodiment, a tablet can comprise a first layer containing, for example, phentermine (e.g., in an immediate release formulation) and a core containing, for example, topiramate in a delayed release or sustained release formulation. Other exemplary embodiments can include, for example, a barrier between the first layer and core, said layer serving the purpose of limiting drug release from the surface of the core. Preferred barriers prevent dissolution of the core when the pharmaceutical formulation is first exposed to gastric fluid. For example, a barrier can comprise a disintegrant, a dissolution-retarding coating (e.g., a polymeric material, for example, an enteric polymer), or a hydrophobic coating or film, and can be selectively soluble in either the stomach or intestinal fluids. Such barriers permit the topiramate to leach out slowly and can cover substantially the whole surface of the core.

The above-described pharmaceutical compositions are designed to release the two effective agents of the combination therapy of the present invention sequentially, i.e., releasing topiramate after releasing phentermine, both agents being contained in the same pharmaceutical composition. Preferred amounts of phentermine and topiramate are as described above with particularly preferred compositions comprising from about 5 mg to about 60 mg phentermine and from about 50 mg to 1500 mg topiramate. Particularly preferred compositions include at least 15 mg phentermine and at least about 50 mg, 100 mg or 200 mg topiramate.

Pharmaceutical compositions so formulated may contain additional additives, suspending agents, diluents, binders or adjuvants, disintegrants, lubricants, glidants, stabilizers, coloring agents, flavors, etc. These are conventional materials which may be incorporated in conventional amounts.

In one embodiment, a method of the present invention is carried out, practiced or performed such that weight loss in the subject or patient occurs. Accordingly, the methods of the present invention are particularly useful for the treatment of overweight or obese patients. As defined herein, "overweight" subjects or patients are between about 1 and 20 percent overweight (e.g., weighs 1-20% in excess of their ideal body weight). Also as defined herein, an "obese" subject or patient is greater than 20 percent overweight (e.g., weighs>20% in excess of his or her ideal body weight). Alternatively, the methods of the present invention are useful in the treatment of subjects or patients in need of losing weight, but who are not necessarily overweight or obese. For example, it may be desirable to achieve weight loss in subjects or patients having arthritis or prostheses such that the individual experiences less adverse effects resulting from bearing weight.

The combination therapies of the present invention will generally be administered until the patient has experienced the desired weight loss, and preferably has achieved an ideal body weight. Alternatively, the combination therapies of the present invention can be administered until the patient has achieved a weight loss of 5-10%, 10-15%, 15-20% or 20-25% of their initial body mass (e.g., the patient's starting weight).

The present inventor has also recognized that the combination therapy of the present invention ameliorates symptoms associated with Syndrome X. Syndrome X consists of a complex of medical problems that are largely associated with obesity, including, hypertension, diabetes or glucose intolerance and insulin resistance, hyperlipidemia, and often tiredness and sleepiness associated with sleep apnea. Patients are often treated with combinations of antihypertensives, lipid lowering agents, insulin or oral diabetic drugs, and various mechanical and surgical treatments of sleep apnea. However, such treatments are often costly and do not treat the underlying problem of obesity. Moreover, some of the treatments for diabetes, including insulin and oral diabetic agents, actually aggravate Syndrome X by increasing insulin levels, increasing appetite, and increasing weight. This can lead to higher blood pressure and even higher cholesterol. Accordingly, one aspect of the present invention features a method of treating Syndrome X using the combination therapies described herein. In one embodiment, the invention features a method of treating Syndrome X in a subject or patient which includes treating the subject with a therapeutically effective amount of a combination of an anticonvulsant sulfamate derivative (e.g., topiramate) and a sympathomimetic agent (e.g., phentermine or a phentermine-like compound), such that at least one symptom associated with Syndrome X is affected. As defined herein, "affecting a symptom" (e.g., affecting a symptom associated with Syndrome X) refers to lessening, decreasing the severity of the symptom or reversing, ameliorating, or improving the symptom (e.g., decreasing hypertension, ameliorating diabetes, reversing glucose intolerance or insulin resistance, lessening hyperlipidemia, or decreasing tiredness and sleepiness associated with sleep apnea).

Treatment of Syndrome X according to the methods of the present invention includes affecting at least one, preferably two, more preferably three, more preferably four, five or six symptoms associated with Syndrome X. In a particularly preferred embodiment, all symptoms associated with Syndrome X are affected (e.g., lessened, reversed, ameliorated, etc.).

The present inventor has also recognized that the combination therapy of the present invention ameliorates some side effects associated with obesity, as described herein. Accordingly, one aspect of the present invention features a method of treating at least one side effect associated with obesity using the combination therapies described herein. In one embodiment, the invention features a method of treating at least one obesity-related side effect in a subject or patient which includes treating the subject with a therapeutically effective amount of a combination of an anticonvulsant sulfamate derivative (e.g., topiramate) and a sympathomimetic agent (e.g., phentermine or a phentermine-like compound), such that at least one obesity-related side effect is effected. As defined herein, a "side effect associated with obesity" includes a symptom or disorder in a subject (e.g., a patient) which is secondary and/or results from (e.g., directly and/or indirectly results from) a medical condition for which the subject is obese and/or being treated. In a preferred embodiment, the subject is obese and/or is being treated for obesity. In another embodiment, the subject has at least one or more (e.g., two, three, four, five or more) side effect(s) selected from the group consisting of sleep apnea, high blood pressure and high blood sugar, high blood lipid, high HgbA1C or other art-recognized side effects associated with obesity.

Whether in the treatment of Syndrome X or in the practicing of the methods of the present invention to effect weight loss (e.g., in the treatment of overweight and/or obesity) or in treatment of side effects associated with obesity, it will be apparent to the skilled artisan (e.g., physician) that monitoring of the patient is needed to determine the effectiveness of the treatments and to potentially modify the treatments (e.g., modify the dosing, time of drug administration, sequence of drug administration, as defined herein). Accordingly, in certain embodiments, the patient is monitored about every 2-6,

preferably every 3-5 and more preferably every 4 weeks. Monitoring the effective of treatment to achieve weight loss includes, but is not limited to monitoring the subject or patient's body weight (e.g., comparing the patient's initial body weight to that at a follow-up visit, for example, four weeks after the initiation of treatment). Additional features of the subject or patient's health can also be monitored (i.e., monitoring the patient's overall health and/or monitoring the effectiveness of treatment of an undesired side effect of obesity) including, but not limited to the patient's blood pressure, blood sugar, serum lipid levels, etc. Likewise, monitoring a subject or patient for treatment of Syndrome X can include monitoring of at least one, preferably more than one symptom associated with Syndrome X.

This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patents and published patent applications cited throughout this application are hereby incorporated by reference.

EXAMPLE 1

Patients as part of the following trial were treated according to the following dosage regimen. Patients took phentermine at a dose of 15 mg daily throughout the weight loss program, before breakfast. For the first 6 days, patients took one 25 mg tablet of topiramate before supper. For the next 6 days, patients took two 25 mg tablets of topiramate before supper. For the next 7 days (days 13-19), patients took 100 mg before supper daily using 4-25 mg tablets of topiramate daily. For days 20-26, patients took 150 mg of topiramate daily consisting of one-half of a 200 mg tablet and two 25-mg mg tablets of topiramate. From that point on, unless instructed otherwise by the physician, patients continued to take one 200 mg topiramate tablet daily before supper and continued the 15 mg phentermine daily in the morning. Patients were advised to drink at least eight (8) full glasses of water daily to reduce the risk of kidney stones which may result from taking topiramate.

Patients were advised that while the effect of phentermine is fairly rapid, the effect of topiramate is slower in onset. The weight reduction effect of topiramate will continue for as long as 18 months on the medication. That is, the patient can expect to continue gradual weight loss for up to 18 months on the medication. Of course, weight loss is maximal if the patient follows diet and/or exercise programs. The weight loss should exceed 15% of the patients starting weight. Thus, if the patient weighs about 200 pounds as of the start date, he/she might expect to lose at least 30 pounds in a period of 12-18 months. The following patient data has been collected.

TABLE 11

Patient's Initials	Age	Sex	Start Weight (lbs)	Start Blood Pressure	Follow-Up Date	Follow-Up Weight (lbs)	% Weight Loss	Follow-Up Blood Pressure
M.O.[1]	48	F	182	115/70	5 weeks	177	2.7%	120/80
					9 weeks	176	3.3%	110/70
T.M.	37	F	190	122/84	2 weeks, 5 days	178	6.3%	110/80
					6 weeks, 2 days	168	11.6%	125/80
D.M.(A)	28	M	286	138/90	4 weeks	279	2.4%	128/86
P.L.	55	F	144	132/84	4 weeks	141	2.1%	138/85
					9 weeks	137	4.9%	122/82
E.K.	52	F	181	130/100	5 weeks	175	3.3%	140/88
I.F.	41	F	196	95/60	6 weeks, 5 days			
D.M.(B)[2]	56	M	295	150/80	4 weeks, 2 days	297	(+0.7%)	148/82
					8 weeks, 2 days	287	2.7%	140/70

[1]Patient M.O. was being treated with Meridia ® at the onset of the study, which continued through the first 5 weeks of the study. At the 5-week follow up, M.O. was switched to the phentermine/topiramate regime described above.
[2]Patient D.M.(B) was being treated with phentermine alone at the onset of the study and was taking the full dose of topiramate by the fourth week of the study.

As is apparent from the above-described data, patients not previously treated with an anorexient at the outset of the study experienced an average of about 3.5% weight loss after only 2-6 weeks (e.g., patient T.M. lost 6.3% body weight, patient D.M.(A) lost 2.4% body weight, patient P.L. lost 2.1% body weight and patient E.K. lost 3.3% body weight). After only 6-9 weeks of treatment, patients (not previously treated with an anorexient at the outset of the study experienced an average of about 8.3% weight loss (e.g., patient T.M. lost 11.6% body weight and patient P.L. lost 4.9% body weight). The patient previously on Meridia® (patient M.O.) lost 3.3% body weight after being enrolled in the program for 9 weeks. Moreover, the patient previously on phentermine (patient D.M.(B)) lost a total of 2.7% body weight after being enrolled in the program for about 8 weeks. This particular patient reported that this is the most significant weight loss he has achieved to date, the patient having previously tried other conventional therapies.

In addition to the weight loss reported above, almost all patients enrolled in the study experienced decreased blood pressure. Moreover, patients involved in the study who had previously taken Redux, phen-fen, Meridia and/or other weight loss treatments report that they have not previously experienced the benefits of the combined phentermine/topiramate therapy. Patients report that they have no appetite, can resist food easily, can concentrate and function at work (even in attention-intensive jobs such as computer programming), have more energy and feel better. Patients also report experiencing fewer side effects than any previous weight loss treatments tried.

EXAMPLE 2

Extended results of the trial described in Example 1.

A total of thirteen patients were treated for 1-9 months with phentermine (15 mg daily) in the morning and up to 400 mg of topiramate (median dose 200 mg), in the evening. [Note: Patient D.M.(B) discussed above is not included in this data as he was on phentermine treatment prior to treatment with the combination therapy of the present invention.] Topiramate dose was gradually increased from 25 mg per day in increments of 25-50 mg weekly until either desirable weight loss took place or until side effects limited dose increases. [Note: A fourteenth patient discontinued treatment after 3 days due to nausea.] All thirteen patients tolerated treatment well with minimal side effects. Along with taking medication, patients were instructed to walk at least 30 minutes three times per week and to follow a low fat diet. No patients had taken diet medication for at least 3 months prior to treatment. Average baseline BMI was 32.5 (range 26-48).

Average weight loss for the thirteen patients was 11.8%. For seven patients who were on treatment the longest (range 5-9 months), the average weight loss was 14.4%. Patients reported that they had little or no appetite and that they actually felt better (Topiramate's usefulness is also being investigated as a mood stabilizer) than before therapy. Blood pressure, lipid, glucose, and Hgb A1C values were also favorably affected by this treatment.

Table lll sets forth patient data for the thirteen above-described patients treated with the combination therapy of the present invention.

TABLE lll

Patient Data: Combination Therapy*

Patient No.	% of Weight Loss	Baseline BMI	Current BMI	Weeks on Rx	Current Status
1	7.7	38	35	10	on Rx
2	10.3	25	23	4	Finished
3	6.8	48	44	5	d/c early - dropped out
4	16.8	30	24	35	on taper
5	23.2	30	23	41	on taper
6	8	41	38	40	on Rx
7	9.7	28	25	33	on taper
8	14.4	30	26	44	on Rx
9	15.9	27	21	32	on taper
10	9	33	31	7	d/c early - will restart
11	12.9	28	24	22	Finished
12	7	29	27	5	on Rx
13	12.1	34	31	6	on Rx

*data for thirteen patients
Average weight loss = 11.8% (13 patients)
Average weight loss ≧ 22 weeks on Rx = 14.4% (7 patients)
Average baseline BMI = 32.4

Table lV sets forth for the average blood pressure, blood glucose, Hgb A1C and blood lipid value for the thirteen patients.

TABLE lV

	BP mmHg	GLUCOSE mg/dL	HGBA1C %*	CHOL mg/dL	TRIG mg/dL
Average Pre-Treatment Value	131.3/ 85.9	107	6.48	212	189
Average On Treatment Value	122.6/ 78.4	102	5.05	210	172

*Numbers include 1 diabetic patient whose oral hypoglycemic was reduced by 50% while on the weight loss treatment.

One of the thirteen patients in the study also had severe sleep apnea with the usual complications of daytime sleepiness and fatigue. His symptoms have disappeared with the weight loss treatment.

Of the six patients (i.e., finished or on taper) who have completed the combination therapy of the present invention, five of the six achieved a body mass index (BMI) of 24 or better. The average pre-treatment or baseline BMI for these six patients was 28. The final average BMI was 23.3. The average weight loss was 17%.

EXAMPLE 3

The 56-year old male patient described previously (D.M.(B)) who was initially taking phentermine alone and had topiramate added to his regimen had a good effect from the combination. He once weighed as much as 395 pounds. When Redux was still on the mark in the United States, he was treated with a combination of diet, exercise, Redux and phentermine. His lowest weight attained was 285 pounds. When Redux was withdrawn from the market, he remained on phentermine but gained weight back to 295-300 pounds. When topiramate was added to his regimen, he managed to lose 25 pounds and is currently at 271 pounds, his lowest weight since he was in his 20s. He, along with most of the patients treated so far, reported that the treatment with topiramate and phentermine had fewer side effects and was more effective than any previous weight loss treatment using medications that he and others had tried. This 56-year old man exhibited lowered blood pressure (approx. 15 mm Hg systolic and 10 mm Hg diastolic).

EXAMPLE 4

Extended results of the trial described in Examples 1 and 2.

The cumulative data from a total of seventeen patients treated with the combination weight loss treatment of the present invention are set forth in Table V.

TABLE V

Patient Data: Combination Therapy*

PATIENT	% WEIGHT LOSS	BASE-LINE BMI	CURRENT BMI	WEEKS ON Rx	CURRENT STATUS
1	7.7	38	35	33	on Rx
2	10.3	25	23	4	Finished
3	6.8	48	44	5	d/c early - dropped out
4	16.8	30	24	58	on taper
5	23.2	30	23	64	on taper
6	17.5	41	33	63	on Rx
7	9.7	28	25	56	on taper
8	18.6	30	24	67	on Rx
9	15.9	27	21	55	on taper
10	9	33	31	7	d/c early - will restart
11	12.9	28	24	22	Finished
12	7	29	27	5	d/c early - will restart
13	12.1	34	31	6	d/c early - will restart
14	22.5	46	32	16	on Rx
15	10.1	50	45	12	on Rx
16	6.4	27	24	4	Finished
17	6.3	27	25	6	on Rx

*data for seventeen patients
AVERAGE WEIGHT LOSS = 12.5% (17 patients)
AVERAGE WEIGHT LOSS ≧ 22 WEEKS ON Rx = 15.3% (8 patients)
AVERAGE BASELINE BMI = 33.6

The present invention provides a novel combination therapy for the treatment of obese or overweight patients that can result in weight losses of greater than 5-10%, perhaps even as great as 15-20%. The therapy combines phentermine or a phentermine-like drug with drug previously recognized for the treatment of epileptic seizures, known as topiramate. The combination therapy results in greater initial weight loss than other recognized therapies, potential greater overall weight loss and can be continued for significant periods of time with fewer and less serious side effects than other recognized weight loss treatments. ln particular, the combination therapy far surpasses the modest anorexient effects of phentermine monotherapy and can be continued for significant periods of time without the loss of effectiveness experienced by patients being treated with phentermine alone. Moreover, the combination therapy has been found to ameliorate symptoms associated with Syndrome X and accordingly, has potential use in the treatment of Syndrome X.

Equivalents:

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

l claim:

1. A method for effecting a weight loss in a subject in need thereof comprising administering to said subject continually over a significant period of time an 8 mg daily dose of phentermine and in combination therewith a daily amount of topiramate selected to prevent the loss of effectiveness of phentermine alone.

2. The method of claim **1** wherein the significant period of time is from 4 weeks to 67 weeks.

3. The method of claim **1** wherein the daily amount of topiramate selected to prevent the loss of effectiveness of phentermine alone is at least about 50 mg.

4. The method of claim **3** wherein the daily amount of topiramate selected to prevent the loss of effectiveness of phentermine alone is from about 50 mg to about 400 mg.

5. The method of claim **1** wherein the daily amount of topiramate selected to prevent the loss of effectiveness of phentermine alone is at least about 100 mg.

6. The method of claim **1** wherein the daily amount of topiramate selected to prevent the loss of effectiveness of phentermine alone is at least about 200 mg.

7. A method for effecting weight loss in a subject in need thereof comprising administering to said subject continuously over a significant period of time a 10 mg daily dose of phentermine and in combination therewith a daily amount of topiramate selected to prevent the loss of effectiveness of phentermine alone.

8. The method of claim **7** wherein the significant period of time is from 4 weeks to 67 weeks.

9. The method of claim **7** wherein the daily amount of topiramate selected to prevent the loss of effectiveness of phenetermine alone is at least about 50 mg.

10. The method of claim **9** wherein the daily amount of topiramate selected to prevent the loss of effectiveness of phentermine alone is from about 50 mg to about 400 mg.

11. The method of claim **7** wherein the daily amount of topiramate selected to prevent the loss of effectiveness of phentermine alone is at least about 100 mg.

12. The method of claim **7** wherein the daily amount of topiramate selected to prevent the loss of effectiveness of phentermine alone is at least about 200 mg.

13. A method for effecting weight loss in a subject in need thereof comprising administering to said subject continuously over a significant period of time a 15 mg daily dose of phentermine and in combination therewith a daily amount of topiramate selected to prevent the loss of effectiveness of phentermine alone.

14. The method of claim **13** wherein the significant period of time is from 4 weeks to 67 weeks.

15. The method of claim **13** wherein the daily amount of topiramate selected to prevent the loss of effectiveness of phentermine alone is at least about 50 mg.

16. The method of claim **15** wherein the daily amount of topiramate selected to prevent the loss of effectiveness of phentermine alone is from about 50 mg to about 400 mg.

17. The method of claim **13** wherein the daily amount of topiramate selected to prevent the loss of effectiveness of phentermine alone is at least about 100 mg.

18. The method of claim **13** wherein the daily amount of topiramate selected to prevent the loss of effectiveness of phentermine alone is at least about 200 mg.

19. A method for effecting weight loss in a subject in need thereof comprising administering to said subject continuously over a significant period of time a 20 mg daily dose of phentermine and in combination therewith a daily amount of topiramate selected to prevent the loss of effectiveness of phentermine alone.

20. The method of claim **19** wherein the significant period of time is from 4 weeks to 67 weeks.

21. The method of claim **19** wherein the daily amount of topiramate selected to prevent the loss of effectiveness of phentermine alone is at least about 50 mg.

22. The method of claim **21** wherein the daily amount of topiramate selected to prevent the loss of effectiveness of phentermine alone is from about 50 mg to about 400 mg.

23. The method of claim **19** wherein the daily amount of topiramate selected to prevent the loss of effectiveness of phentermine alone is at least about 100 mg.

24. The method of claim **19** wherein the daily amount of topiramate selected to prevent the loss of effectiveness of phentermine alone is at least about 200 mg.

* * * * *

EXHIBIT C

US007659256B2

(12) **United States Patent**
Najarian

(10) **Patent No.: US 7,659,256 B2**
(45) **Date of Patent: *Feb. 9, 2010**

(54) **COMBINATION THERAPY FOR EFFECTING WEIGHT LOSS AND TREATING OBESITY**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 583 days.

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(63) Continuation-in-part of application No. 10/454,368, filed on Jun. 3, 2003, now Pat. No. 7,056,890, which is a continuation-in-part of application No. 09/593,555, filed on Jun. 14, 2000, now abandoned.

(60) Provisional application No. 60/181,265, filed on Feb. 9, 2000, provisional application No. 60/178,563, filed on Jan. 26, 2000, provisional application No. 60/139,022, filed on Jun. 14, 1999.

(51) **Int. Cl.**
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A61K 31/70 (2006.01)

(52) **U.S. Cl.** **514/23**; 514/646

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

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(57) **ABSTRACT**

The present invention features a novel therapy for effecting weight loss which involves treating a subject with a sympathomimetic agent (e.g., phentermine or a phentermine-like drug) in combination with an anticonvulsant sulfamate derivative (e.g., topiramate) such that the subject experiences weight loss.

The combination methods of the present invention also are effective against symptoms associated with Syndrome X. The invention also features pharmaceutical compositions and kits for use in the practice of these novel therapies.

29 Claims, No Drawings

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COMBINATION THERAPY FOR EFFECTING WEIGHT LOSS AND TREATING OBESITY

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. patent application Ser. No. 10/454,368, filed Jun. 3, 2003, which is a continuation-in-part of U.S. patent application Ser. No. 09/593,555, filed Jun. 14, 2000, now abandoned, which claims priority under 35 U.S.C. §119(e)(1) to provisional U.S. Patent Applications Ser. No. 60/139,022, filed Jun. 14, 1999, Ser. No. 60/178,563, filed Jan. 26, 2000, and Ser. No. 60/181,265, filed Feb. 9, 2000. The aforementioned patent applications are incorporated herein by reference in their entireties.

BACKGROUND OF THE INVENTION

About 97 million adults in the United States are overweight or obese. The medical problems caused by overweight and obesity can be serious and often life-threatening, and include diabetes, shortness of breath, gallbladder disease, hypertension, elevated blood cholesterol levels, cancer, arthritis, other orthopedic problems, reflux esophagitis (heartburn), snoring, sleep apnea, menstrual irregularities, infertility and heart trouble. Moreover, obesity and overweight substantially increase the risk of morbidity from hypertension, dyslipidemia, type 2 diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis and endometrial, breast, prostate, and colon cancers. Higher body weights are also associated with increases in all-cause mortality. Most or all of these problems are relieved or improved by permanent significant weight loss. Longevity is likewise significantly increased by permanent significant weight loss.

Weight loss treatments vary depending, at least in part, on the degree of weight loss one is attempting to achieve in a subject as well as on the severity of overweight or obesity exhibited by the subject. For example, treatments such as low-fat diet and/or regular exercise are often adequate in cases where a subject is only mildly overweight. Such treatments can be enhanced by controlled use of over-the-counter appetite suppressants including caffeine, ephedrine and phenylpropanolamine (Acutrim®, Dexatrim®). Moreover, prescription medications including amphetamine, diethylpropion (Tenuate®), mazindol (Mazanor®, Sanorex®), phentermine (Fastin®, Ionamin®), phenmetrazine (Preludin®), phendimetrazine (Bontrol®, Plegine®, Adipost®, Dital®, Dyrexan®, Melfiat®, Prelu-2®, Rexigen Forte®), benzphetamine (Didrex®) and fluoxetine (Prozac®) are often used in the treatment of seriously overweight and/or obese subjects or patients. However, such treatments, at best, result in only ~5-10% weight loss (when accompanied with diet and exercise). Moreover, most of these treatments ultimately prove inadequate because they are either dangerous, ineffective or quickly lose their anorexient effect.

At least one class of these prescription medications, the phentermines (Fastin®, Ionamin®), have been used as monotherapy in the treatment of obesity for about 30 years. The phentermines are members of a class of drugs known as the sympathomimetics for their ability to mimic stimulation of the central nervous system. The phentermines act on the hypothalamus, an appetite control center of the brain. Phentermine monotherapy can increase weight loss when used in combination with diet and exercise, as compared to diet and exercise alone. However, the drug loses effectiveness after about two weeks and, in fact, is not approved by the FDA for use beyond six weeks. Moreover, weight loss may not be permanent, especially after the drug is discontinued. Phentermine treatment is also associated with side effects including nervousness, irritability, headache, sweating, dry-mouth, nausea, and constipation.

In general, available weight loss drugs have limited efficacy and some clinically significant side effects. Studies of the weight loss medications dexfenfluramine (Guy-Grand, B. et al. (1989) *Lancet* 2:1142-5), orlistat (Davidson, M. H. et al. (1999) *JAMA* 281:235-42), sibutramine (Bray, G. A. et al. (1999) *Obes. Res.* 7:189-98), and phentermine (Douglas, A. et al. (1983) *Int. J. Obes.* 7:591-5) have shown similar effectiveness. Studies for each demonstrated a weight loss of about 5% of body weight for drug compared with placebo. Other serious considerations limit the clinical use of these drugs. Dexfenfluramine was withdrawn from the market because of suspected heart valvulopathy, orlistat is limited by GI side effects, sibutramine can cause hypertension, and phentermine has limited efficacy.

Various combination therapies that include phentermine as one of the agents have been investigated and have met with mixed success. The phentermines were, up until around 1997, often prescribed along with fenfluramine (Pondimin®) or dexfenfluramine (Redux®), nicknamed "fen", as a combination therapy known as fen-phen. Fenfluramine is a potent releaser of serotonin from serotonergic neurons which acts on a cerebral appetite center. When combined with phentermine, fenfluramine had the effect of enhancing and extending the anorexient action of phentermine. However in 1997, the Food and Drug Administration ("FDA") asked manufacturers to withdraw Pondimin® and Redux® due to studies which strongly suggested that the drugs cause damage to the mitral valve of the heart and pulmonary hypertension.

More recently, it has been suggested that phentermine in combination with anti depressants is a potentially effective therapy for effecting weight loss, U.S. Pat. No. 5,795,895. In particular, the anti-depressants suggested for use in this new combination therapy are members of a class of compounds known as selective serotonin reuptake inhibitors (SSRIs) which include fluoxetine (Prozac®), sertraline (Zoloft®), fluvoxamine maleate (Luvox®) and trazodone hydrochloride (Desyrel®). The combination therapy is also suggested to treat coexisting depression and/or obsessive-compulsive disorder.

Phentermine has also recently been tested in combination with bupropion (Wellbutrin®) for the treatment of obesity. Bupropion is an antidepressant that inhibits dopamine reuptake, as compared to serotonin uptake. It is also used to treat Attention Deficit Disorder (ADHD), bipolar depression, chronic fatigue syndrome, cocaine addiction, nicotine addiction, and lower back pain. While bupropion alone had a modest effect as a weight loss agent (when prescribed to patients following a 1200 calorie per day diet), patients receiving phentermine in combination with bupropion experienced no greater weight loss than those receiving bupropion alone. Moreover, bupropion use has been associated with drug-induced seizures causing it to be removed from the market by the FDA for at least five years before its re-introduction in 1989.

Accordingly, there exists a need for new, more effective weight loss treatments which are accompanied by fewer adverse or undesirable side effects or less serious side effects. In particular, there exists a need for developing medical weight loss treatments which can potentially lower major endpoints such as death and/or myocardial infarction rates by

directly treating obesity rather than treating the consequences of obesity (e.g., diabetes, hypertension, hyperlipidemia), as is currently the practice.

SUMMARY OF THE INVENTION

The present invention features a novel therapy for effecting weight loss which involves treating a subject with a sympathomimetic agent in combination with an anticonvulsant sulfamate derivative such that the subject experiences weight loss. In one aspect, the sympathomimetic agent is a compound having anorectic activity (e.g., amphetamine, methamphetamine, benzphetamine, phentermine, chlorphentermine, diethylpropran, phenmetrazine, and phendimetrazine). Preferably, the sympathomimetic agent is the drug phentermine (nicknamed "phen"). In another aspect, the anticonvulsant sulfamate derivative is the drug topiramate.

The combination methods of the present invention also are effective against symptoms associated with Syndrome X. Accordingly, in another aspect the invention features methods for treating Syndrome X with a combination of a sympathomimetic agent and an anticonvulsant sulfamate derivative (e.g., phentermine and topiramate, respectively) such that at least one symptom associated with Syndrome X is affected. Moreover, the combination methods of the present invention have been shown to have beneficial side effects, such as ameliorating sleep apnea and lowering blood pressure, blood glucose, blood lipid, and Hgb A1C levels. Accordingly, in another aspect the invention features methods for treating at least one side effect associated with obesity. In a preferred embodiment, at least one side effect of obesity is treated with a combination of a sympathomimetic agent in combination with an anticonvulsant sulfamate derivative.

The invention also features pharmaceutical compositions including therapeutically effective amounts of a sympathomimetic agent in combination with an anticonvulsant sulfamate derivative. Kits including the pharmaceutical compositions of the present invention are also featured (e.g., kits including the compositions packaged in a daily dosing regimen).

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a novel combination therapy for effecting weight loss in a subject. In particular, the present invention provides methods which involve treating the subject with a therapeutically effective amount of a combination of a sympathomimetic agent (e.g., phentermine or a phentermine-like compound) and an anticonvulsant sulfamate derivative (e.g., topiramate). The methods are particularly useful for the treatment of overweight and/or obesity, as well as in the treatment of Syndrome X.

The phrase "therapeutically effective amount" as used herein refers to the amount of an agent, compound, drug, composition, or combination of the invention which is effective for producing some desired therapeutic effect upon administration to a subject or patient (e.g., a human subject or patient). The phrase administering to a subject or administering to a patient refers to the process of introducing an agent, compound, drug, composition or combination of the invention into the subject or patient's body via an art-recognized means of introduction (e.g., orally, transdermally, via injection, etc.).

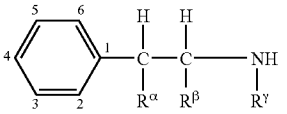
The term sympathomimetic agent is a term of art and refers to agents or compounds which "mimic" or alter stimulation of the sympathetic nervous system (e.g., stimulates the peripheral nervous system) of an organism (e.g., mimic the stimulation naturally effected by physical activity, psychological stress, generalized allergic reaction and other situations in which the organism is provoked).

Preferred sympathomimetic agents for use in the present invention as well as there general clinical uses or effects are set forth in Table 1.

TABLE I

Sympathomimetic Agents and Clinical Uses Thereof

General structure:

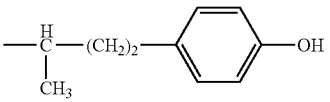


Agent name	Ring substituent(s)	R^{α}	R^{β}	R^{γ}	Main Clinical Uses: α Receptor A N P V	Main Clinical Uses: β Receptor B C	CNS, 0
Phenylethylamine		H	H	H			
Epinephrine	3-OH, 4-OH	OH	H	CH_3	A, P, V	B, C	
Norepinephrine	3-OH, 4-OH	OH	H	H	P		
Epinine	3-OH, 4-OH	H	H	CH_3			
Dopamine	3-OH, 4-OH	H	H	H	P		
Dobutamine	3-OH, 4-OH	H	H	1*		C	
Nordefrin	3-OH, 4-OH	OH	CH_3	H	V		
Ethylnorepinephrine	3-OH, 4-OH	OH	CH_2CH_3	H		B	
Isoproterenol	3-OH, 4-OH	OH	H	$CH(CH_3)_2$		B, C	
Protokylol	3-OH, 4-OH	OH	H	2*		B	
Isoetharine	3-OH, 4-OH	OH	CH_2CH_3	$CH(CH_3)_2$		B	
Metaproterenol	3-OH, 5-OH	OH	H	$CH(CH_3)_2$		B	
Terbutaline	3-OH, 5-OH	OH	H	$C(CH_3)_3$		B	
Metaraminol	3-OH	OH	CH_3	H	P		
Phenylephrine	3-OH	OH	H	CH_3	N, P		
Tyramine	4-OH	H	H	H			
Hydroxyamphetamine	4-OH	H	CH_3	H	N, P	C	
Methoxyphenamine	2-OCH_3	H	CH_3	CH_3		B	

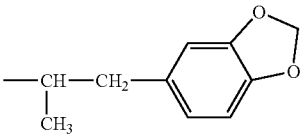
TABLE I-continued

Methoxamine	2-OCH_3, 5-OCH_3	OH	CH_3	H	P		
Albuterol	3-CH_2OH, 4-OH	OH	H	$C(CH_3)_3$		B	
Amphetamine		H	CH_3	H			CNS, 0
Methamphetamine		H	CH_3	CH_3	P		CNS, 0
Benzphetamine		H	CH_3	—NHR^{γ} is replaced with 3*			0
Ephedrine		OH	CH_3	CH_3	N, P	B,C	
Phenylpropanolamine		OH	CH_3	H	N		
Mephentermine		H	—CHR^{β}— is replaced with 4*	CH_3	N, P		
Phentermine		H	—CHR^{β}— is replaced with 4*	H			0
Chlorphentermine	4-Cl	H	—CHR^{β}— is replaced with 4*	H			0
Fenfluramine	3-CF_3	H	CH_3	C_2H_5			0
Propylhexedrine	5*: phenyl ring is replaced with cyclohexyl	H	CH_3	CH_3	N		
Diethylpropion		6*: The substituent at the 1-position is replaced with 6, below.					0
Phenmetrazine		7*: The substituent at the 1-position is replaced with 7, below.					0
Phendimetrazine		8*: The substituent at the 1-position is replaced with 8, below.					0

*1:



*2:



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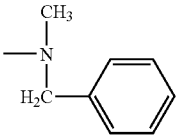

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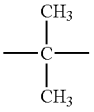
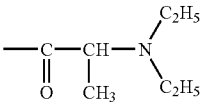
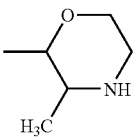


*5:

*6:

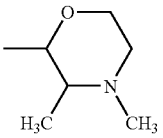


*7:



*8:

TABLE I-continued



α Activity
A = Allergic reactions (includes β action)
N = Nasal decongestion
P = Pressor (may include β action)
V = Other local vasoconstriction
(e.g. in local anesthesia)

β Activity
B = Bronchodilator
C = Cardiac

CNS = Central nervous system
0 = Anorectic

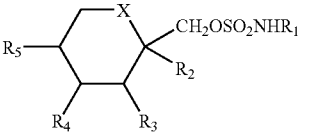
*Numbers bearing an asterisk refer to the substituents numbered in the bottom rows of the table; substituent 5 replaces the phenyl rings, and 6, 7 and 8 are attached directly to the phenyl ring, replacing the ethylamine side chain.
†The α and β in the prototype formula refer to positions of the C atoms in the ethylamine side chain.

In preferred embodiments, the sympathomimetic agent has anorexient properties (e.g., suppresses appetite) or is anorectic without significant toxicity to a subject or patient (e.g., a human) at therapeutically effective doses. In a more preferred embodiment, the sympathomimetic agent has anorexient properties (e.g., suppresses appetite) or is anorectic without loss of efficacy or without adverse or undesirable side effects to a subject or patient (e.g., a human subject or patient) at therapeutically effective doses when prescribed in combination with topiramate. In yet another embodiment, the sympathomimetic agent is phentermine or a phentermine-like compound. As defined herein, a phentermine-like compound is a compound structurally related to phentermine (e.g., an analog or derivative) which maintains an anorectic activity similar to that of phentermine. A preferred phentermine-like compound is chlorphentermine. In yet another embodiment, the sympathomimetic agent is amphetamine or an amphetamine-like compound. As used herein, an amphetamine-like compound is a compound structurally related to amphetamine (e.g., an analog or derivative) which maintains an anorectic effect of amphetamine. In yet another embodiment, the sympathomimetic agent is phenmetrazine or a phenmetrazine-like compound. As defined herein, a "phenmetrazine-like compound" is a compound structurally related to phenmetrazine (e.g., an analog or derivative) which maintains an anorectic effect of phenmetrazine. A preferred phenmetrazine-like compound is phendimetrazine. Analogs and/or derivatives of the compounds of the present invention can be tested for their ability to suppress appetite (e.g., suppress food intake) in a subject (e.g., a mammalian subject).

In an exemplary preferred embodiment, the sympathonimetic agent is selected from the group consisting of amphetamine, methamphetamine, benzphetamine, phenylpropanolamine, phentermine, chlorphentermine, diethylpropion, phenmetrazine, and phendimetrazine (as set forth in Table I. In a particularly preferred embodiment, the sympathomimetic agent is phentermine. It is also within the scope of the present invention to utilize other sympathomimetic agents including pseudo ephedrine (a stereoisomer of ephedrine, SUDAFED®), methylphenidate (RITALIN®), tuaminoheptane, and other CNS stimulants including, for example, caffeine.

The terms "anticonvulsant sulfamate derivative" and "anticonvulsant sulfamate derivatives" are terms of art and refer to a class of sulfamate-derived compounds that possess anticonvulsant activity and have an art-recognized use in the treatment of epilepsy. In particular, the anticonvulsant sulfamate derivatives are monosaccharide derivatives with sulfamate functionality. The anticonvulsant sulfamate derivatives for use in the present invention have one or more of the following modes of activity: modulation of voltage-dependent sodium conductance; potentiation of gamma-aminobutyric acid-evoked currents; inhibition of the kainate/alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) subtype of the glutamate receptor; and/or inhibition of carbonic anhydrase (e.g, a mechanism by which the anticonvulsant derivative of the present invention may decrease the sensation of taste). The anticonvulsant sulfamate derivatives for use in the present invention are described further in U.S. Pat. Nos. 4,513,006, 5,384,327, 5,498,629, 5,753,693 and 5,753,694, as are methods of synthesizing such anticonvulsant sulfamate derivatives. The aforementioned patents are incorporated by reference herein in their entireties.

In preferred embodiments, the anticonvulsant sulfamate derivative is a compound having the following formula (I):



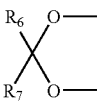
(I)

wherein:

X is CH_2 or O;

R_1 is H or alkyl; and

R_2, R_3, R_4 and R_5 are independently H or lower alkyl, with the proviso that when X is O, then R_2 and R_3 and/or R_4 and R_5 together may be a methylenedioxy group of the following formula (II):



(II)

in which R_6 and R_7 are the same or different and are H or lower alkyl, or are joined to form a cyclopentyl or cyclohexyl ring.

R_1 in particular is hydrogen or alkyl of about 1 to 4 carbons, such as methyl, ethyl, or isopropyl. Alkyl includes both straight and branched chain alkyl. Alkyl groups R_2, R_3, R_4, R_5, R_6 and R_7 are about 1 to 3 carbons and include methyl, ethyl, isopropyl and n-propyl.

A particular group of compounds of the formula (I) are those wherein X is oxygen and both R_2 and R_3, and R_4 and R_5

together are methylenedioxy groups of the formula (II), wherein R_6 and R_7 are both hydrogen, both alkyl, or combine to form a spiro cyclopentyl or cyclohexyl ring, in particular, where R_6 and R_7 are both alkyl such as methyl. A second group of compounds are those wherein X is CH_2 and R_4 and R_5 are joined to form a benzene ring. A third group of compounds of the formula (I) are those wherein both R_2 and R_3 are hydrogen.

In preferred embodiments, the anticonvulsant sulfamate derivatives have anorexient properties (e.g., suppress appetite) without significant toxicity to a subject or patient (e.g., a human) at therapeutically effective doses. In a more preferred embodiment, the anticonvulsant sulfamate derivatives have anorexient properties (e.g., suppress appetite) without significant adverse or undesirable side effects to a subject or patient (e.g., a human) at therapeutically effective doses when prescribed in combination with phentermine. In a particularly preferred embodiment the anticonvulsant sulfamate derivative is topiramate (Topamax®). Topiramate, also referred to in the art as 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate, has been demonstrated in clinical trials of human epilepsy to be effective as an adjunctive therapy or as monotherapy in treating simple and complex partial seizures and secondarily generalized seizures (E. Faught et al. (1995) *Epilepsia* 36(suppl 4):33; S. Sachdeo et al. (1995) *Epilepsia* 36(suppl 4):33) and is currently marketed for the treatment of simple and complex partial seizure epilepsy with or without secondary generalized seizures.

Dosages, Administration and Pharmaceutical Compositions:

The choice of appropriate dosages for the drugs used in combination therapy according to the present invention can be determined and optimized by the skilled artisan, e.g., by observation of the patient, including the patient's overall health, the response to the combination therapy, and the like. Optimization, for example, may be necessary if it is determined that a patient is not exhibiting the desired therapeutic effect or conversely, if the patient is experiencing undesirable or adverse side effects that are too many in number or are of a troublesome severity.

Preferably, a sympathomimetic drug (e.g., a drug set forth in Table I) is prescribed at a dosage routinely used by the skilled artisan (e.g., physician) to promote the desired therapeutic effect of the drug, when the drug is used as a monotherapy. Preferably, an anticonvulsant sulfamate derivative (e.g., a compound having formula I) is prescribed at a lower dosage than routinely used by the skilled artisan (e.g., physician) to promote the desired therapeutic effect of the drug, when the drug is used as a monotherapy (e.g., in the treatment of epilepsy). In a preferred embodiment, a sympathomimetic drug or anticonvulsant sulfamate derivative is prescribed at a dose of between 5-1000, preferably between 10-1500, more preferably between 20-1000 and most preferably between 25-50 mg daily.

It is especially advantageous to formulate compositions of the invention in unit dosage form for ease of administration and uniformity of dosage. The term "unit dosage forms" as used herein refers to physically discrete units suited as unitary dosages for the individuals to be treated. That is, the compositions are formulated into discrete dosage units each containing a predetermined, "unit dosage" of an active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specifications of the novel dosage unit forms of the invention are dependent on the unique characteristics of the composition containing the anticonvulsant or sympathomimetic agent and the particular therapeutic effect to be achieved. Dosages can further be determined by reference to the usual dose and manner of administration of the ingredients. It is also within the scope of the present invention to formulate a single physically discrete dosage form having each of the active ingredients of the combination treatment (e.g., a single dosage form having an anticonvulsant agent and a sympathomimetic agent).

The method of administration of compositions or combinations of the invention will depend, in particular, on the type of sympathomimetic agent used and the chosen anticonvulsant sulfamate derivative. The sympathomimetic agent and the anticonvulsant sulfamate derivative may be administered together in the same composition or simultaneously or sequentially in two separate compositions. Also, one or more sympathomimetic agents or one or more anticonvulsant sulfamate derivatives may be administered to a subject or patient either in the form of a therapeutic composition or in combination, e.g., in the form of one or more separate compositions administered simultaneously or sequentially. The schedule of administration will be dependent on the type of sympathomimetic agent(s) and anticonvulsant sulfamate derivative(s) chosen. For example, a sympathomimetic agent can have a stimulant effect and the degree of such stimulant effect may vary depending on the sympathomimetic agent chosen. Accordingly, a sympathomimetic agent having a significant stimulant effect might be administered earlier in the day than administration of a sympathomimetic agent having a lesser stimulant effect. Likewise, an anticonvulsant sulfamate derivative can have a sedative effect and the degree of such sedative effect may vary depending on the anticonvulsant sulfamate derivative chosen. Accordingly, an anticonvulsant sulfamate derivative having a significant sedative effect might be administered later in the day than administration of an anticonvulsant sulfamate derivative having a lesser sedative effect. Moreover, sympathomimetic agents and/or anticonvulsant agents having lesser stimulant or sedative effects, respectively, may be administered simultaneously.

Sympathomimetic agents and/or anticonvulsant sulfamate derivatives can also be administered along with a pharmaceutically acceptable carrier. As used herein "pharmaceutically acceptable carrier" includes any solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in compositions of the invention is contemplated.

A sympathomimetic agent alone, or in combination with an anticonvulsant sulfamate derivative in the form of a composition, is preferably administered orally. When the composition(s) are orally administered, an inert diluent or an assimilable edible carrier may be included. The composition and other ingredients may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the individual's diet. For oral therapeutic administration, the composition may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The percentage of the compositions and preparations may, of course, be varied. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. In a particularly preferred embodiment, the present invention includes pharmaceutical composition comprising a therapeutically effective amount of a sympathomimetic agent and an anticonvulsant sulfamate derivative. In one embodiment, the present invention includes a therapeutically-effective amount of a sympathomimetic

agent and an anticonvulsant sulfamate derivative packaged in a daily dosing regimen (e.g., packaged on cards, packaged with dosing cards, packaged on blisters or blow-molded plastics, etc.). Such packaging promotes products and increases patient compliance with drug regimens. Such packaging can also reduce patient confusion. The present invention also features such kits further containing instructions for use.

The tablets, troches, pills, capsules and the like may also contain a binder, an excipient, a lubricant, or a sweetening agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed.

A sympathomimetic agent, alone or in combination with an anticonvulsant sulfamate derivative, can also be administered in a convenient manner such as by injection (subcutaneous, intravenous, etc.), inhalation, transdermal application, or rectal administration. Depending on the route of administration, the composition containing the sympathomimetic agent and/or anticonvulsant sulfamate derivative may be coated with a material to protect the compound from the action of acids and other natural conditions which may inactivate the compounds or compositions.

To administer the compositions, for example, transdermally or by injection, it may be necessary to coat the composition with, or co-administer the composition with, a material to prevent its inactivation. For example, the composition may be administered to an individual in an appropriate diluent or in an appropriate carrier such as liposomes. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Liposomes include water-in-oil-in-water CGF emulsions as well as conventional liposomes (Strejan et al. (1984) *J. Neuroimmunol.* 7:27). To administer the compositions containing the sympathomimetic agents and/or anticonvulsant sulfamate derivatives parenterally or intraperitoneally, dispersions can be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

Compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. In all cases, the composition must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene gloycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol and sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

A preferred aspect of the present invention features prescribing phentermine in combination with topiramate to effect weight loss and/or to treat Syndrome X and/or a subset of symptoms thereof. A preferred dose for phentermine is between about 5-60 mg daily, including but not limited to doses of 8, 10, 15, 20, 25, 30, 35, 40, 45, 50 and 55 mg daily. A particularly preferred dose for phentermine is about 15 mg daily. In an exemplary embodiment, the phentermine is of an immediate release form.

Preferably, the phentermine is taken by the patent in the morning and more preferably, is taken before breakfast. The phentermine is best taken in the morning because the drug is a stimulant as well as an appetite suppressant. When phentermine is prescribed (e.g., as part of the combination therapy described herein), physicians should be aware and may want to advise patients that the drug can be mildly habit forming. Phentermine can also cause increased nervousness, increased energy, irritability and, rarely, insomnia. Stopping phentermine may also cause tiredness lasting for up to 1-2 weeks. Phentermine can also raise blood pressure (e.g., during the early phases of treatment).

A preferred dose for topiramate is between about 50-1500 mg daily. As discussed previously, prescription of topiramate at dosages of ≧400 mg daily results is promotion of undesirable side effects (e.g., sedation, mental clouding). Accordingly, in a preferred embodiment, topiramate is prescribed at a dose of about 50-400 mg daily. In another preferred embodiment, the dosage of topiramate is increased gradually at the outset of the therapy in order to reduce the chance of undesirable side effects associated with higher doses of the drug. In an exemplary embodiment, the topiramate is administered at a dose of 25 mg daily for about the first 5-7 days (e.g., 6 days) of treatment, at a dose of about 50 mg daily for the next 5-7 days (e.g., 6 days), at a dose of 100 mg daily for about the next 6-8 days (e.g., 7 days) and about 150 mg daily for the next 20-26 days. From this point forward, the topiramate can be administered at a dose of 150-250 mg daily, including but not limited to doses of 175, 200, and 225 mg daily. A particularly preferred dose for continued therapy is about 200 mg of topiramate daily. In another exemplary embodiment, the topiramate is of an immediate release form. In yet another exemplary embodiment, the topiramate is of a sustained release form.

In a preferred embodiment, topiramate is taken later in the day than the phentermine. Preferably, the patient takes the topiramate just before supper or later in the evening. Topiramate is best given later in the day because the drug can be sedating. In other embodiments, the topiramate is given BID (e.g., twice daily), TID (three times daily) or QID (four time daily). When prescribing topiramate, physicians should be aware and may want to advise patients that the drug can cause tiredness, fatigue, dizziness, difficulty with speech or finding words, difficulty concentrating, difficulty with balance, and/or numbness or tingling in the hands or feet. Less common side effects are nausea, coordination problems, abdominal pain, slowed thinking nervousness, depression, breast pain, painful periods, double or blurred vision, palpitations, low white blood count and kidney stones. A physician should also advise patients that the drug may not be taken if the patient is also taking Diamox (acetazolamide). No female patient should become pregnant while taking this drug as it may cause birth defects. If a female patient misses a period she should immediately discontinue taking the medication and inform the physician. Female patients should not be treated according to the methods of the present invention if breast feeding a child. Patients should not drink alcohol or take sedating medications while taking topiramate since excess sedation can occur. Patients should also refrain from performing dangerous tasks (e.g. operating heavy machinery or driv-

ing) until they are comfortable with the side effects of the full dose (e.g., 200-400 mg daily). Patients should be advised not to increase the dosage beyond what is prescribed. Topiramate is not habit forming.

Yet another embodiment of the present invention features pharmaceutical compositions (e.g., for oral administration) comprising phentermine and topiramate in a single pharmaceutical formulation. Such compositions may be preferred, for example, to increase patient compliance (e.g., by reducing the number of administrations necessary to achieve the desired pharmacologic effect).

In a preferred embodiment, the pharmaceutical composition includes phentermine in an immediate release form and further includes topiramate in a controlled release formulation. As defined herein, an "immediate release formulation" is one which has been formulated to allow, for example, the phentermine, to act as quickly as possible. Preferred immediate release formulations include, but are not limited to, readily dissolvable formulations. As defined herein, a "controlled release formulation" includes a pharmaceutical formulation that has been adapted such that drug release rates and drug release profiles can be matched to physiological and chronotherapeutic requirements or, alternatively, has been formulated to effect release of a drug at a programmed rate. Preferred controlled release formulations include, but are not limited to, granules, delayed release granules, hydrogels (e.g., of synthetic or natural origin), other gelling agents (e.g., gel-forming dietary fibers), matrix-based formulations (e.g., formulations comprising a polymeric material having at least one active ingredient dispersed therethrough), granules within a matrix, polymeric mixtures, granular masses, and the like.

In one embodiment, a controlled release formulation is a delayed release form. As defined herein, a "delayed release form" is formulated in such a way as to delay, for example, topiramate's action for an extended period of time. A delayed release form can be formulated in such a way as to delay the release of an effective dose of topiramate for 4, 8, 12, 16 or 24 hours following the release of phentermine. In yet another preferred embodiment, a controlled release formulation is a sustained release form. As defined herein, a "sustained release form" is formulated in such a way as to sustain, for example, the topiramate's action over an extended period of time. A sustained release form can be formulated in such a way as to provide an effective dose of topiramate (e.g., provide a physiologically effective blood level) over a 4, 8, 12, 16 or 24 hour period.

Preferred compositions include a tablet core consisting essentially of topiramate, said core being in association with a layer of phentermine. Preferably, the core has a delayed or sustained dissolution rate. In an exemplary embodiment, a tablet can comprise a first layer containing, for example, phentermine (e.g., in an immediate release formulation) and a core containing, for example, topiramate in a delayed release or sustained release formulation. Other exemplary embodiments can include, for example, a barrier between the first layer and core, said layer serving the purpose of limiting drug release from the surface of the core. Preferred barriers prevent dissolution of the core when the pharmaceutical formulation is first exposed to gastric fluid. For example, a barrier can comprise a disintegrant, a dissolution-retarding coating (e.g., a polymeric material, for example, an enteric polymer), or a hydrophobic coating or film, and can be selectively soluble in either the stomach or intestinal fluids. Such barriers permit the topiramate to leach out slowly and can cover substantially the whole surface of the core.

The above-described pharmaceutical compositions are designed to release the two effective agents of the combination therapy of the present invention sequentially, i.e., releasing topiramate after releasing phentermine, both agents being contained in the same pharmaceutical composition. Preferred amounts of phentermine and topiramate are as described above with particularly preferred compositions comprising from about 5 mg to about 60 mg phentermine and from about 50 mg to 1500 mg topiramate. Particularly preferred compositions include at least 15 mg phentermine and at least about 50 mg, 100 mg or 200 mg topiramate.

Pharmaceutical compositions so formulated may contain additional additives, suspending agents, diluents, binders or adjuvants, disintegrants, lubricants, glidants, stabilizers, coloring agents, flavors, etc. These are conventional materials which may be incorporated in conventional amounts.

In one embodiment, a method of the present invention is carried out, practiced or performed such that weight loss in the subject or patient occurs. Accordingly, the methods of the present invention are particularly useful for the treatment of overweight or obese patients. As defined herein, "overweight" subjects or patients are between about I and 20 percent overweight (e.g., weighs 1-20% in excess of their ideal body weight). Also as defined herein, an "obese" subject or patient is greater than 20 percent overweight (e.g., weighs >20% in excess of his or her ideal body weight). Alternatively, the methods of the present invention are useful in the treatment of subjects or patients in need of losing weight, but who are not necessarily overweight or obese. For example, it may be desirable to achieve weight loss in subjects or patients having arthritis or prostheses such that the individual experiences less adverse effects resulting from bearing weight.

The combination therapies of the present invention will generally be administered until the patient has experienced the desired weight loss, and preferably has achieved an ideal body weight. Alternatively, the combination therapies of the present invention can be administered until the patient has achieved a weight loss of 5-10%, 10-15%, 15-20% or 20-25% of their initial body mass (e.g., the patient's starting weight).

The present inventor has also recognized that the combination therapy of the present invention ameliorates symptoms associated with Syndrome X. Syndrome X consists of a complex of medical problems that are largely associated with obesity, including, hypertension, diabetes or glucose intolerance and insulin resistance, hyperlipidemia, and often tiredness and sleepiness associated with sleep apnea. Patients are often treated with combinations of antihypertensives, lipid lowering agents, insulin or oral diabetic drugs, and various mechanical and surgical treatments of sleep apnea. However, such treatments are often costly and do not treat the underlying problem of obesity. Moreover, some of the treatments for diabetes, including insulin and oral diabetic agents, actually aggravate Syndrome X by increasing insulin levels, increasing appetite, and increasing weight. This can lead to higher blood pressure and even higher cholesterol. Accordingly, one aspect of the present invention features a method of treating Syndrome X using the combination therapies described herein. In one embodiment, the invention features a method of treating Syndrome X in a subject or patient which includes treating the subject with a therapeutically effective amount of a combination of an anticonvulsant sulfamate derivative (e.g., topiramate) and a sympathomimetic agent (e.g., phentermine or a phentermine-like compound), such that at least one symptom associated with Syndrome X is affected. As defined herein, "affecting a symptom" (e.g., affecting a symptom associated with Syndrome X) refers to lessening, decreasing the severity of the symptom or reversing, ameliorating, or improving the symptom (e.g., decreasing hypertension, ameliorating diabetes, reversing glucose intolerance or insulin resistance, lessening hyperlipidemia, or decreasing tiredness and sleepiness associated with sleep apnea).

Treatment of Syndrome X according to the methods of the present invention includes affecting at least one, preferably two, more preferably three, more preferably four, five or six

symptoms associated with Syndrome X. In a particularly preferred embodiment, all symptoms associated with Syndrome X are affected (e.g., lessened, reversed, ameliorated, etc.).

The present inventor has also recognized that the combination therapy of the present invention ameliorates some side effects associated with obesity, as described herein. Accordingly, one aspect of the present invention features a method of treating at least one side effect associated with obesity using the combination therapies described herein. In one embodiment, the invention features a method of treating at least one obesity-related side effect in a subject or patient which includes treating the subject with a therapeutically effective amount of a combination of an anticonvulsant sulfamate derivative (e.g., topiramate) and a sympathomimetic agent (e.g., phentermine or a phentermine-like compound), such that at least one obesity-related side effect is effected. As defined herein, a "side effect associated with obesity" includes a symptom or disorder in a subject (e.g., a patient) which is secondary and/or results from (e.g., directly and/or indirectly results from) a medical condition for which the subject is obese and/or being treated. In a preferred embodiment, the subject is obese and/or is being treated for obesity. In another embodiment, the subject has at least one or more (e.g., two, three, four, five or more) side effect(s) selected from the group consisting of sleep apnea, high blood pressure and high blood sugar, high blood lipid, high Hgb AIC or other art-recognized side effects associated with obesity.

Whether in the treatment of Syndrome X or in the practicing of the methods of the present invention to effect weight loss (e.g., in the treatment of overweight and/or obesity) or in treatment of side effects associated with obesity, it will be apparent to the skilled artisan (e.g., physician) that monitoring of the patient is needed to determine the effectiveness of the treatments and to potentially modify the treatments (e.g., modify the dosing, time of drug administration, sequence of drug administration, as defined herein). Accordingly, in certain embodiments, the patient is monitored about every 2-6, preferably every 3-5 and more preferably every 4 weeks. Monitoring the effective of treatment to achieve weight loss includes, but is not limited to monitoring the subject or patient's body weight (e.g., comparing the patient's initial body weight to that at a follow-up visit, for example, four weeks after the initiation of treatment). Additional features of the subject or patient's health can also be monitored (i.e., monitoring the patient's overall health and/or monitoring the effectiveness of treatment of an undesired side effect of obesity) including, but not limited to the patient's blood pressure, blood sugar, serum lipid levels, etc. Likewise, monitoring a subject or patient for treatment of Syndrome X can include monitoring of at least one, preferably more than one symptom associated with Syndrome X.

This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patents, and published patent applications cited throughout this application are hereby incorporated by reference.

EXAMPLE 1

Patients as part of the following trial were treated according to the following dosage regimen. Patients took phentermine at a dose of 15 mg daily throughout the weight loss program, before breakfast. For the first 6 days, patients took one 25 mg tablet of topiramate before supper. For the next 6 days, patients took two 25 mg tablets of topiramate before supper. For the next 7 days (days 13-19), patients took 100 mg before supper daily using 4-25 mg tablets of topiramate daily. For days 20-26, patients took 150 mg of topiramate daily consisting of one-half of a 200 mg tablet and two 25-mg mg tablets of topiramate. From that point on, unless instructed otherwise by the physician, patients continued to take one 200 mg topiramate tablet daily before supper and continued the 15 mg phentermine daily in the morning. Patients were advised to drink at least eight (8) full glasses of water daily to reduce the risk of kidney stones which may result from taking topiramate.

Patients were advised that while the effect of phentermine is fairly rapid, the effect of topiramate is slower in onset. The weight reduction effect of topiramate will continue for as long as 18 months on the medication. That is, the patient can expect to continue gradual weight loss for up to 18 months on the medication. Of course, weight loss is maximal if the patient follows diet and/or exercise programs. The weight loss should exceed 15% of the patients starting weight. Thus, if the patient weighs about 200 pounds as of the start date, he/she might expect to lose at least 30 pounds in a period of 12-18 months. The following patient data has been collected.

TABLE II

Patient's Initials	Age	Sex	Start Weight (lbs)	Start Blood Pressure	Follow-Up Date	Follow-Up Weight (lbs)	% Weight Loss	Follow-Up Blood Pressure
M. O.[1]	48	F	182	115/70	5 weeks	177	2.7%	120/80
					9 weeks	176	3.3%	110/70
T. M.	37	F	190	122/84	2 weeks, 5 days	178	6.3%	110/80
					6 weeks, 2 days	168	11.6%	125/80
D. M. (A)	28	M	286	138/90	4 weeks	279	2.4%	128/86
P. L.	55	F	144	132/84	4 weeks	141	2.1%	138/85
					9 weeks	137	4.9%	122/82
E. K.	52	F	181	130/100	5 weeks	175	3.3%	140/88
I. F.	41	F	196	95/60	6 weeks, 5 days			
D. M. (B)[2]	56	M	295	150/80	4 weeks, 2 days	297	(+0.7%)	148/82
					8 weeks, 2 days	287	2.7%	140/70

[1]Patient M. O. was being treated with Meridia ® at the onset of the study, which continued through the first 5 weeks of the study. At the 5-week follow up, M. O. was switched to the phentermine/topiramate regime described above.
[2]Patient D. M. (B) was being treated with phentermine alone at the onset of the study and was taking the full dose of topiramate by the fourth week of the study.

As is apparent from the above-described data, patients not previously treated with an anorexient at the outset of the study experienced an average of about 3.5% weight loss after only 2-6 weeks (e.g., patient T.M. lost 6.3% body weight, patient D.M.(A) lost 2.4% body weight, patient P.L. lost 2.1% body weight and patient E.K. lost 3.3% body weight). After only 6-9 weeks of treatment, patients (not previously treated with an anorexient at the outset of the study experienced an average of about 8.3% weight loss (e.g., patient T.M. lost 11.6% body weight and patient P.L. lost 4.9% body weight). The patient previously on Meridia® (patient M.O.) lost 3.3% body weight after being enrolled in the program for 9 weeks. Moreover, the patient previously on phentermine (patient D.M.(B)) lost a total of 2.7% body weight after being enrolled in the program for about 8 weeks. This particular patient reported that this is the most significant weight loss he has achieved to date, the patient having previously tried other conventional therapies.

In addition to the weight loss reported above, almost all patients enrolled in the study experienced decreased blood pressure. Moreover, patients involved in the study who had previously taken Redux, phen-fen, Meridia and/or other weight loss treatments report that they have not previously experienced the benefits of the combined phentermine/topiramate therapy. Patients report that they have no appetite, can resist food easily, can concentrate and function at work (even in attention-intensive jobs such as computer programming), have more energy and feel better. Patients also report experiencing fewer side effects than any previous weight loss treatments tried.

EXAMPLE 2

Extended results of the trial described in Example 1.

A total of thirteen patients were treated for 1-9 months with phentermine (15 mg daily) in the morning and up to 400 mg of topiramate (median dose 200 mg), in the evening. [Note: Patient D.M.(B) discussed above is not included in this data as he was on phentermine treatment prior to treatment with the combination therapy of the present invention.] Topiramate dose was gradually increased from 25 mg per day in increments of 25-50 mg weekly until either desirable weight loss took place or until side effects limited dose increases. [Note: A fourteenth patient discontinued treatment after 3 days due to nausea.] All thirteen patients tolerated treatment well with minimal side effects. Along with taking medication, patients were instructed to walk at least 30 minutes three times per week and to follow a low fat diet. No patients had taken diet medication for at least 3 months prior to treatment. Average baseline BMI was 32.5 (range 26-48).

Average weight loss for the thirteen patients was 11.8%. For seven patients who were on treatment the longest (range 5-9 months), the average weight loss was 14.4%. Patients reported that they had little or no appetite and that they actually felt better (Topiramate's usefulness is also being investigated as a mood stabilizer) than before therapy. Blood pressure, lipid, glucose, and Hgb A1C values were also favorably affected by this treatment.

Table III sets forth patient data for the thirteen above-described patients treated with the combination therapy of the present invention.

TABLE III

Patient Data: Combination Therapy*

Patient No.	% of Weight Loss	Baseline BMI	Current BMI	Weeks on Rx	Current Status
1	7.7	38	35	10	on Rx
2	10.3	25	23	4	Finished
3	6.8	48	44	5	d/c early - dropped out
4	16.8	30	24	35	on taper
5	23.2	30	23	41	on taper
6	8	41	38	40	on Rx
7	9.7	28	25	33	on taper
8	14.4	30	26	44	on Rx
9	15.9	27	21	32	on taper
10	9	33	31	7	d/c early - will restart
11	12.9	28	24	22	Finished
12	7	29	27	5	on Rx
13	12.1	34	31	6	on Rx

*data for thirteen patients
Average weight loss = 11.8% (13 patients)
Average weight loss ≧ 22 weeks on Rx = 14.4% (7 patients)
Average baseline BMI = 32.4

Table IV sets forth for the average blood pressure, blood glucose, Hgb A1C and blood lipid value for the thirteen patients.

TABLE IV

	BP mm Hg	GLUCOSE mg/dL	HGBA1C %*	CHOL mg/dL	TRIG mg/dL
Average Pre-Treatment Value	131.3/85.9	107	6.48	212	189
Average On Treatment Value	122.6/78.4	102	5.05	210	172

*Numbers include 1 diabetic patient whose oral hypoglycemic was reduced by 50% while on the weight loss treatment.

One of the thirteen patients in the study also had severe sleep apnea with the usual complications of daytime sleepiness and fatigue. His symptoms have disappeared with the weight loss treatment.

Of the six patients (i.e., finished or on taper) who have completed the combination therapy of the present invention, five of the six achieved a body mass index (BMI) of 24 or better. The average pre-treatment or baseline BMI for these six patients was 28. The final average BMI was 23.3. The average weight loss was 17%.

EXAMPLE 3

The 56-year old male patient described previously (D.M.(B)) who was initially taking phentermine alone and had topiramate added to his regimen had a good effect from the combination. He once weighed as much as 395 pounds. When Redux was still on the mark in the United States, he was treated with a combination of diet, exercise, Redux and phentermine. His lowest weight attained was 285 pounds. When Redux was withdrawn from the market, he remained on phentermine but gained weight back to 295-300 pounds. When topiramate was added to his regimen, he managed to lose 25 pounds and is currently at 271 pounds, his lowest weight since he was in his 20s. He, along with most of the patients treated so far, reported that the treatment with topiramate and phentermine had fewer side effects and was more effective than

any previous weight loss treatment using medications that he and others had tried. This 56-year old man exhibited lowered blood pressure (approx. 15 mm Hg systolic and 10 mm Hg diastolic).

EXAMPLE 4

Extended results of the trial described in Examples 1 and 2.

The cumulative data from a total of seventeen patients treated with the combination weight loss treatment of the present invention are set forth in Table V.

TABLE V

Patient Data: Combination Therapy*

PATIENT	% WEIGHT LOSS	BASELINE BMI	CURRENT BMI	WEEKS ON Rx	CURRENT STATUS
1	7.7	38	35	33	on Rx
2	10.3	25	23	4	Finished
3	6.8	48	44	5	d/c early - dropped out
4	16.8	30	24	58	on taper
5	23.2	30	23	64	on taper
6	17.5	41	33	63	on Rx
7	9.7	28	25	56	on taper
8	18.6	30	24	67	on Rx
9	15.9	27	21	55	on taper
10	9	33	31	7	d/c early- will restart
11	12.9	28	24	22	Finished
12	7	29	27	5	d/c early- will restart
13	12.1	34	31	6	d/c early- will restart
14	22.5	46	32	16	on Rx
15	10.1	50	45	12	on Rx
16	6.4	27	24	4	Finished
17	6.3	27	25	6	on Rx

*data for seventeen patients
AVERAGE WEIGHT LOSS = 12.5% (17 patients)
AVERAGE WEIGHT LOSS ≧ 22 WEEKS ON Rx = 15.3% (8 patients)
AVERAGE BASELINE BMI = 33.6

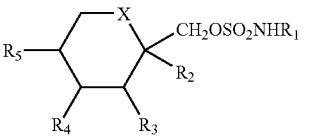
The present invention provides a novel combination therapy for the treatment of obese or overweight patients that can result in weight losses of greater than 5-10%, perhaps even as great as 15-20%. The therapy combines phentermine or a phentermine-like drug with drug previously recognized for the treatment of epileptic seizures, known as topiramate. The combination therapy results in greater initial weight loss than other recognized therapies, potential greater overall weight loss and can be continued for significant periods of time with fewer and less serious side effects than other recognized weight loss treatments. In particular, the combination therapy far surpasses the modeset anorexient effects of phentermine monotherapy and can be continued for significant periods of time without the loss of effectiveness experienced by patients being treated with phentermine alone. Moreover, the combination therapy has been found to ameliorate symptoms associated with Syndrome X and accordingly, has potential use in the treatment of Syndrome X.

Equivalents:

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

I claim:

1. A method for effecting weight loss in a subject comprising administering to the subject a combination of: (a) a therapeutically effective amount of phentermine, and (b) a therapeutically effective amount of an anticonvulsant sulfamate derivative having the structure of formula I



(I)

wherein X is CH_2 or O, R_1, R_2, R_3, R_4, and R_5 are independently H or C_1-C_4 alkyl, and further wherein when X is O, then R_2 and R_3, and/or R_4 and R_5, may be taken together to form a methylene dioxy linkage of the formula —O—CR_6R_7—O— in which R_6 and R_7 are independently H or C_1-C_3 alkyl, or may be taken together to form a cyclopentyl or cyclohexyl ring.

2. The method of claim **1**, wherein X is O, R_1 is H, R_2 and R_3 taken together form the methylene dioxy linkage —O—CH_2—O—, R_4 and R_5 taken together form the methylene dioxy linkage —O—CH_2—O—, and the anticonvulsant sulfamate derivative is topiramate.

3. The method of claim **2**, wherein the therapeutically effective amount of phentermine is from 5 to 60 mg daily.

4. The method of claim **2**, wherein the therapeutically effective amount of topiramate is from 50 to 1500 mg daily.

5. The method of claim **4**, wherein the therapeutically effective amount of topiramate is less than 400 mg daily.

6. The method of claim **5**, wherein the therapeutically effective amount of topiramate is from 50 to 400 mg daily.

7. The method of claim **2**, wherein the therapeutically effective amount of phentermine is 15 mg daily.

8. The method of claim **7**, wherein the therapeutically effective amount of topiramate is from 50 to 1500 mg daily.

9. The method of claim **8**, wherein the therapeutically effective amount of topiramate is less than 400 mg daily.

10. The method of claim **9**, wherein the therapeutically effective amount of topiramate is from 50 to 400 mg daily.

11. The method of claim **1**, wherein the subject is overweight.

12. The method of claim **1**, wherein the subject is obese.

13. The method of claim **1**, wherein the subject is neither overweight nor obese.

14. The method of claim **1**, wherein the subject suffers from a condition that can be alleviated with loss of body weight.

15. The method of claim **1**, wherein the phentermine and the anti-convulsant sulfamate derivative are administered simultaneously.

16. The method of claim **15**, wherein the phentermine amine and the anti-convulsant sulfamate derivative are administered in a single pharmaceutical formulation.

17. The method of claim **1**, wherein the phentermine and the anti-convulsant sulfamate derivative are administered separately.

18. The method of claim **17**, wherein the phentermine and the anti-convulsant sulfamate derivative are administered at different times of day.

19. The method of claim **18**, wherein the phentermine is administered in the morning and the anti-convulsant sulfamate derivative is administered at least once later in the day.

20. The method of claim **2**, wherein the phentermine and the topiramate are administered simultaneously.

21. The method of claim **20**, wherein the phentermine and the topiramate are contained in a single pharmaceutical formulation.

22. The method of claim **2**, wherein the phentermine and the topiramate are administered separately.

23. The method of claim **22**, wherein the phentermine and the topiramate are administered at different times of the day.

24. The method of claim **23**, wherein the phentermine is administered in the morning and the topiramate is administered at least once later in the day.

25. The method of claim **2**, wherein the amount of topiramate administered to the subject is gradually increased, over an extended time period, from an initial daily dosage up to a final daily dosage suitable for continued therapy.

26. The method of claim **2**, wherein the phentermine is contained in an immediate release dosage form.

27. The method of claim **26**, wherein the topiramate is contained in an immediate release dosage form or a controlled release dosage form.

28. The method of claim **2**, wherein the phentermine and the topiramate are administered orally.

29. A pharmaceutical composition comprising topiramate and phentermine.

* * * * *

EXHIBIT D

US007674776B2

(12) **United States Patent**
Najarian

(10) **Patent No.: US 7,674,776 B2**
(45) **Date of Patent: *Mar. 9, 2010**

(54) **COMBINATION THERAPY FOR EFFECTING WEIGHT LOSS AND TREATING OBESITY**

(75) Inventor: **Thomas Najarian**, Los Osos, CA (US)

(73) Assignee: **Vivus, Inc.**, Mountain View, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 945 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/385,233**

(22) Filed: **Mar. 20, 2006**

(65) **Prior Publication Data**

US 2006/0234952 A1 Oct. 19, 2006

Related U.S. Application Data

(63) Continuation-in-part of application No. 10/454,368, filed on Jun. 3, 2003, now Pat. No. 7,056,890, which is a continuation-in-part of application No. 09/593,555, filed on Jun. 14, 2000, now abandoned.

(60) Provisional application No. 60/139,022, filed on Jun. 14, 1999, provisional application No. 60/178,563, filed on Jan. 26, 2000, provisional application No. 60/181,265, filed on Feb. 9, 2000.

(51) **Int. Cl.**
A61K 31/135 (2006.01)
A61K 31/70 (2006.01)

(52) **U.S. Cl.** **514/23**; 514/646

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

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(57) **ABSTRACT**

The present invention features a novel therapy for effecting weight loss which involves treating a subject with a sympathomimetic agent (e.g., phentermine or a phentermine-like drug) in combination with an anticonvulsant sulfamate derivative (e.g., topiramate) such that the subject experiences weight loss.

The combination methods of the present invention also are effective against symptoms associated with Syndrome X. The invention also features pharmaceutical compositions and kits for use in the practice of these novel therapies.

59 Claims, No Drawings

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COMBINATION THERAPY FOR EFFECTING WEIGHT LOSS AND TREATING OBESITY

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. patent application Ser. No. 10/454,368, filed Jun. 3, 2003, which is a continuation-in-part of U.S. patent application Ser. No. 09/593,555, filed Jun. 14, 2000, now abandoned, which claims priority under 35 U.S.C. §119(e)(1) to provisional U.S. Patent Application Ser. No. 60/139,022, filed Jun. 14, 1999, Ser. No. 60/178,563, filed Jan. 26, 2000, and Ser. No. 60/181,265, filed Feb. 9, 2000. The aforementioned patent applications are incorporated herein by reference in their entireties.

BACKGROUND OF THE INVENTION

About 97 million adults in the United States are overweight or obese. The medical problems caused by overweight and obesity can be serious and often life-threatening, and include diabetes, shortness of breath, gallbladder disease, hypertension, elevated blood cholesterol levels, cancer, arthritis, other orthopedic problems, reflux esophagitis (heartburn), snoring, sleep apnea, menstrual irregularities, infertility and heart trouble. Moreover, obesity and overweight substantially increase the risk of morbidity from hypertension, dyslipidemia, type 2 diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis and endometrial, breast, prostate, and colon cancers. Higher body weights are also associated with increases in all-cause mortality. Most or all of these problems are relieved or improved by permanent significant weight loss. Longevity is likewise significantly increased by permanent significant weight loss.

Weight loss treatments vary depending, at least in part, on the degree of weight loss one is attempting to achieve in a subject as well as on the severity of overweight or obesity exhibited by the subject. For example, treatments such as low-fat diet and/or regular exercise are often adequate in cases where a subject is only mildly overweight. Such treatments can be enhanced by controlled use of over-the-counter appetite suppressants including caffeine, ephedrine and phenylpropanolamine (Acutrim®, Dexatrim®). Moreover, prescription medications including amphetamine, diethylpropion (Tenuate®), mazindol (Mazanor®, Sanorex®), phentermine (Fastin®, Ionamin®), phenmetrazine (Preludin®), phendimetrazine (Bontrol®, Plegine®, Adipost®, Dital®, Dyrexan®, Melfiat®, Prelu-2®, Rexigen Forte®), benzphetamine (Didrex®) and fluoxetine (Prozac®) are often used in the treatment of seriously overweight and/or obese subjects or patients. However, such treatments, at best, result in only ~5-10% weight loss (when accompanied with diet and exercise). Moreover, most of these treatments ultimately prove inadequate because they are either dangerous, ineffective or quickly lose their anorexient effect.

At least one class of these prescription medications, the phentermines (Fastin®, Ionamin®), have been used as monotherapy in the treatment of obesity for about 30 years. The phentermines are members of a class of drugs known as the sympathomimetics for their ability to mimic stimulation of the central nervous system. The phentermines act on the hypothalamus, an appetite control center of the brain. Phentermine monotherapy can increase weight loss when used in combination with diet and exercise, as compared to diet and exercise alone. However, the drug loses effectiveness after about two weeks and, in fact, is not approved by the FDA for use beyond six weeks. Moreover, weight loss may not be permanent, especially after the drug is discontinued. Phentermine treatment is also associated with side effects including nervousness, irritability, headache, sweating, dry-mouth, nausea, and constipation.

In general, available weight loss drugs have limited efficacy and some clinically significant side effects. Studies of the weight loss medications dexfenfluramine (Guy-Grand, B. et al. (1989) *Lancet* 2:1142-5), orlistat (Davidson, M. H. et al. (1999) *JAMA* 281:235-42), sibutramine (Bray, G. A. et al. (1999) *Obes. Res.* 7:189-98), and phentermine (Douglas, A. et al. (1983) *Int. J. Obes.* 7:591-5) have shown similar effectiveness. Studies for each demonstrated a weight loss of about 5% of body weight for drug compared with placebo. Other serious considerations limit the clinical use of these drugs. Dexfenfluramine was withdrawn from the market because of suspected heart valvulopathy, orlistat is limited by GI side effects, sibutramine can cause hypertension, and phentermine has limited efficacy.

Various combination therapies that include phentermine as one of the agents have been investigated and have met with mixed success. The phentermines were, up until around 1997, often prescribed along with fenfluramine (Pondimin®) or dexfenfluramine (Redux®), nicknamed "fen", as a combination therapy known as fen-phen. Fenfluramine is a potent releaser of serotonin from serotonergic neurons which acts on a cerebral appetite center. When combined with phentermine, fenfluramine had the effect of enhancing and extending the anorexient action of phentermine. However in 1997, the Food and Drug Administration ("FDA") asked manufacturers to withdraw Pondimin® and Redux® due to studies which strongly suggested that the drugs cause damage to the mitral valve of the heart and pulmonary hypertension.

More recently, it has been suggested that phentermine in combination with anti depressants is a potentially effective therapy for effecting weight loss, U.S. Pat. No. 5,795,895. In particular, the anti-depressants suggested for use in this new combination therapy are members of a class of compounds known as selective serotonin reuptake inhibitors (SSRIs) which include fluoxetine (Prozac®), sertraline (Zoloft®), fluvoxamine maleate (Luvox®) and trazodone hydrochloride (Desyrel®). The combination therapy is also suggested to treat coexisting depression and/or obsessive-compulsive disorder.

Phentermine has also recently been tested in combination with bupropion (Wellbutrin®) for the treatment of obesity. Bupropion is an antidepressant that inhibits dopamine reuptake, as compared to serotonin uptake. It is also used to treat Attention Deficit Disorder (ADHD), bipolar depression, chronic fatigue syndrome, cocaine addiction, nicotine addiction, and lower back pain. While bupropion alone had a modest effect as a weight loss agent (when prescribed to patients following a 1200 calorie per day diet), patients receiving phentermine in combination with bupropion experienced no greater weight loss than those receiving bupropion alone. Moreover, bupropion use has been associated with drug-induced seizures causing it to be removed from the market by the FDA for at least five years before its re-introduction in 1989.

Accordingly, there exists a need for new, more effective weight loss treatments which are accompanied by fewer adverse or undesirable side effects or less serious side effects. In particular, there exists a need for developing medical weight loss treatments which can potentially lower major endpoints such as death and/or myocardial infarction rates by

directly treating obesity rather than treating the consequences of obesity (e.g., diabetes, hypertension, hyperlipidemia), as is currently the practice.

SUMMARY OF THE INVENTION

The present invention features a novel therapy for effecting weight loss which involves treating a subject with a sympathomimetic agent in combination with an anticonvulsant sulfamate derivative such that the subject experiences weight loss. In one aspect, the sympathomimetic agent is a compound having anorectic activity (e.g., amphetamine, methamphetamine, benzphetamine, phentermine, chlorphentermine, diethylpropran, phenmetrazine, and phendimetrazine). Preferably, the sympathomimetic agent is the drug phentermine (nicknamed "phen"). In another aspect, the anticonvulsant sulfamate derivative is the drug topiramate.

The combination methods of the present invention also are effective against symptoms associated with Syndrome X. Accordingly, in another aspect the invention features methods for treating Syndrome X with a combination of a sympathomimetic agent and an anticonvulsant sulfamate derivative (e.g., phentermine and topiramate, respectively) such that at least one symptom associated with Syndrome X is affected. Moreover, the combination methods of the present invention have been shown to have beneficial side effects, such as ameliorating sleep apnea and lowering blood pressure, blood glucose, blood lipid, and Hgb A1C levels. Accordingly, in another aspect the invention features methods for treating at least one side effect associated with obesity. In a preferred embodiment, at least one side effect of obesity is treated with a combination of a sympathomimetic agent in combination with an anticonvulsant sulfamate derivative.

The invention also features pharmaceutical compositions including therapeutically effective amounts of a sympathomimetic agent in combination with an anticonvulsant sulfamate derivative. Kits including the pharmaceutical compositions of the present invention are also featured (e.g., kits including the compositions packaged in a daily dosing regimen).

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a novel combination therapy for effecting weight loss in a subject. In particular, the present invention provides methods which involve treating the subject with a therapeutically effective amount of a combination of a sympathomimetic agent (e.g., phentermine or a phentermine-like compound) and an anticonvulsant sulfamate derivative (e.g., topiramate). The methods are particularly useful for the treatment of overweight and/or obesity, as well as in the treatment of Syndrome X.

The phrase "therapeutically effective amount" as used herein refers to the amount of an agent, compound, drug, composition, or combination of the invention which is effective for producing some desired therapeutic effect upon administration to a subject or patient (e.g., a human subject or patient). The phrase "administering to a subject" or "administering to a patient" refers to the process of introducing an agent, compound, drug, composition or combination of the invention into the subject or patient's body via an art-recognized means of introduction (e.g., orally, transdermally, via injection, etc.).

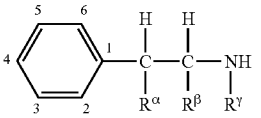
The term "sympathomimetic agent" is a term of art and refers to agents or compounds which "mimic" or alter stimulation of the sympathetic nervous system (e.g., stimulates the peripheral nervous system) of an organism (e.g., mimic the stimulation naturally effected by physical activity, psychological stress, generalized allergic reaction and other situations in which the organism is provoked).

Preferred sympathomimetic agents for use in the present invention as well as there general clinical uses or effects are set forth in Table I.

TABLE I

Sympathomimetic Agents and Clinical Uses Thereof

General structure:

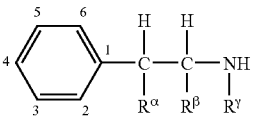


Agent name	Ring substituent(s)	R^{α}	R^{β}	R^{γ}	Main Clinical Uses: α Receptor A N P V	Main Clinical Uses: β Receptor B C	Main Clinical Uses: CNS, 0
Phenylethylamine		H	H	H			
Epinephrine	3-OH, 4-OH	OH	H	CH_3	A, P, V	B, C	
Norepinephrine	3-OH, 4-OH	OH	H	H	P		
Epinine	3-OH, 4-OH	H	H	CH_3			
Dopamine	3-OH, 4-OH	H	H	H	P		
Dobutamine	3-OH, 4-OH	H	H	1*		C	
Nordefrin	3-OH, 4-OH	OH	CH_3	H	V		
Ethylnorepinephrine	3-OH, 4-OH	OH	CH_2CH_3	H		B	
Isoproterenol	3-OH, 4-OH	OH	H	$CH(CH_3)_2$		B, C	
Protokylol	3-OH, 4-OH	OH	H	2*		B	
Isoetharine	3-OH, 4-OH	OH	CH_2CH_3	$CH(CH_3)_2$		B	
Metaproterenol	3-OH, 5-OH	OH	H	$CH(CH_3)_2$		B	
Terbutaline	3-OH, 5-OH	OH	H	$C(CH_3)_3$		B	
Metaraminol	3-OH	OH	CH_3	H	P		
Phenylephrine	3-OH	OH	H	CH_3	N, P		
Tyramine	4-OH	H	H	H			
Hydroxyamphetamine	4-OH	H	CH_3	H	N, P	C	
Methoxyphenamine	2-OCH_3	H	CH_3	CH_3		B	

TABLE I-continued

Sympathomimetic Agents and Clinical Uses Thereof

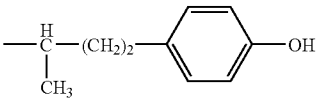
General structure:



Main Clinical Uses

Agent name	Ring substituent(s)	R^{α}	R^{β}	R^{γ}	α Receptor A N P V	β Receptor B C	CNS, 0
Methoxamine	2-OCH_3, 5-OCH_3	OH	CH_3	H	P		
Albuterol	3-CH_2OH, 4-OH	OH	H	$C(CH_3)_3$		B	
Amphetamine		H	CH_3	H			CNS, 0
Methamphetamine		H	CH_3	CH_3	P		CNS, 0
Benzphetamine		H	CH_3	—NHR^{γ} is replaced with 3*			0
Ephedrine		OH	CH_3	CH_3	N, P	B, C	
Phenylpropanolamine		OH	CH_3	H	N		
Mephentermine		H	—CHR^{β}— is replaced with 4*	CH_3	N, P		
Phentermine		H	"	H			0
Chlorphentermine	4-Cl	H	"	H			0
Fenfluramine	3-CF_3	H	CH_3	C_2H_5			0
Propylhexedrine	5*: phenyl ring is replaced with cyclohexyl	H	CH_3	CH_3	N		
Diethylpropion		6*: The substituent at the 1-position is replaced with 6, below.					0
Phenmetrazine		7*: The substituent at the 1-position is replaced with 7, below.					0
Phendimetrazine		8*: The substituent at the 1-position is replaced with 8, below.					0

*1:



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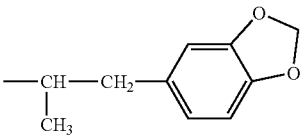

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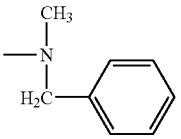

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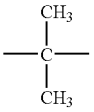

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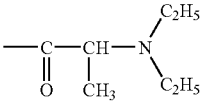
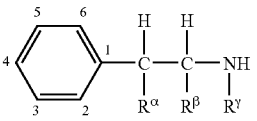


*7:

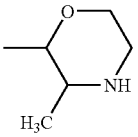
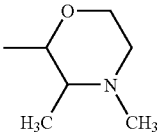
TABLE I-continued

Sympathomimetic Agents and Clinical Uses Thereof

General structure:



Main Clinical Uses

Agent name	Ring substituent(s)	R^{α}	R^{β}	R^{γ}	α Receptor A N P V	β Receptor B C	CNS, 0
							
*8: 							

α Activity
A = Allergic reactions (includes β action)
N = Nasal decongestion
P = Pressor (may include β action)
V = Other local vasoconstriction (e.g. in local anesthesia)
β Activity
B = Bronchodilator
C = Cardiac
CNS = Central nervous system
0 = Anorectic
*Numbers bearing an asterisk refer to the substituents numbered in the bottom rows of the table; substituent 5 replaces the phenyl rings, and 6, 7 and 8 are attached directly to the phenyl ring, replacing the ethylamine side chain.
†The α and β in the prototype formula refer to positions of the C atoms in the ethylamine side chain.

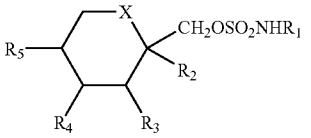
In preferred embodiments, the sympathomimetic agent has anorexient properties (e.g., suppresses appetite) or is anorectic without significant toxicity to a subject or patient (e.g., a human) at therapeutically effective doses. In a more preferred embodiment, the sympathomimetic agent has anorexient properties (e.g., suppresses appetite) or is anorectic without loss of efficacy or without adverse or undesirable side effects to a subject or patient (e.g., a human subject or patient) at therapeutically effective doses when prescribed in combination with topiramate. In yet another embodiment, the sympathomimetic agent is phentermine or a phentermine-like compound. As defined herein, a "phentermine-like compound" is a compound structurally related to phentermine (e.g., an analog or derivative) which maintains an anorectic activity similar to that of phentermine. A preferred phentermine-like compound is chlorphentermine. In yet another embodiment, the sympathomimetic agent is amphetamine or an amphetamine-like compound. As used herein, an "amphetamine-like compound" is a compound structurally related to amphetamine (e.g., an analog or derivative) which maintains an anorectic effect of amphetamine. In yet another embodiment, the sympathomimetic agent is phenmetrazine or a phenmetrazine-like compound. As defined herein, a "phenmetrazine-like compound" is a compound structurally related to phenmetrazine (e.g., an analog or derivative) which maintains an anorectic effect of phenmetrazine. A preferred phenmetrazine-like compound is phendimetrazine. Analogs and/or derivatives of the compounds of the present invention can be tested for their ability to suppress appetite (e.g., suppress food intake) in a subject (e.g., a mammalian subject).

In an exemplary preferred embodiment, the sympathomimetic agent is selected from the group consisting of amphetamine, methamphetamine, benzphetamine, phenylpropanolamine, phentermine, chlorphentermine, diethylpropion, phenmetrazine, and phendimetrazine (as set forth in Table I. In a particularly preferred embodiment, the sympathomimetic agent is phentermine. It is also within the scope of the present invention to utilize other sympathomimetic agents including pseudo ephedrine (a stereoisomer of ephedrine, SUDAFED®), methylphenidate (RITALIN®), tuaminoheptane, and other CNS stimulants including, for example, caffeine.

The terms "anticonvulsant sulfamate derivative" and "anticonvulsant sulfamate derivatives" are terms of art and refer to a class of sulfamate-derived compounds that possess anticonvulsant activity and have an art-recognized use in the treatment of epilepsy. In particular, the anticonvulsant sulfamate derivatives are monosaccharide derivatives with sulfamate functionality. The anticonvulsant sulfamate derivatives for use in the present invention have one or more of the following modes of activity: modulation of voltage-dependent sodium conductance; potentiation of gamma-aminobutyric acid-evoked currents; inhibition of the kainate/alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) subtype of the glutamate receptor; and/or inhibition of carbonic anhydrase (e.g, a mechanism by which the anticonvulsant derivative of the present invention may decrease the sensation of

taste). The anticonvulsant sulfamate derivatives for use in the present invention are described further in U.S. Pat. Nos. 4,513,006, 5,384,327, 5,498,629, 5,753,693 and 5,753,694, as are methods of synthesizing such anticonvulsant sulfamate derivatives. The aforementioned patents are incorporated by reference herein in their entireties.

In preferred embodiments, the anticonvulsant sulfamate derivative is a compound having the following formula (I):



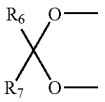
(I)

wherein:

X is CH_2 or O;

R_1 is H or alkyl; and

R_2, R_3, R_4 and R_5 are independently H or lower alkyl, with the proviso that when X is O, then R_2 and R_3 and/or R_4 and R_5 together may be a methylenedioxy group of the following formula (II):



(II)

in which R_6 and R_7 are the same or different and are H or lower alkyl, or are joined to form a cyclopentyl or cyclohexyl ring.

R_1 in particular is hydrogen or alkyl of about 1 to 4 carbons, such as methyl, ethyl, or isopropyl. Alkyl includes both straight and branched chain alkyl. Alkyl groups R_2, R_3, R_4, R_5, R_6 and R_7 are about 1 to 3 carbons and include methyl, ethyl, isopropyl and n-propyl.

A particular group of compounds of the formula (I) are those wherein X is oxygen and both R_2 and R_3, and R_4 and R_5 together are methylenedioxy groups of the formula (II), wherein R_6 and R_7 are both hydrogen, both alkyl, or combine to form a spiro cyclopentyl or cyclohexyl ring, in particular, where R_6 and R_7 are both alkyl such as methyl. A second group of compounds are those wherein X is CH_2 and R_4 and R_5 are joined to form a benzene ring. A third group of compounds of the formula (I) are those wherein both R_2 and R_3 are hydrogen.

In preferred embodiments, the anticonvulsant sulfamate derivatives have anorexient properties (e.g., suppress appetite) without significant toxicity to a subject or patient (e.g., a human) at therapeutically effective doses. In a more preferred embodiment, the anticonvulsant sulfamate derivatives have anorexient properties (e.g., suppress appetite) without significant adverse or undesirable side effects to a subject or patient (e.g., a human) at therapeutically effective doses when prescribed in combination with phentermine. In a particularly preferred embodiment the anticonvulsant sulfamate derivative is topiramate (Topamax®). Topiramate, also referred to in the art as 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate, has been demonstrated in clinical trials of human epilepsy to be effective as an adjunctive therapy or as monotherapy in treating simple and complex partial seizures and secondarily generalized seizures (E. Faught et al. (1995) *Epilepsia* 36(suppl 4):33; S. Sachdeo et al. (1995) *Epilepsia* 36(suppl 4):33) and is currently marketed for the treatment of simple and complex partial seizure epilepsy with or without secondary generalized seizures.

Dosages, Administration and Pharmaceutical Compositions:

The choice of appropriate dosages for the drugs used in combination therapy according to the present invention can be determined and optimized by the skilled artisan, e.g., by observation of the patient, including the patient's overall health, the response to the combination therapy, and the like. Optimization, for example, may be necessary if it is determined that a patient is not exhibiting the desired therapeutic effect or conversely, if the patient is experiencing undesirable or adverse side effects that are too many in number or are of a troublesome severity.

Preferably, a sympathomimetic drug (e.g., a drug set forth in Table I) is prescribed at a dosage routinely used by the skilled artisan (e.g., physician) to promote the desired therapeutic effect of the drug, when the drug is used as a monotherapy. Preferably, an anticonvulsant sulfamate derivative (e.g., a compound having formula I) is prescribed at a lower dosage than routinely used by the skilled artisan (e.g., physician) to promote the desired therapeutic effect of the drug, when the drug is used as a monotherapy (e.g., in the treatment of epilepsy). In a preferred embodiment, a sympathomimetic drug or anticonvulsant sulfamate derivative is prescribed at a dose of between 5-1000, preferably between 10-1500, more preferably between 20-1000 and most preferably between 25-50 mg daily.

It is especially advantageous to formulate compositions of the invention in unit dosage form for ease of administration and uniformity of dosage. The term "unit dosage forms" as used herein refers to physically discrete units suited as unitary dosages for the individuals to be treated. That is, the compositions are formulated into discrete dosage units each containing a predetermined, "unit dosage" of an active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specifications of the novel dosage unit forms of the invention are dependent on the unique characteristics of the composition containing the anticonvulsant or sympathomimetic agent and the particular therapeutic effect to be achieved. Dosages can further be determined by reference to the usual dose and manner of administration of the ingredients. It is also within the scope of the present invention to formulate a single physically discrete dosage form having each of the active ingredients of the combination treatment (e.g., a single dosage form having an anticonvulsant agent and a sympathomimetic agent).

The method of administration of compositions or combinations of the invention will depend, in particular, on the type of sympathomimetic agent used and the chosen anticonvulsant sulfamate derivative. The sympathomimetic agent and the anticonvulsant sulfamate derivative may be administered together in the same composition or simultaneously or sequentially in two separate compositions. Also, one or more sympathomimetic agents or one or more anticonvulsant sulfamate derivatives may be administered to a subject or patient either in the form of a therapeutic composition or in combination, e.g., in the form of one or more separate compositions administered simultaneously or sequentially. The schedule of administration will be dependent on the type of sympathomimetic agent(s) and anticonvulsant sulfamate derivative(s) chosen. For example, a sympathomimetic agent can have a stimulant effect and the degree of such stimulant effect may vary depending on the sympathomimetic agent chosen.

Accordingly, a sympathomimetic agent having a significant stimulant effect might be administered earlier in the day than administration of a sympathomimetic agent having a lesser stimulant effect. Likewise, an anticonvulsant sulfamate derivative can have a sedative effect and the degree of such sedative effect may vary depending on the anticonvulsant sulfamate derivative chosen. Accordingly, an anticonvulsant sulfamate derivative having a significant sedative effect might be administered later in the day than administration of an anticonvulsant sulfamate derivative having a lesser sedative effect. Moreover, sympathomimetic agents and/or anticonvulsant agents having lesser stimulant or sedative effects, respectively, may be administered simultaneously.

Sympathomimetic agents and/or anticonvulsant sulfamate derivatives can also be administered along with a pharmaceutically acceptable carrier. As used herein "pharmaceutically acceptable carrier" includes any solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in compositions of the invention is contemplated.

A sympathomimetic agent alone, or in combination with an anticonvulsant sulfamate derivative in the form of a composition, is preferably administered orally. When the composition(s) are orally administered, an inert diluent or an assimilable edible carrier may be included. The composition and other ingredients may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the individual's diet. For oral therapeutic administration, the composition may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The percentage of the compositions and preparations may, of course, be varied. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. In a particularly preferred embodiment, the present invention includes pharmaceutical composition comprising a therapeutically effective amount of a sympathomimetic agent and an anticonvulsant sulfamate derivative. In one embodiment, the present invention includes a therapeutically-effective amount of a sympathomimetic agent and an anticonvulsant sulfamate derivative packaged in a daily dosing regimen (e.g., packaged on cards, packaged with dosing cards, packaged on blisters or blow-molded plastics, etc.). Such packaging promotes products and increases patient compliance with drug regimens. Such packaging can also reduce patient confusion. The present invention also features such kits further containing instructions for use.

The tablets, troches, pills, capsules and the like may also contain a binder, an excipient, a lubricant, or a sweetening agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed.

A sympathomimetic agent, alone or in combination with an anticonvulsant sulfamate derivative, can also be administered in a convenient manner such as by injection (subcutaneous, intravenous, etc.), inhalation, transdermal application, or rectal administration. Depending on the route of administration, the composition containing the sympathomimetic agent and/or anticonvulsant sulfamate derivative may be coated with a material to protect the compound from the action of acids and other natural conditions which may inactivate the compounds or compositions.

To administer the compositions, for example, transdermally or by injection, it may be necessary to coat the composition with, or co-administer the composition with, a material to prevent its inactivation. For example, the composition may be administered to an individual in an appropriate diluent or in an appropriate carrier such as liposomes. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Liposomes include water-in-oil-in-water CGF emulsions as well as conventional liposomes (Strejan et al. (1984) *J. Neuroimmunol.* 7:27). To administer the compositions containing the sympathomimetic agents and/or anticonvulsant sulfamate derivatives parenterally or intraperitoneally, dispersions can be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

Compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. In all cases, the composition must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene gloycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol and sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

A preferred aspect of the present invention features prescribing phentermine in combination with topiramate to effect weight loss and/or to treat Syndrome X and/or a subset of symptoms thereof. A preferred dose for phentermine is between about 5-60 mg daily, including but not limited to doses of 8, 10, 15, 20, 25, 30, 35, 40, 45, 50 and 55 mg daily. A particularly preferred dose for phentermine is about 15 mg daily. In an exemplary embodiment, the phentermine is of an immediate release form.

Preferably, the phentermine is taken by the patent in the morning and more preferably, is taken before breakfast. The phentermine is best taken in the morning because the drug is a stimulant as well as an appetite suppressant. When phentermine is prescribed (e.g., as part of the combination therapy described herein), physicians should be aware and may want to advise patients that the drug can be mildly habit forming. Phentermine can also cause increased nervousness, increased energy, irritability and, rarely, insomnia. Stopping phentermine may also cause tiredness lasting for up to 1-2 weeks. Phentermine can also raise blood pressure (e.g., during the early phases of treatment).

A preferred dose for topiramate is between about 50-1500 mg daily. As discussed previously, prescription of topiramate at dosages of ≧400 mg daily results is promotion of undesir-

able side effects (e.g., sedation, mental clouding). Accordingly, in a preferred embodiment, topiramate is prescribed at a dose of about 50-400 mg daily. In another preferred embodiment, the dosage of topiramate is increased gradually at the outset of the therapy in order to reduce the chance of undesirable side effects associated with higher doses of the drug. In an exemplary embodiment, the topiramate is administered at a dose of 25 mg daily for about the first 5-7 days (e.g., 6 days) of treatment, at a dose of about 50 mg daily for the next 5-7 days (e.g., 6 days), at a dose of 100 mg daily for about the next 6-8 days (e.g., 7 days) and about 150 mg daily for the next 20-26 days. From this point forward, the topiramate can be administered at a dose of 150-250 mg daily, including but not limited to doses of 175, 200, and 225 mg daily. A particularly preferred dose for continued therapy is about 200 mg of topiramate daily. In another exemplary embodiment, the topiramate is of an immediate release form. In yet another exemplary embodiment, the topiramate is of a sustained release form.

In a preferred embodiment, topiramate is taken later in the day than the phentermine. Preferably, the patient takes the topiramate just before supper or later in the evening. Topiramate is best given later in the day because the drug can be sedating. In other embodiments, the topiramate is given BID (e.g., twice daily), TID (three times daily) or QID (four time daily). When prescribing topiramate, physicians should be aware and may want to advise patients that the drug can cause tiredness, fatigue, dizziness, difficulty with speech or finding words, difficulty concentrating, difficulty with balance, and/or numbness or tingling in the hands or feet. Less common side effects are nausea, coordination problems, abdominal pain, slowed thinking nervousness, depression, breast pain, painful periods, double or blurred vision, palpitations, low white blood count and kidney stones. A physician should also advise patients that the drug may not be taken if the patient is also taking Diamox (acetazolamide). No female patient should become pregnant while taking this drug as it may cause birth defects. If a female patient misses a period she should immediately discontinue taking the medication and inform the physician. Female patients should not be treated according to the methods of the present invention if breast feeding a child. Patients should not drink alcohol or take sedating medications while taking topiramate since excess sedation can occur. Patients should also refrain from performing dangerous tasks (e.g. operating heavy machinery or driving) until they are comfortable with the side effects of the full dose (e.g., 200-400 mg daily). Patients should be advised not to increase the dosage beyond what is prescribed. Topiramate is not habit forming.

Yet another embodiment of the present invention features pharmaceutical compositions (e.g., for oral administration) comprising phentermine and topiramate in a single pharmaceutical formulation. Such compositions may be preferred, for example, to increase patient compliance (e.g., by reducing the number of administrations necessary to achieve the desired pharmacologic effect).

In a preferred embodiment, the pharmaceutical composition includes phentermine in an immediate release form and further includes topiramate in a controlled release formulation. As defined herein, an "immediate release formulation" is one which has been formulated to allow, for example, the phentermine, to act as quickly as possible. Preferred immediate release formulations include, but are not limited to, readily dissolvable formulations. As defined herein, a "controlled release formulation" includes a pharmaceutical formulation that has been adapted such that drug release rates and drug release profiles can be matched to physiological and chronotherapeutic requirements or, alternatively, has been formulated to effect release of a drug at a programmed rate. Preferred controlled release formulations include, but are not limited to, granules, delayed release granules, hydrogels (e.g., of synthetic or natural origin), other gelling agents (e.g., gel-forming dietary fibers), matrix-based formulations (e.g., formulations comprising a polymeric material having at least one active ingredient dispersed therethrough), granules within a matrix, polymeric mixtures, granular masses, and the like.

In one embodiment, a controlled release formulation is a delayed release form. As defined herein, a "delayed release form" is formulated in such a way as to delay, for example, topiramate's action for an extended period of time. A delayed release form can be formulated in such a way as to delay the release of an effective dose of topiramate for 4, 8, 12, 16 or 24 hours following the release of phentermine. In yet another preferred embodiment, a controlled release formulation is a sustained release form. As defined herein, a "sustained release form" is formulated in such a way as to sustain, for example, the topiramate's action over an extended period of time. A sustained release form can be formulated in such a way as to provide an effective dose of topiramate (e.g., provide a physiologically effective blood level) over a 4, 8, 12, 16 or 24 hour period.

Preferred compositions include a tablet core consisting essentially of topiramate, said core being in association with a layer of phentermine. Preferably, the core has a delayed or sustained dissolution rate. In an exemplary embodiment, a tablet can comprise a first layer containing, for example, phentermine (e.g., in an immediate release formulation) and a core containing, for example, topiramate in a delayed release or sustained release formulation. Other exemplary embodiments can include, for example, a barrier between the first layer and core, said layer serving the purpose of limiting drug release from the surface of the core. Preferred barriers prevent dissolution of the core when the pharmaceutical formulation is first exposed to gastric fluid. For example, a barrier can comprise a disintegrant, a dissolution-retarding coating (e.g., a polymeric material, for example, an enteric polymer), or a hydrophobic coating or film, and can be selectively soluble in either the stomach or intestinal fluids. Such barriers permit the topiramate to leach out slowly and can cover substantially the whole surface of the core.

The above-described pharmaceutical compositions are designed to release the two effective agents of the combination therapy of the present invention sequentially, i.e., releasing topiramate after releasing phentermine, both agents being contained in the same pharmaceutical composition. Preferred amounts of phentermine and topiramate are as described above with particularly preferred compositions comprising from about 5 mg to about 60 mg phentermine and from about 50 mg to 1500 mg topiramate. Particularly preferred compositions include at least 15 mg phentermine and at least about 50 mg, 100 mg or 200 mg topiramate.

Pharmaceutical compositions so formulated may contain additional additives, suspending agents, diluents, binders or adjuvants, disintegrants, lubricants, glidants, stabilizers, coloring agents, flavors, etc. These are conventional materials which may be incorporated in conventional amounts.

In one embodiment, a method of the present invention is carried out, practiced or performed such that weight loss in the subject or patient occurs. Accordingly, the methods of the present invention are particularly useful for the treatment of overweight or obese patients. As defined herein, "overweight" subjects or patients are between about 1 and 20 percent overweight (e.g., weighs 1-20% in excess of their

ideal body weight). Also as defined herein, an "obese" subject or patient is greater than 20 percent overweight (e.g., weighs >20% in excess of his or her ideal body weight). Alternatively, the methods of the present invention are useful in the treatment of subjects or patients in need of losing weight, but who are not necessarily overweight or obese. For example, it may be desirable to achieve weight loss in subjects or patients having arthritis or prostheses such that the individual experiences less adverse effects resulting from bearing weight.

The combination therapies of the present invention will generally be administered until the patient has experienced the desired weight loss, and preferably has achieved an ideal body weight. Alternatively, the combination therapies of the present invention can be administered until the patient has achieved a weight loss of 5-10%, 10-15%, 15-20% or 20-25% of their initial body mass (e.g., the patient's starting weight).

The present inventor has also recognized that the combination therapy of the present invention ameliorates symptoms associated with Syndrome X. Syndrome X consists of a complex of medical problems that are largely associated with obesity, including, hypertension, diabetes or glucose intolerance and insulin resistance, hyperlipidemia, and often tiredness and sleepiness associated with sleep apnea. Patients are often treated with combinations of antihypertensives, lipid lowering agents, insulin or oral diabetic drugs, and various mechanical and surgical treatments of sleep apnea. However, such treatments are often costly and do not treat the underlying problem of obesity. Moreover, some of the treatments for diabetes, including insulin and oral diabetic agents, actually aggravate Syndrome X by increasing insulin levels, increasing appetite, and increasing weight. This can lead to higher blood pressure and even higher cholesterol. Accordingly, one aspect of the present invention features a method of treating Syndrome X using the combination therapies described herein. In one embodiment, the invention features a method of treating Syndrome X in a subject or patient which includes treating the subject with a therapeutically effective amount of a combination of an anticonvulsant sulfamate derivative (e.g., topiramate) and a sympathomimetic agent (e.g., phentermine or a phentermine-like compound), such that at least one symptom associated with Syndrome X is affected. As defined herein, "affecting a symptom" (e.g., affecting a symptom associated with Syndrome X) refers to lessening, decreasing the severity of the symptom or reversing, ameliorating, or improving the symptom (e.g., decreasing hypertension, ameliorating diabetes, reversing glucose intolerance or insulin resistance, lessening hyperlipidemia, or decreasing tiredness and sleepiness associated with sleep apnea).

Treatment of Syndrome X according to the methods of the present invention includes affecting at least one, preferably two, more preferably three, more preferably four, five or six symptoms associated with Syndrome X. In a particularly preferred embodiment, all symptoms associated with Syndrome X are affected (e.g., lessened, reversed, ameliorated, etc.).

The present inventor has also recognized that the combination therapy of the present invention ameliorates some side effects associated with obesity, as described herein. Accordingly, one aspect of the present invention features a method of treating at least one side effect associated with obesity using the combination therapies described herein. In one embodiment, the invention features a method of treating at least one obesity-related side effect in a subject or patient which includes treating the subject with a therapeutically effective amount of a combination of an anticonvulsant sulfamate derivative (e.g., topiramate) and a sympathomimetic agent (e.g., phentermine or a phentermine-like compound), such that at least one obesity-related side effect is effected. As defined herein, a "side effect associated with obesity" includes a symptom or disorder in a subject (e.g., a patient) which is secondary and/or results from (e.g., directly and/or indirectly results from) a medical condition for which the subject is obese and/or being treated. In a preferred embodiment, the subject is obese and/or is being treated for obesity. In another embodiment, the subject has at least one or more (e.g., two, three, four, five or more) side effect(s) selected from the group consisting of sleep apnea, high blood pressure and high blood sugar, high blood lipid, high Hgb A1C or other art-recognized side effects associated with obesity.

Whether in the treatment of Syndrome X or in the practicing of the methods of the present invention to effect weight loss (e.g., in the treatment of overweight and/or obesity) or in treatment of side effects associated with obesity, it will be apparent to the skilled artisan (e.g., physician) that monitoring of the patient is needed to determine the effectiveness of the treatments and to potentially modify the treatments (e.g., modify the dosing, time of drug administration, sequence of drug administration, as defined herein). Accordingly, in certain embodiments, the patient is monitored about every 2-6, preferably every 3-5 and more preferably every 4 weeks. Monitoring the effective of treatment to achieve weight loss includes, but is not limited to monitoring the subject or patient's body weight (e.g., comparing the patient's initial body weight to that at a follow-up visit, for example, four weeks after the initiation of treatment). Additional features of the subject or patient's health can also be monitored (i.e., monitoring the patient's overall health and/or monitoring the effectiveness of treatment of an undesired side effect of obesity) including, but not limited to the patient's blood pressure, blood sugar, serum lipid levels, etc. Likewise, monitoring a subject or patient for treatment of Syndrome X can include monitoring of at least one, preferably more than one symptom associated with Syndrome X.

This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patents and published patent applications cited throughout this application are hereby incorporated by reference.

EXAMPLE 1

Patients as part of the following trial were treated according to the following dosage regimen. Patients took phentermine at a dose of 15 mg daily throughout the weight loss program, before breakfast. For the first 6 days, patients took one 25 mg tablet of topiramate before supper. For the next 6 days, patients took two 25 mg tablets of topiramate before supper. For the next 7 days (days 13-19), patients took 100 mg before supper daily using 4-25 mg tablets of topiramate daily. For days 20-26, patients took 150 mg of topiramate daily consisting of one-half of a 200 mg tablet and two 25-mg mg tablets of topiramate. From that point on, unless instructed otherwise by the physician, patients continued to take one 200 mg topiramate tablet daily before supper and continued the 15 mg phentermine daily in the morning. Patients were advised to drink at least eight (8) full glasses of water daily to reduce the risk of kidney stones which may result from taking topiramate.

Patients were advised that while the effect of phentermine is fairly rapid, the effect of topiramate is slower in onset. The weight reduction effect of topiramate will continue for as long as 18 months on the medication. That is, the patient can expect to continue gradual weight loss for up to 18 months on the medication. Of course, weight loss is maximal if the patient

follows diet and/or exercise programs. The weight loss should exceed 15% of the patients starting weight. Thus, if the patient weighs about 200 pounds as of the start date, he/she might expect to lose at least 30 pounds in a period of 12-18 months. The following patient data has been collected.

TABLE II

Patient's Initials	Age	Sex	Start Weight (lbs)	Start Blood Pressure	Follow-Up Date	Follow-Up Weight (lbs)	% Weight Loss	Follow-Up Blood Pressure
M. O.[1]	48	F	182	115/70	5 weeks	177	2.7%	120/80
					9 weeks	176	3.3%	110/70
T. M.	37	F	190	122/84	2 weeks, 5 days	178	6.3%	110/80
					6 weeks, 2 days	168	11.6%	125/80
D. M. (A)	28	M	286	138/90	4 weeks	279	2.4%	128/86
P. L.	55	F	144	132/84	4 weeks	141	2.1%	138/85
					9 weeks	137	4.9%	122/82
E. K.	52	F	181	130/100	5 weeks	175	3.3%	140/88
I. F.	41	F	196	95/60	6 weeks, 5 days			
D. M. (B)[2]	56	M	295	150/80	4 weeks, 2 days	297	(+0.7%)	148/82
					8 weeks, 2 days	287	2.7%	140/70

[1]Patient M. O. was being treated with Meridia ® at the onset of the study, which continued through the first 5 weeks of the study. At the 5-week follow up, M. O. was switched to the phentermine/topiramate regime described above.
[2]Patient D. M. (B) was being treated with phentermine alone at the onset of the study and was taking the full dose of topiramate by the fourth week of the study.

As is apparent from the above-described data, patients not previously treated with an anorexient at the outset of the study experienced an average of about 3.5% weight loss after only 2-6 weeks (e.g., patient T.M. lost 6.3% body weight, patient D.M.(A) lost 2.4% body weight, patient P.L. lost 2.1% body weight and patient E.K. lost 3.3% body weight). After only 6-9 weeks of treatment, patients (not previously treated with an anorexient at the outset of the study experienced an average of about 8.3% weight loss (e.g., patient T.M. lost 11.6% body weight and patient P.L. lost 4.9% body weight). The patient previously on Meridia® (patient M.O.) lost 3.3% body weight after being enrolled in the program for 9 weeks. Moreover, the patient previously on phentermine (patient D.M.(B)) lost a total of 2.7% body weight after being enrolled in the program for about 8 weeks. This particular patient reported that this is the most significant weight loss he has achieved to date, the patient having previously tried other conventional therapies.

In addition to the weight loss reported above, almost all patients enrolled in the study experienced decreased blood pressure. Moreover, patients involved in the study who had previously taken Redux, phen-fen, Meridia and/or other weight loss treatments report that they have not previously experienced the benefits of the combined phentermine/topiramate therapy. Patients report that they have no appetite, can resist food easily, can concentrate and function at work (even in attention-intensive jobs such as computer programming), have more energy and feel better. Patients also report experiencing fewer side effects than any previous weight loss treatments tried.

EXAMPLE 2

Extended results of the trial described in Example 1.

A total of thirteen patients were treated for 1-9 months with phentermine (15 mg daily) in the morning and up to 400 mg of topiramate (median dose 200 mg), in the evening. [Note: Patient D.M.(B) discussed above is not included in this data as he was on phentermine treatment prior to treatment with the combination therapy of the present invention.] Topiramate dose was gradually increased from 25 mg per day in increments of 25-50 mg weekly until either desirable weight loss took place or until side effects limited dose increases. [Note: A fourteenth patient discontinued treatment after 3 days due to nausea.] All thirteen patients tolerated treatment well with minimal side effects. Along with taking medication, patients were instructed to walk at least 30 minutes three times per week and to follow a low fat diet. No patients had taken diet medication for at least 3 months prior to treatment. Average baseline BMI was 32.5 (range 26-48).

Average weight loss for the thirteen patients was 11.8%. For seven patients who were on treatment the longest (range 5-9 months), the average weight loss was 14.4%. Patients reported that they had little or no appetite and that they actually felt better (Topiramate's usefulness is also being investigated as a mood stabilizer) than before therapy. Blood pressure, lipid, glucose, and Hgb A1C values were also favorably affected by this treatment.

Table III sets forth patient data for the thirteen above-described patients treated with the combination therapy of the present invention.

TABLE III

Patient Data: Combination Therapy*

Patient No.	% of Weight Loss	Baseline BMI	Current BMI	Weeks on Rx	Current Status
1	7.7	38	35	10	on Rx
2	10.3	25	23	4	Finished
3	6.8	48	44	5	d/c early - dropped out
4	16.8	30	24	35	on taper
5	23.2	30	23	41	on taper
6	8	41	38	40	on Rx
7	9.7	28	25	33	on taper
8	14.4	30	26	44	on Rx
9	15.9	27	21	32	on taper
10	9	33	31	7	d/c early - will restart
11	12.9	28	24	22	Finished

TABLE III-continued

Patient Data: Combination Therapy*

Patient No.	% of Weight Loss	Baseline BMI	Current BMI	Weeks on Rx	Current Status
12	7	29	27	5	on Rx
13	12.1	34	31	6	on Rx

*data for thirteen patients
Average weight loss = 11.8% (13 patients)
Average weight loss ≧ 22 weeks on Rx = 14.4% (7 patients)
Average baseline BMI = 32.4

Table IV sets forth for the average blood pressure, blood glucose, Hgb A1C and blood lipid value for the thirteen patients.

TABLE IV

	BP mm Hg	GLUCOSE mg/dL	HGBA1C %*	CHOL mg/dL	TRIG mg/dL
Average Pre-Treatment Value	131.3/85.9	107	6.48	212	189
Average On Treatment Value	122.6/78.4	102	5.05	210	172

*Numbers include 1 diabetic patient whose oral hypoglycemic was reduced by 50% while on the weight loss treatment.

One of the thirteen patients in the study also had severe sleep apnea with the usual complications of daytime sleepiness and fatigue. His symptoms have disappeared with the weight loss treatment.

Of the six patients (i.e., finished or on taper) who have completed the combination therapy of the present invention, five of the six achieved a body mass index (BMI) of 24 or better. The average pre-treatment or baseline BMI for these six patients was 28. The final average BMI was 23.3. The average weight loss was 17%.

EXAMPLE 3

The 56-year old male patient described previously (D.M. (B)) who was initially taking phentermine alone and had topiramate added to his regimen had a good effect from the combination. He once weighed as much as 395 pounds. When Redux was still on the mark in the United States, he was treated with a combination of diet, exercise, Redux and phentermine. His lowest weight attained was 285 pounds. When Redux was withdrawn from the market, he remained on phentermine but gained weight back to 295-300 pounds. When topiramate was added to his regimen, he managed to lose 25 pounds and is currently at 271 pounds, his lowest weight since he was in his 20s. He, along with most of the patients treated so far, reported that the treatment with topiramate and phentermine had fewer side effects and was more effective than any previous weight loss treatment using medications that he and others had tried. This 56-year old man exhibited lowered blood pressure (approx. 15 mm Hg systolic and 10 mm Hg diastolic).

EXAMPLE 4

Extended results of the trial described in Examples 1 and 2.

The cumulative data from a total of seventeen patients treated with the combination weight loss treatment of the present invention are set forth in Table V.

TABLE V

Patient Data: Combination Therapy*

PATIENT	% WEIGHT LOSS	BASELINE BMI	CURRENT BMI	WEEKS ON Rx	CURRENT STATUS
1	7.7	38	35	33	on Rx
2	10.3	25	23	4	Finished
3	6.8	48	44	5	d/c early - dropped out
4	16.8	30	24	58	on taper
5	23.2	30	23	64	on taper
6	17.5	41	33	63	on Rx
7	9.7	28	25	56	on taper
8	18.6	30	24	67	on Rx
9	15.9	27	21	55	on taper
10	9	33	31	7	d/c early- will restart
11	12.9	28	24	22	Finished
12	7	29	27	5	d/c early- will restart
13	12.1	34	31	6	d/c early- will restart
14	22.5	46	32	16	on Rx
15	10.1	50	45	12	on Rx
16	6.4	27	24	4	Finished
17	6.3	27	25	6	on Rx

*data for seventeen patients
AVERAGE WEIGHT LOSS = 12.5% (17 patients)
AVERAGE WEIGHT LOSS ≧ 22 WEEKS ON Rx = 15.3% (8 patients)
AVERAGE BASELINE BMI = 33.6

The present invention provides a novel combination therapy for the treatment of obese or overweight patients that can result in weight losses of greater than 5-10%, perhaps even as great as 15-20%. The therapy combines phentermine or a phentermine-like drug with drug previously recognized for the treatment of epileptic seizures, known as topiramate. The combination therapy results in greater initial weight loss

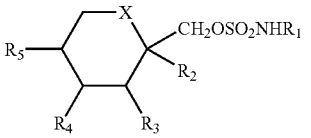
than other recognized therapies, potential greater overall weight loss and can be continued for significant periods of time with fewer and less serious side effects than other recognized weight loss treatments. In particular, the combination therapy far surpasses the modest anorexient effects of phentermine monotherapy and can be continued for significant periods of time without the loss of effectiveness experienced by patients being treated with phentermine alone. Moreover, the combination therapy has been found to ameliorate symptoms associated with Syndrome X and accordingly, has potential use in the treatment of Syndrome X.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

I claim:

1. A composition comprising an anticonvulsant agent and phentermine in amounts that in combination are effective to induce weight loss in a patient, wherein the anticonvulsant agent is an anticonvulsant sulfamate derivative having the structure of formula (I)



wherein X is CH_2 or O, R_1, R_2, R_3, R_4, and R_5 are independently H or C_1-C_4 alkyl, and further wherein when X is O, then R_2 and R_3, and/or R_4 and R_5, may be taken together to form a methylene dioxy linkage of the formula —O—CR_6R_7—O— in which R_6 and R_7 are independently H or C_1-C_3 alkyl, or may be taken together to form a cyclopentyl or cyclohexyl ring.

2. The composition of claim **1**, comprising a dosage form that provides for immediate release of the phentermine and controlled release of the anticonvulsant agent.

3. The composition of claim **2**, wherein the dosage form provides for delayed release of the anticonvulsant agent.

4. The composition of claim **3**, wherein the dosage form additionally provides for sustained release of the anticonvulsant agent.

5. A method for effecting a desired weight loss in a subject, comprising a administering once daily to the subject the composition of claim **1** until the subject has experienced the desired weight loss.

6. The method of claim **5**, wherein the subject is overweight.

7. The method of claim **6**, wherein the subject is obese.

8. The method of claim **5**, wherein the subject is neither overweight nor obese.

9. The method of claim **5**, wherein the subject suffers from a condition that can be alleviated with loss of body weight.

10. A controlled release dosage form comprising phentermine and topiramate in amounts that in combination are effective to induce weight loss in a patient, wherein the dosage form provides for immediate release of the phentermine and delayed release of the topiramate.

11. The dosage form of claim **10**, which further provides for sustained release of the topiramate.

12. The dosage form of claim **11**, wherein a physiologically effective blood level of topiramate is provided over a 4-hour period.

13. The dosage form of claim **11**, wherein a physiologically effective blood level of topiramate is provided over an 8-hour period.

14. The dosage form of claim **11**, wherein a physiologically effective blood level of topiramate is provided over a 12-hour period.

15. The dosage form of claim **10**, wherein release of topiramate is delayed by 4 hours following release of phentermine.

16. The dosage form of claim **10**, wherein release of topiramate is delayed by 8 hours following release of phentermme.

17. The dosage form of claim **10**, wherein release of topiramate is delayed by 12 hours following release of phentermine.

18. A method for effecting a desired weight loss in a subject, comprising administering once daily to the subject the controlled release dosage form of claim **10**, until the subject has experienced the desired weight loss.

19. The method of claim **18**, wherein the subject is overweight.

20. The method of claim **19**, wherein the subject is obese.

21. The method of claim **18**, wherein the subject is neither overweight nor obese.

22. The method of claim **18**, wherein the subject suffers from a condition that can be alleviated with loss of body weight.

23. A controlled release dosage form comprising 15 mg of phentermine and 100 mg of topiramate, wherein the dosage form provides for immediate release of the phentermine and delayed release of the topiramate.

24. A controlled release dosage form comprising 8 mg of phentermine and 50 mg of topiramate, wherein the dosage form provides for immediate release of the phentermine and delayed release of the topiramate.

25. A controlled release formulation comprising phentermine and topiramate, wherein oral administration of the formulation results in immediate release of the phentermine and controlled release of the topiramate, and further wherein the topiramate is present in the form of granules, delayed release granules, granules within a matrix, or a combination with a polymeric mixture.

26. The formulation of claim **25**, wherein the topiramate is present in the form of delayed release granules.

27. The formulation of claim **25**, wherein the phentermine is in readily dissolvable form.

28. The formulation of claim **26**, wherein the phentermine is in readily dissolvable form.

29. A controlled release formulation comprising 15 mg phentermine and 100 mg topiramate, wherein oral administration of the formulation results in immediate release of the phentermine and delayed release of the topiramate, and further wherein the topiramate is present in the form of granules, delayed release granules, granules within a matrix, or a combination with a polymeric mixture.

30. The formulation of claim **29**, wherein the topiramate is present in the form of delayed release granules.

31. The formulation of claim **30**, wherein the phentermine is in readily dissolvable form.

32. The formulation of claim **29**, wherein the phentermine is in readily dissolvable form.

33. A controlled release formulation comprising a topiramate core and a layer of phentermine such that oral administration of the formulation provides for immediate release of the phentermine and delayed or sustained release of the topiramate.

34. The formulation of claim **33**, wherein the formulation provides for delayed release of the topiramate.

35. The formulation of claim **34**, further including a barrier layer between the core surface and the phentermine layer, said barrier layer serving to limit drug release from the surface of the core.

36. The formulation of claim **35**, wherein the barrier layer prevents dissolution of the core when the formulation is first exposed to gastric fluid in the body.

37. The formulation of claim **35**, wherein the barrier layer comprises a disintegrant.

38. The formulation of claim **35**, wherein the barrier layer comprises a dissolution-retardant coating.

39. The formulation of claim **35**, wherein the dissolution-retardant coating is polymeric.

40. The formulation of claim **39**, wherein the dissolution-retardant coating is composed of an enteric polymer.

41. The formulation of claim **35**, wherein the baffler layer comprises a hydrophobic coating.

42. A dosage form comprising phentermine in an immediate release, readily dissolvable form and delayed release granules of topiramate.

43. The dosage form of claim **42**, comprising 8 mg phentermine.

44. The dosage form of claim **43**, comprising 50 mg topiramate.

45. The dosage form of claim **44**, comprising 15 mg phentermine.

46. The dosage form of claim **45**, comprising 100 mg topiramate.

47. A method for effecting a desired weight loss in a subject, comprising administering 15 mg of phentermine and 100 mg topiramate to said subject on a daily basis until the subject has experienced the desired weight loss.

48. The method of claim **47**, wherein the subject is overweight.

49. The method of claim **48**, wherein the subject is obese.

50. The method of claim **47**, wherein the subject is neither overweight nor obese.

51. The method of claim **47**, wherein the subject suffers from a condition that can be alleviated with loss of body weight.

52. A method for effecting a desired weight loss in a subject, comprising administering 8 mg of phentermine and 50 mg topiramate to said subject on a daily basis until the subject has experienced the desired weight loss.

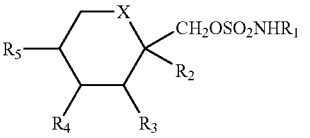
53. The method of claim **52**, wherein the subject is overweight.

54. The method of claim **53**, wherein the subject is obese.

55. The method of claim **52**, wherein the subject is neither overweight nor obese.

56. The method of claim **52**, wherein the subject suffers from a condition that can be alleviated with loss of body weight.

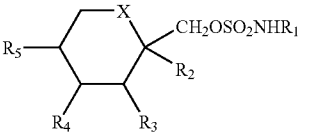
57. A method for effecting a desired weight loss in a subject in need thereof comprising administering to said subject, on a daily basis and until the desired weight loss is achieved, a therapeutically effective amount of phentermine, and an amount of an anticonvulsant agent selected to prevent the loss of effectiveness of the phentermine, wherein the anticonvulsant agent is an anticonvulsant sulfamate derivative having the structure of formula (I)



(I)

wherein X is CH_2 or O, R_1, R_2, R_3, R_4, and R_5 are independently H or C_1-C_4 alkyl, and further wherein when X is O, then R_2 and R_3, and/or R_4 and R_5 may be taken together to form a methylene dioxy linkage of the formula —O—CR_6R_7—O— in which R_6 and R_7 are independently H or C_1-C_3 alkyl, or may be taken together to form a cyclopentyl or cyclohexyl ring.

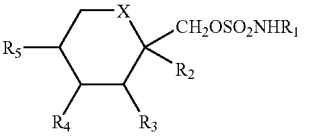
58. A method for treating at least one side effect associated with obesity comprising administering to a subject, on a daily basis and until the side effect associated with obesity is effectively treated, a therapeutically effective amount of phentermine, and an amount of an anticonvulsant agent selected to prevent the loss of effectiveness of the phentermine, wherein the anticonvulsant agent is an anticonvulsant sulfamate derivative having the structure of formula (I)



(I)

wherein X is CH_2 or O, R_1, R_2, R_3, R_4, and R_5 are independently H or C_1-C_4 alkyl, and further wherein when X is O, then R_2 and R_3, and/or R_4 and R_5 may be taken together to form a methylene dioxy linkage of the formula —O—CR_6R_7—O— in which R_6 and R_7 are independently H or C_1-C_3 alkyl, or may be taken together to form a cyclopentyl or cyclohexyl ring.

59. A method for treating Syndrome X in a subject comprising administering to the subject, on a daily basis and until Syndrome X is effectively treated, a therapeutically effective amount of phentermine, and an amount of an anticonvulsant agent selected to prevent the loss of effectiveness of the phentermine, wherein the anticonvulsant agent is an anticonvulsant sulfamate derivative having the structure of formula (I)



(I)

wherein X is CH_2 or O, R_1, R_2, R_3, R_4, and R_5 are independently H or C_1-C_4 alkyl, and further wherein when X is O, then R_2 and R_3, and/or R_4 and R_5, may be taken together to form a methylene dioxy linkage of the formula —O—CR_6R_7—O— in which R_6 and R_7 are indevendently H or C_1-C_3 alkyl, or may be taken together to form a cyclopentyl or cyclohexyl ring.

* * * * *

EXHIBIT E

US008580298B2

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

(10) **Patent No.: US 8,580,298 B2**
(45) **Date of Patent: *Nov. 12, 2013**

(54) **LOW DOSE TOPIRAMATE/PHENTERMINE COMPOSITION AND METHODS OF USE THEREOF**

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(73) Assignee: **Vivus, Inc.**, Mountain View, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 340 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/481,540**

(22) Filed: **Jun. 9, 2009**

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A61K 9/48 (2006.01)

(52) **U.S. Cl.**
USPC **424/451**; 424/490; 514/23; 514/646; 514/455

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

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Primary Examiner — Hasan Ahmed

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(57) **ABSTRACT**

A method for effecting weight loss by administering a combination of topiramate and phentermine is provided. The phentermine is generally administered in immediate release form, in a daily dose in the range of 2 mg to 8 mg, in combination with a daily dose of topiramate selected to prevent the loss of effectiveness of phentermine alone. Methods for treating obesity, conditions associated with obesity, and other indications are also provided, as are compositions and dosage forms containing low doses of phentermine and topiramate, e.g., 3.75 mg phentermine and 23 mg topiramate.

26 Claims, 2 Drawing Sheets

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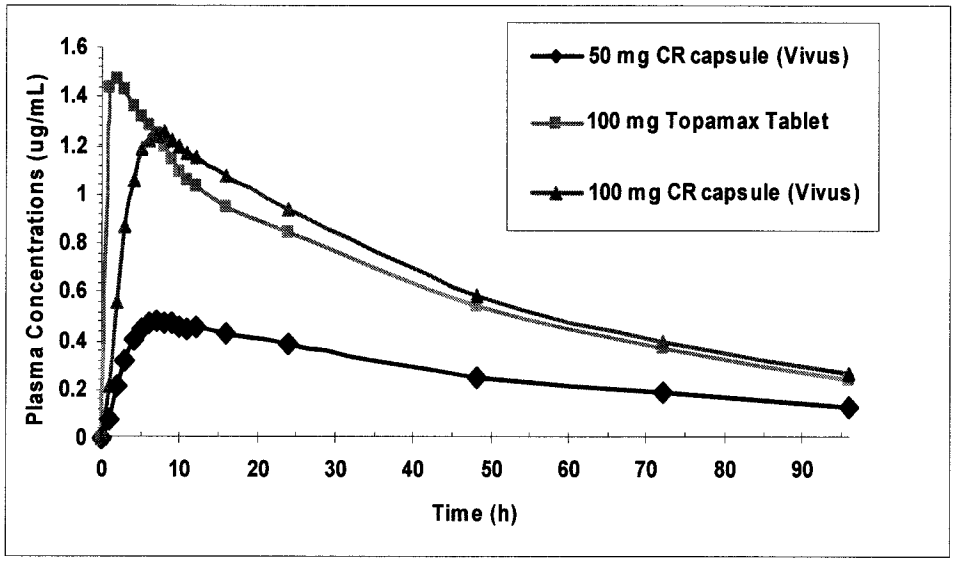
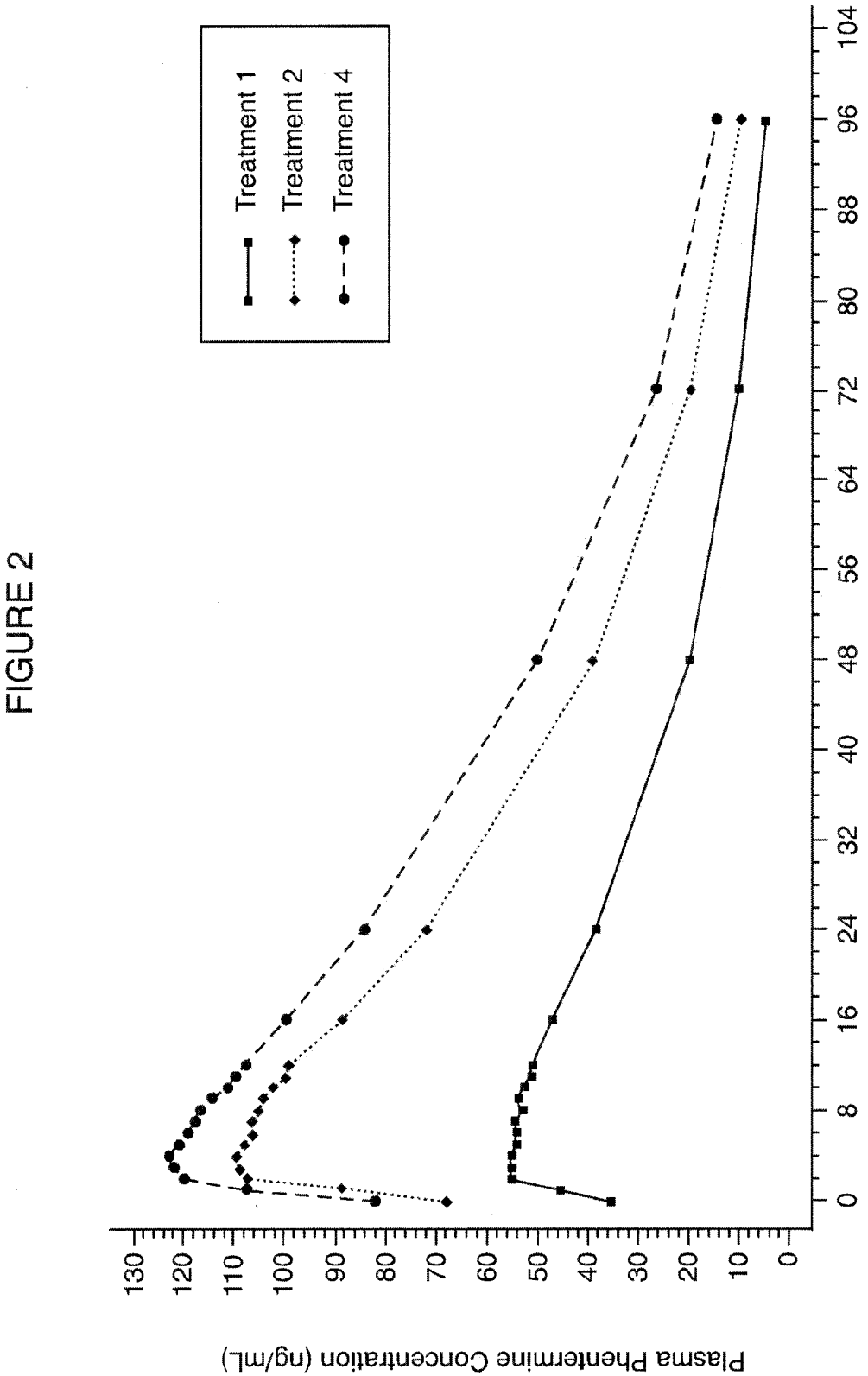

50 mg CR capsule (Vivus)
100 mg Topamax Tablet
100 mg CR capsule (Vivus)
Plasma Concentrations (ug/mL)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
10
20
30
40
50
60
70
80
90
Time (h)

FIGURE 1

FIGURE 2


Treatment 1
Treatment 2
Treatment 4
Plasma Phentermine Concentration (ng/mL)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
0
8
16
24
32
40
48
56
64
72
80
88
96
104

LOW DOSE TOPIRAMATE/PHENTERMINE COMPOSITION AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a continuation-in-part of U.S. patent application Ser. No. 12/135,953, filed Jun. 9, 2008, the disclosure of which is incorporated by reference.

BACKGROUND OF THE INVENTION

The prevalence of obesity in both children and adults is on the rise in first world countries, especially in the United States, as well as in many developing countries such as China and India. Many aspects of a person's life are affected by obesity, from physical problems such as knee and ankle joint deterioration, to emotional problems resulting from self-esteem issues and society's attitude towards heavy people. The medical problems caused by obesity can be serious and often life-threatening and include diabetes, shortness of breath and other respiratory problems such as asthma and pulmonary hypertension, gallbladder disease, dyslipidemia (for example, high cholesterol or high levels of triglycerides) and dyslipidemic hypertension, osteoarthritis and other orthopedic problems, reflux esophagitis (heartburn), snoring, sleep apnea, menstrual irregularities, infertility, problems associated with pregnancy, gout, cardiovascular problems such as coronary artery disease and other heart trouble, muscular dystrophy, and metabolic disorders such as hypoalphalipoproteinemia, familial combined hyperlipidemia, and Syndrome X, including insulin-resistant Syndrome X. In addition, obesity has been associated with an increased incidence of certain cancers, notably cancers of the colon, rectum, prostate, breast, uterus, and cervix.

Obesity substantially increases the risk of morbidity from hypertension, dyslipidemia, type II diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis and endometrial, breast, prostate, and colon cancers. Higher body weights are also associated with increases in all-cause mortality. Many of these problems are relieved or improved when the afflicted individual undergoes permanent significant weight loss. Weight loss in these individuals can also promote a significant increase in longevity.

Strategies for treating obesity and related disorders have included dietary restriction, increased physical activity, pharmacological approaches, and even surgery, with the choice depending, at least in part, on the degree of weight loss one is attempting to achieve as well as on the severity of obesity exhibited by the subject. For example, treatments such as a low-calorie, low-fat diet and/or regular exercise are often adequate with individuals who are only mildly overweight. The difficulty in maintaining long-term weight loss through diet and behavior modification, however, has led to an increasing interest in other avenues for treatment, particularly pharmacotherapy.

Traditional pharmacological interventions typically induce a weight loss of between five and fifteen kilograms; if the medication is discontinued, renewed weight gain often ensues. Surgical treatments are comparatively successful and are reserved for patients with extreme obesity and/or with serious medical complications.

The above treatments can be enhanced by controlled use of over-the-counter appetite suppressants including caffeine, ephedrine and phenylpropanolamine (Acutrim®, Dexatrim®). Moreover, prescription medications including

amphetamine, diethylpropion (Tenuate®), mazindol (Mazanor®, Sanorex®), phentermine (Fastin®, Ionamin®), phenmetrazine (Preludin®), phendimetrazine (Bontrol®, Plegine®, Adipost®, Dital®, Dyrexan®, Melfiat®, Prelu-2®, Rexigen Forte®), benzphetamine (Didrex®) and fluoxetine (Prozac®) are often used in the treatment of seriously overweight and/or obese subjects or patients.

While society has seen tremendous advances in the field of pharmaceuticals, there are, of course, drawbacks to the administration of any given pharmaceutical agent. Sometimes, the disadvantages, or "side effects," are so severe as to preclude administration of a particular agent at a therapeutically effective dose. Furthermore, many agents in the same therapeutic class display similar side effect profiles, meaning that patients either have to forego therapy or suffer from varying degrees of side effects associated with the medication of choice.

In U.S. Pat. No. 7,056,890 to Najarian and U.S. Patent Publication Nos. US 2006/0234950 A1, US 2006/0234951 A1, and US 2006/0234952 A1 to Najarian, all of common assignment herewith to Vivus, Inc. (Mountain View, Calif.), a combination therapy for treating obesity and effecting weight loss is provided wherein a synergistic effect between the active agents enables dose reduction and a concomitant alleviation of side effects typically associated with each active agent. One of the active agents is an anti-convulsant agent, e.g., topiramate, and the second active agent is a sympathomimetic agent, typically a sympathomimetic amine such as phentermine. In U.S. patent application Ser. No. 12/135,935, also of common assignment herewith, an escalating dosing regimen is described for administering topiramate alone or in combination with a second therapeutic agent such as phentermine, wherein the second agent is selected so as to directly or indirectly reduce the side effects associated with one or both of the agents administered. By "indirectly" reducing side effects is meant that a first pharmaceutical agent allows the second agent to be administered at a lower dose without compromising therapeutic efficacy, thus reducing dose-dependent unwanted effects.

Topiramate (2,3,4,5-bis-O-(1-methylethylidene)-(3-D-fructopyranose sulfamate) is a broad-spectrum neurotherapeutic agent approved by the FDA and the regulatory agencies of many other countries for the treatment of certain seizure disorders and the prevention of migraine headaches. E. Faught et al. (1996) Neurology 46:1684-90; Karim et al. (1995) Epilepsia 36 (54):33; S. K. Sachdeo et al. (1995) Epilepsia 36 (54):33; T. A. Glauser (1999) Epilepsia 40 (55): 571-80; R. C. Sachdeo (1998) Clin. Pharmacokinet 34:335-346). There has also been evidence that topiramate is effective in the treatment of diabetes (U.S. Pat. Nos. 7,109,174 and 6,362,220), neurological disorders (U.S. Pat. No. 6,908,902), depression (U.S. Pat. No. 6,627,653), psychosis (U.S. Pat. No. 6,620,819), headaches (U.S. Pat. No. 6,319,903) and hypertension (U.S. Pat. No. 6,201,010). However there have been adverse effects associated with the use of topiramate in humans, such as cognitive dulling and word finding difficulties, which can discourage many obese patients from taking this drug.

Phentermine was approved by the FDA as an appetite suppressant in 1959, and phentermine hydrochloride has been used as a weight loss agent since the 1970s, e.g., under the brand names Adipex-P®, Fastin®, Zantril®, and others. Although the FDA warned against combining phentermine with a second active agent following the reports of cardiac and pulmonary problems associated with the "Fen-Phen" product (in which phentermine was combined with fenfluramine, and later with a related drug, dexfenfluramine), it has

since been found that a safe and effective weight loss treatment is provided by combining phentermine with an active agent that mitigates phentermine's side effects and enables administration of a much lower dose of phentermine than in "Fen-Phen" (containing 30 mg or 37.5 mg phentermine hydrochloride). See U.S. Pat. No. 7,056,890 to Najarian and U.S. Patent Publication Nos. US 2006/0234950 A1, US 2006/0234951 A1, and US 2006/0234952 A1 to Najarian, cited above.

It has now been discovered that a significantly lower dose combination product is effective in achieving weight loss, treating obesity, and treating conditions associated with obesity and excessive weight. The present invention is directed to this product and methods of using the product. The invention provides a number of important advantages vis-à-vis prior weight loss therapies, as will be described in detail herein.

SUMMARY OF THE INVENTION

Accordingly, in a first embodiment, the present invention is directed to a method for effecting weight loss in a subject by administering continually over a significant period of time a daily dose of phentermine in the range of 2 mg to 8 mg and in combination therewith a daily amount of topiramate selected to prevent the loss of effectiveness of phentermine alone. Generally, the combination of these active agents is administered orally. The agents may be administered at different times of day, with the phentermine administered earlier in the day and the topiramate administered later in the day, in the afternoon or evening. Normally, however, the two agents are administered simultaneously using one or more dosage forms that provide for immediate release of the phentermine and controlled release of the topiramate. In an exemplary embodiment, the phentermine and topiramate are administered in a single dosage form that provides for immediate release of the phentermine and both delayed and sustained release of the topiramate.

In another embodiment, the invention is directed to a method for effecting weight loss in a subject by administering continually over a significant period of time a daily dose of 3.75 mg phentermine and, in combination therewith, a daily dose of 23 mg topiramate.

In another embodiment, the invention is directed to a method for effecting weight loss in a subject by administering continually over a significant period of time a daily dose of 7.5 mg phentermine and, in combination therewith, a daily dose of 46 mg topiramate.

In these methods, the daily doses of topiramate and phentermine may also be administered to treat one or more conditions associated with excess weight or obesity. These conditions include, without limitation, diabetes, respiratory disorders, gallbladder disease, dyslipidemia, orthopedic problems, reflux esophagitis, snoring, sleep apnea, menstrual irregularities, infertility, pregnancy complications, gout, cardiovascular problems, muscular dystrophy, metabolic disorders, and certain cancers. Accordingly, in a further embodiment, the invention relates to a method as enumerated above which further involves simultaneously treating the subject for a condition associated with excess weight or obesity.

In another embodiment, a composition is provided for administration to a subject in order to effect weight loss, wherein the composition contains 2 mg to 5 mg phentermine and 17 mg to 23 mg topiramate. An exemplary such composition contains 3.75 mg phentermine and 23 mg topiramate. Generally, the composition is an orally administrable unit dosage form that contains both active agents. Certain dosage forms of the invention provide for immediate release of the phentermine and controlled release of the topiramate.

In a further embodiment, a packaged pharmaceutical preparation is provided that contains a composition of the invention in a sealed container, with instructions for administration, typically self-administration, of the composition. Generally, the packaged preparation contains a plurality of orally administrable unit dosage forms, with, preferably, each individual dosage form in a separate sealed housing, e.g., as in a blister pack.

In still another embodiment, the method, composition, and packaged preparation of the invention are adapted to administer phentermine and topiramate to treat epilepsy.

In still another embodiment, the method, composition, and packaged preparation of the invention are adapted to administer phentermine and topiramate to treat an impulse control disorder.

In still another embodiment, the method, composition, and packaged preparation of the invention are adapted to administer phentermine and topiramate to treat a psychiatric disorder such as depression, panic syndrome, generally anxiety disorder, phobic syndromes, mania, manic depressive illness, hypomania, unipolar depression, stress disorders including post-traumatic stress disorder ("PTSD"), somatoform disorders, personality disorders, psychosis, and schizophrenia.

In still another embodiment, the method, composition, and packaged preparation of the invention are adapted to administer phentermine and topiramate to treat adolescent and juvenile obesity.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** provides a summary of the plasma concentration of controlled release topiramate according to the present invention versus topiramate (Topamax®) in normal obese subjects.

FIG. **2** depicts the mean plasma phentermine concentrations versus time for subjects administered phentermine in combination with controlled release topiramate and phentermine in combination with immediate release topiramate (Topamax®).

DETAILED DESCRIPTION OF THE INVENTION

Definitions and Nomenclature:

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, "an active agent" refers not only to a single active agent but also to a combination of two or more different active agents, "a dosage form" refers to a combination of dosage forms as well as to a single dosage form, and the like.

Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by one of ordinary skill in the art to which the invention pertains. Specific terminology of particular importance to the description of the present invention is defined below.

When referring to an active agent, applicants intend the term "active agent" to encompass not only the specified molecular entity but also its pharmaceutically acceptable, pharmacologically active analogs, including, but not limited to, salts, esters, amides, prodrugs, conjugates, active metabolites, and other such derivatives, analogs, and related compounds as will be discussed infra. Therefore, reference to "phentermine" encompasses not only phentermine per se but also salts and other derivatives of phentermine, e.g., phentermine hydrochloride. It is to be understood that when amounts

or doses of phentermine are specified, that those amounts or doses refer to the amount or dose of phentermine per se and not to a phentermine salt or the like. For example, when it is indicated that a dose or amount of phentermine is 3.75 mg, that would correspond to 4.92 phentermine hydrochloride and not 3.75 phentermine hydrochloride.

The terms "treating" and "treatment" as used herein refer to reduction in severity and/or frequency of symptoms, elimination of symptoms and/or underlying cause, and improvement or remediation of damage. In certain aspects, the term "treating" and "treatment" as used herein refer to the prevention of the occurrence of symptoms. In other aspects, the term "treating" and "treatment" as used herein refer to the prevention of the underlying cause of symptoms associated with obesity, excess weight, and/or a related condition. The phrase "administering to a subject" refers to the process of introducing a composition or dosage form of the invention into the subject (e.g., a human or other mammalian subject) via an art-recognized means of introduction

By the terms "effective amount" and "therapeutically effective amount" of an agent, compound, drug, composition or combination of the invention which is nontoxic and effective for producing some desired therapeutic effect upon administration to a subject or patient (e.g., a human subject or patient).

The term "dosage form" denotes any form of a pharmaceutical composition that contains an amount of active agent sufficient to achieve a therapeutic effect with a single administration. When the formulation is a tablet or capsule, the dosage form is usually one such tablet or capsule. The frequency of administration that will provide the most effective results in an efficient manner without overdosing will vary with the characteristics of the particular active agent, including both its pharmacological characteristics and its physical characteristics, such as hydrophilicity.

The term "controlled release" refers to a drug-containing formulation or fraction thereof in which release of the drug is not immediate, i.e., with a "controlled release" formulation, administration does not result in immediate release of the drug into an absorption pool. The term is used interchangeably with "nonimmediate release" as defined in Remington: The Science and Practice of Pharmacy, Nineteenth Ed. (Easton, Pa.: Mack Publishing Company, 1995). In general, the term "controlled release" as used herein includes sustained release, modified release and delayed release formulations.

The term "sustained release" (synonymous with "extended release") is used in its conventional sense to refer to a drug formulation that provides for gradual release of a drug over an extended period of time, and that preferably, although not necessarily, results in substantially constant blood levels of a drug over an extended time period. The term "delayed release" is also used in its conventional sense, to refer to a drug formulation which, following administration to a patient provides a measurable time delay before drug is released from the formulation into the patient's body.

By "pharmaceutically acceptable" is meant a material that is not biologically or otherwise undesirable, i.e., the material may be incorporated into a pharmaceutical composition administered to a patient without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. When the term "pharmaceutically acceptable" is used to refer to a pharmaceutical carrier or excipient, it is implied that the carrier or excipient has met the required standards of toxicological and manufacturing testing or that it is included on the Inactive Ingredient Guide prepared by the U.S. Food and Drug administration. "Pharmacologically active" (or simply "active") as in a "pharmacologically active" (or "active") derivative or analog, refers to a derivative or analog having the same type of pharmacological activity as the parent compound and approximately equivalent in degree. The term "pharmaceutically acceptable salts" include acid addition salts which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

As used herein, "subject" or "individual" or "patient" refers to any subject for whom or which therapy is desired, and generally refers to the recipient of the therapy to be practiced according to the invention. The subject can be any vertebrate, but will typically be a mammal. If a mammal, the subject will in many embodiments be a human, but may also be a domestic livestock, laboratory subject or pet animal.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

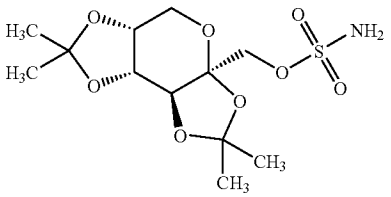
Methods and Formulations of the Invention:

The present invention provides novel methods and compositions to effect weight loss and treat obesity, conditions related to excess weight or obesity, diabetes (whether or not related to obesity), and other conditions and disorders as will be explained infra According to the U.S. Centers for Disease Control, the clinical definition of being overweight (the term being used synonymously herein with the term "excess weight") is having a body mass index (BMI) between 25.0 and 29.9 kg/m; BMI is calculated by multiplying an individual's weight, in kilograms, by height, in meters. The CDC defines obesity as having a BMI of 30 or higher. In one embodiment, the invention provides a method for effecting weight loss and treating overweight, obesity, and conditions associated with excess weight and obesity, and involves administration of a combination of the sympathomimetic agent phentermine and the anti-convulsant agent topiramate.

Topiramate is an anticonvulsant sulfamate compound that is sold in the United States under the trade name Topamax® (Ortho-McNeil Pharmaceutical, Inc., Raritan, N.J., U.S.A). Topiramate has been approved for use as an antiepileptic agent as an adjuvant therapy for patients with partial onset seizures or primary generalized tonic-clonic seizures, and for the prevention of migraine headache. See Physician's Desk Reference, 56th ed. (2002); see also U.S. Pat. No. 4,513,006 to Maryanoff et al. and U.S. Pat. No. 7,351,695 to Almarssoo et al.

"Topiramate" generally refers to the sulfamate-substituted monosaccharide having the chemical name 2,3,4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate and the molecular formula C12H21NO8S. The structure of the compound is represented by Formula (I)

(I)

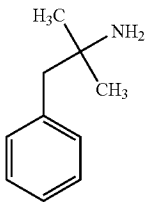


As used herein, the term "topiramate" encompasses 2,3,4,5-bis-(O)-(1-methylethylidene)-β-D-fructopyranose sulfamate as well as individual enantiomers, individual diastereomers, or mixtures thereof. The term "topiramate" as used herein also encompasses topiramate salts as well as polymorphs, solvates (including hydrates and mixed solvates, as well as hydrates of salts), co-crystals (for instance, with other compounds or other forms of topiramate), amorphous, and anhydrous forms of the compound of Formula (I). Topiramate salts useful in conjunction with the present invention, as will be appreciated from the fact that the compound is a sulfamic acid derivative, are pharmaceutically acceptable basic addition salts. Such salts are prepared from bases that provide a pharmaceutically acceptable cation that associates with the sulfamic acid group of the compound of Formula (I). Suitable pharmaceutically acceptable cations include both organic and inorganic cations, including, without limitation, sodium, sodium, potassium, lithium, magnesium, calcium, aluminum, zinc, procaine, benzathine, chloroprocaine, choline, diethylamine, ethylenediamine, N-methylglucamine, benethamine, clemizole, diethylamine, piperazine, tromethamine, triethylamine, ethanolamine, triethanolamine, arginine, lysine, histidine, tributylamine, 2-amino-2-pentylpropanol, 2-amino-2-methyl-1,3-propanediol, tris(hydroxymethyl) aminomethane, benzylamine, 2-(dimethylamino)ethanol, barium or bismuth counter ions. Particularly preferred cations are sodium, lithium, and potassium. Other forms of topiramate referenced above may be prepared using methods known in the art; see, e.g., U.S. Pat. No. 7,351,695.

At dosages previously believed to be required for therapeutic efficacy, administration of topiramate has been associated with significant adverse effects, as noted above, including, without limitation, dizziness, psychomotor slowing, difficulty with memory, fatigue, and somnolence. See U.S. Pat. No. 7,351,695, supra, and Physicians' Desk Reference, supra.

Phentermine is a sympathomimetic agent that has been used as an appetite suppressant, but, like topiramate, has been associated with significant adverse effects at doses previously believed to be required for efficacy; these effects are generally associated with the catecholamine-releasing properties of the drug, including, for instance, tachycardia, elevated blood pressure, anxiety, and insomnia. Phentermine is a shortened version of the compound's chemical name, phenyl-tertiary-butylamine, and is also referred to as 2-methyl-1-phenylpropan-2-amine and 2-methyl-amphetamine. Phentermine has the molecular formula C10 H15N, the chemical structure of Formula (II)

(II)



and is an achiral primary amine. As such, phentermine may be in the form of either the free base or an acid addition salt prepared with an acid that yields a pharmaceutically acceptable anion. Suitable acid addition salts may be prepared from organic acids, e.g., acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like, as well as inorganic acids, e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, etc. As with topiramate, phentermine may take on various other forms as well.

It has now been surprisingly discovered that a combination of a low daily dose of topiramate and a low daily dose of phentermine is effective in achieving weight loss, treating obesity, treating conditions related to overweight and obesity, and addressing other indications as will be discussed herein. The incidence of adverse effects previously associated with each active agent is significantly reduced because of the lowered daily dosage as well as the offsetting effect each active agent has on the potential adverse effects of the other active agent. Even at the low doses of the present methods, phentermine has anorexient properties (e.g., suppresses appetite) and is anorectic without loss of efficacy or without adverse or undesirable side effects to a subject when administered according to the dosage regimens described herein when the phentermine is administered in combination with topiramate.

The present method for effecting weight loss in a subject involves administering a daily dose of phentermine in the range of 2 mg to 8 mg, e.g., 2 mg to 5 mg, in combination with a daily dose of topiramate selected to prevent the loss of effectiveness of phentermine alone. An example of a suitable daily dose of topiramate that would prevent the loss of effectiveness of phentermine alone is 15 mg to 50 mg, e.g., 15 mg to 25 mg or 17 mg to 23 mg. An exemplary dosage regimen involves administration of daily doses of 3.75 mg phentermine and 23 mg topiramate. Another exemplary dosage regimen involves administration of daily doses of 7.5 mg and 46 mg topiramate.

When the topiramate and/or the phentermine are associated with additional moieties, e.g., are in the form of salts, hydrates, or the like, the dosage herein refers to the compound per se and does not include the associated moieties, e.g., cations, anions, hydrates, etc. Thus, if phentermine hydrochloride is used in the methods and compositions of the invention, 4.92 mg of phentermine hydrochloride (having a molecular weight of 195.69 g/mol) will be necessary to provide the 3.75 mg daily dose of phentermine (having a molecular weight of 149.23 g/mol).

The dosage regimen involves continual, i.e., ongoing, administration, over a significant period of time, e.g., in the range of about 4 weeks to about 67 weeks, depending on the severity of an individual's weight problem, the amount of weight that should be lost, and the rate at which weight is lost. Generally, although not necessarily, the combination of the active agents is administered orally.

The method of administration can involve simultaneous administration of the two active agents, in a single composition or in two discrete compositions each containing one of the active agents. The method of administration may also involve administration of the two active agents at different times of day, with the phentermine generally administered earlier in the day and the topiramate generally administered later in the day. Normally, however, the two agents are administered simultaneously using one or more dosage forms that provide for immediate release of the phentermine and con-

trolled release of the topiramate. In an exemplary embodiment, the phentermine and topiramate are administered in a single dosage form that provides for immediate release of the phentermine and sustained release and/or delayed release of the topiramate.

Examples of compositions that contain a combination of phentermine and topiramate include, without limitation: (1) 2 mg to 5 mg phentermine and 17 mg to 23 mg topiramate; (2) 3.75 mg phentermine and 23 mg topiramate; (3) 3.75 mg phentermine in the form of 4.92 mg phentermine hydrochloride and 23 mg topiramate; (4) 7.5 mg phentermine and 46 mg topiramate; and (5) 7.5 mg phentermine in the form of 9.84 mg phentermine hydrochloride and 46 mg topiramate.

These and other compositions of the invention exhibit a lower maximum concentration (Cmax) of topiramate without decreasing total drug exposure defined by the area under the concentration-time curve (AUC). Further, preferred compositions of the present invention can provide for delayed, sustained release of topiramate such that the maximum plasma concentration (Tmax) is reached 6 to 10, typically 6 to 8, hours after administration. As depicted in FIG. **1**, drug exposure as measured by AUC for a controlled release (CR) formulation capsule prepared as described in Example 1 is the same as that observed with an immediate release topiramate (Topamax®) tablet despite a 20% reduction in the Cmax. Therefore, formulations of the invention are capable of reducing the Cmax of topiramate, enabling a reduction in side effects without compromising the efficacy of the treatment, since the AUC is the same. This reduction in Cmax is preferred as topiramate can be sedating, as noted above, and a delay in the time to reach maximum plasma concentration to the late afternoon or evening time improves the tolerability of the drug. On the other hand, the preferred formulations of the invention provide for immediate release of phentermine, with the medication administered early in the day, such that any stimulant effects that may be experienced do not occur in the evening.

In another embodiment of the invention, a composition is provided that contains 7.5 mg phentermine and 46 mg topiramate.

Depending on the intended mode of administration, the pharmaceutical formulation may be a solid, semi-solid or liquid, such as, for example, a tablet, a capsule, a caplet, a liquid, a suspension, an emulsion, a suppository, granules, pellets, beads, a powder, or the like, preferably in unit dosage form suitable for single administration of a precise dosage. Suitable pharmaceutical compositions and dosage forms may be prepared using conventional methods known to those in the field of pharmaceutical formulation and described in the pertinent texts and literature, e.g., in Remington: The Science and Practice of Pharmacy (Easton, Pa.: Mack Publishing Co., 1995). Oral administration and therefore oral dosage forms are generally preferred, and include tablets, capsules, caplets, solutions, suspensions and syrups, and may also comprise a plurality of granules, beads, powders, or pellets that may or may not be encapsulated. Preferred oral dosage forms are capsules and tablets, particularly controlled release capsules and tablets, as noted above.

As noted above, it is especially advantageous to formulate compositions of the invention in unit dosage form for ease of administration and uniformity of dosage. The term "unit dosage forms" as used herein refers to physically discrete units suited as unitary dosages for the individuals to be treated. That is, the compositions are formulated into discrete dosage units each containing a predetermined, "unit dosage" quantity of an active agent calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specifications of unit dosage forms of the invention are dependent on the unique characteristics of the active agent to be delivered. Dosages can further be determined by reference to the usual dose and manner of administration of the ingredients. It should be noted that, in some cases, two or more individual dosage units in combination provide a therapeutically effective amount of the active agent, e.g., two tablets or capsules taken together may provide a therapeutically effective dosage of topiramate, such that the unit dosage in each tablet or capsule is approximately 50% of the therapeutically effective amount.

Tablets may be manufactured using standard tablet processing procedures and equipment. Direct compression and granulation techniques are preferred. In addition to the active agent, tablets will generally contain inactive, pharmaceutically acceptable carrier materials such as binders, lubricants, disintegrants, fillers, stabilizers, surfactants, coloring agents, and the like.

Capsules are also preferred oral dosage forms, in which case the active agent-containing composition may be encapsulated in the form of a liquid or solid (including particulates such as granules, beads, powders or pellets). Suitable capsules may be either hard or soft, and are generally made of gelatin, starch, or a cellulosic material, with gelatin capsules preferred. Two-piece hard gelatin capsules are preferably sealed, such as with gelatin bands or the like. See, for example, Remington: The Science and Practice of Pharmacy, cited earlier herein, which describes materials and methods for preparing encapsulated pharmaceuticals.

Oral dosage forms, whether tablets, capsules, caplets, or particulates, can, if desired, be formulated so as to provide for controlled release of topiramate, and in a preferred embodiment, the present formulations are controlled release oral dosage forms. Generally, the dosage forms provide for sustained release, i.e., gradual, release of topiramate, from the dosage form to the patient's body over an extended time period, typically providing for a substantially constant blood level of the agent over a time period in the range of about 4 to about 12 hours, typically in the range of about 6 to about 10 hours or 6 to about 8 hours. Release of the topiramate may also be delayed; that is, there is a time lag between administration and the start of topiramate release. In this way, for instance, an individual will not experience sleepiness or other side effects of topiramate during the school or work day. Preferred dosage forms thus involve sustained release of the topiramate, delayed release of the topiramate, or both sustained and delayed release of the topiramate.

Generally, as will be appreciated by those of ordinary skill in the art, sustained release dosage forms can be formulated by dispersing the active agent within a matrix of a gradually hydrolyzable material such as a hydrophilic polymer, or by coating a solid, drug-containing dosage form with such a material. Hydrophilic polymers useful for providing a sustained release coating or matrix include, by way of example: cellulosic polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, ethyl cellulose, cellulose acetate, and carboxymethylcellulose sodium; acrylic acid polymers and copolymers, preferably formed from acrylic acid, methacrylic acid, acrylic acid alkyl esters, methacrylic acid alkyl esters, and the like, e.g. copolymers of acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate; and vinyl polymers and copolymers such as polyvinyl pyrrolidone e.g., Povidone K30, polyvinyl acetate, and ethylene-vinyl acetate copolymer. Preferred sustained release polymers herein include those available as "Methocel" polymers from Dow Chemical,

particularly the methylcellulose ether polymers in the Methocel™ A group, having a viscosity grade of about 4,000 cps and a methoxyl content of about 27.5% to 31.5%, e.g., Methocel™ A15LV, Methocel™ A15C, and Methocel™ A4M.

When sustained release preparations are prepared, tablets, granules, powder, capsules, and the like can be produced according to a conventional method after adding excipient, and as necessary, binder, disintegrating agent, lubricant, coloring agent, taste-modifying agent, flavoring agent, and the like. These additives may be ones generally used in the field, and for example, lactose, sodium chloride, glucose, starch, microcrystalline cellulose, and silicic acid as the excipient, water, ethanol, propanol, simple syrup, gelatin solution, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, shellac, calcium phosphate, and polyvinylpyrrolidone as the binder, agar powder, sodium hydrogen carbonate, sodium lauryl sulfate, and stearic acid monoglyceride as the disintegrating agent, purified talc, stearic acid salt, borax, and polyethylene glycol as the lubricant, β-carotene, yellow iron sesquioxide, and caramel as the coloring agent, and saccharose and orange peel as the taste-modifying agent can be listed as examples. It should be noted that various grades of microcrystalline cellulose are preferred fillers herein, e.g., Avicel® PH101, Avicel® PH102, and Avicel® PH200 (FMC), with particle sizes of about 50 microns, 100 microns, and 190 microns, respectively. Microcrystalline cellulose having a particle size in the range of about 50 microns to 200 microns is preferred herein.

The dosage forms may also be provided with a delayed release coating, e.g., composed of an acrylate and/or methacrylate copolymers. Examples of such polymers are those available under the trade name "Eudragit" from Rohm Pharma (Germany). The Eudragit series E, L, S, RL, RS, and NE copolymers are available as solubilized in organic solvent, in an aqueous dispersion, or as a dry powder. Preferred acrylate polymers are copolymers of methacrylic acid and methyl methacrylate, such as the Eudragit L and Eudragit S series polymers. Other preferred Eudragit polymers are cationic, such as the Eudragit E, RS, and RL series polymers. Eudragit E100 and E PO are cationic copolymers of dimethylaminoethyl methacrylate and neutral methacrylates (e.g., methyl methacrylate), while Eudragit RS and Eudragit RL polymers are analogous polymers, composed of neutral methacrylic acid esters and a small proportion of trimethylammonioethyl methacrylate.

In a specific embodiment, controlled release topiramate beads for oral administration, e.g., by incorporation in an orally administrable capsule or compaction into an orally administrable tablet, are made using an extrusion spheronization process to produce a matrix core comprised of: topiramate, 40.0% w/w; microcrystalline cellulose, e.g., Avicel® PH102, 56.5% w/w; and methylcellulose, e.g., Methocel™ A15 LV, 3.5% w/w. The topiramate cores are then coated with ethyl cellulose, 5.47% w/w and Povidone K30: 2.39% w/w. The phentermine beads are composed of an immediate release drug coating onto sugar spheres or analogous non-active cores. Both sets of beads may then be encapsulated into one capsule.

Preparations according to this invention for parenteral administration include sterile aqueous and nonaqueous solutions, suspensions, and emulsions. Injectable aqueous solutions contain the active agent in water-soluble form. Examples of nonaqueous solvents or vehicles include fatty oils, such as olive oil and corn oil, synthetic fatty acid esters, such as ethyl oleate or triglycerides, low molecular weight alcohols such as propylene glycol, synthetic hydrophilic polymers such as polyethylene glycol, liposomes, and the like. Parenteral formulations may also contain adjuvants such as solubilizers, preservatives, wetting agents, emulsifiers, dispersants, and stabilizers, and aqueous suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, and dextran. Injectable formulations are rendered sterile by incorporation of a sterilizing agent, filtration through a bacteria-retaining filter, irradiation, or heat. They can also be manufactured using a sterile injectable medium. The active agent may also be in dried, e.g., lyophilized, form that may be rehydrated with a suitable vehicle immediately prior to administration via injection.

The active agents may also be administered through the skin using conventional transdermal drug delivery systems, wherein the active agent is contained within a laminated structure that serves as a drug delivery device to be affixed to the skin. In such a structure, the drug composition is contained in a layer, or "reservoir," underlying an upper backing layer. The laminated structure may contain a single reservoir, or it may contain multiple reservoirs. In one embodiment, the reservoir comprises a polymeric matrix of a pharmaceutically acceptable contact adhesive material that serves to affix the system to the skin during drug delivery. Alternatively, the drug-containing reservoir and skin contact adhesive are present as separate and distinct layers, with the adhesive underlying the reservoir which, in this case, may be either a polymeric matrix as described above, or it may be a liquid or hydrogel reservoir, or may take some other form. Transdermal drug delivery systems may in addition contain a skin permeation enhancer.

In addition to the formulations described previously, the active agent may be formulated as a depot preparation for controlled release of the active agent, preferably sustained release over an extended time period. These sustained release dosage forms are generally administered by implantation (e.g., subcutaneously or intramuscularly or by intramuscular injection).

Although the present compositions will generally be administered orally, parenterally, transdermally, or via an implanted depot, other modes of administration are suitable as well. For example, administration may be transmucosal, e.g., rectal or vaginal, preferably using a suppository that contains, in addition to the active agent, excipients such as a suppository wax. Formulations for nasal or sublingual administration are also prepared with standard excipients well known in the art. The pharmaceutical compositions of the invention may also be formulated for inhalation, e.g., as a solution in saline, as a dry powder, or as an aerosol.

Indications:

Conditions of particular interest for which the invention finds utility include overweight, obesity and conditions often associated with and/or caused by excess weight and obesity. The combination of topiramate and phentermine in the dosages provided herein give rise to significant therapeutic effects and reduced adverse effects, making these pharmaceutical combinations extremely effective therapeutics, especially in the treatment of overweight, obesity and/or related conditions, including conditions associated with and/or caused by excess weight or obesity per se. Subjects suitable for treatment with the subject combination therapy treatment regimen thus include individuals suffering from conditions associated with obesity, such conditions including, without limitation:

- diabetes, insulin resistance, and impaired glucose tolerance;
- respiratory problems such as pulmonary hypertension, asthma, and shortness of breath;

gallbladder disease;
dyslipidemia, e.g., high cholesterol, high levels of triglycerides, etc.;
osteoarthritis and other orthopedic problems;
reflux esophagitis;
adverse conditions related to sleep, including sleep apnea and loud snoring;
menstrual irregularities, infertility, and complications in pregnancy;
gout;
high blood pressure, i.e., hypertension;
cardiovascular problems such as coronary artery disease and other heart trouble;
muscular dystrophy;
stroke, particularly thrombotic stroke and deep vein thrombosis (DVT);
migraines;
metabolic disorders such as hypoalphalipoproteinemia, familial combined hyperlipidemia, and Syndrome X, including insulin-resistant Syndrome X; and
colon, rectal, renal, esophageal, gallbladder, pancreatic, prostate, breast, uterine, ovarian, endometrial, and cervical cancers.

Higher body weights are also associated with increases in all-cause mortality. Most or all of these problems are relieved or improved by permanent significant weight loss. Longevity is likewise significantly increased by permanent significant weight loss.

Diabetes mellitus is very commonly seen in obese individuals, and is associated with continuous and pathologically elevated blood glucose concentration. It is one of the leading causes of death in the United States and is responsible for about 5% of all mortality. Diabetes is divided into two major sub-classes: Type I, also known as juvenile diabetes, or Insulin-Dependent Diabetes Mellitus (IDDM); and Type II, also known as adult onset diabetes, or Non-Insulin-Dependent Diabetes Mellitus (NIDDM).

According to the American Diabetes Association, there are over one million juvenile diabetics in the United States. Type I Diabetes is a form of autoimmune disease. Autoantibodies produced by the patients completely or partially destroy the insulin producing cells of the pancreas. Juvenile diabetics must, therefore, receive exogenous insulin during their lifetime. Without treatment, excessive acidosis, dehydration, kidney damage, and death may result. Even with treatment, complications such as blindness, atherosclerosis, and impotence can occur.

There are more than five million Type II (adult onset) diabetics diagnosed in the United States. Type II disease usually begins during middle age; the principal cause is now known to be overweight and obesity. In Type II diabetics, rising blood glucose levels after meals do not properly stimulate insulin production by the pancreas. Additionally, peripheral tissues are generally resistant to the effects of insulin. The resulting high blood glucose levels (hyperglycemia) can cause extensive tissue damage. Type II diabetics are often referred to as insulin resistant. They often have higher than normal plasma insulin levels (hyperinsulinemia) as the body attempts to overcome its insulin resistance. Some researchers now believe that hyperinsulinemia may be a causative factor in the development of high blood pressure, high levels of circulating low density lipoproteins (LDLs), and lower than normal levels of the beneficial high density lipoproteins (HDLs). While moderate insulin resistance can be compensated for in the early stages of Type II diabetes by increased insulin secretion, in more advanced disease states insulin secretion is also impaired.

Insulin resistance and hyperinsulinemia have also been linked with two other metabolic disorders that pose considerable health risks: impaired glucose tolerance and metabolic obesity. Impaired glucose tolerance is characterized by normal glucose levels before eating, with a tendency toward elevated levels (hyperglycemia) following a meal. According to the World Health Organization, approximately 11% of the U.S. population between the ages of 20 and 74 are estimated to have impaired glucose tolerance. These individuals are considered to be at higher risk for diabetes and coronary artery disease.

Obesity may also be associated with insulin resistance. A causal linkage among obesity, impaired glucose tolerance, and Type II diabetes has been proposed, but a physiological basis has not yet been established. Some researchers believe that impaired glucose tolerance and diabetes are clinically observed and diagnosed only later in the disease process after a person has developed insulin resistance and hyperinsulinemia.

Insulin resistance is frequently associated with hypertension, coronary artery disease (arteriosclerosis), and lactic acidosis, as well as related disease states. The fundamental relationship between these disease states, and a method of treatment, has not been established.

Hypertension is another condition that is frequently seen in obese individuals, and occurs when the blood pressure inside the large arteries is chronically elevated. Hypertension affects about 50 million people in the United States alone. It is more common as people grow older and is both more common and more serious in African Americans. Most cases of hypertension are of unknown etiology. It is known that the tendency to develop hypertension can be inherited. Environment also plays a very important role in hypertension. For example, hypertension may be avoided by keeping body weight under control, keeping physically fit, eating a healthy diet, limiting alcohol intake, and avoiding medications that might increase blood pressure. Other less common causes of hypertension include disorders of the kidneys or endocrine glands. Hypertension has been called “the silent killer” because it has no specific symptoms and yet can lead to death. People with untreated hypertension are much more likely to die from or be disabled by cardiovascular complications such as strokes, heart attacks, heart failure, heart rhythm irregularities, and kidney failure, than people who have normal blood pressure.

Current treatments for hypertension include lifestyle changes (diet, exercise, nonsmoking, etc.) as well as drug therapy. The major classes of medications currently used to treat hypertension include adrenergic neuron antagonists (which are peripherally acting), alpha adrenergic agonists (which are centrally acting), alpha adrenergic blockers, alpha and beta blockers, angiotensin II receptor blockers, angiotensin converting enzyme (ACE) inhibitors, beta adrenergic blockers, calcium channel blockers, thiazides (benzothiadiazine derivatives) and related diuretics, and vasodilators (which act by direct relaxation of vascular smooth muscles).

A particularly serious hypertensive disorder is primary pulmonary hypertension, also known as idiopathic pulmonary hypertension. This is a condition in which the blood pressure in the pulmonary arteries is abnormally high in the absence of other diseases of the heart or lungs. The cause of primary pulmonary hypertension is unknown. Pulmonary hypertension develops in response to increased resistance to blood flow. Narrowing of the pulmonary arterioles occurs and the right side of the heart becomes enlarged due to the increased work of pumping blood against the resistance. Eventually, progressive heart failure develops. Currently, there is no known cure for primary pulmonary hypertension.

Treatment is primarily directed towards controlling the symptoms, although some success has occurred with the use of vasodilators. Other medications used to treat the symptoms of primary pulmonary hypertension include diuretics and calcium channel blockers. Typically, as the disease progresses, oxygen is often required. In certain cases, a heart-lung transplant may be indicated for certain suitable candidates, although the availability of donor organs continues to be extremely limited. Unfortunately, primary pulmonary hypertension is a progressive disease, usually leading to congestive heart failure and respiratory failure.

Secondary pulmonary hypertension is a serious disorder that arises as a complication of other conditions such as, for example, scleroderma. Treatments are similar as those for primary pulmonary hypertension and, unfortunately, the prognosis is the same as well.

Other respiratory disorders that are frequently seen in obese individuals include asthma and shortness of breath, both of which conditions are often alleviated by weight loss.

With respect to adverse conditions and disorders associated with sleep, sleep apnea is perhaps the most concerning. Sleep apnea is classified as either obstructive sleep apnea, the more common form that occurs when throat muscles relax, or central sleep apnea, which occurs when the brain doesn't send proper signals to the muscles that control breathing. Additionally, some people have mixed sleep apnea, which is a combination of both obstructive and central sleep apneas. Sleep apnea literally means "cessation of breath." It is characterized by repetitive episodes of upper airway obstruction that occur during sleep, usually associated with a reduction in blood oxygen saturation. In other words, the airway becomes obstructed at several possible sites. The upper airway can be obstructed by excess tissue in the airway, large tonsils, and a large tongue and usually includes the airway muscles relaxing and collapsing when asleep. Another site of obstruction can be the nasal passages. Sometimes the structure of the jaw and airway can be a factor in sleep apnea.

The signs and symptoms of obstructive and central sleep apneas overlap, sometimes making the type of sleep apnea more difficult to determine. The most common signs and symptoms of obstructive and central sleep apneas include: excessive daytime sleepiness (hypersomnia); loud snoring; observed episodes of breathing cessation during sleep; abrupt awakenings accompanied by shortness of breath; awakening with a dry mouth or sore throat; morning headache; and/or difficulty staying asleep (insomnia). Disruptive snoring may be a more prominent characteristic of obstructive sleep apnea, while awakening with shortness of breath may be more common with central sleep apnea.

Sleep apnea is a progressive condition and can be very serious; it is a potentially life-threatening condition that requires immediate medical attention. The risks of undiagnosed obstructive sleep apnea include heart attacks, strokes, high blood pressure, heart disease, irregular heartbeat, and impotence. In addition, obstructive sleep apnea causes daytime sleepiness that can result in accidents, lost productivity and interpersonal relationship problems. The severity of the symptoms may be mild, moderate or severe.

Sleep apnea is diagnosed utilizing a sleep test, called polysomnography but treatment methodologies differ depending on the severity of the disorder. Mild Sleep Apnea is usually treated by some behavioral changes; losing weight and sleeping on one's side are often recommended. There are oral mouth devices (that help keep the airway open) that may help to reduce snoring in three different ways. Some devices (1) bring the jaw forward or (2) elevate the soft palate or (3) retain the tongue (from falling back in the airway and blocking breathing).

Moderate to severe sleep apnea is usually treated with a continuous positive airway pressure (C-PAP). C-PAP is a machine that blows air into your nose via a nose mask, keeping the airway open and unobstructed. For more severe apnea, there is a Bi-level (Bi-PAP) machine. The Bi-level machine is different in that it blows air at two different pressures. When a person inhales, the pressure is higher and in exhaling, the pressure is lower.

Some people have facial deformities that may cause the sleep apnea. It simply may be that their jaw is smaller than it should be or they could have a smaller opening at the back of the throat. Some people have enlarged tonsils, a large tongue or some other tissues partially blocking the airway. Fixing a deviated septum may help to open the nasal passages. Removing the tonsils and adenoids or polyps may help also. Children are much more likely to have their tonsils and adenoids removed. Surgical procedures, such as tracheostomy, uvulopalatopharyngoplasty (UPPP), laser assisted uvuloplasty (LAUP), somnoplasty, and mandibular myotomy are often required to effectively treat sleep apnea. Weight loss, however, particularly in an obese person, can significantly alleviate sleep apnea and other sleep-related adverse conditions such as loud snoring and the like.

Relatively recently, a connection between obesity and the occurrence or increased incidence of migraine headaches has been noted. Migraine headaches begin with mild pain, which increases in intensity over a short period of time. There are two major types of migraines. The common migraine affects 80-85% of migraine sufferers and classical migraine with aura affects 15% of migraine sufferers. Symptoms associated with migraines include headaches, psychological symptomology such as irritability, depression, fatigue, drowsiness, restlessness; neurological symptoms such as photophobia, phonophobia or gastrointestinal symptoms such as change in bowel habit, change of food intake or urinary symptoms such as urinary frequency, auras which are neurological deficits and can be a variety of deficits for the migraine population but in the individual is usually stereotyped. These deficits may be visual scotoma or visual designs, hemiplegia, migrating paraesthesia, dysarthria, dysphasia, or déjàvu. The headache is usually accompanied by light or sound sensitivity, photophobia or phonophobia, irritability and impaired concentration. For those individuals whose migraine headaches are caused by or exacerbated by obesity, treatment according to the methodology of the present invention can be effective.

Other indications for which the present invention is readily adapted include epilepsy and certain psychiatric indications such as impulse control disorders.

Topiramate has long been known as an anti-epileptic agent. At dosages previously required or believed to be required for efficacy, however, topiramate therapy resulted in significant side effects, as noted elsewhere herein. The present invention, according to which topiramate dosage may be reduced by concomitant administration of phentermine, significantly reduces those side effects of topiramate, most if not all of which are dose-related.

Among psychiatric indications, depression is particularly common. "Depression," as is well known, is manifested by a combination of symptoms that interfere with the ability to work, study, sleep, eat, and enjoy once pleasurable activities. Depression includes major depression, especially refractory depression, bipolar depression, and the degeneration associated with depression. Symptoms of depression include persistent sad, anxious, or "empty" mood, feelings of hopeless-

ness, pessimism, feelings of guilt, worthlessness, helplessness, loss of interest or pleasure in hobbies and activities that were once enjoyed, including sex, decreased energy, fatigue, being "slowed down", difficulty concentrating, remembering, making decisions, insomnia, early-morning awakening, or oversleeping, appetite and/or weight loss or overeating and weight gain, thoughts of death or suicide; suicide attempts, restlessness, irritability, persistent physical symptoms that do not respond to treatment, such as headaches, digestive disorders, and chronic pain.

Other psychiatric disorders may also be treated using the compositions and methods of the invention. These disorders include impulse control disorders, panic syndrome, general anxiety disorder, phobic syndromes of all types, mania, manic depressive illness, hypomania, unipolar depression, stress disorders, PTSD, somatoform disorders, personality disorders, psychosis, and schizophrenia.

"Impulse Control Disorders" are characterized by harmful behaviors performed in response to irresistible impulses. The essential feature of an impulse control disorder is the failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person or to others. Symptoms include an increasing sense of tension or arousal before committing an act, and then experiences pleasure, gratification, or release at the time of committing the act. After the act is performed, there may or may not be regret or guilt. Numerous disorders can be characterized as impulse control disorders including intermittent explosive disorder, kleptomania, pathological gambling, pyromania, trichotillomania, compulsive buying or shopping, repetitive self-mutilation, nonparaphilic sexual addictions, severe nail biting, compulsive skin picking, personality disorders with impulsive features, attention deficit/hyperactivity disorder, eating disorders characterized by binge eating, and substance abuse disorders such as alcoholism and drug addiction. Binge eating disorder and bulimia are also sometimes classified as impulse control disorders.

Packaged Pharmaceutical Preparations:

Also provided are packaged pharmaceutical preparations for practicing the subject methods. The packaged preparation contains a composition of the invention in a sealed container, and typically contains a plurality of individual dosage forms each in a sealed housing, as in a blister pack, but could also contain one or more dosage forms in a single sealed container. The dosage forms might be, for instance, dosage forms containing 3.75 mg phentermine in immediate release form and 23 mg topiramate in controlled release form, or, in an alternative example, 7.5 mg phentermine in immediate release form and 46 mg topiramate in controlled release form. Optionally, dosage forms with lower doses of one or both active agents can also be included, for dose titration and dose escalation.

In certain embodiments, the packaged pharmaceutical preparations include instructions for a patient to carry out drug administration to achieve weight loss, treat obesity, treat conditions associated with obesity, or treat other conditions as explained earlier herein. For instance, the instructions may include the daily dose of topiramate to be taken, the daily dose of phentermine to be taken, and/or the dosing regimen for self-administration of a controlled release dosage form containing both active agents. The instructions may be recorded on a suitable recording medium or printed on a substrate such as paper or plastic. As such, the instructions may be present as a package insert, in the labeling of the package, container(s), or components thereof (i.e., associated with the packaging or sub-packaging), etc. In other embodiments, the instructions are present as an electronic storage data file present on a suitable computer readable storage medium, e.g. CD-ROM, diskette, etc. In yet other embodiments, the actual instructions are not present, but means for obtaining the instructions from a remote source, e.g. via the internet, are provided. As an example, a web address might be included to direct patients to a website where the instructions can be viewed and/or from which the instructions can be downloaded. As with the instructions per se, this means for obtaining the instructions is recorded on a suitable substrate.

Some or all of the included components may be packaged in suitable packaging to maintain sterility. In many embodiments, the components are packaged in a containment element to provide a single, easily handled unit, where the containment element, e.g., box or analogous structure, may or may not be an airtight container, e.g., to further preserve the sterility of some or all of the components. In certain aspects, a sealed package of controlled release dosage forms is provided wherein the dosage forms contain phentermine in immediate release form and topiramate in controlled release, e.g., sustained release and delayed release form. Alternatively, separate phentermine-containing and topiramate-containing dosage forms may be included.

This invention is further illustrated by the following examples which should not be construed as limiting. Although any methods and materials similar or equivalent to those described herein may be useful in the practice or testing of the present invention, preferred methods and materials are described below.

The contents of all references, patents and published patent applications cited throughout this application are hereby incorporated by reference.

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (e.g. amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Celsius, and pressure is at or near atmospheric.

Example 1

Controlled release topiramate beads are made using an extrusion spheronization process to produce a matrix core comprised of topiramate, 40.0% w/w; microcrystalline cellulose (Avicel® PH102), 56.5% w/w; and Methocel™ A15 LV, 3.5% w/w. The topiramate cores were then coated with ethyl cellulose, 5.47% w/w, and Povidone K30, 2.39% w/w.

The composition of the topiramate beads so prepared is as follows:

Component	% w/w
topiramate	36.85
microcrystalline cellulose, (Avicel ® PH102)	52.05
methylcellulose (Methocel ™ A15 LV)	3.22
ethylcellulose	5.47

-continued

Component	% w/w
polyvinylpyrrolidone (Povidone K30)	2.39

Phentermine hydrochloride is coated onto sugar spheres to provide immediate release phentermine beads. Both sets of beads are then encapsulated into each of a plurality of capsules, with each capsule containing 3.75 mg phentermine (as 4.92 mg phentermine HCl) and 23 mg topiramate.

Example 2

Controlled release topiramate beads and immediate release phentermine beads are prepared as in Example 1. Both sets of beads are then encapsulated into each of a plurality of capsules, with each capsule containing 7.5 mg phentermine and 46 mg topiramate.

Example 3

In a study comparing controlled-release formulation of topiramate according to the present invention versus immediate release topiramate (Topamax®) in combination with phentermine, the controlled release formulation of the instant invention of topiramate had a 10-15% lower effect on phentermine exposure (FIG. **2**).

The mean and statistical comparisons for plasma phentermine PK parameters at steady state in multiple dose administrations are summarized in Table 1.

TABLE 1

Arithmetic Mean (SD) and Statistical Comparison of Pharmacokinetic Parameters for Plasma Phentermine

		Treatment 2 Versus Treatment 4		
Pharmacokinetic Parameters	Mean +/− SD Treatment 2 (N = 13)	Treatment 4 (N = 12)	90% Confidence Intervals	% Mean Ratio
$AUC_{0\text{-}tau}$ (ng * hr/mL)	2250 +/− 563	2530 +/− 644	(75.6, 105.3)	89.2
$AUC_{0\text{-}96}$ (ng * hr/mL)	4640 +/− 1570	5550 +/− 1960	(67.1, 105.0)	84.0
$AUC_{0\text{-}t}$ (ng * hr/mL)	4640 +/− 1570	5550 +/− 1960	(67.1, 105.0)	84.0
C_{max_ss} (ng * hr/mL)	114 +/− 23.6	127 +/− 27.6	(78.8, 104.5)	90.7
C_{min_ss} (ng * hr/mL)	9.84 +/− 7.24	14.6 +/− 11.3	(42.5, 109.0)	68.1
t_{max} (hr)	4.01 (1.04, 7.00)	4.54 (1.00, 10.0)		
$T_{1/2}$ (hr)	23.3 +/− 6.17	26.3 +/− 7.43		
CL_{ss}/F (L/hr)	7.10 +/− 1.89	6.38 +/− 2.00		
V_2/F (L/hr)	229 +/− 45.3	232 +/− 58.5		

t_{max} is presented as median (minimum, maximum)
Parameters were dose-normalized and ln-transformed prior to analysis.
% Mean Ratio = 100 * ex[(Treatment 2 − Treatment 4) for ln-transformed parameters
Treatment 1 (Test): 7.5 mg phentermine/50 mg topiramate (Formulation A)
Treatment 2 (Test): 15 mg phentermine/100 mg topiramate (Formulation A)
Treatment 4 (Reference): 15 mg phentermine/100 mg topiramate
Source: Tables 14.2.1.8, 14.2.1.10, 14.2.1.12, and 14.2.1.17

These data indicate a lower maximum and extent of phentermine exposure between tests versus reference treatments after multiple-dose administration. As such, the controlled release formulation of topiramate reduced drug interaction with phentermine which in turn will reduce further side effects associated with phentermine.

Example 4

A patient with obesity and elevated lipids exhibiting a heart murmur, shortness of breath out of proportion to weight and age, low blood pressure, leg edema, and a BMI of 46 undergoes an echocardiogram, which shows mitral regurgitation of 1-2+ and mild elevation in pulmonary artery pressure of 36 mm

The composition prepared in Example 1 is administered to the patient on a daily basis, and the patient additionally proceeds with a low fat, low carbohydrate diet and daily exercise. Two weeks after the start of her weight loss program she reports that her exercise tolerance is markedly improved and previous chest pressure and shortness of breath on exertion are gone. The patient loses weight continuously on the program and after four months can be expected to lose at least 20 pounds. Ongoing continuation of the program can be expected to result in further weight loss and additional improvement in obesity-related conditions.

Example 5

The procedure of Example 4 is repeated with a second patient having a BMI over 40 and suffering from similar conditions related to obesity.

The composition prepared in Example 2 is administered to the patient on a daily basis, and the patient additionally proceeds with a low fat, low carbohydrate diet and daily exercise. Two weeks after the start of his weight loss program he reports that her exercise tolerance is markedly improved. The patient loses weight continuously on the program and after four months can be expected to lose at least 25 pounds. Ongoing continuation of the program can be expected to result in further weight loss and additional improvement in obesity-related conditions.

The invention claimed is:

1. A unit dosage form for weight loss for oral administration to a patient having a body mass index of at least 30 kg/m^2 and a condition associated with obesity, comprising a combination of:

an immediate release phentermine formulation containing a unit dosage of phentermine in the range of 2 mg to 8 mg; and

a controlled release topiramate formulation containing a unit dosage of topiramate in the range of 15 mg to 50 mg,

wherein the dosage of phentermine in mg/day is about 16% of the dosage of topiramate in mg/day, and

wherein the controlled release topiramate formulation reaches a maximum plasma concentration (Cmax) at about 6 to about 10 hours (Tmax) after administration and exhibits a lower Cmax, than non-controlled release topiramate, without decreasing total drug exposure defined by the area under the concentration-time curve (AUC), thereby enabling reduction of concentration-dependent side effects without a decrease in efficacy.

2. The dosage form of claim **1**, wherein the immediate release phentermine formulation comprises beads of inactive cores coated with the immediate release phentermine formulation.

3. The dosage form of claim **2**, comprising a capsule housing the immediate release phentermine beads and the controlled release topiramate beads.

4. The dosage form of claim **1**, wherein following oral administration to a patient, the dosage form provides for a substantially constant blood level of topiramate over a time period in the range of about 4 to about 12 hours.

5. The dosage form of claim **4**, wherein the time period is in the range of about 6 to about 10 hours.

6. The dosage form of claim **1**, wherein the controlled release topiramate formulation reaches a maximum plasma concentration at about 8 hours to about 10 hours (Tmax) after administration.

7. The dosage form of claim **1**, wherein the controlled release topiramate formulation comprises controlled release beads of the topiramate, a binder, and a polymeric filler in a matrix core, wherein the matrix core is provided with a delayed release coating comprising ethyl cellulose and polyvinyl pyrrolidone.

8. The dosage form of claim **7**, wherein the polymeric filler comprises microcrystalline cellulose.

9. The dosage form of claim **7**, wherein the binder comprises methylcellulose.

10. The dosage form of claim **1**, wherein the unit dosage of phentermine is in the range of 2 mg to 5 mg.

11. The dosage form of claim **1**, wherein the unit dosage of topiramate is in the range of 15 mg to 25 mg.

12. The dosage form of claim **11**, wherein the unit dosage of topiramate is in the range of 17 mg to 23 mg.

13. The dosage form of claim **10**, wherein the unit dosage of topiramate is in the range of 15 mg to 25 mg.

14. The dosage form of claim **13**, wherein the unit dosage of topiramate is in the range of 17 mg to 23 mg.

15. The dosage form of claim **1**, wherein the unit dosage of phentermine is 3.75 mg and the unit dosage of topiramate is 23 mg.

16. The dosage form of claim **15**, wherein the 3.75 mg phentermine is in the form of 4.92 mg phentermine hydrochloride.

17. The dosage form of claim **1**, wherein the unit dosage of phentermine is 7.5 mg and the unit dosage of topiramate is 46 mg.

18. The dosage form of claim **17**, wherein the 7.5 mg phentermine is in the form of 9.84 mg phentermine hydrochloride.

19. The dosage form of claim **7**, wherein the ethyl cellulose and the polyvinyl pyrrolidone in the delayed release coating are in a weight ratio of approximately 2.3:1.

20. The dosage form of claim **1**, comprising a tablet with at least two discrete segments, at least one of which contains the immediate release phentermine formulation and at least another of which contains the controlled release topiramate formulation.

21. A unit dosage form for weight loss for oral administration to a patient having a body mass index of at least 30 kg/m^2 and a condition associated with obesity, comprising a combination of:

an immediate release phentermine formulation containing a unit dosage of phentermine in the range of 2 mg to 8 mg; and

a controlled release topiramate formulation containing a unit dosage of topiramate in the range of 15 mg to 50 mg, comprising controlled release beads of the topiramate, a binder, and a polymeric filler in a matrix core, wherein the matrix core is provided with a delayed release coating comprising ethyl cellulose and polyvinyl pyrrolidone, and

wherein the dosage of phentermine in mg/day is about 16% of the dosage of topiramate in mg/day, and

wherein the controlled release topiramate formulation exhibits a maximum plasma concentration (Cmax) at about 6 to about 10 hours (Tmax) after administration and exhibits a lower Cmax, than non-controlled release topiramate, without decreasing total drug exposure defined by the area under the concentration-time curve (AUC), thereby enabling reduction of concentration-dependent side effects without a decrease in efficacy.

22. A packaged pharmaceutical preparation comprising a plurality of the unit dosage forms of claim **1** in a sealed container and instructions for administering the dosage forms orally to effect weight loss.

23. A packaged pharmaceutical preparation, comprising a plurality of the unit dosage forms of claim **1** each in a discrete sealed housing, and instructions for administering the dosage forms orally to effect weight loss.

24. A packaged pharmaceutical preparation comprising a plurality of the unit dosage forms of claim **21** in a sealed container and instructions for administering the dosage forms orally to effect weight loss.

25. A packaged pharmaceutical preparation, comprising a plurality of the unit dosage forms of claim **21** each in a discrete sealed housing, and instructions for administering the dosage forms orally to effect weight loss.

26. The dosage form of claim **1** or **21**, wherein the condition associated with obesity is selected group consisting of diabetes, elevated fasting blood glucose, insulin resistance, impaired glucose tolerance, pulmonary hypertension, asthma, shortness of breath, gallbladder disease, dyslipidemia, high cholesterol, high levels of triglycerides, osteoarthritis, reflux esophagitis, sleep apnea, menstrual irregularities, infertility, complications in pregnancy, gout, high blood pressure, hypertension, coronary artery disease, heart disease, muscular dystrophy, stroke, thrombotic stroke, deep vein thrombosis (DVT), migraines, metabolic disorders, hypoalphalipoproteinemia, familial combined hyperlipidemia, Syndrome X, insulin-resistant Syndrome X, colon cancer, rectal cancer, renal cancer, esophageal cancer, gall-

bladder cancer, pancreatic cancer, prostate cancer, breast cancer, uterine cancer, ovarian cancer, endometrial cancer, and cervical cancer.

* * * * *

EXHIBIT F

US008580299B2

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

(10) **Patent No.: US 8,580,299 B2**
(45) **Date of Patent: Nov. 12, 2013**

(54) **ESCALATING DOSING REGIMEN FOR EFFECTING WEIGHT LOSS AND TREATING OBESITY**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 370 days.

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A61K 9/48 (2006.01)

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

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(57) **ABSTRACT**

The present invention is drawn to novel topiramate compositions as well as methods for effecting weight loss, e.g., in the treatment of obesity and related conditions, including conditions associated with and/or caused by obesity per se. The present invention features an escalating dosing regimen adapted for the administration of topiramate and optionally a sympathomimetic agent such as phentermine or bupropion, in the treatment of obesity and related conditions.

9 Claims, 2 Drawing Sheets

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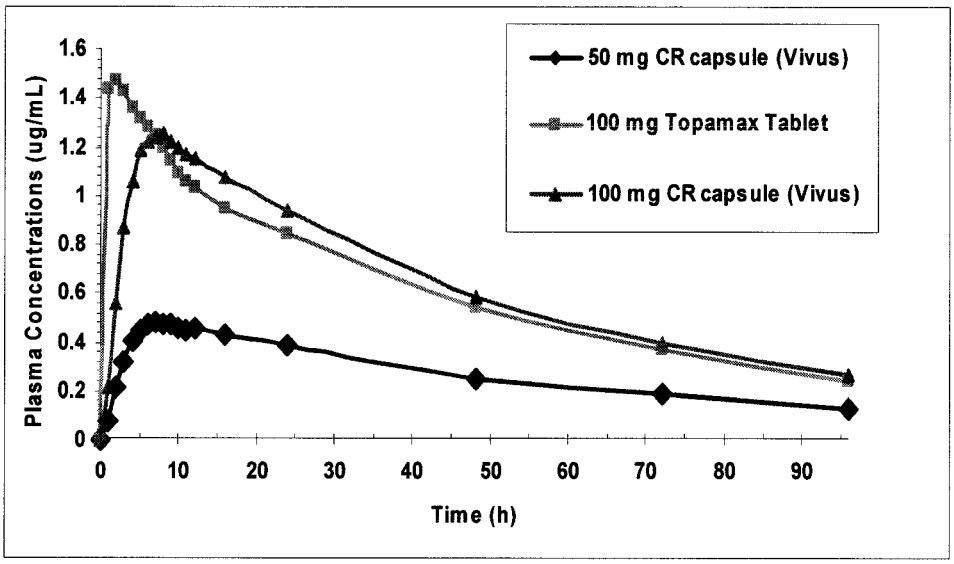
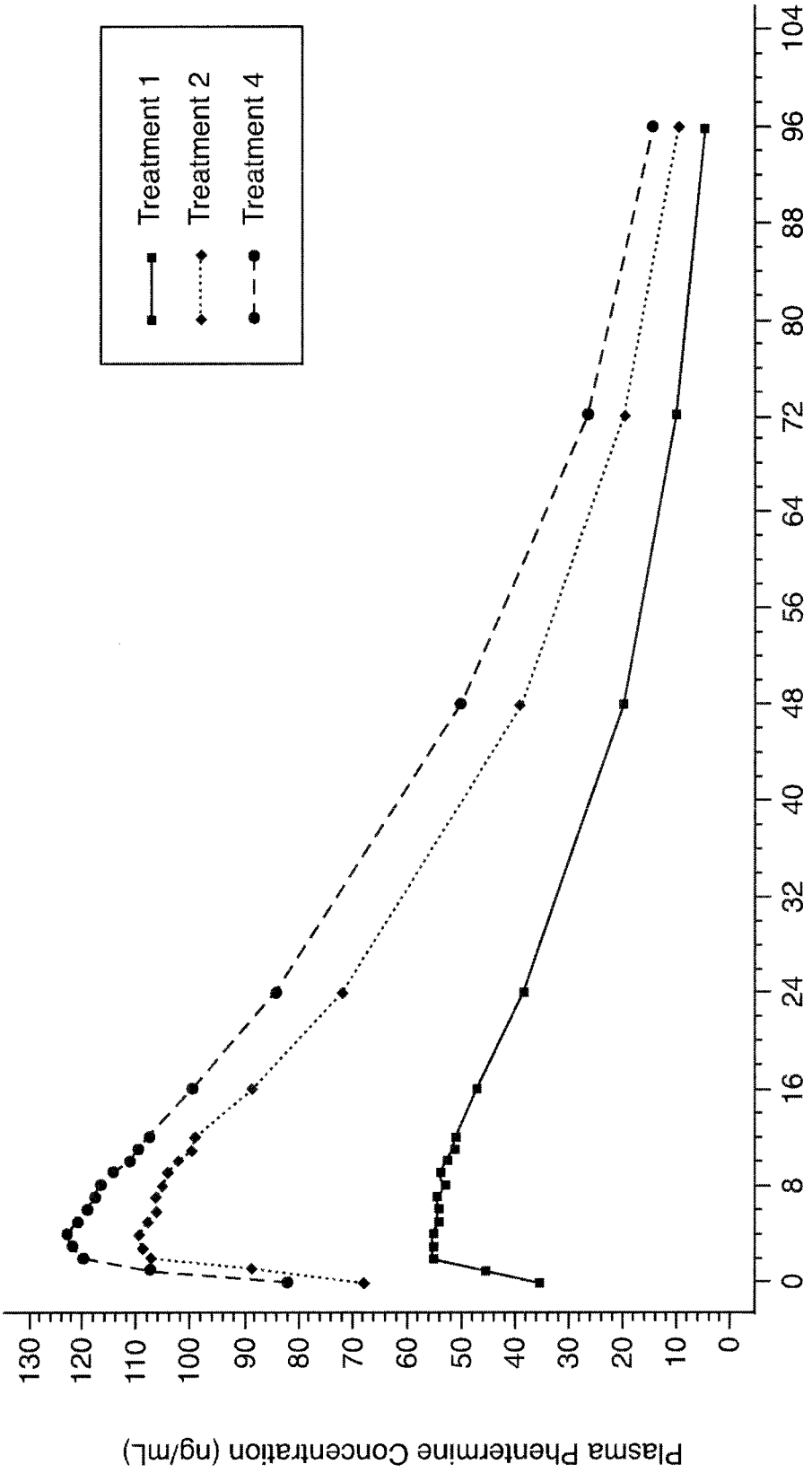

50 mg CR capsule (Vivus)
100 mg Topamax Tablet
100 mg CR capsule (Vivus)
Plasma Concentrations (ug/mL)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
10
20
30
40
50
60
70
80
90
Time (h)

FIGURE 1

FIGURE 2


Treatment 1
Treatment 2
Treatment 4
Plasma Phentermine Concentration (ng/mL)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
0
8
16
24
32
40
48
56
64
72
80
88
96
104

ESCALATING DOSING REGIMEN FOR EFFECTING WEIGHT LOSS AND TREATING OBESITY

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a continuation-in-part of U.S. patent application Ser. No. 12/135,953, filed Jun. 9, 2008, the disclosure of which is incorporated by reference.

BACKGROUND OF THE INVENTION

The prevalence of obesity in both children and adults is on the rise in first world countries, especially in the United States, as well as in many developing countries such as China and India. Many aspects of a person's life are affected by obesity, from physical problems such as knee and ankle joint deterioration, to emotional problems resulting from self-esteem issues and society's attitude towards heavy people. The medical problems caused by obesity can be serious and often life-threatening and include diabetes, shortness of breath and other respiratory problems such as asthma and pulmonary hypertension, gallbladder disease, dyslipidemia (for example, high cholesterol or high levels of triglycerides) and dyslipidemic hypertension, osteoarthritis and other orthopedic problems, reflux esophagitis (heartburn), snoring, sleep apnea, menstrual irregularities, infertility, problems associated with pregnancy, gout, cardiovascular problems such as coronary artery disease and other heart trouble, muscular dystrophy, and metabolic disorders such as hypoalphalipoproteinemia, familial combined hyperlipidemia, and Syndrome X, including insulin-resistant Syndrome X. In addition, obesity has been associated with an increased incidence of certain cancers, notably cancers of the colon, rectum, prostate, breast, uterus, and cervix.

Obesity substantially increases the risk of morbidity from hypertension, dyslipidemia, type II diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis and endometrial, breast, prostate, and colon cancers. Higher body weights are also associated with increases in all-cause mortality. Many of these problems are relieved or improved when the afflicted individual undergoes permanent significant weight loss. Weight loss in these individuals can also promote a significant increase in longevity.

Strategies for treating obesity and related disorders have included dietary restriction, increased physical activity, pharmacological approaches, and even surgery, with the choice depending, at least in part, on the degree of weight loss one is attempting to achieve as well as on the severity of obesity exhibited by the subject. For example, treatments such as a low-calorie, low-fat diet and/or regular exercise are often adequate with individuals who are only mildly overweight. The difficulty in maintaining long-term weight loss through diet and behavior modification, however, has led to an increasing interest in other avenues for treatment, particularly pharmacotherapy.

Traditional pharmacological interventions typically induce a weight loss of between five and fifteen kilograms; if the medication is discontinued, renewed weight gain often ensues. Surgical treatments are comparatively successful and are reserved for patients with extreme obesity and/or with serious medical complications.

The above treatments can be enhanced by controlled use of over-the-counter appetite suppressants including caffeine, ephedrine and phenylpropanolamine (Acutrim®), Dexatrim®). Moreover, prescription medications including

amphetamine, diethylpropion (Tenuate®), mazindol (Mazanor®, Sanorex®), phentermine (Fastin®), Ionamin®), phenmetrazine (Preludin®), phendimetrazine (Bontrol®, Plegine®, Adipost®), Dital®, Dyrexan®, Melfiat®, Prelu-2®, Rexigen Forte®), benzphetamine (Didrex®) and fluoxetine (Prozac®) are often used in the treatment of seriously overweight and/or obese subjects or patients.

While society has seen tremendous advances in the field of pharmaceuticals, there are, of course, drawbacks to the administration of any given pharmaceutical agent. Sometimes, the disadvantages, or "side effects," are so severe as to preclude administration of a particular agent at a therapeutically effective dose. Furthermore, many agents in the same therapeutic class display similar side effect profiles, meaning that patients either have to forego therapy or suffer from varying degrees of side effects associated with the medication of choice.

The present invention is directed to an escalating dosing regimen for administering topiramate alone or in combination with a second therapeutic agent that directly or indirectly reduces the side effects associated with one or both of the agents administered. By "indirectly" reducing side effects is meant that the second therapeutic agent allows the first pharmaceutical agent to be administered at a lower dose without compromising therapeutic efficacy, thus resulting dose-dependent unwanted effects.

Topiramate (2,3,4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate) is a broad-spectrum neurotherapeutic agent approved by the FDA and the regulatory agencies of many other countries for the treatment of certain seizure disorders and the prevention of migraine headaches. E. Faught et al. (1996) Neurology 46:1684-90; Karim et al. (1995) Epilepsia 36 (S4):33; S. K. Sachdeo et al. (1995) Epilepsia 36(S4):33; T. A. Glauser (1999) Epilepsia 40 (S5): S71-80; R. C. Sachdeo (1998) Clin. Pharmacokinet. 34:335-346). There has also been evidence that topiramate is effective in the treatment of diabetes (U.S. Pat. Nos. 7,109,174 and 6,362,220), neurological disorders (U.S. Pat. No. 6,908,902), depression (U.S. Pat. No. 6,627,653), psychosis (U.S. Pat. No. 6,620,819), headaches (U.S. Pat. No. 6,319,903) and hypertension (U.S. Pat. No. 6,201,010). However there have been adverse effects associated with the use of topiramate in humans, such as cognitive dulling and word finding difficulties, which can discourage many obese patients from taking this drug.

As such, there is considerable interest in the development of additional methods and compositions for treating obesity and related conditions in which the therapeutic efficacy of known therapeutic agents and compositions are improved. In addition, combination therapy, wherein two or more active agents are administered in combination, may be employed to decrease the dose of each individual active agent administered and mitigate one or more side effects of the other active agent or agents. Given that the incidence of obesity and conditions caused by or related to obesity has reached epidemic proportions, there is an urgent need for effective methods for the treatment of obesity and/or a related condition, including combination treatments that result in reduction of toxicity, decreased side effects and effective treatment.

SUMMARY OF THE INVENTION

The present invention provides novel topiramate compositions and methods for effecting weight loss, treating obesity, and treating conditions caused by or associated with excess weight or obesity. The compositions can contain topiramate as a single active agent but more typically contain topiramate

in combination with at least one sympathomimetic agent. The term "sympathomimetic agent" is a term of art and refers to agents or compounds that mimic or alter stimulation of the sympathetic nervous system. Exemplary sympathomimetic agents include phentermine and bupropion. Optimally, the topiramate and the sympathomimetic agent are contained in a single dosage form, which provides for immediate release of the sympathomimetic agent and controlled release, e.g., sustained release, delayed release, or both sustained release and delayed release, of the topiramate.

In another aspect of the invention, a controlled release topiramate composition is provided that is composed of an effective amount of topiramate, microcrystalline cellulose, and methylcellulose. Such a composition will provide for sustained release of the topiramate. The composition, in the form of, for instance, a bead or tablet, may be coated with ethyl cellulose, polyvinyl pyrrolidone, or the like, to provide for delayed release of the topiramate as well. A sympathomimetic agent is preferably although not necessarily included, and, if present, is preferably in immediate release form.

The present invention features an escalating dosing regimen for administering topiramate alone or in combination with a sympathomimetic agent, wherein the dosing regimen is in the context of a method for effecting weight loss, e.g., in a method for treating obesity, overweight, or a condition associated with obesity, or in an alternative method, e.g., a method for treating epilepsy, a method for treating an impulse control disorder, or the like. The method involves administration of a topiramate composition as described above, wherein the topiramate is generally although not necessarily administered in a controlled release composition and/or in combination with a sympathomimetic agent. The escalating dosing regimen involves administration of an initial daily dosage to an individual for a specific time period and incrementally increasing the dosage at various designated time points.

The invention also provides a packaged pharmaceutical preparation comprising topiramate, optionally a sympathomimetic agent as well, and instructions for administering, e.g., self-administering, the active agent(s). Generally, the instructions for administration include reference to an escalating dosing regimen wherein a lower daily dosage of topiramate is administered initially, with incremental increases at various designated time points thereafter. Ideally, a titration card is provided that sets forth the recommended dosages for at least four weeks.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** provides a summary of the plasma concentration of controlled release topiramate according to the present invention versus topiramate (Topamax®) in normal obese subjects.

FIG. **2** depicts the mean plasma phentermine concentrations versus time for subjects administered phentermine in combination with controlled release topiramate and phentermine in combination with immediate release topiramate (Topamax®).

DETAILED DESCRIPTION OF THE INVENTION

Definitions and Nomenclature

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, "an active agent" refers not only to a single active agent but also to a combination of two or more different active agents, "a dosage form" refers to a combination of dosage forms as well as to a single dosage form, and the like.

Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by one of ordinary skill in the art to which the invention pertains. Specific terminology of particular importance to the description of the present invention is defined below.

When referring to an active agent, applicants intend the term "active agent" to encompass not only the specified molecular entity but also its pharmaceutically acceptable, pharmacologically active analogs, including, but not limited to, salts, esters, amides, prodrugs, conjugates, active metabolites, and other such derivatives, analogs, and related compounds as will be discussed infra. Therefore, reference to "phentermine," for example, or "bupropion," encompasses not only phentermine and bupropion per se but also salts and other derivatives of phentermine and bupropion, e.g., phentermine hydrochloride and bupropion hydrochloride, respectively. It is to be understood that when amounts or doses are specified, that those amounts or doses refer to the amount or dose of active agent per se and not to a salt or the like. For example, when it is indicated that a dose or amount of phentermine is 7.5 mg, that would correspond to 9.84 phentermine hydrochloride and not 7.5 phentermine hydrochloride.

The terms "treating" and "treatment" as used herein refer to reduction in severity and/or frequency of symptoms, elimination of symptoms and/or underlying cause, and improvement or remediation of damage. In certain aspects, the term "treating" and "treatment" as used herein refer to the prevention of the occurrence of symptoms. In other aspects, the term "treating" and "treatment" as used herein refer to the prevention of the underlying cause of symptoms associated with obesity, excess weight, and/or a related condition. The phrase "administering to a subject" refers to the process of introducing a composition or dosage form of the invention into the subject (e.g., a human or other mammalian subject) via an art-recognized means of introduction

By the terms "effective amount" and "therapeutically effective amount" of an agent, compound, drug, composition or combination of the invention which is nontoxic and effective for producing some desired therapeutic effect upon administration to a subject or patient (e.g., a human subject or patient).

The term "dosage form" denotes any form of a pharmaceutical composition that contains an amount of active agent sufficient to achieve a therapeutic effect with a single administration. When the formulation is a tablet or capsule, the dosage form is usually one such tablet or capsule. The frequency of administration that will provide the most effective results in an efficient manner without overdosing will vary with the characteristics of the particular active agent, including both its pharmacological characteristics and its physical characteristics, such as hydrophilicity.

The term "controlled release" refers to a drug-containing formulation or fraction thereof in which release of the drug is not immediate, i.e., with a "controlled release" formulation, administration does not result in immediate release of the drug into an absorption pool. The term is used interchangeably with "nonimmediate release" as defined in Remington: The Science and Practice of Pharmacy, Nineteenth Ed. (Easton, Pa.: Mack Publishing Company, 1995). In general, the term "controlled release" as used herein includes sustained release, modified release and delayed release formulations.

The term "sustained release" (synonymous with "extended release") is used in its conventional sense to refer to a drug formulation that provides for gradual release of a drug over an

extended period of time, and that preferably, although not necessarily, results in substantially constant blood levels of a drug over an extended time period. The term "delayed release" is also used in its conventional sense, to refer to a drug formulation which, following administration to a patient provides a measurable time delay before drug is released from the formulation into the patient's body.

By "pharmaceutically acceptable" is meant a material that is not biologically or otherwise undesirable, i.e., the material may be incorporated into a pharmaceutical composition administered to a patient without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. When the term "pharmaceutically acceptable" is used to refer to a pharmaceutical carrier or excipient, it is implied that the carrier or excipient has met the required standards of toxicological and manufacturing testing or that it is included on the Inactive Ingredient Guide prepared by the U.S. Food and Drug administration. "Pharmacologically active" (or simply "active") as in a "pharmacologically active" (or "active") derivative or analog, refers to a derivative or analog having the same type of pharmacological activity as the parent compound and approximately equivalent in degree. The term "pharmaceutically acceptable salts" include acid addition salts which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

As used herein, "subject" or "individual" or "patient" refers to any subject for whom or which therapy is desired, and generally refers to the recipient of the therapy to be practiced according to the invention. The subject can be any vertebrate, but will typically be a mammal. If a mammal, the subject will in many embodiments be a human, but may also be a domestic livestock, laboratory subject or pet animal.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

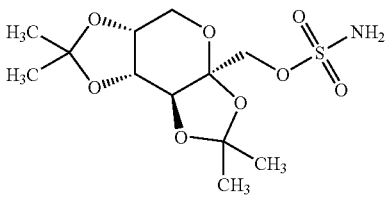
Methods and Formulations of the Invention:

The present invention provides novel methods and compositions to effect weight loss and treat obesity, conditions related to excess weight or obesity, diabetes (whether or not related to obesity), and other conditions and disorders as will be explained infra. According to the U.S. Centers for Disease Control, the clinical definition of being overweight (the term being used synonymously herein with the term "excess weight") is having a body mass index (BMI) between 25.0 and 29.9 kg/m; BMI is calculated by multiplying an individual's weight, in kilograms, by height, in meters. The CDC defines obesity as having a BMI of 30 or higher. In one embodiment, the invention provides a method for effecting weight loss and treating overweight, obesity, and conditions associated with excess weight and obesity, and involves administration of a combination of the sympathomimetic agent phentermine and the anti-convulsant agent topiramate.

Topiramate is an anticonvulsant sulfamate compound that is sold in the United States under the trade name Topamax® (Ortho-McNeil Pharmaceutical, Inc., Raritan, N.J., U.S.A). Topiramate has been approved for use as an antiepileptic agent as an adjuvant therapy for patients with partial onset seizures or primary generalized tonic-clonic seizures, and for the prevention of migraine headache. See Physician's Desk Reference, 56th ed. (2002); see also U.S. Pat. No. 4,513,006 to Maryanoff et al. and U.S. Pat. No. 7,351,695 to Almarssoo et al.

"Topiramate" generally refers to the sulfamate-substituted monosaccharide having the chemical name 2,3,4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate and the molecular formula C12H21NO8S. The structure of the compound is represented by Formula (I)

(I)



As used herein, the term "topiramate" encompasses 2,3,4,5-bis-(O)-(1-methylethylidene)-β-D-fructopyranose sulfamate as well as individual enantiomers, individual diastereomers, or mixtures thereof. The term "topiramate" as used herein also encompasses topiramate salts as well as polymorphs, solvates (including hydrates and mixed solvates, as well as hydrates of salts), co-crystals (for instance, with other compounds or other forms of topiramate), amorphous, and anhydrous forms of the compound of Formula (I). Topiramate salts useful in conjunction with the present invention, as will be appreciated from the fact that the compound is a sulfamic acid derivative, are pharmaceutically acceptable basic addition

salts. Such salts are prepared from bases that provide a pharmaceutically acceptable cation that associates with the sulfamic acid group of the compound of Formula (I). Suitable pharmaceutically acceptable cations include both organic and inorganic cations, including, without limitation, sodium, sodium, potassium, lithium, magnesium, calcium, aluminum, zinc, procaine, benzathine, chloroprocaine, choline, diethylamine, ethylenediamine, N-methylglucamine, benethamine, clemizole, diethylamine, piperazine, tromethamine, triethylamine, ethanolamine, triethanolamine, arginine, lysine, histidine, tributylamine, 2-amino-2-pentylpropanol, 2-amino-2-methyl-1,3-propanediol, tris(hydroxymethyl) aminomethane, benzylamine, 2-(dimethylamino)ethanol, barium or bismuth counter ions. Particularly preferred cations are sodium, lithium, and potassium. Other forms of topiramate referenced above may be prepared using methods known in the art; see, e.g., U.S. Pat. No. 7,351,695. The subject methods include a dosing regimen for the administration of topiramate alone or, more preferably, in combination with a sympathomimetic agent. In certain aspects, the present invention provides a dosing regimen for the administration of a pharmaceutical composition that includes, e.g., topiramate in combination with bupropion or phentermine.

In one embodiment of the invention, directed to an escalating dosage regimen, the dosing strategy involves administering to a patient a lower daily dosage of topiramate alone or in combination with a sympathomimetic agent for a specific period of time and then incrementally increasing the dosage at various designated time points.

For example, when treating a patient who is overweight or obese, and who may suffer from a condition associated with or caused by excess weight or obesity, the patient receives a dosage of 15 mg/day to 30 mg/day, e.g., 23 mg/day, of topiramate for 1 week. Next, the patient receives a dosage of 35 mg/day to 55 mg/day, e.g., 46 mg/day, of topiramate for a second week. Thereafter, the patient receives a dosage of 60 mg/day to 80 mg/day, e.g., 69 mg/day, of topiramate for a third week, which is followed by a final dosage of 85 mg to 125 mg/day, e.g., 92 mg/day of topiramate for a fourth week.

In another example, when treating a patient for obesity and/or a related condition, the patient receives a dosage of 15 mg/day to 30 mg/day, e.g., 23 mg/day, of topiramate in combination with a dosage of 3.75 mg/day of phentermine for 1 week. The patient next receives a dosage of 35 mg/day to 55 mg/day, e.g., 46 mg/day, of topiramate in combination with a dosage of 7.5 mg/day of phentermine for a second week. Thereafter, the patient receives a dosage of 60 mg/day to 80 mg/day, e.g., 69 mg/day, of topiramate in combination with a dosage of 11.25 mg/day of phentermine for a third week which is followed by a final dosage of 85 mg to 125 mg/day, e.g., 92 mg/day, topiramate in combination with a dosage of 15 mg/day of phentermine for a fourth week.

After the fourth week of administration, the further administration of topiramate alone or topiramate in combination with phentermine is carried on indefinitely or, more typically, until a sufficient reduction of symptoms has been achieved. In certain aspects, the final dose of 92 mg/day of topiramate alone or in combination with a dosage of 15 mg/day of phentermine indefinitely or until a sufficient reduction of symptoms has been achieved. In other aspects, the final dose of topiramate alone or topiramate in combination with phentermine is decreased to the initial starting dose of the regimen and maintained indefinitely or until a sufficient reduction of symptoms has been achieved. In a weight loss regimen, the dosage regimen generally involves continual, i.e., ongoing, administration, over a significant period of time, e.g., in the range of about 4 weeks to about 67 weeks, depending on the severity of an individual's weight problem, the amount of weight that should be lost, and the rate at which weight is lost.

In another embodiment of the invention, topiramate is administered on an ongoing basis, i.e., generally following the escalating dosage regimen described above. In either of these methods, i.e., the escalating dosage regimen or an ongoing maintenance dosage regimen, pharmaceutical compositions are administered that include an effective amount of topiramate as the active agent, wherein an "effective amount" of topiramate is generally an amount that results in a reduction of at least one pathological parameter associated with obesity, excess weight, and/or a related disorder. In the methods of the invention, e.g., in a method for effecting weight loss such as in the treatment of obesity and/or a condition related to obesity, an effective amount of topiramate is an amount that is effective to achieve a reduction of at least about 10%, at least about 15%, at least about 20%, or at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95%, compared to the expected reduction in the parameter, e.g., loss of weight, in an individual suffering from obesity, excess weight, and/or a related disorder and not treated with the topiramate compositions.

A suitable daily dose of topiramate is in the range of 10 mg to 1500 mg. For example, 10 mg, 20 mg, 30 mg, 60 mg, 90 mg, 120 mg, 150 mg, 180 mg, 210 mg, 240 mg, 270 mg, 300 mg, 330 mg, 360 mg, 390 mg, 420 mg, 450 mg, 480 mg, 500 mg, 600 mg, 800 mg, 1000 mg, 1200 mg, 1500 mg or the like is administered to a patient as a daily dosage. In another example, 23 mg, 46 mg, 69 mg and 92 mg or the like is administered to a patient as a daily dosage. In some embodiments, the daily dosage of topiramate is in the range of 10 mg to 150. In certain embodiments, the daily dosage of topiramate is in the range of 10 mg to 100 mg. Each of the aforementioned "daily dosages" is generally although not necessarily administered as a single daily dose.

The patient may receive a specific dosage of topiramate over a period of weeks, months, or years, e.g., 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 2 years, 3 years, 4 years, 5 years and the like.

Aspects of the invention provide a topiramate monotherapy or combination therapy in which the subject topiramate formulation is effective when administered at a initial dose as low as 10-23 mg. In certain aspects, the topiramate formulation is effective at a dose of approximately 20 mg. The novel topiramate formulations of the present invention have a lower maximum concentration (Cmax) without decreasing total drug exposure defined by the area under the concentration-time curve (AUC). Further, the novel topiramate formulations of the present invention have a delay in time after administration of a drug when the maximum plasma concentration is reached (Tmax) by six to eight hours. As depicted in FIG. **1**, drug exposure as measured by AUC for the control release (CR) formulation capsule is the same as the 100 mg of immediate release topiramate (Topamax®) tablet despite a 20% reduction in the Cmax. Therefore, this formulation is capable of reducing the Cmax which would reduce side effects without compromising the efficacy of the treatment, since the AUC is the same. This reduction in Cmax is preferred as topiramate can be sedating and a delay in the time to reach maximum plasma concentration to the late afternoon or evening time would improve the tolerability of the drug.

As such, the effective amount of topiramate is decreased, thereby further reducing any toxicity or harmful side effects in the patient. The amount of topiramate administered to the patient is less than an amount that would cause toxicity in the patient. In certain embodiments, the amount of the compound that is administered to the patient is less than the amount that causes a concentration of the compound in the patient's plasma to equal or exceed the toxic level of the compound. The optimal amount of the compound that should be administered to the patient in the practice of the present invention will depend on the individual as well as the severity of the individual's symptoms.

Depending on the intended mode of administration, the pharmaceutical formulation may be a solid, semi-solid or liquid, such as, for example, a tablet, a capsule, a caplet, a liquid, a suspension, an emulsion, a suppository, granules, pellets, beads, a powder, or the like, preferably in unit dosage form suitable for single administration of a precise dosage. Suitable pharmaceutical compositions and dosage forms may be prepared using conventional methods known to those in the field of pharmaceutical formulation and described in the pertinent texts and literature, e.g., in Remington: The Science and Practice of Pharmacy (Easton, Pa.: Mack Publishing Co., 1995). Oral administration and therefore oral dosage forms are generally preferred, and include tablets, capsules, caplets, solutions, suspensions and syrups, and may also comprise a plurality of granules, beads, powders, or pellets that may or may not be encapsulated. Preferred oral dosage forms are capsules and tablets, particularly controlled release capsules and tablets, as noted above.

As noted above, it is especially advantageous to formulate compositions of the invention in unit dosage form for ease of administration and uniformity of dosage. The term "unit dosage forms" as used herein refers to physically discrete units suited as unitary dosages for the individuals to be treated. That is, the compositions are formulated into discrete dosage units each containing a predetermined, "unit dosage" quantity of an active agent calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specifications of unit dosage forms of the invention are dependent on the unique characteristics of the active agent to be delivered. Dosages can further be determined by reference to the usual dose and manner of administration of the ingredients. It should be noted that, in some cases, two or more individual dosage units in combination provide a therapeutically effective amount of the active agent, e.g., two tablets or capsules taken together may provide a therapeutically effective dosage of topiramate, such that the unit dosage in each tablet or capsule is approximately 50% of the therapeutically effective amount.

Tablets may be manufactured using standard tablet processing procedures and equipment. Direct compression and granulation techniques are preferred. In addition to the active agent, tablets will generally contain inactive, pharmaceutically acceptable carrier materials such as binders, lubricants, disintegrants, fillers, stabilizers, surfactants, coloring agents, and the like.

Capsules are also preferred oral dosage forms, in which case the active agent-containing composition may be encapsulated in the form of a liquid or solid (including particulates such as granules, beads, powders or pellets). Suitable capsules may be either hard or soft, and are generally made of gelatin, starch, or a cellulosic material, with gelatin capsules preferred. Two-piece hard gelatin capsules are preferably sealed, such as with gelatin bands or the like. See, for example, *Remington: The Science and Practice of Pharmacy*, cited earlier herein, which describes materials and methods for preparing encapsulated pharmaceuticals.

Oral dosage forms, whether tablets, capsules, caplets, or particulates, can, if desired, be formulated so as to provide for controlled release of topiramate, and in a preferred embodiment, the present formulations are controlled release oral dosage forms. Generally, the dosage forms provide for sustained release, i.e., gradual, release of topiramate, from the dosage form to the patient's body over an extended time period, typically providing for a substantially constant blood level of the agent over a time period in the range of about 4 to about 12 hours, typically in the range of about 6 to about 10 hours or 6 to about 8 hours. Release of the topiramate may also be delayed; that is, there is a time lag between administration and the start of topiramate release. In this way, for instance, an individual will not experience sleepiness or other side effects of topiramate during the school or work day. Preferred dosage forms thus involve sustained release of the topiramate, delayed release of the topiramate, or both sustained and delayed release of the topiramate.

Generally, as will be appreciated by those of ordinary skill in the art, sustained release dosage forms are formulated by dispersing the active agent within a matrix of a gradually hydrolyzable material such as a hydrophilic polymer, or by coating a solid, drug-containing dosage form with such a material. Hydrophilic polymers useful for providing a sustained release coating or matrix include, by way of example: cellulosic polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, ethyl cellulose, cellulose acetate, and carboxymethylcellulose sodium; acrylic acid polymers and copolymers, preferably formed from acrylic acid, methacrylic acid, acrylic acid alkyl esters, methacrylic acid alkyl esters, and the like, e.g. copolymers of acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate; and vinyl polymers and copolymers such as polyvinyl pyrrolidone e.g., Povidone K30, polyvinyl acetate, and ethylene-vinyl acetate copolymer. Preferred sustained release polymers herein include those available as "Methocel" polymers from Dow Chemical, particularly the methylcellulose ether polymers in the Methocel™ A group, having a viscosity grade of about 4,000 cps and a methoxyl content of about 27.5% to 31.5%, e.g., Methocel™ A15LV, Methocel™ A15C, and Methocel™ A4M.

When sustained release preparations are prepared, tablets, granules, powder, capsules, and the like can be produced according to a conventional method after adding excipient, and as necessary, binder, disintegrating agent, lubricant, coloring agent, taste-modifying agent, flavoring agent, and the like. These additives may be ones generally used in the field, and for example, lactose, sodium chloride, glucose, starch, microcrystalline cellulose, and silicic acid as the excipient, water, ethanol, propanol, simple syrup, gelatin solution, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, shellac, calcium phosphate, and polyvinylpyrrolidone as the binder, agar powder, sodium hydrogen carbonate, sodium lauryl sulfate, and stearic acid monoglyceride as the disintegrating agent, purified talc, stearic acid salt, borax, and polyethylene glycol as the lubricant, β-carotene, yellow iron sesquioxide, and caramel as the coloring agent, and saccharose and orange peel as the taste-modifying agent can be listed as examples. It should be noted that various grades of microcrystalline cellulose are preferred fillers herein, e.g., Avicel® PH101, Avicel® PH102, and Avicel® PH200 (FMC), with particle sizes of about 50 microns, 100 microns, and 190

microns, respectively. Microcrystalline cellulose having a particle size in the range of about 50 microns to 200 microns is preferred herein.

The dosage forms may also be provided with a delayed release coating, e.g., composed of an acrylate and/or methacrylate copolymers. Examples of such polymers are those available under the trade name "Eudragit" from Rohm Pharma (Germany). The Eudragit series E, L, S, RL, RS, and NE copolymers are available as solubilized in organic solvent, in an aqueous dispersion, or as a dry powder. Preferred acrylate polymers are copolymers of methacrylic acid and methyl methacrylate, such as the Eudragit L and Eudragit S series polymers. Other preferred Eudragit polymers are cationic, such as the Eudragit E, RS, and RL series polymers. Eudragit E100 and E PO are cationic copolymers of dimethylaminoethyl methacrylate and neutral methacrylates (e.g., methyl methacrylate), while Eudragit RS and Eudragit RL polymers are analogous polymers, composed of neutral methacrylic acid esters and a small proportion of trimethylammonioethyl methacrylate.

In a specific embodiment, controlled release topiramate beads for oral administration, e.g., by incorporation in an orally administrable capsule or compaction into an orally administrable tablet, are made using an extrusion spheronization process to produce a matrix core comprised of: topiramate, 40.0% w/w; microcrystalline cellulose, e.g., Avicel® PH102, 56.5% w/w; and methylcellulose, e.g., Methocel™ A15 LV, 3.5% w/w. The topiramate cores are then coated with ethyl cellulose, 5.47% w/w and Povidone K30:2.39% w/w. As will be described in detail infra, beads of a second active agent, e.g., a sympathomimetic agent, may also be prepared and incorporated into the capsule. For instance, phentermine or bupropion beads having an immediate release drug coating on sugar spheres or analogous non-active cores may be employed. Both sets of beads may then be encapsulated into one capsule.

Preparations according to this invention for parenteral administration include sterile aqueous and nonaqueous solutions, suspensions, and emulsions. Injectable aqueous solutions contain the active agent in water-soluble form. Examples of nonaqueous solvents or vehicles include fatty oils, such as olive oil and corn oil, synthetic fatty acid esters, such as ethyl oleate or triglycerides, low molecular weight alcohols such as propylene glycol, synthetic hydrophilic polymers such as polyethylene glycol, liposomes, and the like. Parenteral formulations may also contain adjuvants such as solubilizers, preservatives, wetting agents, emulsifiers, dispersants, and stabilizers, and aqueous suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, and dextran. Injectable formulations are rendered sterile by incorporation of a sterilizing agent, filtration through a bacteria-retaining filter, irradiation, or heat. They can also be manufactured using a sterile injectable medium. The active agent may also be in dried, e.g., lyophilized, form that may be rehydrated with a suitable vehicle immediately prior to administration via injection.

The active agents may also be administered through the skin using conventional transdermal drug delivery systems, wherein the active agent is contained within a laminated structure that serves as a drug delivery device to be affixed to the skin. In such a structure, the drug composition is contained in a layer, or "reservoir," underlying an upper backing layer. The laminated structure may contain a single reservoir, or it may contain multiple reservoirs. In one embodiment, the reservoir comprises a polymeric matrix of a pharmaceutically acceptable contact adhesive material that serves to affix the system to the skin during drug delivery. Alternatively, the drug-containing reservoir and skin contact adhesive are present as separate and distinct layers, with the adhesive underlying the reservoir which, in this case, may be either a polymeric matrix as described above, or it may be a liquid or hydrogel reservoir, or may take some other form. Transdermal drug delivery systems may in addition contain a skin permeation enhancer.

In addition to the formulations described previously, the active agent may be formulated as a depot preparation for controlled release of the active agent, preferably sustained release over an extended time period. These sustained release dosage forms are generally administered by implantation (e.g., subcutaneously or intramuscularly or by intramuscular injection).

Although the present compositions will generally be administered orally, parenterally, transdermally, or via an implanted depot, other modes of administration are suitable as well. For example, administration may be transmucosal, e.g., rectal or vaginal, preferably using a suppository that contains, in addition to the active agent, excipients such as a suppository wax. Formulations for nasal or sublingual administration are also prepared with standard excipients well known in the art. The pharmaceutical compositions of the invention may also be formulated for inhalation, e.g., as a solution in saline, as a dry powder, or as an aerosol.

In another embodiment, the methods of the invention, i.e., the escalating dosage regimen or ongoing maintenance dosing, involve administration of a combination of topiramate and a sympathomimetic agent.

Sympathomimetic agents for use in the present invention and their general clinical uses or effects are set forth in Table 1.

TABLE 1

Sympathomimetic Agents and Clinical Uses Thereof
General structure: Main Clinical Uses

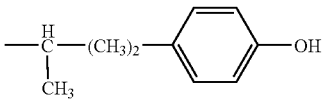
Agent name	Ring substituent(s)	R^{α}	R^{β}	R^{γ}	<Receptor A N P V	® Receptor B C	CNS, 0
Bupropion	3-Cl	=O	CH_3	$C(CH_3)_3$			
Phenylethylamine		H	H	H			
Epinephrine	3-OH, 4-OH	OH	H	CH_3	A, P, V	B, C	
Norepinephrine	3-OH, 4-OH	OH	H	H	P		
Epinine	3-OH, 4-OH	H	H	CH_3			
Dopamine	3-OH, 4-OH	H	H	H	P		
Dobutamine	3-OH, 4-OH	H	H	1*		C	
Nordefrin	3-OH, 4-OH	OH	CH_3	H	V		
Ethylnorepinephrine	3-OH, 4-OH	OH	CH_2CH_3	H		B	
Isoproterenol	3-OH, 4-OH	OH	H	$CH(CH_3)_2$		B, C	
Protokylol	3-OH, 4-OH	OH	H	2*		B	

TABLE 1-continued

Sympathomimetic Agents and Clinical Uses Thereof
General structure: Main Clinical Uses

Agent name	Ring substituent(s)	R^{α}	R^{β}	R^{γ}	<Receptor A N P V	® Receptor B C	CNS, 0
Isoetharine	3-OH, 4-OH	OH	CH_2CH_3	$CH(CH_3)_2$		B	
Metaproterenol	3-OH, 5-OH	OH	H	$CH(CH_3)_2$		B	
Terbutaline	3-OH, 5-OH	OH	H	$C(CH_3)_3$		B	
Metaraminol	3-OH	OH	CH_3	H	P		
Phenylephrine	3-OH	OH	H	CH_3	N, P		
Tyramine	4-OH	H	H	H			
Hydroxyamphetamine	4-OH	H	CH_3	H	N, P	C	
Methoxyphenamine	2-OCH_3	H	CH_3	CH_3		B	
Methoxamine	2-OCH_3, 5-OCH_3	OH	CH_3	H	P		
Albuterol	3-CH_2OH, 4-OH	OH	H	$C(CH_3)_3$		B	
Amphetamine		H	CH_3	H			CNS, 0
Methamphetamine		H	CH_3	CH_3	P		CNS, 0
Benzphetamine		H	CH_3	—NHR^{γ} is replaced with 3*			0
Ephedrine		OH	CH_3	CH_3	N, P	B,C	
Phenylpropanolamine		OH	CH_3	H	N		
Mephentermine		H	—CHR^{β}— is replaced with 4*	CH_3	N, P		
Phentermine		H	—CHR^{β}— is replaced with 4*	H			0
Chlorphentermine	4-Cl	H	—CHR^{β}— is replaced with 4*	H			0
Fenfluramine	3-CF3	H	CH_3	C_2H_5			0
Propylhexedrine	5*: phenyl ring is replaced with cyclohexyl	H	CH_3	CH_3	N		
Diethylpropion		6*: The substituent at the 1-position is replaced with 6, below.					0
Phenmetrazine		7*: The substituent at the 1-position is replaced with 7, below.					0
Phendimetrazine		8*: The substituent at the 1-position is replaced with 8, below.					0

*1:



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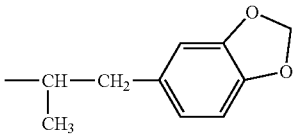

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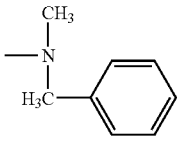

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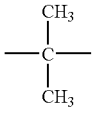
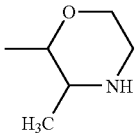


TABLE 1-continued

Sympathomimetic Agents and Clinical Uses Thereof General structure: Main Clinical Uses							
Agent name	Ring substituent(s)	R^{α}	R^{β}	R^{γ}	<Receptor A N P V	® Receptor B C	CNS, 0
*5: 							
*6:							
*7: 							

<Activity
A = Allergic reactions (includes ® action)
N = Nasal decongestion
P = Pressor (may include ® action)
V = Other local vasoconstriction (e.g. in local anesthesia)
® Activity
B = Bronchodilator
C = Cardiac
CNS = Central nervous system
0 = Anorectic
*Numbers bearing an asterisk refer to the substituents numbered in the bottom rows of the table; substituent 5 replaces the phenyl rings, and 6, 7 and 8 are attached directly to the phenyl ring, replacing the ethylamine side chain.
†The < and ® in the prototype formula refer to positions of the C atoms in the ethylamine side chain.

In certain embodiments, the sympathomimetic agent is phentermine or a phentermine-like compound. As defined herein, a "phentermine-like compound" is a compound structurally related to phentermine (e.g., an analog or derivative) which maintains an anorectic activity similar to that of phentermine. One phentermine-like compound is chlorphentermine. In yet another embodiment, the sympathomimetic agent is amphetamine or an amphetamine-like compound. As used herein, an "amphetamine-like compound" is a compound structurally related to amphetamine (e.g., an analog or derivative) which maintains an anorectic effect of amphetamine. In yet another embodiment, the sympathomimetic agent is phenmetrazine or a phenmetrazine-like compound. As defined herein, a "phenmetrazine-like compound" is a compound structurally related to phenmetrazine (e.g., an analog or derivative) which maintains an anorectic effect of phenmetrazine. One phenmetrazine-like compound is phendimetrazine. Analogs and/or derivatives of the compounds of the present invention can be tested for their ability to suppress appetite (e.g., suppress food intake) in a subject (e.g., a mammalian subject).

In other embodiments, the sympathomimetic agent is bupropion or a bupropion-like compound. As defined herein, a "bupropion-like compound" is a compound structurally related to bupropion (e.g., an analog or derivative) which maintains an anti-depressive activity similar to that of bupropion.

In an exemplary embodiment, the sympathomimetic agent is selected from bupropion, amphetamine, methamphetamine, benzphetamine, phenylpropanolamine, phentermine, chlorphentermine, diethylpropion, phenmetrazine, and phendimetrazine (as set forth in Table 1).

In one embodiment, the sympathomimetic agent is phentermine. It is also within the scope of the present invention to utilize other sympathomimetic agents including pseudoephedrine (a stereoisomer of ephedrine), methylphenidate, dexmethylphenidate, tuaminoheptane, and other CNS stimulants including, for example, caffeine and bupropion.

The selection of appropriate dosages for the drugs used in combination therapy according to the present invention can be determined and optimized by the skilled artisan, e.g., by observation of the patient, including the patient's overall health, the response to the combination therapy, and the like. Optimization may be necessary if it is determined that a patient is not exhibiting the desired therapeutic effect or, conversely, if the patient is experiencing undesirable or adverse side effects that are too many in number or are of troublesome severity.

Although the dosage used will vary depending on the clinical goals to be achieved, a suitable daily dose range for the sympathomimetic agent is generally in the range of 2 mg to 1500 mg, administered to a patient over an ongoing time period. For example, 2 mg, 4 mg, 10 mg, 20 mg, 30 mg, 60 mg, 90 mg, 120 mg, 150 mg, 180 mg, 210 mg, 240 mg, 270 mg, 300 mg, 330 mg, 360 mg, 390 mg, 420 mg, 450 mg, 480 mg, 500 mg, 600 mg, 800 mg, 1000 mg, 1200 mg, 1500 mg or the like is administered to a patient as a daily dosage, which may be a single daily dosage. In another example, 3.75 mg, 7.5 mg, 11.75 mg, 15 mg or the like is administered to a patient as a daily dosage, which, again, may be a single daily dosage.

In one embodiment, each component of the combination (e.g., (i) topiramate, and (ii) a sympathomimetic drug) is prescribed at a dose that is below the typically described dose for each component as a monotherapy. The components may be prescribed separately or as a combination dosage. In one embodiment, each component of the combination (e.g., (i) topiramate, and (ii) a sympathomimetic drug) is prescribed at a dose that is above the typically described dose for each component as a monotherapy. The components may be prescribed separately or as a combination dosage.

In another embodiment, the prescribed dosage of the sympathomimetic drug is above the typically described dose for monotherapy, and topiramate is prescribed at a dosage that is at or below the typically described dose for monotherapy. In another embodiment, the prescribed dosage of the sympatho-

mimetic drug is at or below the typically described dose for monotherapy, and topiramate is prescribed at a dosage that is above the typically described dose for monotherapy.

In certain embodiments, when phentermine is the sympathomimetic agent, phentermine may be, for example, administered at a daily dosage, e.g., a single daily dosage, in the range of 2 mg to 60 mg. In one aspect, the phentermine is administered at a daily dosage, e.g., a single daily dosage, in the range of 2 mg to 30 mg. In another aspect, the phentermine is administered at a daily dosage, e.g., a single daily dosage, in the range of 2 mg to 15 mg.

In certain embodiments, when bupropion is the sympathomimetic agent, bupropion may be, for example, administered at a daily dosage, e.g., a single daily dosage, in the range of 50 mg to 400 mg, more typically in the range of 50 mg to 200 mg.

The method of administration of pharmaceutical combinations of the invention will depend, in particular, on the type of sympathomimetic agent used. Topiramate and the sympathomimetic agent may be administered together in the same composition or simultaneously or sequentially in two separate compositions. Also, one or more sympathomimetic agents may be administered to a subject or patient either in the form of a therapeutic composition or in combination, e.g., in the form of one or more separate compositions administered simultaneously or sequentially. The schedule of administration will be dependent on the type of sympathomimetic agent(s) chosen. For example, a sympathomimetic agent can have a stimulant effect and the degree of the stimulant effect may vary depending on the sympathomimetic agent chosen. A sympathomimetic agent having a significant stimulant effect would preferably be administered earlier in the day than would a sympathomimetic agent having a lesser stimulant effect. Topiramate, which typically has at least some sedative effect even at lower doses, may be administered later in the day than administration of a compound having a lesser sedative effect.

In one embodiment, topiramate is administered in a controlled release form, i.e., in sustained release and/or delayed release form, preferably both, and phentermine is administered in an immediate release form. As such, the phentermine may be taken in the morning because the drug is a stimulant as well as an appetite suppressant. In this embodiment, topiramate may be taken later in the day than the phentermine. Preferably, the patient takes the topiramate just before dinner or later in the evening because the drug is sedating.

In yet another embodiment, topiramate is administered in a controlled release form, i.e., in sustained release and/or delayed release form, and bupropion is administered in an immediate release form. As such, the bupropion may be taken in the morning because the drug is a stimulant as well as an appetite suppressant. In this embodiment, topiramate may be taken later in the day than the bupropion. Preferably, the patient takes the topiramate just before dinner or later in the evening because the drug is sedating.

As described supra, a controlled release dosage form of the invention wherein combination therapy is indicated can be a capsule containing controlled release topiramate beads and immediate release phentermine beads, bupropion beads, or the like. The topiramate beads may be made using an extrusion spheronization process to produce a matrix core comprised of: topiramate, 40.0% w/w; microcrystalline cellulose, e.g., Avicel® PH102, 56.5% w/w; and methylcellulose, e.g., Methocel™ A15 LV, 3.5% w/w. The topiramate cores are then coated with ethyl cellulose, 5.47% w/w and Povidone K30: 2.39% w/w. The phentermine beads, bupropion beads, or the like, are composed of an immediate release drug coating on sugar spheres or analogous non-active cores. Both sets of beads are then encapsulated into one capsule.

In certain embodiments, the phentermine beads may be provided with a controlled release drug coating on sugar spheres or other non-active cores. In other aspects, the phentermine beads may be coated onto the controlled release topiramate beads.

In combination therapy, then, a preferred method of administration involves simultaneous administration of the two active agents, in a single composition or in two discrete compositions each containing one of the active agents. The method of administration may also involve administration of the two active agents at different times of day, with the sympathomimetic agent generally administered earlier in the day and the topiramate generally administered later in the day. Normally, however, the two agents are administered simultaneously using one or more dosage forms that provide for immediate release of the sympathomimetic agent and controlled release of the topiramate. In an exemplary embodiment, the sympathomimetic agent and the topiramate are administered in a single dosage form that provides for immediate release of the sympathomimetic agent and sustained release and/or delayed release, preferably both sustained release and delayed release, of the topiramate. Such dosage forms may be coated cores or encapsulated beads, as described above, or they may be tablets, wherein, for example, the tablets contain at least two discrete segments, at least one of which contains the sympathomimetic agent such as phentermine or bupropion in immediate release form, and another of which contains topiramate in controlled release form.

Indications:

Conditions of particular interest for which the invention finds utility include overweight, obesity and conditions often associated with and/or caused by excess weight and obesity. Topiramate compositions and combinations administered according to the dosage regimens provided herein give rise to significant therapeutic effects and reduced adverse effects, making these pharmaceutical compositions extremely effective therapeutics, especially in the treatment of overweight, obesity and/or related conditions, including conditions associated with and/or caused by excess weight or obesity per se. Subjects suitable for treatment with the subject combination therapy treatment regimen thus include individuals suffering from conditions associated with obesity, such conditions including, without limitation:

diabetes, insulin resistance, and impaired glucose tolerance;

respiratory problems such as pulmonary hypertension, asthma, and shortness of breath;

gallbladder disease;

dyslipidemia, e.g., high cholesterol, high levels of triglycerides, etc.;

osteoarthritis and other orthopedic problems;

reflux esophagitis;

adverse conditions related to sleep, including sleep apnea and loud snoring;

menstrual irregularities, infertility, and complications in pregnancy;

gout;

high blood pressure, i.e., hypertension;

cardiovascular problems such as coronary artery disease and other heart trouble;

muscular dystrophy;

stroke, particularly thrombotic stroke and deep vein thrombosis (DVT);

migraines;

metabolic disorders such as hypoalphalipoproteinemia, familial combined hyperlipidemia, and Syndrome X, including insulin-resistant Syndrome X; and

colon, rectal, renal, esophageal, gallbladder, pancreatic, prostate, breast, uterine, ovarian, endometrial, and cervical cancers.

Higher body weights are also associated with increases in all-cause mortality. Most or all of these problems are relieved or improved by permanent significant weight loss. Longevity is likewise significantly increased by permanent significant weight loss.

Diabetes mellitus is very commonly seen in obese individuals, and is associated with continuous and pathologically elevated blood glucose concentration. It is one of the leading causes of death in the United States and is responsible for about 5% of all mortality. Diabetes is divided into two major sub-classes: Type I, also known as juvenile diabetes, or Insulin-Dependent Diabetes Mellitus (IDDM); and Type II, also known as adult onset diabetes, or Non-Insulin-Dependent Diabetes Mellitus (NIDDM).

According to the American Diabetes Association, there are over one million juvenile diabetics in the United States. Type I Diabetes is a form of autoimmune disease. Autoantibodies produced by the patients completely or partially destroy the insulin producing cells of the pancreas. Juvenile diabetics must, therefore, receive exogenous insulin during their lifetime. Without treatment, excessive acidosis, dehydration, kidney damage, and death may result. Even with treatment, complications such as blindness, atherosclerosis, and impotence can occur.

There are more than five million Type II (adult onset) diabetics diagnosed in the United States. Type II disease usually begins during middle age; the principal cause is now known to be overweight and obesity. In Type II diabetics, rising blood glucose levels after meals do not properly stimulate insulin production by the pancreas. Additionally, peripheral tissues are generally resistant to the effects of insulin. The resulting high blood glucose levels (hyperglycemia) can cause extensive tissue damage. Type II diabetics are often referred to as insulin resistant. They often have higher than normal plasma insulin levels (hyperinsulinemia) as the body attempts to overcome its insulin resistance. Some researchers now believe that hyperinsulinemia may be a causative factor in the development of high blood pressure, high levels of circulating low density lipoproteins (LDLs), and lower than normal levels of the beneficial high density lipoproteins (HDLs). While moderate insulin resistance can be compensated for in the early stages of Type II diabetes by increased insulin secretion, in more advanced disease states insulin secretion is also impaired.

Insulin resistance and hyperinsulinemia have also been linked with two other metabolic disorders that pose considerable health risks: impaired glucose tolerance and metabolic obesity. Impaired glucose tolerance is characterized by normal glucose levels before eating, with a tendency toward elevated levels (hyperglycemia) following a meal. According to the World Health Organization, approximately 11% of the U.S. population between the ages of 20 and 74 are estimated to have impaired glucose tolerance. These individuals are considered to be at higher risk for diabetes and coronary artery disease.

Obesity may also be associated with insulin resistance. A causal linkage among obesity, impaired glucose tolerance, and Type II diabetes has been proposed, but a physiological basis has not yet been established. Some researchers believe that impaired glucose tolerance and diabetes are clinically observed and diagnosed only later in the disease process after a person has developed insulin resistance and hyperinsulinemia.

Insulin resistance is frequently associated with hypertension, coronary artery disease (arteriosclerosis), and lactic acidosis, as well as related disease states. The fundamental relationship between these disease states, and a method of treatment, has not been established.

Hypertension is another condition that is frequently seen in obese individuals, and occurs when the blood pressure inside the large arteries is chronically elevated. Hypertension affects about 50 million people in the United States alone. It is more common as people grow older and is both more common and more serious in African Americans. Most cases of hypertension are of unknown etiology. It is known that the tendency to develop hypertension can be inherited. Environment also plays a very important role in hypertension. For example, hypertension may be avoided by keeping body weight under control, keeping physically fit, eating a healthy diet, limiting alcohol intake, and avoiding medications that might increase blood pressure. Other less common causes of hypertension include disorders of the kidneys or endocrine glands. Hypertension has been called "the silent killer" because it has no specific symptoms and yet can lead to death. People with untreated hypertension are much more likely to die from or be disabled by cardiovascular complications such as strokes, heart attacks, heart failure, heart rhythm irregularities, and kidney failure, than people who have normal blood pressure.

Current treatments for hypertension include lifestyle changes (diet, exercise, nonsmoking, etc.) as well as drug therapy. The major classes of medications currently used to treat hypertension include adrenergic neuron antagonists (which are peripherally acting), alpha adrenergic agonists (which are centrally acting), alpha adrenergic blockers, alpha and beta blockers, angiotensin II receptor blockers, angiotensin converting enzyme (ACE) inhibitors, beta adrenergic blockers, calcium channel blockers, thiazides (benzothiadiazine derivatives) and related diuretics, and vasodilators (which act by direct relaxation of vascular smooth muscles).

A particularly serious hypertensive disorder is primary pulmonary hypertension, also known as idiopathic pulmonary hypertension. This is a condition in which the blood pressure in the pulmonary arteries is abnormally high in the absence of other diseases of the heart or lungs. The cause of primary pulmonary hypertension is unknown. Pulmonary hypertension develops in response to increased resistance to blood flow. Narrowing of the pulmonary arterioles occurs and the right side of the heart becomes enlarged due to the increased work of pumping blood against the resistance. Eventually, progressive heart failure develops. Currently, there is no known cure for primary pulmonary hypertension. Treatment is primarily directed towards controlling the symptoms, although some success has occurred with the use of vasodilators. Other medications used to treat the symptoms of primary pulmonary hypertension include diuretics and calcium channel blockers. Typically, as the disease progresses, oxygen is often required. In certain cases, a heart-lung transplant may be indicated for certain suitable candidates, although the availability of donor organs continues to be extremely limited. Unfortunately, primary pulmonary hypertension is a progressive disease, usually leading to congestive heart failure and respiratory failure.

Secondary pulmonary hypertension is a serious disorder that arises as a complication of other conditions such as, for example, scleroderma. Treatments are similar as those for primary pulmonary hypertension and, unfortunately, the prognosis is the same as well.

Other respiratory disorders that are frequently seen in obese individuals include asthma and shortness of breath, both of which conditions are often alleviated by weight loss.

With respect to adverse conditions and disorders associated with sleep, sleep apnea is perhaps the most concerning. Sleep apnea is classified as either obstructive sleep apnea, the more common form that occurs when throat muscles relax, or central sleep apnea, which occurs when the brain doesn't send proper signals to the muscles that control breathing. Additionally, some people have mixed sleep apnea, which is a combination of both obstructive and central sleep apneas. Sleep apnea literally means "cessation of breath." It is characterized by repetitive episodes of upper airway obstruction that occur during sleep, usually associated with a reduction in blood oxygen saturation. In other words, the airway becomes obstructed at several possible sites. The upper airway can be obstructed by excess tissue in the airway, large tonsils, and a large tongue and usually includes the airway muscles relaxing and collapsing when asleep. Another site of obstruction can be the nasal passages. Sometimes the structure of the jaw and airway can be a factor in sleep apnea.

The signs and symptoms of obstructive and central sleep apneas overlap, sometimes making the type of sleep apnea more difficult to determine. The most common signs and symptoms of obstructive and central sleep apneas include: excessive daytime sleepiness (hypersomnia); loud snoring; observed episodes of breathing cessation during sleep; abrupt awakenings accompanied by shortness of breath; awakening with a dry mouth or sore throat; morning headache; and/or difficulty staying asleep (insomnia). Disruptive snoring may be a more prominent characteristic of obstructive sleep apnea, while awakening with shortness of breath may be more common with central sleep apnea.

Sleep apnea is a progressive condition and can be very serious; it is a potentially life-threatening condition that requires immediate medical attention. The risks of undiagnosed obstructive sleep apnea include heart attacks, strokes, high blood pressure, heart disease, irregular heartbeat, and impotence. In addition, obstructive sleep apnea causes daytime sleepiness that can result in accidents, lost productivity and interpersonal relationship problems. The severity of the symptoms may be mild, moderate or severe.

Sleep apnea is diagnosed utilizing a sleep test, called polysomnography but treatment methodologies differ depending on the severity of the disorder. Mild Sleep Apnea is usually treated by some behavioral changes; losing weight and sleeping on one's side are often recommended. There are oral mouth devices (that help keep the airway open) that may help to reduce snoring in three different ways. Some devices (1) bring the jaw forward or (2) elevate the soft palate or (3) retain the tongue (from falling back in the airway and blocking breathing).

Moderate to severe sleep apnea is usually treated with a continuous positive airway pressure (C-PAP). C-PAP is a machine that blows air into your nose via a nose mask, keeping the airway open and unobstructed. For more severe apnea, there is a Bi-level (Bi-PAP) machine. The Bi-level machine is different in that it blows air at two different pressures. When a person inhales, the pressure is higher and in exhaling, the pressure is lower.

Some people have facial deformities that may cause the sleep apnea. It simply may be that their jaw is smaller than it should be or they could have a smaller opening at the back of the throat. Some people have enlarged tonsils, a large tongue or some other tissues partially blocking the airway. Fixing a deviated septum may help to open the nasal passages. Removing the tonsils and adenoids or polyps may help also. Children are much more likely to have their tonsils and adenoids removed. Surgical procedures, such as tracheostomy, uvulopalatopharyngoplasty (UPPP), laser assisted uvuloplasty (LAUP), somnoplasty, and mandibular myotomy are often required to effectively treat sleep apnea. Weight loss, however, particularly in an obese person, can significantly alleviate sleep apnea and other sleep-related adverse conditions such as loud snoring and the like.

Relatively recently, a connection between obesity and the occurrence or increased incidence of migraine headaches has been noted. Migraine headaches begin with mild pain, which increases in intensity over a short period of time. There are two major types of migraines. The common migraine affects 80-85% of migraine sufferers and classical migraine with aura affects 15% of migraine sufferers. Symptoms associated with migraines include headaches, psychological symptomology such as irritability, depression, fatigue, drowsiness, restlessness; neurological symptoms such as photophobia, phonophobia or gastrointestinal symptoms such as change in bowel habit, change of food intake or urinary symptoms such as urinary frequency, auras which are neurological deficits and can be a variety of deficits for the migraine population but in the individual is usually stereotyped. These deficits may be visual scotoma or visual designs, hemiplegia, migrating paraesthesia, dysarthria, dysphasia, or déjà vu. The headache is usually accompanied by light or sound sensitivity, photophobia or phonophobia, irritability and impaired concentration. For those individuals whose migraine headaches are caused by or exacerbated by obesity, treatment according to the methodology of the present invention can be effective.

Other indications for which the present invention is readily adapted include epilepsy and certain psychiatric indications such as impulse control disorders.

Topiramate has long been known as an anti-epileptic agent. At dosages previously required or believed to be required for efficacy, however, topiramate therapy resulted in significant side effects, as noted elsewhere herein. The present invention, according to which topiramate dosage may be reduced by concomitant administration of phentermine, significantly reduces those side effects of topiramate, most if not all of which are dose-related.

Among psychiatric indications, depression is particularly common. "Depression," as is well known, is manifested by a combination of symptoms that interfere with the ability to work, study, sleep, eat, and enjoy once pleasurable activities. Depression includes major depression, especially refractory depression, bipolar depression, and the degeneration associated with depression. Symptoms of depression include persistent sad, anxious, or "empty" mood, feelings of hopelessness, pessimism, feelings of guilt, worthlessness, helplessness, loss of interest or pleasure in hobbies and activities that were once enjoyed, including sex, decreased energy, fatigue, being "slowed down", difficulty concentrating, remembering, making decisions, insomnia, early-morning awakening, or oversleeping, appetite and/or weight loss or overeating and weight gain, thoughts of death or suicide; suicide attempts, restlessness, irritability, persistent physical symptoms that do not respond to treatment, such as headaches, digestive disorders, and chronic pain.

Other psychiatric disorders may also be treated using the compositions and methods of the invention. These disorders include impulse control disorders, panic syndrome, general anxiety disorder, phobic syndromes of all types, mania, manic depressive illness, hypomania, unipolar depression, stress disorders, PTSD, somatoform disorders, personality disorders, psychosis, and schizophrenia.

"Impulse Control Disorders" are characterized by harmful behaviors performed in response to irresistible impulses. The essential feature of an impulse control disorder is the failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person or to others. Symptoms include an increasing sense of tension or arousal before committing an act, and then experiences pleasure, gratification, or release at the time of committing the act. After the act is performed, there may or may not be regret or guilt. Numerous disorders can be characterized as impulse control disorders including intermittent explosive disorder, kleptomania, pathological gambling, pyromania, trichotillomania, compulsive buying or shopping, repetitive self-mutilation, nonparaphilic sexual addictions, severe nail biting, compulsive skin picking, personality disorders with impulsive features, attention deficit/hyperactivity disorder, eating disorders characterized by binge eating, and substance abuse disorders such as alcoholism and drug addiction. Binge eating disorder and bulimia are also sometimes classified as impulse control disorders.

Packaged Pharmaceutical Preparations:

Also provided are packaged pharmaceutical preparations for practicing the subject methods. The packaged preparation contains a composition of the invention in a sealed container, and typically contains a plurality of individual dosage forms each in a sealed housing, as in a blister pack, but could also contain one or more dosage forms in a single sealed container. Optionally, dosage forms with lower doses of one or both active agents can also be included, for dose titration and dose escalation.

In certain embodiments, the packaged pharmaceutical preparations include instructions for a patient to carry out drug administration to achieve weight loss, treat obesity, treat conditions associated with obesity, or treat other conditions as explained earlier herein. For instance, the instructions may include the daily dose of topiramate to be taken, the daily dose of phentermine or other sympathomimetic agent to be taken, and/or the dosing regimen for self-administration of a controlled release dosage form containing topiramate and optionally the second active agent. The instructions may be recorded on a suitable recording medium or printed on a substrate such as paper or plastic. As such, the instructions may be present as a package insert, in the labeling of the package, container(s), or components thereof (i.e., associated with the packaging or sub-packaging), etc. In other embodiments, the instructions are present as an electronic storage data file present on a suitable computer readable storage medium, e.g. CD-ROM, diskette, etc. In yet other embodiments, the actual instructions are not present, but means for obtaining the instructions from a remote source, e.g. via the internet, are provided. As an example, a web address might be included to direct patients to a website where the instructions can be viewed and/or from which the instructions can be downloaded. As with the instructions per se, this means for obtaining the instructions is recorded on a suitable substrate.

Some or all of the included components may be packaged in suitable packaging to maintain sterility. In many embodiments, the components are packaged in a containment element to provide a single, easily handled unit, where the containment element, e.g., box or analogous structure, may or may not be an airtight container, e.g., to further preserve the sterility of some or all of the components. In certain aspects, a sealed package of controlled release dosage forms is provided wherein the dosage forms contain phentermine in immediate release form and topiramate in controlled release, e.g., sustained release and delayed release form. Alternatively, separate phentermine-containing and topiramate-containing dosage forms may be included.

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (e.g. amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Celsius, and pressure is at or near atmospheric.

Example 1

Controlled release topiramate beads are made using an extrusion spheronization process to produce a matrix core comprised of topiramate, 40.0% w/w; microcrystalline cellulose (Avicel® PH102), 56.5% w/w; and Methocel™ A15 LV, 3.5% w/w. The topiramate cores were then coated with ethyl cellulose, 5.47% w/w, and Povidone K30, 2.39% w/w.

The composition of the topiramate beads so prepared is as follows:

Component	% w/w
topiramate	36.85
microcrystalline cellulose, (Avicel ® PH102)	52.05
methylcellulose (Methocel ™ A15 LV)	3.22
ethylcellulose	5.47
polyvinylpyrrolidone (Povidone K30)	2.39

Phentermine hydrochloride was coated onto sugar spheres to provide immediate release phentermine beads. Both sets of beads were then encapsulated into each of a plurality of capsules.

Example 2

In a study comparing controlled-release formulation of topiramate according to the present invention versus immediate release topiramate (Topamax®) in combination with phentermine, the controlled release formulation of the instant invention of topiramate had a 10-15% lower effect on phentermine exposure (FIG. **2**).

The mean and statistical comparisons for plasma phentermine PK parameters at steady state in multiple dose administrations are summarized in Table 2.

TABLE 2

Arithmetic Mean (SD) and Statistical Comparison of Pharmacokinetic Parameters for Plasma Phentermine

		Treatment 2 Versus Treatment 4		
Pharmacokinetic Parameters	Mean +/− SD Treatment 2 (N = 13)	Treatment 4 (N = 12)	90% Confidence Intervals	% Mean Ratio
$AUC_{0\text{-}tau}$ (ng*hr/mL)	2250 +/− 563	2530 +/− 644	(75.6, 105.3)	89.2

TABLE 2-continued

Arithmetic Mean (SD) and Statistical Comparison of Pharmacokinetic Parameters for Plasma Phentermine

Pharmacokinetic Parameters	Mean +/− SD Treatment 2 (N = 13)	Treatment 2 Versus Treatment 4 Treatment 4 (N = 12)	90% Confidence Intervals	% Mean Ratio
AUC_{0-96} (ng*hr/mL)	4640 +/− 1570	5550 +/− 1960	(67.1, 105.0)	84.0
AUC_{0-t} (ng*hr/mL)	4640 +/− 1570	5550 +/− 1960	(67.1, 105.0)	84.0
$C_{max, ss}$ (ng*hr/mL)	114 +/− 23.6	127 +/− 27.6	(78.8, 104.5)	90.7
$C_{min, ss}$ (ng*hr/mL)	9.84 +/− 7.24	14.6 +/− 11.3	(42.5, 109.0)	68.1
t_{max} (hr)	4.01 (1.04, 7.00)	4.54 (1.00, 10.0)		
$T_{1/2}$ (hr)	23.3 +/− 6.17	26.3 +/− 7.43		
CL_{ss}/F (L/hr)	7.10 +/− 1.89	6.38 +/− 2.00		
V_2/F (L/hr)	229 +/− 45.3	232 +/− 58.5		

t_{max} is presented as median (minimum, maximum)
Parameters were dose-normalized and ln-transformed prior to analysis.
% Mean Ratio = 100* ex[(Treatment 2-Treatment 4) for ln-transformed parameters
Treatment 1 (Test): 7.5 mg phentermine/50 mg topiramate (Formulation A)
Treatment 2 (Test): 15 mg phentermine/100 mg topiramate (Formulation A)
Treatment 4 (Reference): 15 mg phentermine/100 mg topiramate
Source: Tables 14.2.1.8, 14.2.1.10, 14.2.1.12, and 14.2.1.17

These data indicate a lower maximum and extent of phentermine exposure between tests versus reference treatments after multiple-dose administration. As such, the controlled release formulation of topiramate reduced drug interaction with phentermine which in turn will reduce further side effects associated with phentermine.

The invention claimed is:

1. A method for effecting weight loss in a subject having a body mass index of at least 30 kg/m^2 and a condition associated with obesity comprising administering an escalating unit dosage form comprising,

(a) a first dosage form, comprising,

23 mg of topiramate, formulated for controlled release, and

3.75 mg of phentermine, formulated for immediate release,

wherein the first dosage form is administered to the subject daily for 2 weeks; and

(b) a second dosage form, comprising either,

46 mg of topiramate, formulated for controlled release, and

7.5 mg of phentermine, formulated for immediate release,

or

92 mg of topiramate, formulated for controlled release, and

15 mg of phentermine, formulated for immediate release,

wherein the topiramate formulated for controlled release reaches maximum plasma concentration (Cmax) at about 6 to about 10 hours (Tmax) after administration and exhibits a lower Cmax, than non-controlled release topiramate, without decreasing total drug exposure defined by the area under the concentration-time curve (AUC), enabling a reduction in side effects without compromising the efficacy of the treatment, and

wherein the second dosage form is administered to the subject daily for at least 2 years, thereby effecting weight loss and treating the condition associated with obesity.

2. The method of claim **1**, wherein the phentermine is phentermine hydrochloride, wherein the amount of phentermine hydrochloride in the first dosage form is about 4.92 mg, and wherein 4.92 mg of phentermine hydrochloride provides 3.75 mg of phentermine.

3. The method of claim **1**, wherein the phentermine is phentermine hydrochloride, wherein the amount of phentermine hydrochloride in the second dosage form is about 9.84 mg, and wherein 9.84 mg of phentermine hydrochloride provides 7.5 mg of phentermine.

4. The method of claim **1**, wherein the condition associated with obesity is selected from the group consisting of diabetes, elevated fasting blood glucose, insulin resistance, impaired glucose tolerance, pulmonary hypertension, asthma, shortness of breath, gallbladder disease, dyslipidemia, high cholesterol, high levels of triglycerides, osteoarthritis, reflux esophagitis, sleep apnea, menstrual irregularities, infertility, complications in pregnancy, gout, high blood pressure, hypertension, coronary artery disease, heart disease, muscular dystrophy, stroke, thrombotic stroke, deep vein thrombosis (DVT), migraines, metabolic disorders, hypoalphalipoproteinemia, familial combined hyperlipidemia, Syndrome X, insulin-resistant Syndrome X, colon cancer, rectal cancer, renal cancer, esophageal cancer, gallbladder cancer, pancreatic cancer, prostate cancer, breast cancer, uterine cancer, ovarian cancer, endometrial cancer, and cervical cancer.

5. The method of claim **1**, wherein the condition associated with obesity is selected from the group consisting of high blood pressure, high levels of triglycerides, elevated fasting blood glucose and diabetes.

6. The method of claim **1**, wherein the subject is suffering from at least two conditions associated with obesity selected from the group consisting of high blood pressure, high levels of triglycerides, elevated fasting blood glucose and diabetes.

7. The method of claim **1**, wherein the topiramate formulated for controlled release is formulated for sustained release, delayed release, or both.

8. The method of claim **1**, wherein the escalating unit dosage form is formulated for oral administration.

9. The method of claim **1**, wherein the weight loss is effective to achieve a reduction of at least about 10% of body weight.

* * * * *

EXHIBIT G

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

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(54) **ESCALATING DOSING REGIMEN FOR EFFECTING WEIGHT LOSS AND TREATING OBESITY**

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(57) **ABSTRACT**

The present invention is drawn to novel topiramate compositions as well as methods for effecting weight loss, e.g., in the treatment of obesity and related conditions, including conditions associated with and/or caused by obesity per se. The present invention features an escalating dosing regimen adapted for the administration of topiramate and optionally a sympathomimetic agent such as phentermine or bupropion, in the treatment of obesity and related conditions.

33 Claims, 2 Drawing Sheets

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FIGURE 1

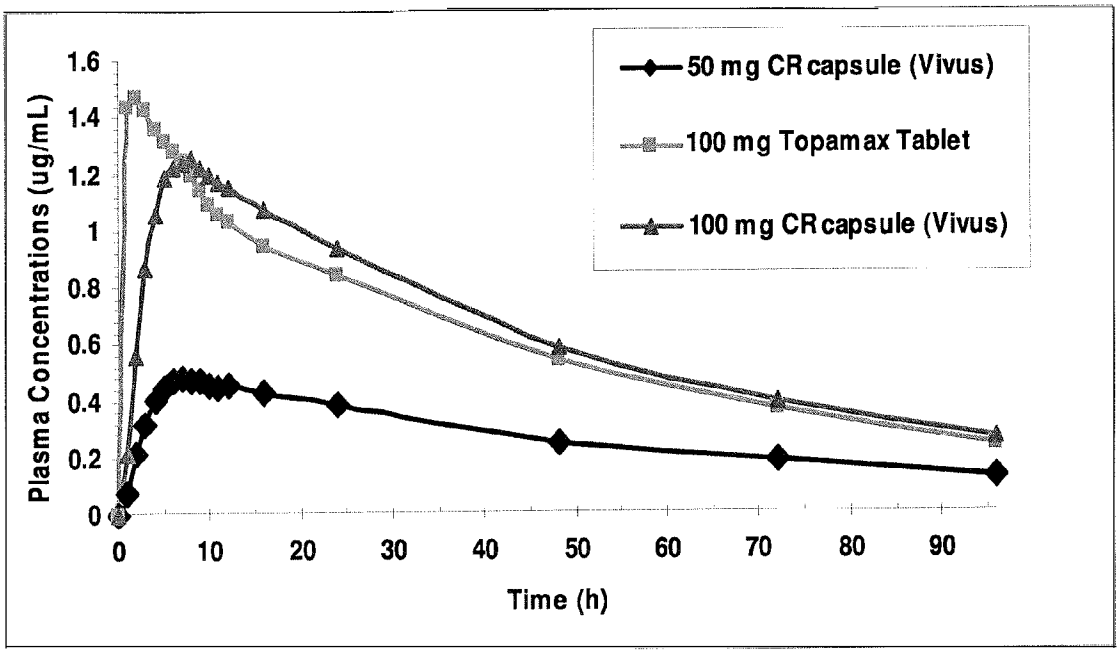
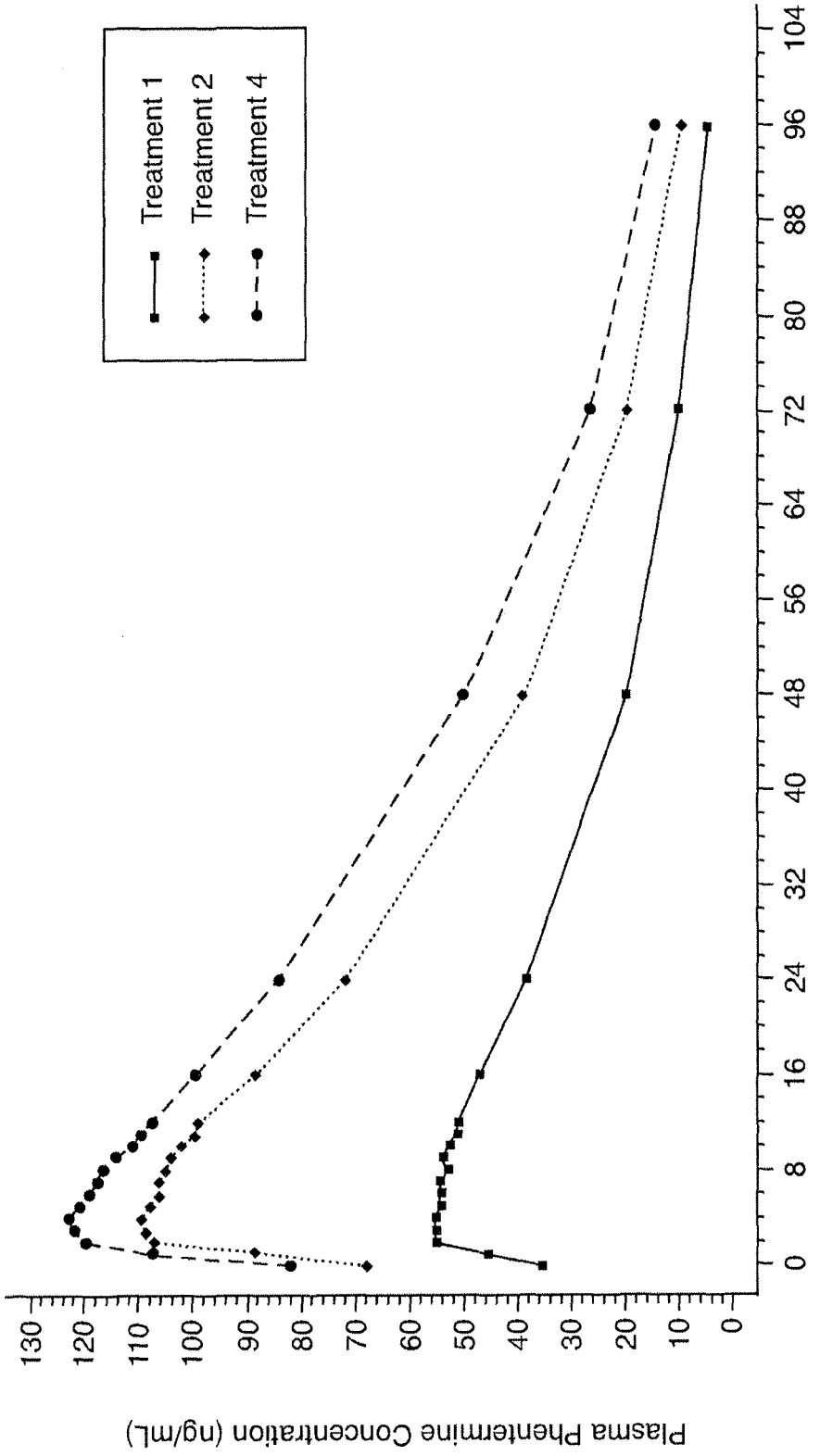

50 mg CR capsule (Vivus)
100 mg Topamax Tablet
100 mg CR capsule (Vivus)
Plasma Concentrations (ug/mL)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
10
20
30
40
50
60
70
80
90
Time (h)

FIGURE 2


Treatment 1
Treatment 2
Treatment 4
Plasma Phentermine Concentration (ng/mL)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
0
8
16
24
32
40
48
56
64
72
80
88
96
104

ESCALATING DOSING REGIMEN FOR EFFECTING WEIGHT LOSS AND TREATING OBESITY

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Ser. No. 12/481,548, filed Jun. 9, 2009, which is a continuation-in-part of U.S. Ser. No. 12/135,953, filed Jun. 9, 2008. The contents of each of these applications are incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

The prevalence of obesity in both children and adults is on the rise in first world countries, especially in the United States, as well as in many developing countries such as China and India. Many aspects of a person's life are affected by obesity, from physical problems such as knee and ankle joint deterioration, to emotional problems resulting from self-esteem issues and society's attitude towards heavy people. The medical problems caused by obesity can be serious and often life-threatening and include diabetes, shortness of breath and other respiratory problems such as asthma and pulmonary hypertension, gallbladder disease, dyslipidemia (for example, high cholesterol or high levels of triglycerides) and dyslipidemic hypertension, osteoarthritis and other orthopedic problems, reflux esophagitis (heartburn), snoring, sleep apnea, menstrual irregularities, infertility, problems associated with pregnancy, gout, cardiovascular problems such as coronary artery disease and other heart trouble, muscular dystrophy, and metabolic disorders such as hypoalphalipoproteinemia, familial combined hyperlipidemia, and Syndrome X, including insulin-resistant Syndrome X. In addition, obesity has been associated with an increased incidence of certain cancers, notably cancers of the colon, rectum, prostate, breast, uterus, and cervix.

Obesity substantially increases the risk of morbidity from hypertension, dyslipidemia, type II diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis and endometrial, breast, prostate, and colon cancers. Higher body weights are also associated with increases in all-cause mortality. Many of these problems are relieved or improved when the afflicted individual undergoes permanent significant weight loss. Weight loss in these individuals can also promote a significant increase in longevity.

Strategies for treating obesity and related disorders have included dietary restriction, increased physical activity, pharmacological approaches, and even surgery, with the choice depending, at least in part, on the degree of weight loss one is attempting to achieve as well as on the severity of obesity exhibited by the subject. For example, treatments such as a low-calorie, low-fat diet and/or regular exercise are often adequate with individuals who are only mildly overweight. The difficulty in maintaining long-term weight loss through diet and behavior modification, however, has led to an increasing interest in other avenues for treatment, particularly pharmacotherapy.

Traditional pharmacological interventions typically induce a weight loss of between five and fifteen kilograms; if the medication is discontinued, renewed weight gain often ensues. Surgical treatments are comparatively successful and are reserved for patients with extreme obesity and/or with serious medical complications.

The above treatments can be enhanced by controlled use of over-the-counter appetite suppressants including caffeine, ephedrine and phenylpropanolamine (Acutrim®, Dexatrim®). Moreover, prescription medications including amphetamine, diethylpropion (Tenuate®), mazindol (Mazanor®, Sanorex®), phentermine (Fasting, Ionamin®), phenmetrazine (Preludin®), phendimetrazine (Bontrol®, Plegine®, Adipost®, Dital®, Dyrexan®, Melfiat®, Prelu-2®, Rexigen Forte®), benzphetamine (Didrex®) and fluoxetine (Prozac®) are often used in the treatment of seriously overweight and/or obese subjects or patients.

While society has seen tremendous advances in the field of pharmaceuticals, there are, of course, drawbacks to the administration of any given pharmaceutical agent. Sometimes, the disadvantages, or "side effects," are so severe as to preclude administration of a particular agent at a therapeutically effective dose. Furthermore, many agents in the same therapeutic class display similar side effect profiles, meaning that patients either have to forego therapy or suffer from varying degrees of side effects associated with the medication of choice.

The present invention is directed to an escalating dosing regimen for administering topiramate alone or in combination with a second therapeutic agent that directly or indirectly reduces the side effects associated with one or both of the agents administered. By "indirectly" reducing side effects is meant that the second therapeutic agent allows the first pharmaceutical agent to be administered at a lower dose without compromising therapeutic efficacy, thus resulting dose-dependent unwanted effects.

Topiramate (2,3,4,5-bis-O-(1-methylethylidene)β-D-fructopyranose sulfamate) is a broad-spectrum neurotherapeutic agent approved by the FDA and the regulatory agencies of many other countries for the treatment of certain seizure disorders and the prevention of migraine headaches. E. Faught et al. (1996) Neurology 46:1684-90; Karim et al. (1995) Epilepsia 36 (S4):33; S. K. Sachdeo et al. (1995) Epilepsia 36(S4):33; T. A. Glauser (1999) Epilepsia 40 (S5): S71-80; R. C. Sachdeo (1998) Clin. Pharmacokinet. 34:335-346). There has also been evidence that topiramate is effective in the treatment of diabetes (U.S. Pat. Nos. 7,109,174 and 6,362,220), neurological disorders (U.S. Pat. No. 6,908,902), depression (U.S. Pat. No. 6,627,653), psychosis (U.S. Pat. No. 6,620,819), headaches (U.S. Pat. No. 6,319,903) and hypertension (U.S. Pat. No. 6,201,010). However there have been adverse effects associated with the use of topiramate in humans, such as cognitive dulling and word finding difficulties, which can discourage many obese patients from taking this drug.

As such, there is considerable interest in the development of additional methods and compositions for treating obesity and related conditions in which the therapeutic efficacy of known therapeutic agents and compositions are improved. In addition, combination therapy, wherein two or more active agents are administered in combination, may be employed to decrease the dose of each individual active agent administered and mitigate one or more side effects of the other active agent or agents. Given that the incidence of obesity and conditions caused by or related to obesity has reached epidemic proportions, there is an urgent need for effective methods for the treatment of obesity and/or a related condition, including combination treatments that result in reduction of toxicity, decreased side effects and effective treatment.

SUMMARY OF THE INVENTION

The present invention provides novel topiramate compositions and methods for effecting weight loss, treating obesity, and treating conditions caused by or associated with excess

weight or obesity. The compositions can contain topiramate as a single active agent but more typically contain topiramate in combination with at least one sympathomimetic agent. The term "sympathomimetic agent" is a term of art and refers to agents or compounds that mimic or alter stimulation of the sympathetic nervous system. Exemplary sympathomimetic agents include phentermine and bupropion. Optimally, the topiramate and the sympathomimetic agent are contained in a single dosage form, which provides for immediate release of the sympathomimetic agent and controlled release, e.g., sustained release, delayed release, or both sustained release and delayed release, of the topiramate.

In another aspect of the invention, a controlled release topiramate composition is provided that is composed of an effective amount of topiramate, microcrystalline cellulose, and methylcellulose. Such a composition will provide for sustained release of the topiramate. The composition, in the form of, for instance, a bead or tablet, may be coated with ethyl cellulose, polyvinyl pyrrolidone, or the like, to provide for delayed release of the topiramate as well. A sympathomimetic agent is preferably although not necessarily included, and, if present, is preferably in immediate release form.

The present invention features an escalating dosing regimen for administering topiramate alone or in combination with a sympathomimetic agent, wherein the dosing regimen is in the context of a method for effecting weight loss, e.g., in a method for treating obesity, overweight, or a condition associated with obesity, or in an alternative method, e.g., a method for treating epilepsy, a method for treating an impulse control disorder, or the like. The method involves administration of a topiramate composition as described above, wherein the topiramate is generally although not necessarily administered in a controlled release composition and/or in combination with a sympathomimetic agent. The escalating dosing regimen involves administration of an initial daily dosage to an individual for a specific time period and incrementally increasing the dosage at various designated time points.

The invention also provides a packaged pharmaceutical preparation comprising topiramate, optionally a sympathomimetic agent as well, and instructions for administering, e.g., self-administering, the active agent(s). Generally, the instructions for administration include reference to an escalating dosing regimen wherein a lower daily dosage of topiramate is administered initially, with incremental increases at various designated time points thereafter. Ideally, a titration card is provided that sets forth the recommended dosages for at least four weeks.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** provides a summary of the plasma concentration of controlled release topiramate according to the present invention versus topiramate (Topamax®) in normal obese subjects.

FIG. **2** depicts the mean plasma phentermine concentrations versus time for subjects administered phentermine in combination with controlled release topiramate and phentermine in combination with immediate release topiramate (Topamax®).

DETAILED DESCRIPTION OF THE INVENTION

Definitions and Nomenclature:

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, "an active agent" refers not only to a single active agent but also to a combination of two or more different active agents, "a dosage form" refers to a combination of dosage forms as well as to a single dosage form, and the like.

Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by one of ordinary skill in the art to which the invention pertains. Specific terminology of particular importance to the description of the present invention is defined below.

When referring to an active agent, applicants intend the term "active agent" to encompass not only the specified molecular entity but also its pharmaceutically acceptable, pharmacologically active analogs, including, but not limited to, salts, esters, amides, prodrugs, conjugates, active metabolites, and other such derivatives, analogs, and related compounds as will be discussed infra. Therefore, reference to "phentermine," for example, or "bupropion," encompasses not only phentermine and bupropion per se but also salts and other derivatives of phentermine and bupropion, e.g., phentermine hydrochloride and bupropion hydrochloride, respectively. It is to be understood that when amounts or doses are specified, that those amounts or doses refer to the amount or dose of active agent per se and not to a salt or the like. For example, when it is indicated that a dose or amount of phentermine is 7.5 mg, that would correspond to 9.84 phentermine hydrochloride and not 7.5 phentermine hydrochloride.

The terms "treating" and "treatment" as used herein refer to reduction in severity and/or frequency of symptoms, elimination of symptoms and/or underlying cause, and improvement or remediation of damage. In certain aspects, the term "treating" and "treatment" as used herein refer to the prevention of the occurrence of symptoms. In other aspects, the term "treating" and "treatment" as used herein refer to the prevention of the underlying cause of symptoms associated with obesity, excess weight, and/or a related condition. The phrase "administering to a subject" refers to the process of introducing a composition or dosage form of the invention into the subject (e.g., a human or other mammalian subject) via an art-recognized means of introduction

By the terms "effective amount" and "therapeutically effective amount" of an agent, compound, drug, composition or combination of the invention which is nontoxic and effective for producing some desired therapeutic effect upon administration to a subject or patient (e.g., a human subject or patient).

The term "dosage form" denotes any form of a pharmaceutical composition that contains an amount of active agent sufficient to achieve a therapeutic effect with a single administration. When the formulation is a tablet or capsule, the dosage form is usually one such tablet or capsule. The frequency of administration that will provide the most effective results in an efficient manner without overdosing will vary with the characteristics of the particular active agent, including both its pharmacological characteristics and its physical characteristics, such as hydrophilicity.

The term "controlled release" refers to a drug-containing formulation or fraction thereof in which release of the drug is not immediate, i.e., with a "controlled release" formulation, administration does not result in immediate release of the drug into an absorption pool. The term is used interchangeably with "nonimmediate release" as defined in Remington: The Science and Practice of Pharmacy, Nineteenth Ed. (Easton, Pa.: Mack Publishing Company, 1995). In general, the term "controlled release" as used herein includes sustained release, modified release and delayed release formulations.

The term "sustained release" (synonymous with "extended release") is used in its conventional sense to refer to a drug formulation that provides for gradual release of a drug over an

extended period of time, and that preferably, although not necessarily, results in substantially constant blood levels of a drug over an extended time period. The term "delayed release" is also used in its conventional sense, to refer to a drug formulation which, following administration to a patient provides a measurable time delay before drug is released from the formulation into the patient's body.

By "pharmaceutically acceptable" is meant a material that is not biologically or otherwise undesirable, i.e., the material may be incorporated into a pharmaceutical composition administered to a patient without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. When the term "pharmaceutically acceptable" is used to refer to a pharmaceutical carrier or excipient, it is implied that the carrier or excipient has met the required standards of toxicological and manufacturing testing or that it is included on the Inactive Ingredient Guide prepared by the U.S. Food and Drug administration. "Pharmacologically active" (or simply "active") as in a "pharmacologically active" (or "active") derivative or analog, refers to a derivative or analog having the same type of pharmacological activity as the parent compound and approximately equivalent in degree. The term "pharmaceutically acceptable salts" include acid addition salts which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

As used herein, "subject" or "individual" or "patient" refers to any subject for whom or which therapy is desired, and generally refers to the recipient of the therapy to be practiced according to the invention. The subject can be any vertebrate, but will typically be a mammal. If a mammal, the subject will in many embodiments be a human, but may also be a domestic livestock, laboratory subject or pet animal.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

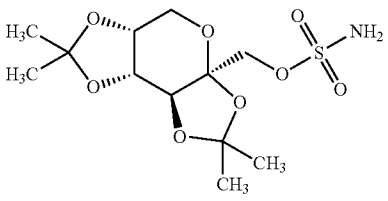
The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

Methods and Formulations of the Invention:

The present invention provides novel methods and compositions to effect weight loss and treat obesity, conditions related to excess weight or obesity, diabetes (whether or not related to obesity), and other conditions and disorders as will be explained infra. According to the U.S. Centers for Disease Control, the clinical definition of being overweight (the term being used synonymously herein with the term "excess weight") is having a body mass index (BMI) between 25.0 and 29.9 kg/m; BMI is calculated by multiplying an individual's weight, in kilograms, by height, in meters. The CDC defines obesity as having a BMI of 30 or higher. In one embodiment, the invention provides a method for effecting weight loss and treating overweight, obesity, and conditions associated with excess weight and obesity, and involves administration of a combination of the sympathomimetic agent phentermine and the anti-convulsant agent topiramate.

Topiramate is an anticonvulsant sulfamate compound that is sold in the United States under the trade name Topamax® (Ortho-McNeil Pharmaceutical, Inc., Raritan, N.J., U.S.A). Topiramate has been approved for use as an antiepileptic agent as an adjuvant therapy for patients with partial onset seizures or primary generalized tonic-clonic seizures, and for the prevention of migraine headache. See Physician's Desk Reference, 56th ed. (2002); see also U.S. Pat. No. 4,513,006 to Maryanoff et al. and U.S. Pat. No. 7,351,695 to Almarssoo et al.

"Topiramate" generally refers to the sulfamate-substituted monosaccharide having the chemical name 2,3,4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate and the molecular formula C12H21NO8S. The structure of the compound is represented by Formula (I)



(I)

As used herein, the term "topiramate" encompasses 2,3,4,5-bis-(O)-(1-methylethylidene)-β-D-fructopyranose sulfamate as well as individual enantiomers, individual diastereomers, or mixtures thereof. The term "topiramate" as used herein also encompasses topiramate salts as well as polymorphs, solvates (including hydrates and mixed solvates, as well as hydrates of salts), co-crystals (for instance, with other compounds or other forms of topiramate), amorphous, and anhydrous forms of the compound of Formula (I). Topiramate salts useful in conjunction with the present invention, as will be appreciated from the fact that the compound is a sulfamic acid derivative, are pharmaceutically acceptable basic addition

salts. Such salts are prepared from bases that provide a pharmaceutically acceptable cation that associates with the sulfamic acid group of the compound of Formula (I). Suitable pharmaceutically acceptable cations include both organic and inorganic cations, including, without limitation, sodium, sodium, potassium, lithium, magnesium, calcium, aluminum, zinc, procaine, benzathine, chloroprocaine, choline, diethylamine, ethylenediamine, N-methylglucamine, benethamine, clemizole, diethylamine, piperazine, tromethamine, triethylamine, ethanolamine, triethanolamine, arginine, lysine, histidine, tributylamine, 2-amino-2-pentylpropanol, 2-amino-2-methyl-1,3-propanediol, tris(hydroxymethyl) aminomethane, benzylamine, 2-(dimethylamino)ethanol, barium or bismuth counter ions. Particularly preferred cations are sodium, lithium, and potassium. Other forms of topiramate referenced above may be prepared using methods known in the art; see, e.g., U.S. Pat. No. 7,351,695. The subject methods include a dosing regimen for the administration of topiramate alone or, more preferably, in combination with a sympathomimetic agent. In certain aspects, the present invention provides a dosing regimen for the administration of a pharmaceutical composition that includes, e.g., topiramate in combination with bupropion or phentermine.

In one embodiment of the invention, directed to an escalating dosage regimen, the dosing strategy involves administering to a patient a lower daily dosage of topiramate alone or in combination with a sympathomimetic agent for a specific period of time and then incrementally increasing the dosage at various designated time points.

For example, when treating a patient who is overweight or obese, and who may suffer from a condition associated with or caused by excess weight or obesity, the patient receives a dosage of 15 mg/day to 30 mg/day, e.g., 23 mg/day, of topiramate for 1 week. Next, the patient receives a dosage of 35 mg/day to 55 mg/day, e.g., 46 mg/day, of topiramate for a second week. Thereafter, the patient receives a dosage of 60 mg/day to 80 mg/day, e.g., 69 mg/day, of topiramate for a third week, which is followed by a final dosage of 85 mg to 125 mg/day, e.g., 92 mg/day of topiramate for a fourth week.

In another example, when treating a patient for obesity and/or a related condition, the patient receives a dosage of 15 mg/day to 30 mg/day, e.g., 23 mg/day, of topiramate in combination with a dosage of 3.75 mg/day of phentermine for 1 week. The patient next receives a dosage of 35 mg/day to 55 mg/day, e.g., 46 mg/day, of topiramate in combination with a dosage of 7.5 mg/day of phentermine for a second week. Thereafter, the patient receives a dosage of 60 mg/day to 80 mg/day, e.g., 69 mg/day, of topiramate in combination with a dosage of 11.25 mg/day of phentermine for a third week which is followed by a final dosage of 85 mg to 125 mg/day, e.g., 92 mg/day, topiramate in combination with a dosage of 15 mg/day of phentermine for a fourth week.

After the fourth week of administration, the further administration of topiramate alone or topiramate in combination with phentermine is carried on indefinitely or, more typically, until a sufficient reduction of symptoms has been achieved. In certain aspects, the final dose of 92 mg/day of topiramate alone or in combination with a dosage of 15 mg/day of phentermine indefinitely or until a sufficient reduction of symptoms has been achieved. In other aspects, the final dose of topiramate alone or topiramate in combination with phentermine is decreased to the initial starting dose of the regimen and maintained indefinitely or until a sufficient reduction of symptoms has been achieved. In a weight loss regimen, the dosage regimen generally involves continual, i.e., ongoing, administration, over a significant period of time, e.g., in the range of about 4 weeks to about 67 weeks, depending on the severity of an individual's weight problem, the amount of weight that should be lost, and the rate at which weight is lost.

In another embodiment of the invention, topiramate is administered on an ongoing basis, i.e., generally following the escalating dosage regimen described above. In either of these methods, i.e., the escalating dosage regimen or an ongoing maintenance dosage regimen, pharmaceutical compositions are administered that include an effective amount of topiramate as the active agent, wherein an "effective amount" of topiramate is generally an amount that results in a reduction of at least one pathological parameter associated with obesity, excess weight, and/or a related disorder. In the methods of the invention, e.g., in a method for effecting weight loss such as in the treatment of obesity and/or a condition related to obesity, an effective amount of topiramate is an amount that is effective to achieve a reduction of at least about 10%, at least about 15%, at least about 20%, or at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95%, compared to the expected reduction in the parameter, e.g., loss of weight, in an individual suffering from obesity, excess weight, and/or a related disorder and not treated with the topiramate compositions.

A suitable daily dose of topiramate is in the range of 10 mg to 1500 mg. For example, 10 mg, 20 mg, 30 mg, 60 mg, 90 mg, 120 mg, 150 mg, 180 mg, 210 mg, 240 mg, 270 mg, 300 mg, 330 mg, 360 mg, 390 mg, 420 mg, 450 mg, 480 mg, 500 mg, 600 mg, 800 mg, 1000 mg, 1200 mg, 1500 mg or the like is administered to a patient as a daily dosage. In another example, 23 mg, 46 mg, 69 mg and 92 mg or the like is administered to a patient as a daily dosage. In some embodiments, the daily dosage of topiramate is in the range of 10 mg to 150. In certain embodiments, the daily dosage of topiramate is in the range of 10 mg to 100 mg. Each of the aforementioned "daily dosages" is generally although not necessarily administered as a single daily dose.

The patient may receive a specific dosage of topiramate over a period of weeks, months, or years, e.g., 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 2 years, 3 years, 4 years, 5 years and the like.

Aspects of the invention provide a topiramate monotherapy or combination therapy in which the subject topiramate formulation is effective when administered at a initial dose as low as 10-23 mg. In certain aspects, the topiramate formulation is effective at a dose of approximately 20 mg. The novel topiramate formulations of the present invention have a lower maximum concentration (Cmax) without decreasing total drug exposure defined by the area under the concentration-time curve (AUC). Further, the novel topiramate formulations of the present invention have a delay in time after administration of a drug when the maximum plasma concentration is reached (Tmax) by six to eight hours. As depicted in FIG. **1**, drug exposure as measured by AUC for the control release (CR) formulation capsule is the same as the 100 mg of immediate release topiramate (Topamax®) tablet despite a 20% reduction in the Cmax. Therefore, this formulation is capable of reducing the Cmax which would reduce side effects without compromising the efficacy of the treatment, since the AUC is the same. This reduction in Cmax is preferred as topiramate can be sedating and a delay in the time to reach maximum plasma concentration to the late afternoon or evening time would improve the tolerability of the drug.

As such, the effective amount of topiramate is decreased, thereby further reducing any toxicity or harmful side effects in the patient. The amount of topiramate administered to the patient is less than an amount that would cause toxicity in the patient. In certain embodiments, the amount of the compound that is administered to the patient is less than the amount that causes a concentration of the compound in the patient's plasma to equal or exceed the toxic level of the compound. The optimal amount of the compound that should be administered to the patient in the practice of the present invention will depend on the individual as well as the severity of the individual's symptoms.

Depending on the intended mode of administration, the pharmaceutical formulation may be a solid, semi-solid or liquid, such as, for example, a tablet, a capsule, a caplet, a liquid, a suspension, an emulsion, a suppository, granules, pellets, beads, a powder, or the like, preferably in unit dosage form suitable for single administration of a precise dosage. Suitable pharmaceutical compositions and dosage forms may be prepared using conventional methods known to those in the field of pharmaceutical formulation and described in the pertinent texts and literature, e.g., in Remington: The Science and Practice of Pharmacy (Easton, Pa.: Mack Publishing Co., 1995). Oral administration and therefore oral dosage forms are generally preferred, and include tablets, capsules, caplets, solutions, suspensions and syrups, and may also comprise a plurality of granules, beads, powders, or pellets that may or may not be encapsulated. Preferred oral dosage forms are capsules and tablets, particularly controlled release capsules and tablets, as noted above.

As noted above, it is especially advantageous to formulate compositions of the invention in unit dosage form for ease of administration and uniformity of dosage. The term "unit dosage forms" as used herein refers to physically discrete units suited as unitary dosages for the individuals to be treated. That is, the compositions are formulated into discrete dosage units each containing a predetermined, "unit dosage" quantity of an active agent calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specifications of unit dosage forms of the invention are dependent on the unique characteristics of the active agent to be delivered. Dosages can further be determined by reference to the usual dose and manner of administration of the ingredients. It should be noted that, in some cases, two or more individual dosage units in combination provide a therapeutically effective amount of the active agent, e.g., two tablets or capsules taken together may provide a therapeutically effective dosage of topiramate, such that the unit dosage in each tablet or capsule is approximately 50% of the therapeutically effective amount.

Tablets may be manufactured using standard tablet processing procedures and equipment. Direct compression and granulation techniques are preferred. In addition to the active agent, tablets will generally contain inactive, pharmaceutically acceptable carrier materials such as binders, lubricants, disintegrants, fillers, stabilizers, surfactants, coloring agents, and the like.

Capsules are also preferred oral dosage forms, in which case the active agent-containing composition may be encapsulated in the form of a liquid or solid (including particulates such as granules, beads, powders or pellets). Suitable capsules may be either hard or soft, and are generally made of gelatin, starch, or a cellulosic material, with gelatin capsules preferred. Two-piece hard gelatin capsules are preferably sealed, such as with gelatin bands or the like. See, for example, *Remington: The Science and Practice of Pharmacy*, cited earlier herein, which describes materials and methods for preparing encapsulated pharmaceuticals.

Oral dosage forms, whether tablets, capsules, caplets, or particulates, can, if desired, be formulated so as to provide for controlled release of topiramate, and in a preferred embodiment, the present formulations are controlled release oral dosage forms. Generally, the dosage forms provide for sustained release, i.e., gradual, release of topiramate, from the dosage form to the patient's body over an extended time period, typically providing for a substantially constant blood level of the agent over a time period in the range of about 4 to about 12 hours, typically in the range of about 6 to about 10 hours or 6 to about 8 hours. Release of the topiramate may also be delayed; that is, there is a time lag between administration and the start of topiramate release. In this way, for instance, an individual will not experience sleepiness or other side effects of topiramate during the school or work day. Preferred dosage forms thus involve sustained release of the topiramate, delayed release of the topiramate, or both sustained and delayed release of the topiramate.

Generally, as will be appreciated by those of ordinary skill in the art, sustained release dosage forms are formulated by dispersing the active agent within a matrix of a gradually hydrolyzable material such as a hydrophilic polymer, or by coating a solid, drug-containing dosage form with such a material. Hydrophilic polymers useful for providing a sustained release coating or matrix include, by way of example: cellulosic polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, ethyl cellulose, cellulose acetate, and carboxymethylcellulose sodium; acrylic acid polymers and copolymers, preferably formed from acrylic acid, methacrylic acid, acrylic acid alkyl esters, methacrylic acid alkyl esters, and the like, e.g. copolymers of acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate; and vinyl polymers and copolymers such as polyvinyl pyrrolidone e.g., Povidone K30, polyvinyl acetate, and ethylene-vinyl acetate copolymer. Preferred sustained release polymers herein include those available as "Methocel" polymers from Dow Chemical, particularly the methylcellulose ether polymers in the Methocel™ A group, having a viscosity grade of about 4,000 cps and a methoxyl content of about 27.5% to 31.5%, e.g., Methocel™ A15LV, Methocel™ A15C, and Methocel™ A4M.

When sustained release preparations are prepared, tablets, granules, powder, capsules, and the like can be produced according to a conventional method after adding excipient, and as necessary, binder, disintegrating agent, lubricant, coloring agent, taste-modifying agent, flavoring agent, and the like. These additives may be ones generally used in the field, and for example, lactose, sodium chloride, glucose, starch, microcrystalline cellulose, and silicic acid as the excipient, water, ethanol, propanol, simple syrup, gelatin solution, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, shellac, calcium phosphate, and polyvinylpyrrolidone as the binder, agar powder, sodium hydrogen carbonate, sodium lauryl sulfate, and stearic acid monoglyceride as the disintegrating agent, purified talc, stearic acid salt, borax, and polyethylene glycol as the lubricant, β-carotene, yellow iron sesquioxide, and caramel as the coloring agent, and saccharose and orange peel as the taste-modifying agent can be listed as examples. It should be noted that various grades of microcrystalline cellulose are preferred fillers herein, e.g., Avicel® PH101, Avicel® PH102, and Avicel® PH200 (FMC), with particle sizes of about 50 microns, 100 microns, and 190

microns, respectively. Microcrystalline cellulose having a particle size in the range of about 50 microns to 200 microns is preferred herein.

The dosage forms may also be provided with a delayed release coating, e.g., composed of an acrylate and/or methacrylate copolymers. Examples of such polymers are those available under the trade name "Eudragit" from Rohm Pharma (Germany). The Eudragit series E, L, S, RL, RS, and NE copolymers are available as solubilized in organic solvent, in an aqueous dispersion, or as a dry powder. Preferred acrylate polymers are copolymers of methacrylic acid and methyl methacrylate, such as the Eudragit L and Eudragit S series polymers. Other preferred Eudragit polymers are cationic, such as the Eudragit E, RS, and RL series polymers. Eudragit E100 and E PO are cationic copolymers of dimethylaminoethyl methacrylate and neutral methacrylates (e.g., methyl methacrylate), while Eudragit RS and Eudragit RL polymers are analogous polymers, composed of neutral methacrylic acid esters and a small proportion of trimethylammonioethyl methacrylate.

In a specific embodiment, controlled release topiramate beads for oral administration, e.g., by incorporation in an orally administrable capsule or compaction into an orally administrable tablet, are made using an extrusion spheronization process to produce a matrix core comprised of: topiramate, 40.0% w/w; microcrystalline cellulose, e.g., Avicel® PH102, 56.5% w/w; and methylcellulose, e.g., Methocel™ A15 LV, 3.5% w/w. The topiramate cores are then coated with ethyl cellulose, 5.47% w/w and Povidone K30: 2.39% w/w. As will be described in detail infra, beads of a second active agent, e.g., a sympathomimetic agent, may also be prepared and incorporated into the capsule. For instance, phentermine or bupropion beads having an immediate release drug coating on sugar spheres or analogous non-active cores may be employed. Both sets of beads may then be encapsulated into one capsule.

Preparations according to this invention for parenteral administration include sterile aqueous and nonaqueous solutions, suspensions, and emulsions. Injectable aqueous solutions contain the active agent in water-soluble form. Examples of nonaqueous solvents or vehicles include fatty oils, such as olive oil and corn oil, synthetic fatty acid esters, such as ethyl oleate or triglycerides, low molecular weight alcohols such as propylene glycol, synthetic hydrophilic polymers such as polyethylene glycol, liposomes, and the like. Parenteral formulations may also contain adjuvants such as solubilizers, preservatives, wetting agents, emulsifiers, dispersants, and stabilizers, and aqueous suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, and dextran. Injectable formulations are rendered sterile by incorporation of a sterilizing agent, filtration through a bacteria-retaining filter, irradiation, or heat. They can also be manufactured using a sterile injectable medium. The active agent may also be in dried, e.g., lyophilized, form that may be rehydrated with a suitable vehicle immediately prior to administration via injection.

The active agents may also be administered through the skin using conventional transdermal drug delivery systems, wherein the active agent is contained within a laminated structure that serves as a drug delivery device to be affixed to the skin. In such a structure, the drug composition is contained in a layer, or "reservoir," underlying an upper backing layer. The laminated structure may contain a single reservoir, or it may contain multiple reservoirs. In one embodiment, the reservoir comprises a polymeric matrix of a pharmaceutically acceptable contact adhesive material that serves to affix the system to the skin during drug delivery. Alternatively, the drug-containing reservoir and skin contact adhesive are present as separate and distinct layers, with the adhesive underlying the reservoir which, in this case, may be either a polymeric matrix as described above, or it may be a liquid or hydrogel reservoir, or may take some other form. Transdermal drug delivery systems may in addition contain a skin permeation enhancer.

In addition to the formulations described previously, the active agent may be formulated as a depot preparation for controlled release of the active agent, preferably sustained release over an extended time period. These sustained release dosage forms are generally administered by implantation (e.g., subcutaneously or intramuscularly or by intramuscular injection).

Although the present compositions will generally be administered orally, parenterally, transdermally, or via an implanted depot, other modes of administration are suitable as well. For example, administration may be transmucosal, e.g., rectal or vaginal, preferably using a suppository that contains, in addition to the active agent, excipients such as a suppository wax. Formulations for nasal or sublingual administration are also prepared with standard excipients well known in the art. The pharmaceutical compositions of the invention may also be formulated for inhalation, e.g., as a solution in saline, as a dry powder, or as an aerosol.

In another embodiment, the methods of the invention, i.e., the escalating dosage regimen or ongoing maintenance dosing, involve administration of a combination of topiramate and a sympathomimetic agent.

Sympathomimetic agents for use in the present invention and their general clinical uses or effects are set forth in Table 1.

TABLE 1

Sympathomimetic Agents and Clinical Uses Thereof

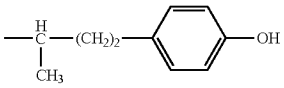
	General structure:				Main Clinical Uses		
Agent name	Ring substituent(s)	R^{α}	R^{β}	R^{γ}	⟨ Receptor A N P V	® Receptor B C	CNS, 0
Bupropion	3-Cl	=O	CH_3	$C(CH_3)_3$			
Phenylethylamine		H	H	H			
Epinephrine	3-OH, 4-OH	OH	H	CH_3	A, P, V	B, C	
Norepinephrine	3-OH, 4-OH	OH	H	H	P		
Epinine	3-OH, 4-OH	H	H	CH_3			
Dopamine	3-OH, 4-OH	H	H	H	P		
Dobutamine	3-OH, 4-OH	H	H	1*		C	
Nordefrin	3-OH, 4-OH	OH	CH_3	H	V		
Ethylnorepinephrine	3-OH, 4-OH	OH	CH_2CH_3	H		B	

TABLE 1-continued

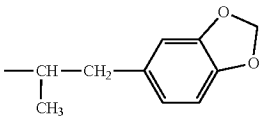
Sympathomimetic Agents and Clinical Uses Thereof

	General structure:				Main Clinical Uses		
Agent name	Ring substituent(s)	R^{α}	R^{β}	R^{γ}	⟨ Receptor A N P V	® Receptor B C	CNS, 0
Isoproterenol	3-OH, 4-OH	OH	H	$CH(CH_3)_2$		B, C	
Protokylol	3-OH, 4-OH	OH	H	2*		B	
Isoetharine	3-OH, 4-OH	OH	CH_2CH_3	$CH(CH_3)_2$		B	
Metaproterenol	3-OH, 5-OH	OH	H	$CH(CH_3)_2$		B	
Terbutaline	3-OH, 5-OH	OH	H	$C(CH_3)_3$		B	
Metaraminol	3-OH	OH	CH_3	H	P		
Phenylephrine	3-OH	OH	H	CH_3	N, P		
Tyramine	4-OH	H	H	H			
Hydroxyamphetamine	4-OH	H	CH_3	H	N, P	C	
Methoxyphenamine	2-OCH_3	H	CH_3	CH_3		B	
Methoxamine	2-OCH_3, 5-OCH_3	OH	CH_3	H	P		
Albuterol	3-CH_2OH, 4-OH	OH	H	$C(CH_3)_3$		B	
Amphetamine		H	CH_3	H			CNS, 0
Methamphetamine		H	CH_3	CH_3	P		CNS, 0
Benzphetamine		H	CH_3	—NHR^{γ} is replaced with 3*			0
Ephedrine		OH	CH_3	CH_3	N, P	B, C	
Phenylpropanolamine		OH	CH_3	H	N		
Mephentermine		H	—CHR^{β}— is replaced with 4*	CH_3	N, P		
Phentermine		H	"	H			0
Chlorphentermine	4-Cl	H	"	H			0
Fenfluramine	3-CF_3	H	CH_3	C_2H_5			0
Propylhexedrine	5*: phenyl ring is replaced with cyclohexyl	H	CH_3	CH_3	N		
Diethylpropion		6*: The substituent at the 1-position is replaced with 6, below.					0
Phenmetrazine		7*: The substituent at the 1-position is replaced with 7, below.					0
Phendimetrazine		8*: The substituent at the 1-position is replaced with 8, below.					0

*1:



*2:



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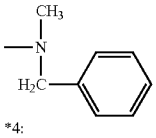

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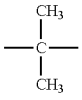

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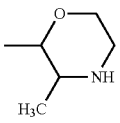

⟨ Activity
A = Allergic reactions (includes ® action)

TABLE 1-continued

Sympathomimetic Agents and Clinical Uses Thereof

General structure:					Main Clinical Uses		
Agent name	Ring substituent(s)	R^{α}	R^{β}	R^{γ}	⟨ Receptor A N P V	® Receptor B C	CNS, 0

N = Nasal decongestion
P = Pressor (may include ® action)
V = Other local vasoconstriction (e.g. in local anesthesia)
® Activity
B = Bronchodilator
C = Cardiac
CNS = Central nervous system
0 = Anorectic

*Numbers bearing an asterisk refer to the substituents numbered in the bottom rows of the table; substituent 5 replaces the phenyl rings, and 6, 7 and 8 are attached directly to the phenyl ring, replacing the ethylamine side chain.

†The⟨ and ® in the prototype formula refer to positions of the C atoms in the ethylamine side chain.

In certain embodiments, the sympathomimetic agent is phentermine or a phentermine-like compound. As defined herein, a "phentermine-like compound" is a compound structurally related to phentermine (e.g., an analog or derivative) which maintains an anorectic activity similar to that of phentermine. One phentermine-like compound is chlorphentermine. In yet another embodiment, the sympathomimetic agent is amphetamine or an amphetamine-like compound. As used herein, an "amphetamine-like compound" is a compound structurally related to amphetamine (e.g., an analog or derivative) which maintains an anorectic effect of amphetamine. In yet another embodiment, the sympathomimetic agent is phenmetrazine or a phenmetrazine-like compound. As defined herein, a "phenmetrazine-like compound" is a compound structurally related to phenmetrazine (e.g., an analog or derivative) which maintains an anorectic effect of phenmetrazine. One phenmetrazine-like compound is phendimetrazine. Analogs and/or derivatives of the compounds of the present invention can be tested for their ability to suppress appetite (e.g., suppress food intake) in a subject (e.g., a mammalian subject).

In other embodiments, the sympathomimetic agent is bupropion or a bupropion-like compound. As defined herein, a "bupropion-like compound" is a compound structurally related to bupropion (e.g., an analog or derivative) which maintains an anti-depressive activity similar to that of bupropion.

In an exemplary embodiment, the sympathomimetic agent is selected from bupropion, amphetamine, methamphetamine, benzphetamine, phenylpropanolamine, phentermine, chlorphentermine, diethylpropion, phenmetrazine, and phendimetrazine (as set forth in Table 1).

In one embodiment, the sympathomimetic agent is phentermine. It is also within the scope of the present invention to utilize other sympathomimetic agents including pseudoephedrine (a stereoisomer of ephedrine), methylphenidate, dexmethylphenidate, tuaminoheptane, and other CNS stimulants including, for example, caffeine and bupropion.

The selection of appropriate dosages for the drugs used in combination therapy according to the present invention can be determined and optimized by the skilled artisan, e.g., by observation of the patient, including the patient's overall health, the response to the combination therapy, and the like. Optimization may be necessary if it is determined that a patient is not exhibiting the desired therapeutic effect or, conversely, if the patient is experiencing undesirable or adverse side effects that are too many in number or are of troublesome severity.

Although the dosage used will vary depending on the clinical goals to be achieved, a suitable daily dose range for the sympathomimetic agent is generally in the range of 2 mg to 1500 mg, administered to a patient over an ongoing time period. For example, 2 mg, 4 mg, 10 mg, 20 mg, 30 mg, 60 mg, 90 mg, 120 mg, 150 mg, 180 mg, 210 mg, 240 mg, 270 mg, 300 mg, 330 mg, 360 mg, 390 mg, 420 mg, 450 mg, 480 mg, 500 mg, 600 mg, 800 mg, 1000 mg, 1200 mg, 1500 mg or the like is administered to a patient as a daily dosage, which may be a single daily dosage. In another example, 3.75 mg, 7.5 mg, 11.75 mg, 15 mg or the like is administered to a patient as a daily dosage, which, again, may be a single daily dosage.

In one embodiment, each component of the combination (e.g., (i) topiramate, and (ii) a sympathomimetic drug) is prescribed at a dose that is below the typically described dose for each component as a monotherapy. The components may be prescribed separately or as a combination dosage. In one embodiment, each component of the combination (e.g., (i) topiramate, and (ii) a sympathomimetic drug) is prescribed at a dose that is above the typically described dose for each component as a monotherapy. The components may be prescribed separately or as a combination dosage.

In another embodiment, the prescribed dosage of the sympathomimetic drug is above the typically described dose for monotherapy, and topiramate is prescribed at a dosage that is at or below the typically described dose for monotherapy. In another embodiment, the prescribed dosage of the sympathomimetic drug is at or below the typically described dose for monotherapy, and topiramate is prescribed at a dosage that is above the typically described dose for monotherapy.

In certain embodiments, when phentermine is the sympathomimetic agent, phentermine may be, for example, administered at a daily dosage, e.g., a single daily dosage, in the range of 2 mg to 60 mg. In one aspect, the phentermine is administered at a daily dosage, e.g., a single daily dosage, in the range of 2 mg to 30 mg. In another aspect, the phentermine is administered at a daily dosage, e.g., a single daily dosage, in the range of 2 mg to 15 mg.

In certain embodiments, when bupropion is the sympathomimetic agent, bupropion may be, for example, administered at a daily dosage, e.g., a single daily dosage, in the range of 50 mg to 400 mg, more typically in the range of 50 mg to 200 mg.

The method of administration of pharmaceutical combinations of the invention will depend, in particular, on the type of sympathomimetic agent used. Topiramate and the sympathomimetic agent may be administered together in the same composition or simultaneously or sequentially in two separate compositions. Also, one or more sympathomimetic

agents may be administered to a subject or patient either in the form of a therapeutic composition or in combination, e.g., in the form of one or more separate compositions administered simultaneously or sequentially. The schedule of administration will be dependent on the type of sympathomimetic agent(s) chosen. For example, a sympathomimetic agent can have a stimulant effect and the degree of the stimulant effect may vary depending on the sympathomimetic agent chosen. A sympathomimetic agent having a significant stimulant effect would preferably be administered earlier in the day than would a sympathomimetic agent having a lesser stimulant effect. Topiramate, which typically has at least some sedative effect even at lower doses, may be administered later in the day than administration of a compound having a lesser sedative effect.

In one embodiment, topiramate is administered in a controlled release form, i.e., in sustained release and/or delayed release form, preferably both, and phentermine is administered in an immediate release form. As such, the phentermine may be taken in the morning because the drug is a stimulant as well as an appetite suppressant. In this embodiment, topiramate may be taken later in the day than the phentermine. Preferably, the patient takes the topiramate just before dinner or later in the evening because the drug is sedating.

In yet another embodiment, topiramate is administered in a controlled release form, i.e., in sustained release and/or delayed release form, and bupropion is administered in an immediate release form. As such, the bupropion may be taken in the morning because the drug is a stimulant as well as an appetite suppressant. In this embodiment, topiramate may be taken later in the day than the bupropion. Preferably, the patient takes the topiramate just before dinner or later in the evening because the drug is sedating.

As described supra, a controlled release dosage form of the invention wherein combination therapy is indicated can be a capsule containing controlled release topiramate beads and immediate release phentermine beads, bupropion beads, or the like. The topiramate beads may be made using an extrusion spheronization process to produce a matrix core comprised of: topiramate, 40.0% w/w; microcrystalline cellulose, e.g., Avicel® PH102, 56.5% w/w; and methylcellulose, e.g., Methocel™ A15 LV, 3.5% w/w. The topiramate cores are then coated with ethyl cellulose, 5.47% w/w and Povidone K30: 2.39% w/w. The phentermine beads, bupropion beads, or the like, are composed of an immediate release drug coating on sugar spheres or analogous non-active cores. Both sets of beads are then encapsulated into one capsule.

In certain embodiments, the phentermine beads may be provided with a controlled release drug coating on sugar spheres or other non-active cores. In other aspects, the phentermine beads may be coated onto the controlled release topiramate beads.

In combination therapy, then, a preferred method of administration involves simultaneous administration of the two active agents, in a single composition or in two discrete compositions each containing one of the active agents. The method of administration may also involve administration of the two active agents at different times of day, with the sympathomimetic agent generally administered earlier in the day and the topiramate generally administered later in the day. Normally, however, the two agents are administered simultaneously using one or more dosage forms that provide for immediate release of the sympathomimetic agent and controlled release of the topiramate. In an exemplary embodiment, the sympathomimetic agent and the topiramate are administered in a single dosage form that provides for immediate release of the sympathomimetic agent and sustained release and/or delayed release, preferably both sustained release and delayed release, of the topiramate. Such dosage forms may be coated cores or encapsulated beads, as described above, or they may be tablets, wherein, for example, the tablets contain at least two discrete segments, at least one of which contains the sympathomimetic agent such as phentermine or bupropion in immediate release form, and another of which contains topiramate in controlled release form.

Indications:

Conditions of particular interest for which the invention finds utility include overweight, obesity and conditions often associated with and/or caused by excess weight and obesity. Topiramate compositions and combinations administered according to the dosage regimens provided herein give rise to significant therapeutic effects and reduced adverse effects, making these pharmaceutical compositions extremely effective therapeutics, especially in the treatment of overweight, obesity and/or related conditions, including conditions associated with and/or caused by excess weight or obesity per se. Subjects suitable for treatment with the subject combination therapy treatment regimen thus include individuals suffering from conditions associated with obesity, such conditions including, without limitation:

diabetes, insulin resistance, and impaired glucose tolerance;

respiratory problems such as pulmonary hypertension, asthma, and shortness of breath;

gallbladder disease;

dyslipidemia, e.g., high cholesterol, high levels of triglycerides, etc.;

osteoarthritis and other orthopedic problems;

reflux esophagitis;

adverse conditions related to sleep, including sleep apnea and loud snoring;

menstrual irregularities, infertility, and complications in pregnancy;

gout;

high blood pressure, i.e., hypertension;

cardiovascular problems such as coronary artery disease and other heart trouble;

muscular dystrophy;

stroke, particularly thrombotic stroke and deep vein thrombosis (DVT);

migraines;

metabolic disorders such as hypoalphalipoproteinemia, familial combined hyperlipidemia, and Syndrome X, including insulin-resistant Syndrome X; and

colon, rectal, renal, esophageal, gallbladder, pancreatic, prostate, breast, uterine, ovarian, endometrial, and cervical cancers.

Higher body weights are also associated with increases in all-cause mortality. Most or all of these problems are relieved or improved by permanent significant weight loss. Longevity is likewise significantly increased by permanent significant weight loss.

Diabetes mellitus is very commonly seen in obese individuals, and is associated with continuous and pathologically elevated blood glucose concentration. It is one of the leading causes of death in the United States and is responsible for about 5% of all mortality. Diabetes is divided into two major sub-classes: Type I, also known as juvenile diabetes, or Insulin-Dependent Diabetes Mellitus (IDDM); and Type II, also known as adult onset diabetes, or Non-Insulin-Dependent Diabetes Mellitus (NIDDM).

According to the American Diabetes Association, there are over one million juvenile diabetics in the United States. Type

I Diabetes is a form of autoimmune disease. Autoantibodies produced by the patients completely or partially destroy the insulin producing cells of the pancreas. Juvenile diabetics must, therefore, receive exogenous insulin during their lifetime. Without treatment, excessive acidosis, dehydration, kidney damage, and death may result. Even with treatment, complications such as blindness, atherosclerosis, and impotence can occur.

There are more than five million Type II (adult onset) diabetics diagnosed in the United States. Type II disease usually begins during middle age; the principal cause is now known to be overweight and obesity. In Type II diabetics, rising blood glucose levels after meals do not properly stimulate insulin production by the pancreas. Additionally, peripheral tissues are generally resistant to the effects of insulin. The resulting high blood glucose levels (hyperglycemia) can cause extensive tissue damage. Type II diabetics are often referred to as insulin resistant. They often have higher than normal plasma insulin levels (hyperinsulinemia) as the body attempts to overcome its insulin resistance. Some researchers now believe that hyperinsulinemia may be a causative factor in the development of high blood pressure, high levels of circulating low density lipoproteins (LDLs), and lower than normal levels of the beneficial high density lipoproteins (HDLs). While moderate insulin resistance can be compensated for in the early stages of Type II diabetes by increased insulin secretion, in more advanced disease states insulin secretion is also impaired.

Insulin resistance and hyperinsulinemia have also been linked with two other metabolic disorders that pose considerable health risks: impaired glucose tolerance and metabolic obesity. Impaired glucose tolerance is characterized by normal glucose levels before eating, with a tendency toward elevated levels (hyperglycemia) following a meal. According to the World Health Organization, approximately 11% of the U.S. population between the ages of 20 and 74 are estimated to have impaired glucose tolerance. These individuals are considered to be at higher risk for diabetes and coronary artery disease.

Obesity may also be associated with insulin resistance. A causal linkage among obesity, impaired glucose tolerance, and Type II diabetes has been proposed, but a physiological basis has not yet been established. Some researchers believe that impaired glucose tolerance and diabetes are clinically observed and diagnosed only later in the disease process after a person has developed insulin resistance and hyperinsulinemia.

Insulin resistance is frequently associated with hypertension, coronary artery disease (arteriosclerosis), and lactic acidosis, as well as related disease states. The fundamental relationship between these disease states, and a method of treatment, has not been established.

Hypertension is another condition that is frequently seen in obese individuals, and occurs when the blood pressure inside the large arteries is chronically elevated. Hypertension affects about 50 million people in the United States alone. It is more common as people grow older and is both more common and more serious in African Americans. Most cases of hypertension are of unknown etiology. It is known that the tendency to develop hypertension can be inherited. Environment also plays a very important role in hypertension. For example, hypertension may be avoided by keeping body weight under control, keeping physically fit, eating a healthy diet, limiting alcohol intake, and avoiding medications that might increase blood pressure. Other less common causes of hypertension include disorders of the kidneys or endocrine glands. Hypertension has been called “the silent killer” because it has no specific symptoms and yet can lead to death. People with untreated hypertension are much more likely to die from or be disabled by cardiovascular complications such as strokes, heart attacks, heart failure, heart rhythm irregularities, and kidney failure, than people who have normal blood pressure.

Current treatments for hypertension include lifestyle changes (diet, exercise, nonsmoking, etc.) as well as drug therapy. The major classes of medications currently used to treat hypertension include adrenergic neuron antagonists (which are peripherally acting), alpha adrenergic agonists (which are centrally acting), alpha adrenergic blockers, alpha and beta blockers, angiotensin II receptor blockers, angiotensin converting enzyme (ACE) inhibitors, beta adrenergic blockers, calcium channel blockers, thiazides (benzothiadiazine derivatives) and related diuretics, and vasodilators (which act by direct relaxation of vascular smooth muscles).

A particularly serious hypertensive disorder is primary pulmonary hypertension, also known as idiopathic pulmonary hypertension. This is a condition in which the blood pressure in the pulmonary arteries is abnormally high in the absence of other diseases of the heart or lungs. The cause of primary pulmonary hypertension is unknown. Pulmonary hypertension develops in response to increased resistance to blood flow. Narrowing of the pulmonary arterioles occurs and the right side of the heart becomes enlarged due to the increased work of pumping blood against the resistance. Eventually, progressive heart failure develops. Currently, there is no known cure for primary pulmonary hypertension. Treatment is primarily directed towards controlling the symptoms, although some success has occurred with the use of vasodilators. Other medications used to treat the symptoms of primary pulmonary hypertension include diuretics and calcium channel blockers. Typically, as the disease progresses, oxygen is often required. In certain cases, a heart-lung transplant may be indicated for certain suitable candidates, although the availability of donor organs continues to be extremely limited. Unfortunately, primary pulmonary hypertension is a progressive disease, usually leading to congestive heart failure and respiratory failure.

Secondary pulmonary hypertension is a serious disorder that arises as a complication of other conditions such as, for example, scleroderma. Treatments are similar as those for primary pulmonary hypertension and, unfortunately, the prognosis is the same as well.

Other respiratory disorders that are frequently seen in obese individuals include asthma and shortness of breath, both of which conditions are often alleviated by weight loss.

With respect to adverse conditions and disorders associated with sleep, sleep apnea is perhaps the most concerning. Sleep apnea is classified as either obstructive sleep apnea, the more common form that occurs when throat muscles relax, or central sleep apnea, which occurs when the brain doesn’t send proper signals to the muscles that control breathing. Additionally, some people have mixed sleep apnea, which is a combination of both obstructive and central sleep apneas. Sleep apnea literally means “cessation of breath.” It is characterized by repetitive episodes of upper airway obstruction that occur during sleep, usually associated with a reduction in blood oxygen saturation. In other words, the airway becomes obstructed at several possible sites. The upper airway can be obstructed by excess tissue in the airway, large tonsils, and a large tongue and usually includes the airway muscles relaxing and collapsing when asleep. Another site of obstruction can be the nasal passages. Sometimes the structure of the jaw and airway can be a factor in sleep apnea.

The signs and symptoms of obstructive and central sleep apneas overlap, sometimes making the type of sleep apnea

more difficult to determine. The most common signs and symptoms of obstructive and central sleep apneas include: excessive daytime sleepiness (hypersomnia); loud snoring; observed episodes of breathing cessation during sleep; abrupt awakenings accompanied by shortness of breath; awakening with a dry mouth or sore throat; morning headache; and/or difficulty staying asleep (insomnia). Disruptive snoring may be a more prominent characteristic of obstructive sleep apnea, while awakening with shortness of breath may be more common with central sleep apnea.

Sleep apnea is a progressive condition and can be very serious; it is a potentially life-threatening condition that requires immediate medical attention. The risks of undiagnosed obstructive sleep apnea include heart attacks, strokes, high blood pressure, heart disease, irregular heartbeat, and impotence. In addition, obstructive sleep apnea causes daytime sleepiness that can result in accidents, lost productivity and interpersonal relationship problems. The severity of the symptoms may be mild, moderate or severe.

Sleep apnea is diagnosed utilizing a sleep test, called polysomnography but treatment methodologies differ depending on the severity of the disorder. Mild Sleep Apnea is usually treated by some behavioral changes; losing weight and sleeping on one's side are often recommended. There are oral mouth devices (that help keep the airway open) that may help to reduce snoring in three different ways. Some devices (1) bring the jaw forward or (2) elevate the soft palate or (3) retain the tongue (from falling back in the airway and blocking breathing).

Moderate to severe sleep apnea is usually treated with a continuous positive airway pressure (C-PAP). C-PAP is a machine that blows air into your nose via a nose mask, keeping the airway open and unobstructed. For more severe apnea, there is a Bi-level (Bi-PAP) machine. The Bi-level machine is different in that it blows air at two different pressures. When a person inhales, the pressure is higher and in exhaling, the pressure is lower.

Some people have facial deformities that may cause the sleep apnea. It simply may be that their jaw is smaller than it should be or they could have a smaller opening at the back of the throat. Some people have enlarged tonsils, a large tongue or some other tissues partially blocking the airway. Fixing a deviated septum may help to open the nasal passages. Removing the tonsils and adenoids or polyps may help also. Children are much more likely to have their tonsils and adenoids removed. Surgical procedures, such as tracheostomy, uvulopalatopharyngoplasty (UPPP), laser assisted uvuloplasty (LAUP), somnoplasty, and mandibular myotomy are often required to effectively treat sleep apnea. Weight loss, however, particularly in an obese person, can significantly alleviate sleep apnea and other sleep-related adverse conditions such as loud snoring and the like.

Relatively recently, a connection between obesity and the occurrence or increased incidence of migraine headaches has been noted. Migraine headaches begin with mild pain, which increases in intensity over a short period of time. There are two major types of migraines. The common migraine affects 80-85% of migraine sufferers and classical migraine with aura affects 15% of migraine sufferers. Symptoms associated with migraines include headaches, psychological symptomology such as irritability, depression, fatigue, drowsiness, restlessness; neurological symptoms such as photophobia, phonophobia or gastrointestinal symptoms such as change in bowel habit, change of food intake or urinary symptoms such as urinary frequency, auras which are neurological deficits and can be a variety of deficits for the migraine population but in the individual is usually stereotyped. These deficits may be visual scotoma or visual designs, hemiplegia, migrating paraesthesia, dysarthria, dysphasia, or déjà vu. The headache is usually accompanied by light or sound sensitivity, photophobia or phonophobia, irritability and impaired concentration. For those individuals whose migraine headaches are caused by or exacerbated by obesity, treatment according to the methodology of the present invention can be effective.

Other indications for which the present invention is readily adapted include epilepsy and certain psychiatric indications such as impulse control disorders.

Topiramate has long been known as an anti-epileptic agent. At dosages previously required or believed to be required for efficacy, however, topiramate therapy resulted in significant side effects, as noted elsewhere herein. The present invention, according to which topiramate dosage may be reduced by concomitant administration of phentermine, significantly reduces those side effects of topiramate, most if not all of which are dose-related.

Among psychiatric indications, depression is particularly common. "Depression," as is well known, is manifested by a combination of symptoms that interfere with the ability to work, study, sleep, eat, and enjoy once pleasurable activities. Depression includes major depression, especially refractory depression, bipolar depression, and the degeneration associated with depression. Symptoms of depression include persistent sad, anxious, or "empty" mood, feelings of hopelessness, pessimism, feelings of guilt, worthlessness, helplessness, loss of interest or pleasure in hobbies and activities that were once enjoyed, including sex, decreased energy, fatigue, being "slowed down", difficulty concentrating, remembering, making decisions, insomnia, early-morning awakening, or oversleeping, appetite and/or weight loss or overeating and weight gain, thoughts of death or suicide; suicide attempts, restlessness, irritability, persistent physical symptoms that do not respond to treatment, such as headaches, digestive disorders, and chronic pain.

Other psychiatric disorders may also be treated using the compositions and methods of the invention. These disorders include impulse control disorders, panic syndrome, general anxiety disorder, phobic syndromes of all types, mania, manic depressive illness, hypomania, unipolar depression, stress disorders, PTSD, somatoform disorders, personality disorders, psychosis, and schizophrenia.

"Impulse Control Disorders" are characterized by harmful behaviors performed in response to irresistible impulses. The essential feature of an impulse control disorder is the failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person or to others. Symptoms include an increasing sense of tension or arousal before committing an act, and then experiences pleasure, gratification, or release at the time of committing the act. After the act is performed, there may or may not be regret or guilt. Numerous disorders can be characterized as impulse control disorders including intermittent explosive disorder, kleptomania, pathological gambling, pyromania, trichotillomania, compulsive buying or shopping, repetitive self-mutilation, nonparaphilic sexual addictions, severe nail biting, compulsive skin picking, personality disorders with impulsive features, attention deficit/hyperactivity disorder, eating disorders characterized by binge eating, and substance abuse disorders such as alcoholism and drug addiction. Binge eating disorder and bulimia are also sometimes classified as impulse control disorders.

Packaged Pharmaceutical Preparations:

Also provided are packaged pharmaceutical preparations for practicing the subject methods. The packaged preparation contains a composition of the invention in a sealed container, and typically contains a plurality of individual dosage forms

each in a sealed housing, as in a blister pack, but could also contain one or more dosage forms in a single sealed container. Optionally, dosage forms with lower doses of one or both active agents can also be included, for dose titration and dose escalation.

In certain embodiments, the packaged pharmaceutical preparations include instructions for a patient to carry out drug administration to achieve weight loss, treat obesity, treat conditions associated with obesity, or treat other conditions as explained earlier herein. For instance, the instructions may include the daily dose of topiramate to be taken, the daily dose of phentermine or other sympathomimetic agent to be taken, and/or the dosing regimen for self-administration of a controlled release dosage form containing topiramate and optionally the second active agent. The instructions may be recorded on a suitable recording medium or printed on a substrate such as paper or plastic. As such, the instructions may be present as a package insert, in the labeling of the package, container(s), or components thereof (i.e., associated with the packaging or sub-packaging), etc. In other embodiments, the instructions are present as an electronic storage data file present on a suitable computer readable storage medium, e.g. CD-ROM, diskette, etc. In yet other embodiments, the actual instructions are not present, but means for obtaining the instructions from a remote source, e.g. via the internet, are provided. As an example, a web address might be included to direct patients to a website where the instructions can be viewed and/or from which the instructions can be downloaded. As with the instructions per se, this means for obtaining the instructions is recorded on a suitable substrate.

Some or all of the included components may be packaged in suitable packaging to maintain sterility. In many embodiments, the components are packaged in a containment element to provide a single, easily handled unit, where the containment element, e.g., box or analogous structure, may or may not be an airtight container, e.g., to further preserve the sterility of some or all of the components. In certain aspects, a sealed package of controlled release dosage forms is provided wherein the dosage forms contain phentermine in immediate release form and topiramate in controlled release, e.g., sustained release and delayed release form. Alternatively, separate phentermine-containing and topiramate-containing dosage forms may be included.

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (e.g. amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Celsius, and pressure is at or near atmospheric.

Example 1

Controlled release topiramate beads are made using an extrusion spheronization process to produce a matrix core comprised of topiramate, 40.0% w/w; microcrystalline cellulose (Avicel® PH102), 56.5% w/w; and Methocel™ A15 LV, 3.5% w/w. The topiramate cores were then coated with ethyl cellulose, 5.47% w/w, and Povidone K30, 2.39% w/w.

The composition of the topiramate beads so prepared is as follows:

Component	% w/w
topiramate	36.85
microcrystalline cellulose, (Avicel ® PH102)	52.05
Methylcellulose (Methocel ™ A15 LV)	3.22
ethylcellulose	5.47
Polyvinylpyrrolidone (Povidone K30)	2.39

Phentermine hydrochloride was coated onto sugar spheres to provide immediate release phentermine beads. Both sets of beads were then encapsulated into each of a plurality of capsules.

Example 2

In a study comparing controlled-release formulation of topiramate according to the present invention versus immediate release topiramate (Topamax®) in combination with phentermine, the controlled release formulation of the instant invention of topiramate had a 10-15% lower effect on phentermine exposure (FIG. **2**).

The mean and statistical comparisons for plasma phentermine PK parameters at steady state in multiple dose administrations are summarized in Table 2.

TABLE 2

Arithmetic Mean (SD) and Statistical Comparison of Pharmacokinetic Parameters for Plasma Phentermine

		Treatment 2 Versus Treatment 4		
Pharmacokinetic Parameters	Mean +/− SD Treatment 2 (N = 13)	Treatment 4 (N = 12)	90% Confidence Intervals	% Mean Ratio
$AUC_{0\text{-}tau}$ (ng * hr/mL)	2250 +/− 563	2530 +/− 644	(75.6, 105.3)	89.2
$AUC_{0\text{-}96}$ (ng * hr/mL)	4640 +/− 1570	5550 +/− 1960	(67.1, 105.0)	84.0
$AUC_{0\text{-}t}$ (ng * hr/mL)	4640 +/− 1570	5550 +/− 1960	(67.1, 105.0)	84.0
$C_{max,\ ss}$ (ng * hr/mL)	114 +/− 23.6	127 +/− 27.6	(78.8, 104.5)	90.7
$C_{min,\ ss}$ (ng * hr/mL)	9.84 +/− 7.24	14.6 +/− 11.3	(42.5, 109.0)	68.1
t_{max} (hr)	4.01 (1.04, 7.00)	4.54 (1.00, 10.0)		
$T_{1/2}$ (hr)	23.3 +/− 6.17	26.3 +/− 7.43		
CL_{ss}/F (L/hr)	7.10 +/− 1.89	6.38 +/− 2.00		
V_2/F (L/hr)	229 +/− 45.3	232 +/− 58.5		

t_{max} is presented as median (minimum, maximum)
Parameters were dose-normalized and ln-transformed prior to analysis.
% Mean Ratio = 100* ex[(Treatment 2-Treatment 4) for ln-transformed parameters
Treatment 1 (Test): 7.5 mg phentermine/50 mg topiramate (Formulation A)
Treatment 2 (Test): 15 mg phentermine/100 mg topiramate (Formulation A)
Treatment 4 (Reference): 15 mg phentermine/100 mg topiramate
Source: Tables 14.2.1.8, 14.2.1.10, 14.2.1.12, and 14.2.1.17

These data indicate a lower maximum and extent of phentermine exposure between tests versus reference treatments after multiple-dose administration. As such, the controlled release formulation of topiramate reduced drug interaction with phentermine which in turn will reduce further side effects associated with phentermine.

The invention claimed is:

1. A method for effecting weight loss in a patient having a body mass index of at least 25 kg/m^2, comprising administering an escalating unit dosage form comprising,

(a) a first dosage form, comprising,

23 mg of topiramate, formulated for controlled release, and

3.75 mg of phentermine, formulated for immediate release,

wherein the first dosage form is administered to the subject daily for at least 2 weeks; and

(b) a second dosage form, comprising,

46 mg of topiramate, formulated for controlled release, and

7.5 mg of phentermine, formulated for immediate release,

wherein the topiramate formulated for controlled release reaches maximum plasma concentration (Cmax) at about 6 to about 10 hours (Tmax) after administration and exhibits a lower Cmax, than non-controlled release topiramate, without decreasing total drug exposure defined by the area under the concentration-time curve (AUC), and

wherein the second dosage form is administered to the subject daily for at least 2 years, thereby effecting weight loss.

2. The method of claim **1**, wherein the subject has a body mass index between 25 kg/m^2 and 29.9 kg/m^2.

3. The method of claim **2**, wherein the subject has a condition associated with obesity.

4. The method of claim **1**, wherein the subject has a body mass index of at least 30 kg/m^2.

5. The method of claim **4**, wherein the subject has a condition associated with obesity.

6. The method of claim **3**, wherein the condition associated with obesity is selected from the group consisting of diabetes, elevated fasting blood glucose, insulin resistance, impaired glucose tolerance, pulmonary hypertension, asthma, shortness of breath, gallbladder disease, dyslipidemia, high cholesterol, high levels of triglycerides, osteoarthritis, reflux esophagitis, sleep apnea, menstrual irregularities, infertility, complications in pregnancy, gout, high blood pressure, hypertension, coronary artery disease, heart disease, muscular dystrophy, stroke, thrombotic stroke, deep vein thrombosis (DVT), migraines, metabolic disorders, hypoalphalipoproteinemia, familial combined hyperlipidemia, Syndrome X, insulin-resistant Syndrome X, colon cancer, rectal cancer, renal cancer, esophageal cancer, gallbladder cancer, pancreatic cancer, prostate cancer, breast cancer, uterine cancer, ovarian cancer, endometrial cancer, and cervical cancer.

7. The method of claim **5**, wherein the condition associated with obesity is selected from the group consisting of diabetes, elevated fasting blood glucose, insulin resistance, impaired glucose tolerance, pulmonary hypertension, asthma, shortness of breath, gallbladder disease, dyslipidemia, high cholesterol, high levels of triglycerides, osteoarthritis, reflux esophagitis, sleep apnea, menstrual irregularities, infertility, complications in pregnancy, gout, high blood pressure, hypertension, coronary artery disease, heart disease, muscular dystrophy, stroke, thrombotic stroke, deep vein thrombosis (DVT), migraines, metabolic disorders, hypoalphalipoproteinemia, familial combined hyperlipidemia, Syndrome X, insulin-resistant Syndrome X, colon cancer, rectal cancer, renal cancer, esophageal cancer, gallbladder cancer, pancreatic cancer, prostate cancer, breast cancer, uterine cancer, ovarian cancer, endometrial cancer, and cervical cancer.

8. The method of claim **6**, wherein the condition associated with obesity is selected from the group consisting of high blood pressure, high levels of triglycerides, elevated fasting blood glucose and diabetes.

9. The method of claim **7**, wherein the condition associated with obesity is selected from the group consisting of high blood pressure, high levels of triglycerides, elevated fasting blood glucose and diabetes.

10. The method of claim **3**, wherein the subject is suffering from at least two conditions associated with obesity selected from the group consisting of high blood pressure, high levels of triglycerides, elevated fasting blood glucose and diabetes.

11. The method of claim **5**, wherein the subject is suffering from at least two conditions associated with obesity selected from the group consisting of high blood pressure, high levels of triglycerides, elevated fasting blood glucose and diabetes.

12. The method of claim **1**, wherein the 3.75 mg phentermine is provided in the first dosage form as about 4.92 mg phentermine hydrochloride, and wherein 4.92 mg of phentermine hydrochloride provides 3.75 mg of phentermine.

13. The method of claim **1**, wherein the 7.5 mg phentermine is provided in the second dosage form as about 9.84 mg phentermine hydrochloride, and wherein 9.84 mg of phentermine hydrochloride provides 7.5 mg of phentermine.

14. The method of claim **1**, wherein the topiramate formulated for controlled release reaches maximum plasma concentration (Cmax) at a time (Tmax) that is delayed by about 6 to about 8 hours compared to the Tmax of non-controlled release topiramate and exhibits a lower Cmax than non-controlled release topiramate.

15. The method of claim **1**, wherein the topiramate formulated for controlled release is formulated for sustained release, delayed release, or both.

16. The method of claim **1**, wherein the escalating unit dosage form is formulated for oral administration.

17. The method of claim **1**, wherein the weight loss is effective to achieve a reduction of at least about 10% of body weight.

18. A method for effecting weight loss in a patient having a body mass index of at least 25 kg/m^2, comprising administering an escalating unit dosage form comprising,

(a) a first dosage form, comprising,

23 mg of topiramate, formulated for controlled release, and

3.75 mg of phentermine, formulated for immediate release,

wherein the first dosage form is administered to the subject daily for at least 2 weeks; and

(b) a second dosage form, comprising,

92 mg of topiramate, formulated for controlled release, and

15 mg of phentermine, formulated for immediate release,

wherein the topiramate formulated for controlled release reaches maximum plasma concentration (Cmax) at about 6 to about 10 hours (Tmax) after administration and exhibits a lower Cmax, than non-controlled release topiramate, without decreasing total drug exposure defined by the area under the concentration-time curve (AUC), and

wherein the second dosage form is administered to the subject daily for at least 2 years, thereby effecting weight loss.

19. The method of claim **18**, wherein the subject has a body mass index between 25 kg/m^2 and 29.9 kg/m^2.

20. The method of claim **19**, wherein the subject has a condition associated with obesity.

21. The method of claim **18**, wherein the subject has a body mass index of at least 30 kg/m^2.

22. The method of claim **21**, wherein the subject has a condition associated with obesity.

23. The method of claim **20**, wherein the condition associated with obesity is selected from the group consisting of diabetes, elevated fasting blood glucose, insulin resistance, impaired glucose tolerance, pulmonary hypertension, asthma, shortness of breath, gallbladder disease, dyslipidemia, high cholesterol, high levels of triglycerides, osteoarthritis, reflux esophagitis, sleep apnea, menstrual irregularities, infertility, complications in pregnancy, gout, high blood pressure, hypertension, coronary artery disease, heart disease, muscular dystrophy, stroke, thrombotic stroke, deep vein thrombosis (DVT), migraines, metabolic disorders, hypoalphalipoproteinemia, familial combined hyperlipidemia, Syndrome X, insulin-resistant Syndrome X, colon cancer, rectal cancer, renal cancer, esophageal cancer, gallbladder cancer, pancreatic cancer, prostate cancer, breast cancer, uterine cancer, ovarian cancer, endometrial cancer, and cervical cancer.

24. The method of claim **22**, wherein the condition associated with obesity is selected from the group consisting of diabetes, elevated fasting blood glucose, insulin resistance, impaired glucose tolerance, pulmonary hypertension, asthma, shortness of breath, gallbladder disease, dyslipidemia, high cholesterol, high levels of triglycerides, osteoarthritis, reflux esophagitis, sleep apnea, menstrual irregularities, infertility, complications in pregnancy, gout, high blood pressure, hypertension, coronary artery disease, heart disease, muscular dystrophy, stroke, thrombotic stroke, deep vein thrombosis (DVT), migraines, metabolic disorders, hypoalphalipoproteinemia, familial combined hyperlipidemia, Syndrome X, insulin-resistant Syndrome X, colon cancer, rectal cancer, renal cancer, esophageal cancer, gallbladder cancer, pancreatic cancer, prostate cancer, breast cancer, uterine cancer, ovarian cancer, endometrial cancer, and cervical cancer.

25. The method of claim **23**, wherein the condition associated with obesity is selected from the group consisting of high blood pressure, high levels of triglycerides, elevated fasting blood glucose and diabetes.

26. The method of claim **24**, wherein the condition associated with obesity is selected from the group consisting of high blood pressure, high levels of triglycerides, elevated fasting blood glucose and diabetes.

27. The method of claim **20**, wherein the subject is suffering from at least two conditions associated with obesity selected from the group consisting of high blood pressure, high levels of triglycerides, elevated fasting blood glucose and diabetes.

28. The method of claim **22**, wherein the subject is suffering from at least two conditions associated with obesity selected from the group consisting of high blood pressure, high levels of triglycerides, elevated fasting blood glucose and diabetes.

29. The method of claim **18**, wherein the 3.75 mg phentermine is provided in the first dosage form as about 4.92 mg phentermine hydrochloride, and wherein 4.92 mg of phentermine hydrochloride provides 3.75 mg of phentermine.

30. The method of claim **18**, wherein the topiramate formulated for controlled release reaches maximum plasma concentration (Cmax) at a time (Tmax) that is delayed by about 6 to about 8 hours compared to the Tmax of non-controlled release topiramate and exhibits a lower Cmax than non-controlled release topiramate.

31. The method of claim **18**, wherein the topiramate formulated for controlled release is formulated for sustained release, delayed release, or both.

32. The method of claim **18**, wherein the escalating unit dosage form is formulated for oral administration.

33. The method of claim **18**, wherein the weight loss is effective to achieve a reduction of at least about 10% of body weight.

* * * * *

EXHIBIT H

US008895058B2

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

(10) **Patent No.: US 8,895,058 B2**
(45) **Date of Patent: *Nov. 25, 2014**

(54) **LOW DOSE TOPIRAMATE/PHENTERMINE COMPOSITION AND METHODS OF USE THEREOF**

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

This patent is subject to a terminal disclaimer.

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A61K 31/357	(2006.01)
A61K 31/35	(2006.01)
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(52) **U.S. Cl.**

CPC ***A61K 9/28*** (2013.01); ***A61K 31/357*** (2013.01); ***A61K 31/35*** (2013.01); ***A61K 31/137*** (2013.01)

USPC **424/451**; 424/490; 514/23; 514/646; 514/455

(58) **Field of Classification Search**

CPC combination set(s) only.

See application file for complete search history.

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(57) **ABSTRACT**

A method for effecting weight loss by administering a combination of topiramate and phentermine is provided. The phentermine is generally administered in immediate release form, in a daily dose in the range of 2 mg to 8 mg, in combination with a daily dose of topiramate selected to prevent the loss of effectiveness of phentermine alone. Methods for treating obesity, conditions associated with obesity, and other indications are also provided, as are compositions and dosage forms containing low doses of phentermine and topiramate, e.g., 3.75 mg phentermine and 23 mg topiramate.

32 Claims, 2 Drawing Sheets

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FIGURE 1

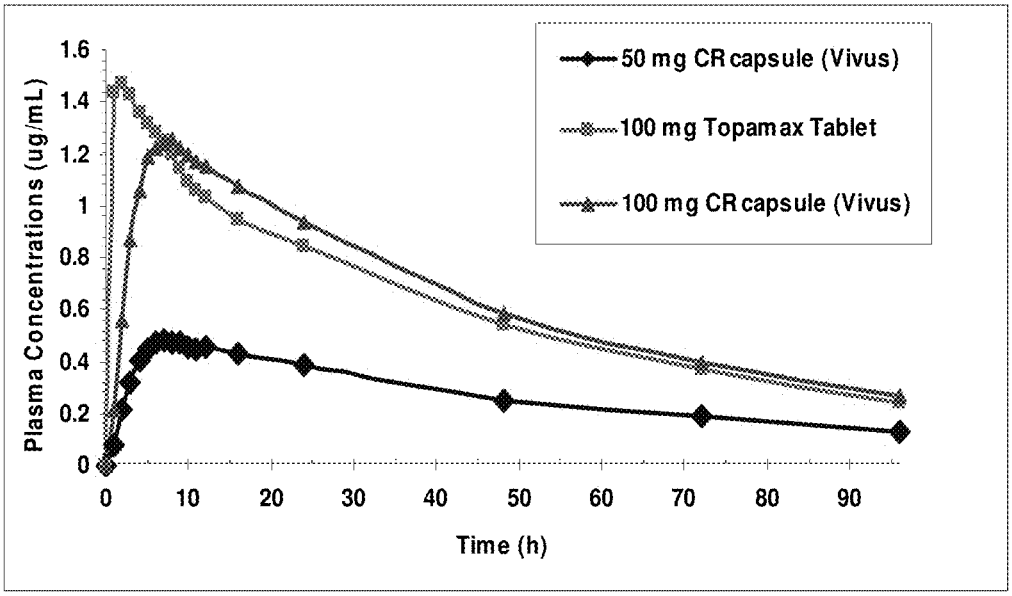
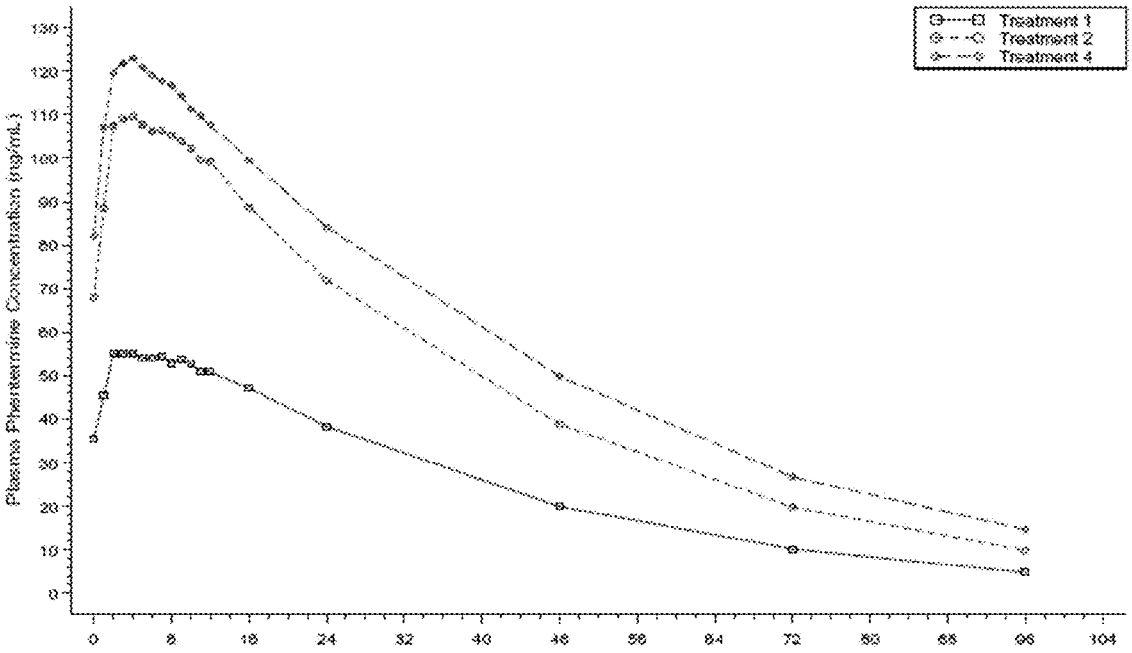

Plasma Concentrations (ug/mL)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
10
20
30
40
50
60
70
80
90
Time (h)
50 mg CR capsule (Vivus)
100 mg Topamax Tablet
100 mg CR capsule (Vivus)

FIGURE 2


Treatment 1
Treatment 2
Treatment 4
Plasma Pheniramine Concentration (ng/mL)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
0
8
16
24
32
40
48
56
64
72
80
88
96
104

LOW DOSE TOPIRAMATE/PHENTERMINE COMPOSITION AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Ser. No. 12/481,540, filed Jun. 9, 2009, which is a continuation-in-part of U.S. Ser. No. 12/135,953, filed Jun. 9, 2008. The contents of each of these applications are incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

The prevalence of obesity in both children and adults is on the rise in first world countries, especially in the United States, as well as in many developing countries such as China and India. Many aspects of a person's life are affected by obesity, from physical problems such as knee and ankle joint deterioration, to emotional problems resulting from self-esteem issues and society's attitude towards heavy people. The medical problems caused by obesity can be serious and often life-threatening and include diabetes, shortness of breath and other respiratory problems such as asthma and pulmonary hypertension, gallbladder disease, dyslipidemia (for example, high cholesterol or high levels of triglycerides) and dyslipidemic hypertension, osteoarthritis and other orthopedic problems, reflux esophagitis (heartburn), snoring, sleep apnea, menstrual irregularities, infertility, problems associated with pregnancy, gout, cardiovascular problems such as coronary artery disease and other heart trouble, muscular dystrophy, and metabolic disorders such as hypoalphalipoproteinemia, familial combined hyperlipidemia, and Syndrome X, including insulin-resistant Syndrome X. In addition, obesity has been associated with an increased incidence of certain cancers, notably cancers of the colon, rectum, prostate, breast, uterus, and cervix.

Obesity substantially increases the risk of morbidity from hypertension, dyslipidemia, type II diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis and endometrial, breast, prostate, and colon cancers. Higher body weights are also associated with increases in all-cause mortality. Many of these problems are relieved or improved when the afflicted individual undergoes permanent significant weight loss. Weight loss in these individuals can also promote a significant increase in longevity.

Strategies for treating obesity and related disorders have included dietary restriction, increased physical activity, pharmacological approaches, and even surgery, with the choice depending, at least in part, on the degree of weight loss one is attempting to achieve as well as on the severity of obesity exhibited by the subject. For example, treatments such as a low-calorie, low-fat diet and/or regular exercise are often adequate with individuals who are only mildly overweight. The difficulty in maintaining long-term weight loss through diet and behavior modification, however, has led to an increasing interest in other avenues for treatment, particularly pharmacotherapy.

Traditional pharmacological interventions typically induce a weight loss of between five and fifteen kilograms; if the medication is discontinued, renewed weight gain often ensues. Surgical treatments are comparatively successful and are reserved for patients with extreme obesity and/or with serious medical complications.

The above treatments can be enhanced by controlled use of over-the-counter appetite suppressants including caffeine, ephedrine and phenylpropanolamine (Acutrim®, Dexatrim®). Moreover, prescription medications including amphetamine, diethylpropion (Tenuate®), mazindol (Mazanor®, Sanorex®), phentermine (Fastin®, Ionamin®), phenmetrazine (Preludin®), phendimetrazine (Bontrol®, Plegine®, Adipost®, Dital®, Dyrexan®, Melfiat®, Prelu-2®, Rexigen Forte®), benzphetamine (Didrex®) and fluoxetine (Prozac®) are often used in the treatment of seriously overweight and/or obese subjects or patients.

While society has seen tremendous advances in the field of pharmaceuticals, there are, of course, drawbacks to the administration of any given pharmaceutical agent. Sometimes, the disadvantages, or "side effects," are so severe as to preclude administration of a particular agent at a therapeutically effective dose. Furthermore, many agents in the same therapeutic class display similar side effect profiles, meaning that patients either have to forego therapy or suffer from varying degrees of side effects associated with the medication of choice.

In U.S. Pat. No. 7,056,890 to Najarian and U.S. Patent Publication Nos. US 2006/0234950 A1, US 2006/0234951 A1, and US 2006/0234952 A1 to Najarian, all of common assignment herewith to Vivus, Inc. (Mountain View, Calif.), a combination therapy for treating obesity and effecting weight loss is provided wherein a synergistic effect between the active agents enables dose reduction and a concomitant alleviation of side effects typically associated with each active agent. One of the active agents is an anti-convulsant agent, e.g., topiramate, and the second active agent is a sympathomimetic agent, typically a sympathomimetic amine such as phentermine. In U.S. patent application Ser. No. 12/135,935, also of common assignment herewith, an escalating dosing regimen is described for administering topiramate alone or in combination with a second therapeutic agent such as phentermine, wherein the second agent is selected so as to directly or indirectly reduce the side effects associated with one or both of the agents administered. By "indirectly" reducing side effects is meant that a first pharmaceutical agent allows the second agent to be administered at a lower dose without compromising therapeutic efficacy, thus reducing dose-dependent unwanted effects.

Topiramate (2,3,4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate) is a broad-spectrum neurotherapeutic agent approved by the FDA and the regulatory agencies of many other countries for the treatment of certain seizure disorders and the prevention of migraine headaches. E. Faught et al. (1996) Neurology 46:1684-90; Karim et al. (1995) Epilepsia 36 (54):33; S. K. Sachdeo et al. (1995) Epilepsia 36(54):33; T. A. Glauser (1999) Epilepsia 40 (S5): S71-80; R. C. Sachdeo (1998) Clin. Pharmacokinet. 34:335-346). There has also been evidence that topiramate is effective in the treatment of diabetes (U.S. Pat. Nos. 7,109,174 and 6,362,220), neurological disorders (U.S. Pat. No. 6,908,902), depression (U.S. Pat. No. 6,627,653), psychosis (U.S. Pat. No. 6,620,819), headaches (U.S. Pat. No. 6,319,903) and hypertension (U.S. Pat. No. 6,201,010). However there have been adverse effects associated with the use of topiramate in humans, such as cognitive dulling and word finding difficulties, which can discourage many obese patients from taking this drug.

Phentermine was approved by the FDA as an appetite suppressant in 1959, and phentermine hydrochloride has been used as a weight loss agent since the 1970s, e.g., under the brand names Adipex-P®, Fastin®, Zantril®, and others. Although the FDA warned against combining phentermine with a second active agent following the reports of cardiac and pulmonary problems associated with the "Fen-Phen"

product (in which phentermine was combined with fenfluramine, and later with a related drug, dexfenfluramine), it has since been found that a safe and effective weight loss treatment is provided by combining phentermine with an active agent that mitigates phentermine's side effects and enables administration of a much lower dose of phentermine than in "Fen-Phen" (containing 30 mg or 37.5 mg phentermine hydrochloride). See U.S. Pat. No. 7,056,890 to Najarian and U.S. Patent Publication Nos. US 2006/0234950 A1, US 2006/0234951 A1, and US 2006/0234952 A1 to Najarian, cited above.

It has now been discovered that a significantly lower dose combination product is effective in achieving weight loss, treating obesity, and treating conditions associated with obesity and excessive weight. The present invention is directed to this product and methods of using the product. The invention provides a number of important advantages vis-à-vis prior weight loss therapies, as will be described in detail herein.

SUMMARY OF THE INVENTION

Accordingly, in a first embodiment, the present invention is directed to a method for effecting weight loss in a subject by administering continually over a significant period of time a daily dose of phentermine in the range of 2 mg to 8 mg and in combination therewith a daily amount of topiramate selected to prevent the loss of effectiveness of phentermine alone. Generally, the combination of these active agents is administered orally. The agents may be administered at different times of day, with the phentermine administered earlier in the day and the topiramate administered later in the day, in the afternoon or evening. Normally, however, the two agents are administered simultaneously using one or more dosage forms that provide for immediate release of the phentermine and controlled release of the topiramate. In an exemplary embodiment, the phentermine and topiramate are administered in a single dosage form that provides for immediate release of the phentermine and both delayed and sustained release of the topiramate.

In another embodiment, the invention is directed to a method for effecting weight loss in a subject by administering continually over a significant period of time a daily dose of 3.75 mg phentermine and, in combination therewith, a daily dose of 23 mg topiramate.

In another embodiment, the invention is directed to a method for effecting weight loss in a subject by administering continually over a significant period of time a daily dose of 7.5 mg phentermine and, in combination therewith, a daily dose of 46 mg topiramate.

In these methods, the daily doses of topiramate and phentermine may also be administered to treat one or more conditions associated with excess weight or obesity. These conditions include, without limitation, diabetes, respiratory disorders, gallbladder disease, dyslipidemia, orthopedic problems, reflux esophagitis, snoring, sleep apnea, menstrual irregularities, infertility, pregnancy complications, gout, cardiovascular problems, muscular dystrophy, metabolic disorders, and certain cancers. Accordingly, in a further embodiment, the invention relates to a method as enumerated above which further involves simultaneously treating the subject for a condition associated with excess weight or obesity.

In another embodiment, a composition is provided for administration to a subject in order to effect weight loss, wherein the composition contains 2 mg to 5 mg phentermine and 17 mg to 23 mg topiramate. An exemplary such composition contains 3.75 mg phentermine and 23 mg topiramate. Generally, the composition is an orally administrable unit dosage form that contains both active agents. Certain dosage forms of the invention provide for immediate release of the phentermine and controlled release of the topiramate.

In a further embodiment, a packaged pharmaceutical preparation is provided that contains a composition of the invention in a sealed container, with instructions for administration, typically self-administration, of the composition. Generally, the packaged preparation contains a plurality of orally administrable unit dosage forms, with, preferably, each individual dosage form in a separate sealed housing, e.g., as in a blister pack.

In still another embodiment, the method, composition, and packaged preparation of the invention are adapted to administer phentermine and topiramate to treat epilepsy.

In still another embodiment, the method, composition, and packaged preparation of the invention are adapted to administer phentermine and topiramate to treat an impulse control disorder.

In still another embodiment, the method, composition, and packaged preparation of the invention are adapted to administer phentermine and topiramate to treat a psychiatric disorder such as depression, panic syndrome, generally anxiety disorder, phobic syndromes, mania, manic depressive illness, hypomania, unipolar depression, stress disorders including post-traumatic stress disorder ("PTSD"), somatoform disorders, personality disorders, psychosis, and schizophrenia.

In still another embodiment, the method, composition, and packaged preparation of the invention are adapted to administer phentermine and topiramate to treat adolescent and juvenile obesity.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** provides a summary of the plasma concentration of controlled release topiramate according to the present invention versus topiramate (Topamax®) in normal obese subjects.

FIG. **2** depicts the mean plasma phentermine concentrations versus time for subjects administered phentermine in combination with controlled release topiramate and phentermine in combination with immediate release topiramate (Topamax®).

DETAILED DESCRIPTION OF THE INVENTION

Definitions and Nomenclature

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, "an active agent" refers not only to a single active agent but also to a combination of two or more different active agents, "a dosage form" refers to a combination of dosage forms as well as to a single dosage form, and the like.

Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by one of ordinary skill in the art to which the invention pertains. Specific terminology of particular importance to the description of the present invention is defined below.

When referring to an active agent, applicants intend the term "active agent" to encompass not only the specified molecular entity but also its pharmaceutically acceptable, pharmacologically active analogs, including, but not limited to, salts, esters, amides, prodrugs, conjugates, active metabolites, and other such derivatives, analogs, and related compounds as will be discussed infra. Therefore, reference to "phentermine" encompasses not only phentermine per se but

also salts and other derivatives of phentermine, e.g., phentermine hydrochloride. It is to be understood that when amounts or doses of phentermine are specified, that those amounts or doses refer to the amount or dose of phentermine per se and not to a phentermine salt or the like. For example, when it is indicated that a dose or amount of phentermine is 3.75 mg, that would correspond to 4.92 phentermine hydrochloride and not 3.75 phentermine hydrochloride.

The terms "treating" and "treatment" as used herein refer to reduction in severity and/or frequency of symptoms, elimination of symptoms and/or underlying cause, and improvement or remediation of damage. In certain aspects, the term "treating" and "treatment" as used herein refer to the prevention of the occurrence of symptoms. In other aspects, the term "treating" and "treatment" as used herein refer to the prevention of the underlying cause of symptoms associated with obesity, excess weight, and/or a related condition. The phrase "administering to a subject" refers to the process of introducing a composition or dosage form of the invention into the subject (e.g., a human or other mammalian subject) via an art-recognized means of introduction

By the terms "effective amount" and "therapeutically effective amount" of an agent, compound, drug, composition or combination of the invention which is nontoxic and effective for producing some desired therapeutic effect upon administration to a subject or patient (e.g., a human subject or patient).

The term "dosage form" denotes any form of a pharmaceutical composition that contains an amount of active agent sufficient to achieve a therapeutic effect with a single administration. When the formulation is a tablet or capsule, the dosage form is usually one such tablet or capsule. The frequency of administration that will provide the most effective results in an efficient manner without overdosing will vary with the characteristics of the particular active agent, including both its pharmacological characteristics and its physical characteristics, such as hydrophilicity.

The term "controlled release" refers to a drug-containing formulation or fraction thereof in which release of the drug is not immediate, i.e., with a "controlled release" formulation, administration does not result in immediate release of the drug into an absorption pool. The term is used interchangeably with "nonimmediate release" as defined in Remington: The Science and Practice of Pharmacy, Nineteenth Ed. (Easton, Pa.: Mack Publishing Company, 1995). In general, the term "controlled release" as used herein includes sustained release, modified release and delayed release formulations.

The term "sustained release" (synonymous with "extended release") is used in its conventional sense to refer to a drug formulation that provides for gradual release of a drug over an extended period of time, and that preferably, although not necessarily, results in substantially constant blood levels of a drug over an extended time period. The term "delayed release" is also used in its conventional sense, to refer to a drug formulation which, following administration to a patient provides a measurable time delay before drug is released from the formulation into the patient's body.

By "pharmaceutically acceptable" is meant a material that is not biologically or otherwise undesirable, i.e., the material may be incorporated into a pharmaceutical composition administered to a patient without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. When the term "pharmaceutically acceptable" is used to refer to a pharmaceutical carrier or excipient, it is implied that the carrier or excipient has met the required standards of toxicological and manufacturing testing or that it is included on the Inactive Ingredient Guide prepared by the U.S. Food and Drug administration. "Pharmacologically active" (or simply "active") as in a "pharmacologically active" (or "active") derivative or analog, refers to a derivative or analog having the same type of pharmacological activity as the parent compound and approximately equivalent in degree. The term "pharmaceutically acceptable salts" include acid addition salts which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

As used herein, "subject" or "individual" or "patient" refers to any subject for whom or which therapy is desired, and generally refers to the recipient of the therapy to be practiced according to the invention. The subject can be any vertebrate, but will typically be a mammal. If a mammal, the subject will in many embodiments be a human, but may also be a domestic livestock, laboratory subject or pet animal.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

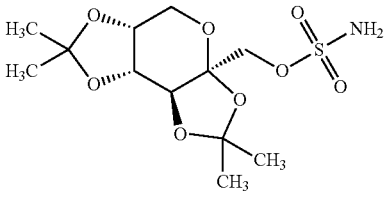
Methods and Formulations of the Invention:

The present invention provides novel methods and compositions to effect weight loss and treat obesity, conditions related to excess weight or obesity, diabetes (whether or not related to obesity), and other conditions and disorders as will be explained infra. According to the U.S. Centers for Disease Control, the clinical definition of being overweight (the term being used synonymously herein with the term "excess weight") is having a body mass index (BMI) between 25.0 and 29.9 kg/m; BMI is calculated by multiplying an individual's weight, in kilograms, by height, in meters. The CDC defines obesity as having a BMI of 30 or higher. In one embodiment, the invention provides a method for effecting weight loss and treating overweight, obesity, and conditions associated with excess weight and obesity, and involves administration of a combination of the sympathomimetic agent phentermine and the anti-convulsant agent topiramate.

Topiramate is an anticonvulsant sulfamate compound that is sold in the United States under the trade name Topamax® (Ortho-McNeil Pharmaceutical, Inc., Raritan, N.J., U.S.A). Topiramate has been approved for use as an antiepileptic agent as an adjuvant therapy for patients with partial onset seizures or primary generalized tonic-clonic seizures, and for the prevention of migraine headache. See Physician's Desk Reference, 56th ed. (2002); see also U.S. Pat. No. 4,513,006 to Maryanoff et al. and U.S. Pat. No. 7,351,695 to Almarssoo et al.

"Topiramate" generally refers to the sulfamate-substituted monosaccharide having the chemical name 2,3,4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate and the molecular formula C12H21NO8S. The structure of the compound is represented by Formula (I)

(I)

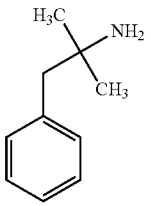


As used herein, the term "topiramate" encompasses 2,3,4,5-bis-(O)-(1-methylethylidene)-β-D-fructopyranose sulfamate as well as individual enantiomers, individual diastereomers, or mixtures thereof. The term "topiramate" as used herein also encompasses topiramate salts as well as polymorphs, solvates (including hydrates and mixed solvates, as well as hydrates of salts), co-crystals (for instance, with other compounds or other forms of topiramate), amorphous, and anhydrous forms of the compound of Formula (I). Topiramate salts useful in conjunction with the present invention, as will be appreciated from the fact that the compound is a sulfamic acid derivative, are pharmaceutically acceptable basic addition salts. Such salts are prepared from bases that provide a pharmaceutically acceptable cation that associates with the sulfamic acid group of the compound of Formula (I). Suitable pharmaceutically acceptable cations include both organic and inorganic cations, including, without limitation, sodium, sodium, potassium, lithium, magnesium, calcium, aluminum, zinc, procaine, benzathine, chloroprocaine, choline, diethylamine, ethylenediamine, N-methylglucamine, benethamine, clemizole, diethylamine, piperazine, tromethamine, triethylamine, ethanolamine, triethanolamine, arginine, lysine, histidine, tributylamine, 2-amino-2-pentylpropanol, 2-amino-2-methyl-1,3-propanediol, tris(hydroxymethyl) aminomethane, benzylamine, 2-(dimethylamino)ethanol, barium or bismuth counter ions. Particularly preferred cations are sodium, lithium, and potassium. Other forms of topiramate referenced above may be prepared using methods known in the art; see, e.g., U.S. Pat. No. 7,351,695.

At dosages previously believed to be required for therapeutic efficacy, administration of topiramate has been associated with significant adverse effects, as noted above, including, without limitation, dizziness, psychomotor slowing, difficulty with memory, fatigue, and somnolence. See U.S. Pat. No. 7,351,695, supra, and Physicians' Desk Reference, supra.

Phentermine is a sympathomimetic agent that has been used as an appetite suppressant, but, like topiramate, has been associated with significant adverse effects at doses previously believed to be required for efficacy; these effects are generally associated with the catecholamine-releasing properties of the drug, including, for instance, tachycardia, elevated blood pressure, anxiety, and insomnia. Phentermine is a shortened version of the compound's chemical name, phenyl-tertiary-butylamine, and is also referred to as 2-methyl-1-phenylpropan-2-amine and 2-methyl-amphetamine. Phentermine has the molecular formula $C_{10}H_{15}N$, the chemical structure of Formula (II)

(II)



and is an achiral primary amine. As such, phentermine may be in the form of either the free base or an acid addition salt prepared with an acid that yields a pharmaceutically acceptable anion. Suitable acid addition salts may be prepared from organic acids, e.g., acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like, as well as inorganic acids, e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, etc. As with topiramate, phentermine may take on various other forms as well.

It has now been surprisingly discovered that a combination of a low daily dose of topiramate and a low daily dose of phentermine is effective in achieving weight loss, treating obesity, treating conditions related to overweight and obesity, and addressing other indications as will be discussed herein. The incidence of adverse effects previously associated with each active agent is significantly reduced because of the lowered daily dosage as well as the offsetting effect each active agent has on the potential adverse effects of the other active agent. Even at the low doses of the present methods, phentermine has anorexient properties (e.g., suppresses appetite) and is anorectic without loss of efficacy or without adverse or undesirable side effects to a subject when administered according to the dosage regimens described herein when the phentermine is administered in combination with topiramate.

The present method for effecting weight loss in a subject involves administering a daily dose of phentermine in the range of 2 mg to 8 mg, e.g., 2 mg to 5 mg, in combination with a daily dose of topiramate selected to prevent the loss of effectiveness of phentermine alone. An example of a suitable daily dose of topiramate that would prevent the loss of effectiveness of phentermine alone is 15 mg to 50 mg, e.g., 15 mg to 25 mg or 17 mg to 23 mg. An exemplary dosage regimen involves administration of daily doses of 3.75 mg phentermine and 23 mg topiramate. Another exemplary dosage regimen involves administration of daily doses of 7.5 mg and 46 mg topiramate.

When the topiramate and/or the phentermine are associated with additional moieties, e.g., are in the form of salts, hydrates, or the like, the dosage herein refers to the compound per se and does not include the associated moieties, e.g., cations, anions, hydrates, etc. Thus, if phentermine hydrochloride is used in the methods and compositions of the invention, 4.92 mg of phentermine hydrochloride (having a molecular weight of 195.69 g/mol) will be necessary to provide the 3.75 mg daily dose of phentermine (having a molecular weight of 149.23 g/mol).

The dosage regimen involves continual, i.e., ongoing, administration, over a significant period of time, e.g., in the range of about 4 weeks to about 67 weeks, depending on the severity of an individual's weight problem, the amount of weight that should be lost, and the rate at which weight is lost. Generally, although not necessarily, the combination of the active agents is administered orally.

The method of administration can involve simultaneous administration of the two active agents, in a single composition or in two discrete compositions each containing one of the active agents. The method of administration may also involve administration of the two active agents at different times of day, with the phentermine generally administered earlier in the day and the topiramate generally administered later in the day. Normally, however, the two agents are administered simultaneously using one or more dosage forms that provide for immediate release of the phentermine and con-

trolled release of the topiramate. In an exemplary embodiment, the phentermine and topiramate are administered in a single dosage form that provides for immediate release of the phentermine and sustained release and/or delayed release of the topiramate.

Examples of compositions that contain a combination of phentermine and topiramate include, without limitation: (1) 2 mg to 5 mg phentermine and 17 mg to 23 mg topiramate; (2) 3.75 mg phentermine and 23 mg topiramate; (3) 3.75 mg phentermine in the form of 4.92 mg phentermine hydrochloride and 23 mg topiramate; (4) 7.5 mg phentermine and 46 mg topiramate; and (5) 7.5 mg phentermine in the form of 9.84 mg phentermine hydrochloride and 46 mg topiramate.

These and other compositions of the invention exhibit a lower maximum concentration (Cmax) of topiramate without decreasing total drug exposure defined by the area under the concentration-time curve (AUC). Further, preferred compositions of the present invention can provide for delayed, sustained release of topiramate such that the maximum plasma concentration (Tmax) is reached 6 to 10, typically 6 to 8, hours after administration. As depicted in FIG. **1**, drug exposure as measured by AUC for a controlled release (CR) formulation capsule prepared as described in Example 1 is the same as that observed with an immediate release topiramate (Topamax®) tablet despite a 20% reduction in the Cmax. Therefore, formulations of the invention are capable of reducing the Cmax of topiramate, enabling a reduction in side effects without compromising the efficacy of the treatment, since the AUC is the same. This reduction in Cmax is preferred as topiramate can be sedating, as noted above, and a delay in the time to reach maximum plasma concentration to the late afternoon or evening time improves the tolerability of the drug. On the other hand, the preferred formulations of the invention provide for immediate release of phentermine, with the medication administered early in the day, such that any stimulant effects that may be experienced do not occur in the evening.

In another embodiment of the invention, a composition is provided that contains 7.5 mg phentermine and 46 mg topiramate.

Depending on the intended mode of administration, the pharmaceutical formulation may be a solid, semi-solid or liquid, such as, for example, a tablet, a capsule, a caplet, a liquid, a suspension, an emulsion, a suppository, granules, pellets, beads, a powder, or the like, preferably in unit dosage form suitable for single administration of a precise dosage. Suitable pharmaceutical compositions and dosage forms may be prepared using conventional methods known to those in the field of pharmaceutical formulation and described in the pertinent texts and literature, e.g., in Remington: The Science and Practice of Pharmacy (Easton, Pa.: Mack Publishing Co., 1995). Oral administration and therefore oral dosage forms are generally preferred, and include tablets, capsules, caplets, solutions, suspensions and syrups, and may also comprise a plurality of granules, beads, powders, or pellets that may or may not be encapsulated. Preferred oral dosage forms are capsules and tablets, particularly controlled release capsules and tablets, as noted above.

As noted above, it is especially advantageous to formulate compositions of the invention in unit dosage form for ease of administration and uniformity of dosage. The term "unit dosage forms" as used herein refers to physically discrete units suited as unitary dosages for the individuals to be treated. That is, the compositions are formulated into discrete dosage units each containing a predetermined, "unit dosage" quantity of an active agent calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specifications of unit dosage forms of the invention are dependent on the unique characteristics of the active agent to be delivered. Dosages can further be determined by reference to the usual dose and manner of administration of the ingredients. It should be noted that, in some cases, two or more individual dosage units in combination provide a therapeutically effective amount of the active agent, e.g., two tablets or capsules taken together may provide a therapeutically effective dosage of topiramate, such that the unit dosage in each tablet or capsule is approximately 50% of the therapeutically effective amount.

Tablets may be manufactured using standard tablet processing procedures and equipment. Direct compression and granulation techniques are preferred. In addition to the active agent, tablets will generally contain inactive, pharmaceutically acceptable carrier materials such as binders, lubricants, disintegrants, fillers, stabilizers, surfactants, coloring agents, and the like.

Capsules are also preferred oral dosage forms, in which case the active agent-containing composition may be encapsulated in the form of a liquid or solid (including particulates such as granules, beads, powders or pellets). Suitable capsules may be either hard or soft, and are generally made of gelatin, starch, or a cellulosic material, with gelatin capsules preferred. Two-piece hard gelatin capsules are preferably sealed, such as with gelatin bands or the like. See, for example, Remington: The Science and Practice of Pharmacy, cited earlier herein, which describes materials and methods for preparing encapsulated pharmaceuticals.

Oral dosage forms, whether tablets, capsules, caplets, or particulates, can, if desired, be formulated so as to provide for controlled release of topiramate, and in a preferred embodiment, the present formulations are controlled release oral dosage forms. Generally, the dosage forms provide for sustained release, i.e., gradual, release of topiramate, from the dosage form to the patient's body over an extended time period, typically providing for a substantially constant blood level of the agent over a time period in the range of about 4 to about 12 hours, typically in the range of about 6 to about 10 hours or 6 to about 8 hours. Release of the topiramate may also be delayed; that is, there is a time lag between administration and the start of topiramate release. In this way, for instance, an individual will not experience sleepiness or other side effects of topiramate during the school or work day. Preferred dosage forms thus involve sustained release of the topiramate, delayed release of the topiramate, or both sustained and delayed release of the topiramate.

Generally, as will be appreciated by those of ordinary skill in the art, sustained release dosage forms can be formulated by dispersing the active agent within a matrix of a gradually hydrolyzable material such as a hydrophilic polymer, or by coating a solid, drug-containing dosage form with such a material. Hydrophilic polymers useful for providing a sustained release coating or matrix include, by way of example: cellulosic polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, ethyl cellulose, cellulose acetate, and carboxymethylcellulose sodium; acrylic acid polymers and copolymers, preferably formed from acrylic acid, methacrylic acid, acrylic acid alkyl esters, methacrylic acid alkyl esters, and the like, e.g. copolymers of acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate; and vinyl polymers and copolymers such as polyvinyl pyrrolidone e.g., Povidone K30, polyvinyl acetate, and ethylene-vinyl acetate copolymer. Preferred sustained release polymers herein include those available as "Methocel" polymers from Dow Chemical,

particularly the methylcellulose ether polymers in the Methocel™ A group, having a viscosity grade of about 4,000 cps and a methoxyl content of about 27.5% to 31.5%, e.g., Methocel™ A15LV, Methocel™ A15C, and Methocel™ A4M.

When sustained release preparations are prepared, tablets, granules, powder, capsules, and the like can be produced according to a conventional method after adding excipient, and as necessary, binder, disintegrating agent, lubricant, coloring agent, taste-modifying agent, flavoring agent, and the like. These additives may be ones generally used in the field, and for example, lactose, sodium chloride, glucose, starch, microcrystalline cellulose, and silicic acid as the excipient, water, ethanol, propanol, simple syrup, gelatin solution, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, shellac, calcium phosphate, and polyvinylpyrrolidone as the binder, agar powder, sodium hydrogen carbonate, sodium lauryl sulfate, and stearic acid monoglyceride as the disintegrating agent, purified talc, stearic acid salt, borax, and polyethylene glycol as the lubricant, β-carotene, yellow iron sesquioxide, and caramel as the coloring agent, and saccharose and orange peel as the taste-modifying agent can be listed as examples. It should be noted that various grades of microcrystalline cellulose are preferred fillers herein, e.g., Avicel® PH101, Avicel® PH102, and Avicel® PH200 (FMC), with particle sizes of about 50 microns, 100 microns, and 190 microns, respectively. Microcrystalline cellulose having a particle size in the range of about 50 microns to 200 microns is preferred herein.

The dosage forms may also be provided with a delayed release coating, e.g., composed of an acrylate and/or methacrylate copolymers. Examples of such polymers are those available under the trade name "Eudragit" from Rohm Pharma (Germany). The Eudragit series E, L, S, RL, RS, and NE copolymers are available as solubilized in organic solvent, in an aqueous dispersion, or as a dry powder. Preferred acrylate polymers are copolymers of methacrylic acid and methyl methacrylate, such as the Eudragit L and Eudragit S series polymers. Other preferred Eudragit polymers are cationic, such as the Eudragit E, RS, and RL series polymers. Eudragit E100 and E PO are cationic copolymers of dimethylaminoethyl methacrylate and neutral methacrylates (e.g., methyl methacrylate), while Eudragit RS and Eudragit RL polymers are analogous polymers, composed of neutral methacrylic acid esters and a small proportion of trimethylammonioethyl methacrylate.

In a specific embodiment, controlled release topiramate beads for oral administration, e.g., by incorporation in an orally administrable capsule or compaction into an orally administrable tablet, are made using an extrusion spheronization process to produce a matrix core comprised of: topiramate, 40.0% w/w; microcrystalline cellulose, e.g., Avicel® PH102, 56.5% w/w; and methylcellulose, e.g., Methocel™ A15 LV, 3.5% w/w. The topiramate cores are then coated with ethyl cellulose, 5.47% w/w and Povidone K30: 2.39% w/w. The phentermine beads are composed of an immediate release drug coating onto sugar spheres or analogous non-active cores. Both sets of beads may then be encapsulated into one capsule.

Preparations according to this invention for parenteral administration include sterile aqueous and nonaqueous solutions, suspensions, and emulsions. Injectable aqueous solutions contain the active agent in water-soluble form. Examples of nonaqueous solvents or vehicles include fatty oils, such as olive oil and corn oil, synthetic fatty acid esters, such as ethyl oleate or triglycerides, low molecular weight alcohols such as propylene glycol, synthetic hydrophilic polymers such as polyethylene glycol, liposomes, and the like. Parenteral formulations may also contain adjuvants such as solubilizers, preservatives, wetting agents, emulsifiers, dispersants, and stabilizers, and aqueous suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, and dextran. Injectable formulations are rendered sterile by incorporation of a sterilizing agent, filtration through a bacteria-retaining filter, irradiation, or heat. They can also be manufactured using a sterile injectable medium. The active agent may also be in dried, e.g., lyophilized, form that may be rehydrated with a suitable vehicle immediately prior to administration via injection.

The active agents may also be administered through the skin using conventional transdermal drug delivery systems, wherein the active agent is contained within a laminated structure that serves as a drug delivery device to be affixed to the skin. In such a structure, the drug composition is contained in a layer, or "reservoir," underlying an upper backing layer. The laminated structure may contain a single reservoir, or it may contain multiple reservoirs. In one embodiment, the reservoir comprises a polymeric matrix of a pharmaceutically acceptable contact adhesive material that serves to affix the system to the skin during drug delivery. Alternatively, the drug-containing reservoir and skin contact adhesive are present as separate and distinct layers, with the adhesive underlying the reservoir which, in this case, may be either a polymeric matrix as described above, or it may be a liquid or hydrogel reservoir, or may take some other form. Transdermal drug delivery systems may in addition contain a skin permeation enhancer.

In addition to the formulations described previously, the active agent may be formulated as a depot preparation for controlled release of the active agent, preferably sustained release over an extended time period. These sustained release dosage forms are generally administered by implantation (e.g., subcutaneously or intramuscularly or by intramuscular injection).

Although the present compositions will generally be administered orally, parenterally, transdermally, or via an implanted depot, other modes of administration are suitable as well. For example, administration may be transmucosal, e.g., rectal or vaginal, preferably using a suppository that contains, in addition to the active agent, excipients such as a suppository wax. Formulations for nasal or sublingual administration are also prepared with standard excipients well known in the art. The pharmaceutical compositions of the invention may also be formulated for inhalation, e.g., as a solution in saline, as a dry powder, or as an aerosol.

Indications:

Conditions of particular interest for which the invention finds utility include overweight, obesity and conditions often associated with and/or caused by excess weight and obesity. The combination of topiramate and phentermine in the dosages provided herein give rise to significant therapeutic effects and reduced adverse effects, making these pharmaceutical combinations extremely effective therapeutics, especially in the treatment of overweight, obesity and/or related conditions, including conditions associated with and/or caused by excess weight or obesity per se. Subjects suitable for treatment with the subject combination therapy treatment regimen thus include individuals suffering from conditions associated with obesity, such conditions including, without limitation:

diabetes, insulin resistance, and impaired glucose tolerance;

respiratory problems such as pulmonary hypertension, asthma, and shortness of breath;

gallbladder disease;

dyslipidemia, e.g., high cholesterol, high levels of triglycerides, etc.;

osteoarthritis and other orthopedic problems;

reflux esophagitis;

adverse conditions related to sleep, including sleep apnea and loud snoring;

menstrual irregularities, infertility, and complications in pregnancy;

gout;

high blood pressure, i.e., hypertension;

cardiovascular problems such as coronary artery disease and other heart trouble;

muscular dystrophy;

stroke, particularly thrombotic stroke and deep vein thrombosis (DVT);

migraines;

metabolic disorders such as hypoalphalipoproteinemia, familial combined hyperlipidemia, and Syndrome X, including insulin-resistant Syndrome X; and

colon, rectal, renal, esophageal, gallbladder, pancreatic, prostate, breast, uterine, ovarian, endometrial, and cervical cancers.

Higher body weights are also associated with increases in all-cause mortality. Most or all of these problems are relieved or improved by permanent significant weight loss. Longevity is likewise significantly increased by permanent significant weight loss.

Diabetes mellitus is very commonly seen in obese individuals, and is associated with continuous and pathologically elevated blood glucose concentration. It is one of the leading causes of death in the United States and is responsible for about 5% of all mortality. Diabetes is divided into two major sub-classes: Type I, also known as juvenile diabetes, or Insulin-Dependent Diabetes Mellitus (IDDM); and Type II, also known as adult onset diabetes, or Non-Insulin-Dependent Diabetes Mellitus (NIDDM).

According to the American Diabetes Association, there are over one million juvenile diabetics in the United States. Type I Diabetes is a form of autoimmune disease. Autoantibodies produced by the patients completely or partially destroy the insulin producing cells of the pancreas. Juvenile diabetics must, therefore, receive exogenous insulin during their lifetime. Without treatment, excessive acidosis, dehydration, kidney damage, and death may result. Even with treatment, complications such as blindness, atherosclerosis, and impotence can occur.

There are more than five million Type II (adult onset) diabetics diagnosed in the United States. Type II disease usually begins during middle age; the principal cause is now known to be overweight and obesity. In Type II diabetics, rising blood glucose levels after meals do not properly stimulate insulin production by the pancreas. Additionally, peripheral tissues are generally resistant to the effects of insulin. The resulting high blood glucose levels (hyperglycemia) can cause extensive tissue damage. Type II diabetics are often referred to as insulin resistant. They often have higher than normal plasma insulin levels (hyperinsulinemia) as the body attempts to overcome its insulin resistance. Some researchers now believe that hyperinsulinemia may be a causative factor in the development of high blood pressure, high levels of circulating low density lipoproteins (LDLs), and lower than normal levels of the beneficial high density lipoproteins (HDLs). While moderate insulin resistance can be compensated for in the early stages of Type II diabetes by increased insulin secretion, in more advanced disease states insulin secretion is also impaired.

Insulin resistance and hyperinsulinemia have also been linked with two other metabolic disorders that pose considerable health risks: impaired glucose tolerance and metabolic obesity. Impaired glucose tolerance is characterized by normal glucose levels before eating, with a tendency toward elevated levels (hyperglycemia) following a meal. According to the World Health Organization, approximately 11% of the U.S. population between the ages of 20 and 74 are estimated to have impaired glucose tolerance. These individuals are considered to be at higher risk for diabetes and coronary artery disease.

Obesity may also be associated with insulin resistance. A causal linkage among obesity, impaired glucose tolerance, and Type II diabetes has been proposed, but a physiological basis has not yet been established. Some researchers believe that impaired glucose tolerance and diabetes are clinically observed and diagnosed only later in the disease process after a person has developed insulin resistance and hyperinsulinemia.

Insulin resistance is frequently associated with hypertension, coronary artery disease (arteriosclerosis), and lactic acidosis, as well as related disease states. The fundamental relationship between these disease states, and a method of treatment, has not been established.

Hypertension is another condition that is frequently seen in obese individuals, and occurs when the blood pressure inside the large arteries is chronically elevated. Hypertension affects about 50 million people in the United States alone. It is more common as people grow older and is both more common and more serious in African Americans. Most cases of hypertension are of unknown etiology. It is known that the tendency to develop hypertension can be inherited. Environment also plays a very important role in hypertension. For example, hypertension may be avoided by keeping body weight under control, keeping physically fit, eating a healthy diet, limiting alcohol intake, and avoiding medications that might increase blood pressure. Other less common causes of hypertension include disorders of the kidneys or endocrine glands. Hypertension has been called “the silent killer” because it has no specific symptoms and yet can lead to death. People with untreated hypertension are much more likely to die from or be disabled by cardiovascular complications such as strokes, heart attacks, heart failure, heart rhythm irregularities, and kidney failure, than people who have normal blood pressure.

Current treatments for hypertension include lifestyle changes (diet, exercise, nonsmoking, etc.) as well as drug therapy. The major classes of medications currently used to treat hypertension include adrenergic neuron antagonists (which are peripherally acting), alpha adrenergic agonists (which are centrally acting), alpha adrenergic blockers, alpha and beta blockers, angiotensin II receptor blockers, angiotensin converting enzyme (ACE) inhibitors, beta adrenergic blockers, calcium channel blockers, thiazides (benzothiadiazine derivatives) and related diuretics, and vasodilators (which act by direct relaxation of vascular smooth muscles).

A particularly serious hypertensive disorder is primary pulmonary hypertension, also known as idiopathic pulmonary hypertension. This is a condition in which the blood pressure in the pulmonary arteries is abnormally high in the absence of other diseases of the heart or lungs. The cause of primary pulmonary hypertension is unknown. Pulmonary hypertension develops in response to increased resistance to blood flow. Narrowing of the pulmonary arterioles occurs and the right side of the heart becomes enlarged due to the increased work of pumping blood against the resistance. Eventually, progressive heart failure develops. Currently, there is no known cure for primary pulmonary hypertension.

Treatment is primarily directed towards controlling the symptoms, although some success has occurred with the use of vasodilators. Other medications used to treat the symptoms of primary pulmonary hypertension include diuretics and calcium channel blockers. Typically, as the disease progresses, oxygen is often required. In certain cases, a heart-lung transplant may be indicated for certain suitable candidates, although the availability of donor organs continues to be extremely limited. Unfortunately, primary pulmonary hypertension is a progressive disease, usually leading to congestive heart failure and respiratory failure.

Secondary pulmonary hypertension is a serious disorder that arises as a complication of other conditions such as, for example, scleroderma. Treatments are similar as those for primary pulmonary hypertension and, unfortunately, the prognosis is the same as well.

Other respiratory disorders that are frequently seen in obese individuals include asthma and shortness of breath, both of which conditions are often alleviated by weight loss.

With respect to adverse conditions and disorders associated with sleep, sleep apnea is perhaps the most concerning. Sleep apnea is classified as either obstructive sleep apnea, the more common form that occurs when throat muscles relax, or central sleep apnea, which occurs when the brain doesn't send proper signals to the muscles that control breathing. Additionally, some people have mixed sleep apnea, which is a combination of both obstructive and central sleep apneas. Sleep apnea literally means "cessation of breath." It is characterized by repetitive episodes of upper airway obstruction that occur during sleep, usually associated with a reduction in blood oxygen saturation. In other words, the airway becomes obstructed at several possible sites. The upper airway can be obstructed by excess tissue in the airway, large tonsils, and a large tongue and usually includes the airway muscles relaxing and collapsing when asleep. Another site of obstruction can be the nasal passages. Sometimes the structure of the jaw and airway can be a factor in sleep apnea.

The signs and symptoms of obstructive and central sleep apneas overlap, sometimes making the type of sleep apnea more difficult to determine. The most common signs and symptoms of obstructive and central sleep apneas include: excessive daytime sleepiness (hypersomnia); loud snoring; observed episodes of breathing cessation during sleep; abrupt awakenings accompanied by shortness of breath; awakening with a dry mouth or sore throat; morning headache; and/or difficulty staying asleep (insomnia). Disruptive snoring may be a more prominent characteristic of obstructive sleep apnea, while awakening with shortness of breath may be more common with central sleep apnea.

Sleep apnea is a progressive condition and can be very serious; it is a potentially life-threatening condition that requires immediate medical attention. The risks of undiagnosed obstructive sleep apnea include heart attacks, strokes, high blood pressure, heart disease, irregular heartbeat, and impotence. In addition, obstructive sleep apnea causes daytime sleepiness that can result in accidents, lost productivity and interpersonal relationship problems. The severity of the symptoms may be mild, moderate or severe.

Sleep apnea is diagnosed utilizing a sleep test, called polysomnography but treatment methodologies differ depending on the severity of the disorder. Mild Sleep Apnea is usually treated by some behavioral changes; losing weight and sleeping on one's side are often recommended. There are oral mouth devices (that help keep the airway open) that may help to reduce snoring in three different ways. Some devices (1) bring the jaw forward or (2) elevate the soft palate or (3) retain the tongue (from falling back in the airway and blocking breathing).

Moderate to severe sleep apnea is usually treated with a continuous positive airway pressure (C-PAP). C-PAP is a machine that blows air into your nose via a nose mask, keeping the airway open and unobstructed. For more severe apnea, there is a Bi-level (Bi-PAP) machine. The Bi-level machine is different in that it blows air at two different pressures. When a person inhales, the pressure is higher and in exhaling, the pressure is lower.

Some people have facial deformities that may cause the sleep apnea. It simply may be that their jaw is smaller than it should be or they could have a smaller opening at the back of the throat. Some people have enlarged tonsils, a large tongue or some other tissues partially blocking the airway. Fixing a deviated septum may help to open the nasal passages. Removing the tonsils and adenoids or polyps may help also. Children are much more likely to have their tonsils and adenoids removed. Surgical procedures, such as tracheostomy, uvulopalatopharyngoplasty (UPPP), laser assisted uvuloplasty (LAUP), somnoplasty, and mandibular myotomy are often required to effectively treat sleep apnea. Weight loss, however, particularly in an obese person, can significantly alleviate sleep apnea and other sleep-related adverse conditions such as loud snoring and the like.

Relatively recently, a connection between obesity and the occurrence or increased incidence of migraine headaches has been noted. Migraine headaches begin with mild pain, which increases in intensity over a short period of time. There are two major types of migraines. The common migraine affects 80-85% of migraine sufferers and classical migraine with aura affects 15% of migraine sufferers. Symptoms associated with migraines include headaches, psychological symptomology such as irritability, depression, fatigue, drowsiness, restlessness; neurological symptoms such as photophobia, phonophobia or gastrointestinal symptoms such as change in bowel habit, change of food intake or urinary symptoms such as urinary frequency, auras which are neurological deficits and can be a variety of deficits for the migraine population but in the individual is usually stereotyped. These deficits may be visual scotoma or visual designs, hemiplegia, migrating paraesthesia, dysarthria, dysphasia, or déjà vu. The headache is usually accompanied by light or sound sensitivity, photophobia or phonophobia, irritability and impaired concentration. For those individuals whose migraine headaches are caused by or exacerbated by obesity, treatment according to the methodology of the present invention can be effective.

Other indications for which the present invention is readily adapted include epilepsy and certain psychiatric indications such as impulse control disorders.

Topiramate has long been known as an anti-epileptic agent. At dosages previously required or believed to be required for efficacy, however, topiramate therapy resulted in significant side effects, as noted elsewhere herein. The present invention, according to which topiramate dosage may be reduced by concomitant administration of phentermine, significantly reduces those side effects of topiramate, most if not all of which are dose-related.

Among psychiatric indications, depression is particularly common. "Depression," as is well known, is manifested by a combination of symptoms that interfere with the ability to work, study, sleep, eat, and enjoy once pleasurable activities. Depression includes major depression, especially refractory depression, bipolar depression, and the degeneration associated with depression. Symptoms of depression include persistent sad, anxious, or "empty" mood, feelings of hopeless-

ness, pessimism, feelings of guilt, worthlessness, helplessness, loss of interest or pleasure in hobbies and activities that were once enjoyed, including sex, decreased energy, fatigue, being "slowed down", difficulty concentrating, remembering, making decisions, insomnia, early-morning awakening, or oversleeping, appetite and/or weight loss or overeating and weight gain, thoughts of death or suicide; suicide attempts, restlessness, irritability, persistent physical symptoms that do not respond to treatment, such as headaches, digestive disorders, and chronic pain.

Other psychiatric disorders may also be treated using the compositions and methods of the invention. These disorders include impulse control disorders, panic syndrome, general anxiety disorder, phobic syndromes of all types, mania, manic depressive illness, hypomania, unipolar depression, stress disorders, PTSD, somatoform disorders, personality disorders, psychosis, and schizophrenia.

"Impulse Control Disorders" are characterized by harmful behaviors performed in response to irresistible impulses. The essential feature of an impulse control disorder is the failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person or to others. Symptoms include an increasing sense of tension or arousal before committing an act, and then experiences pleasure, gratification, or release at the time of committing the act. After the act is performed, there may or may not be regret or guilt. Numerous disorders can be characterized as impulse control disorders including intermittent explosive disorder, kleptomania, pathological gambling, pyromania, trichotillomania, compulsive buying or shopping, repetitive self-mutilation, nonparaphilic sexual addictions, severe nail biting, compulsive skin picking, personality disorders with impulsive features, attention deficit/hyperactivity disorder, eating disorders characterized by binge eating, and substance abuse disorders such as alcoholism and drug addiction. Binge eating disorder and bulimia are also sometimes classified as impulse control disorders.

Packaged Pharmaceutical Preparations:

Also provided are packaged pharmaceutical preparations for practicing the subject methods. The packaged preparation contains a composition of the invention in a sealed container, and typically contains a plurality of individual dosage forms each in a sealed housing, as in a blister pack, but could also contain one or more dosage forms in a single sealed container. The dosage forms might be, for instance, dosage forms containing 3.75 mg phentermine in immediate release form and 23 mg topiramate in controlled release form, or, in an alternative example, 7.5 mg phentermine in immediate release form and 46 mg topiramate in controlled release form. Optionally, dosage forms with lower doses of one or both active agents can also be included, for dose titration and dose escalation.

In certain embodiments, the packaged pharmaceutical preparations include instructions for a patient to carry out drug administration to achieve weight loss, treat obesity, treat conditions associated with obesity, or treat other conditions as explained earlier herein. For instance, the instructions may include the daily dose of topiramate to be taken, the daily dose of phentermine to be taken, and/or the dosing regimen for self-administration of a controlled release dosage form containing both active agents. The instructions may be recorded on a suitable recording medium or printed on a substrate such as paper or plastic. As such, the instructions may be present as a package insert, in the labeling of the package, container(s), or components thereof (i.e., associated with the packaging or sub-packaging), etc. In other embodiments, the instructions are present as an electronic storage data file present on a suitable computer readable storage medium, e.g. CD-ROM, diskette, etc. In yet other embodiments, the actual instructions are not present, but means for obtaining the instructions from a remote source, e.g. via the internet, are provided. As an example, a web address might be included to direct patients to a website where the instructions can be viewed and/or from which the instructions can be downloaded. As with the instructions per se, this means for obtaining the instructions is recorded on a suitable substrate.

Some or all of the included components may be packaged in suitable packaging to maintain sterility. In many embodiments, the components are packaged in a containment element to provide a single, easily handled unit, where the containment element, e.g., box or analogous structure, may or may not be an airtight container, e.g., to further preserve the sterility of some or all of the components. In certain aspects, a sealed package of controlled release dosage forms is provided wherein the dosage forms contain phentermine in immediate release form and topiramate in controlled release, e.g., sustained release and delayed release form. Alternatively, separate phentermine-containing and topiramate-containing dosage forms may be included.

This invention is further illustrated by the following examples which should not be construed as limiting. Although any methods and materials similar or equivalent to those described herein may be useful in the practice or testing of the present invention, preferred methods and materials are described below.

The contents of all references, patents and published patent applications cited throughout this application are hereby incorporated by reference.

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (e.g. amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Celsius, and pressure is at or near atmospheric.

Example 1

Controlled release topiramate beads are made using an extrusion spheronization process to produce a matrix core comprised of topiramate, 40.0% w/w; microcrystalline cellulose (Avicel® PH102), 56.5% w/w; and Methocel™ A15 LV, 3.5% w/w. The topiramate cores were then coated with ethyl cellulose, 5.47% w/w, and Povidone K30, 2.39% w/w.

The composition of the topiramate beads so prepared is as follows:

Component	% w/w
topiramate	36.85
microcrystalline cellulose, (Avicel ® PH102)	52.05
Methylcellulose (Methocel ™ A15 LV)	3.22
ethylcellulose	5.47
Polyvinylpyrrolidone (Povidone K30)	2.39

Phentermine hydrochloride is coated onto sugar spheres to provide immediate release phentermine beads. Both sets of beads are then encapsulated into each of a plurality of capsules, with each capsule containing 3.75 mg phentermine (as 4.92 mg phentermine HCl) and 23 mg topiramate.

Example 2

Controlled release topiramate beads and immediate release phentermine beads are prepared as in Example 1. Both sets of beads are then encapsulated into each of a plurality of capsules, with each capsule containing 7.5 mg phentermine and 46 mg topiramate.

Example 3

In a study comparing controlled-release formulation of topiramate according to the present invention versus immediate release topiramate (Topamax®) in combination with phentermine, the controlled release formulation of the instant invention of topiramate had a 10-15% lower effect on phentermine exposure (FIG. **2**).

The mean and statistical comparisons for plasma phentermine PK parameters at steady state in multiple dose administrations are summarized in Table 1.

TABLE 1

Arithmetic Mean (SD) and Statistical Comparison of Pharmacokinetic Parameters for Plasma Phentermine

		Treatment 2 Versus Treatment 4		
Pharmacokinetic Parameters	Mean +/− SD Treatment 2 (N = 13)	Treatment 4 (N = 12)	90% Confidence Intervals	% Mean Ratio
$AUC_{0\text{-}tau}$ (ng * hr/mL)	2250 +/− 563	2530 +/− 644	(75.6, 105.3)	89.2
$AUC_{0\text{-}96}$ (ng * hr/mL)	4640 +/− 1570	5550 +/− 1960	(67.1, 105.0)	84.0
$AUC_{0\text{-}t}$ (ng * hr/mL)	4640 +/− 1570	5550 +/− 1960	(67.1, 105.0)	84.0
$C_{max,ss}$ (ng * hr/mL)	114 +/− 23.6	127 +/− 27.6	(78.8, 104.5)	90.7
$C_{min,ss}$ (ng * hr/mL)	9.84 +/− 7.24	14.6 +/− 11.3	(42.5, 109.0)	68.1
t_{max} (hr)	4.01 (1.04, 7.00)	4.54 (1.00, 10.0)		
$T_{1/2}$ (hr)	23.3 +/− 6.17	26.3 +/− 7.43		
CL_{ss}/F (L/hr)	7.10 +/− 1.89	6.38 +/− 2.00		
V_2/F (L/hr)	229 +/− 45.3	232 +/− 58.5		

t_{max} is presented as median (minimum, maximum)
Parameters were dose-normalized and ln-transformed prior to analysis.
% Mean Ratio = 100* ex[(Treatment 2 – Treatment 4) for ln-transformed parameters
Treatment 1 (Test): 7.5 mg phentermine/50 mg topiramate (Formulation A)
Treatment 2 (Test): 15 mg phentermine/100 mg topiramate (Formulation A)
Treatment 4 (Reference): 15 mg phentermine/100 mg topiramate
Source: Tables 14.2.1.8, 14.2.1.10, 14.2.1.12, and 14.2.1.17

These data indicate a lower maximum and extent of phentermine exposure between tests versus reference treatments after multiple-dose administration. As such, the controlled release formulation of topiramate reduced drug interaction with phentermine which in turn will reduce further side effects associated with phentermine.

Example 4

A patient with obesity and elevated lipids exhibiting a heart murmur, shortness of breath out of proportion to weight and age, low blood pressure, leg edema, and a BMI of 46 undergoes an echocardiogram, which shows mitral regurgitation of 1-2+ and mild elevation in pulmonary artery pressure of 36 mm

The composition prepared in Example 1 is administered to the patient on a daily basis, and the patient additionally proceeds with a low fat, low carbohydrate diet and daily exercise. Two weeks after the start of her weight loss program she reports that her exercise tolerance is markedly improved and previous chest pressure and shortness of breath on exertion are gone. The patient loses weight continuously on the program and after four months can be expected to lose at least 20 pounds. Ongoing continuation of the program can be expected to result in further weight loss and additional improvement in obesity-related conditions.

Example 5

The procedure of Example 4 is repeated with a second patient having a BMI over 40 and suffering from similar conditions related to obesity.

The composition prepared in Example 2 is administered to the patient on a daily basis, and the patient additionally proceeds with a low fat, low carbohydrate diet and daily exercise. Two weeks after the start of his weight loss program he reports that her exercise tolerance is markedly improved. The patient loses weight continuously on the program and after four months can be expected to lose at least 25 pounds. Ongoing continuation of the program can be expected to result in further weight loss and additional improvement in obesity-related conditions.

The invention claimed is:

1. A unit dosage form for weight loss for oral administration to a patient having a body mass index of at least 25 kg/m^2, comprising a combination of:

an immediate release phentermine formulation containing a unit dosage of phentermine in the range of 2 mg to 8 mg; and

a controlled release topiramate formulation containing a unit dosage of topiramate in the range of 15 mg to 50 mg,

wherein the dosage of phentermine in mg/day is about 16% of the dosage of topiramate in mg/day, and

wherein the controlled release topiramate formulation reaches a maximum plasma concentration (Cmax) at about 6 to about 10 hours (Tmax) after administration and exhibits a lower Cmax, than non-controlled release topiramate, without decreasing total drug exposure defined by the area under the concentration-time curve (AUC).

2. The dosage form of claim **1**, wherein the subject is overweight having a body mass index between 25 kg/m^2 and 29.9 kg/m^2.

3. The dosage form of claim **2**, wherein the subject has a condition associated with obesity.

4. The dosage form of claim **1**, wherein the subject is obese having a body mass index of at least 30 kg/m^2.

5. The dosage form of claim **4**, wherein the subject has a condition associated with obesity.

6. The dosage form of claim **3**, wherein the condition associated with obesity is selected group consisting of diabetes, elevated fasting blood glucose, insulin resistance, impaired glucose tolerance, pulmonary hypertension, asthma, shortness of breath, gallbladder disease, dyslipidemia, high cholesterol, high levels of triglycerides, osteoarthritis, reflux esophagitis, sleep apnea, menstrual irregularities, infertility, complications in pregnancy, gout, high blood pressure, hypertension, coronary artery disease, heart disease, muscular dystrophy, stroke, thrombotic stroke, deep

vein thrombosis (DVT), migraines, metabolic disorders, hypoalphalipoproteinemia, familial combined hyperlipidemia, Syndrome X, insulin-resistant Syndrome X, colon cancer, rectal cancer, renal cancer, esophageal cancer, gallbladder cancer, pancreatic cancer, prostate cancer, breast cancer, uterine cancer, ovarian cancer, endometrial cancer, and cervical cancer.

7. The dosage form of claim **5**, wherein the condition associated with obesity is selected group consisting of diabetes, elevated fasting blood glucose, insulin resistance, impaired glucose tolerance, pulmonary hypertension, asthma, shortness of breath, gallbladder disease, dyslipidemia, high cholesterol, high levels of triglycerides, osteoarthritis, reflux esophagitis, sleep apnea, menstrual irregularities, infertility, complications in pregnancy, gout, high blood pressure, hypertension, coronary artery disease, heart disease, muscular dystrophy, stroke, thrombotic stroke, deep vein thrombosis (DVT), migraines, metabolic disorders, hypoalphalipoproteinemia, familial combined hyperlipidemia, Syndrome X, insulin-resistant Syndrome X, colon cancer, rectal cancer, renal cancer, esophageal cancer, gallbladder cancer, pancreatic cancer, prostate cancer, breast cancer, uterine cancer, ovarian cancer, endometrial cancer, and cervical cancer.

8. The dosage form of claim **6**, wherein the condition associated with obesity is selected from the group consisting of high blood pressure, high levels of triglycerides, elevated fasting blood glucose and diabetes.

9. The dosage form of claim **7**, wherein the condition associated with obesity is selected from the group consisting of high blood pressure, high levels of triglycerides, elevated fasting blood glucose and diabetes.

10. The dosage form of claim **3**, wherein the subject is suffering from at least two conditions associated with obesity selected from the group consisting of high blood pressure, high levels of triglycerides, elevated fasting blood glucose and diabetes.

11. The dosage form of claim **5**, wherein the subject is suffering from at least two conditions associated with obesity selected from the group consisting of high blood pressure, high levels of triglycerides, elevated fasting blood glucose and diabetes.

12. The dosage form of claim **1**, wherein the unit dosage of phentermine is in the range of 2 mg to 5 mg.

13. The dosage form of claim **1**, wherein the unit dosage of topiramate is in the range of 15 mg to 25 mg.

14. The dosage form of claim **13**, wherein the unit dosage of topiramate is in the range of 17 mg to 23 mg.

15. The dosage form of claim **12**, wherein the unit dosage of topiramate is in the range of 15 mg to 25 mg.

16. The dosage form of claim **15**, wherein the unit dosage of topiramate is in the range of 17 mg to 23 mg.

17. The dosage form of claim **1**, wherein the unit dosage of phentermine is 3.75 mg and the unit dosage of topiramate is 23 mg.

18. The dosage form of claim **17**, wherein the 3.75 mg phentermine is provided in the unit dosage form as about 4.92 mg phentermine hydrochloride, and wherein 4.92 mg of phentermine hydrochloride provides 3.75 mg of phentermine.

19. The dosage form of claim **1**, wherein the unit dosage of phentermine is 7.5 mg and the unit dosage of topiramate is 46 mg.

20. The dosage form of claim **19**, wherein the 7.5 mg phentermine is provided in the unit dosage form as about 9.84 mg phentermine hydrochloride, and wherein 9.84 mg of phentermine hydrochloride provides 7.5 mg of phentermine.

21. The dosage form of claim **1**, wherein following oral administration to a patient, the dosage form provides for a substantially constant blood level of topiramate over a time period in the range of about 4 to about 12 hours.

22. The dosage form of claim **21**, wherein the time period is in the range of about 6 to about 10 hours.

23. The dosage form of claim **1**, wherein the controlled release topiramate formulation reaches a maximum plasma concentration at about 8 hours to about 10 hours (Tmax) after administration.

24. The dosage form of claim **1**, wherein the immediate release phentermine formulation comprises beads of inactive cores coated with the immediate release phentermine formulation.

25. The dosage form of claim **24**, comprising a capsule housing the immediate release phentermine beads and the controlled release topiramate beads.

26. The dosage form of claim **1**, wherein the controlled release topiramate formulation comprises controlled release beads of the topiramate, a binder, and a polymeric filler in a matrix core, wherein the matrix core is provided with a delayed release coating comprising ethyl cellulose and polyvinyl pyrrolidone.

27. The dosage form of claim **26**, wherein the polymeric filler comprises microcrystalline cellulose.

28. The dosage form of claim **26**, wherein the binder comprises methylcellulose.

29. The dosage form of claim **26**, wherein the ethyl cellulose and the polyvinyl pyrrolidone in the delayed release coating are in a weight ratio of approximately 2.3:1.

30. The dosage form of claim **1**, comprising a tablet with at least two discrete segments, at least one of which contains the immediate release phentermine formulation and at least another of which contains the controlled release topiramate formulation.

31. A packaged pharmaceutical preparation comprising a plurality of the unit dosage forms of claim **1** in a sealed container and instructions for administering the dosage forms orally to effect weight loss.

32. A packaged pharmaceutical preparation, comprising a plurality of the unit dosage forms of claim **1** each in a discrete sealed housing, and instructions for administering the dosage forms orally to effect weight loss.

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