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

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

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

Plaintiffs,

v.

ANCHEN PHARMACEUTICALS, INC. and ANCHEN, INC.,

Defendants.

Civil Action No. CV09-4931 CBM(MLGX)

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Eurand, Inc., Cephalon, Inc. and Anesta AG (collectively, "Plaintiffs") bring this Complaint against Defendants Anchen Pharmaceuticals, Inc. and Anchen, Inc. (collectively "Anchen" or "Anchen Defendants"), and in support state and allege as follows:

NATURE OF THE ACTION

1. This is an action for patent infringement under the Food and Drug and Patent Laws of the United States, Titles 21 and 35, respectively, arising from Anchen filing an Abbreviated New Drug Application with the United States Food and Drug Administration ("FDA"), seeking approval to commercially market generic versions of the drug product AMRIX® (Cyclobenzaprine HCl extended release capsules) prior to the expiration of United States Patent No. 7,387,793 ("the '793 Patent"), which covers the AMRIX® product.

THE PARTIES

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

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

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

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

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

7. On information and belief, Defendants Anchen Pharmaceuticals, Inc. and Anchen, Inc. closely coordinate their commercial activities and hold themselves out to the marketplace as one company. For example, during prosecution of Anchen

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

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

JURISDICTION AND VENUE

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

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

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

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

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

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

BACKGROUND

Genesis of the Delaware and California Actions

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

16. Cephalon markets and distributes AMRIX® nationwide, including in California. The filing of ANDA 91-281 evidences an intent by Anchen to compete with Cephalon and place its product into every market where AMRIX® is currently found, including California.

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

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

19. On July 7, 2009, within the 45-day window, Plaintiffs filed and served an action against Anchen Pharmaceuticals, Inc. and Anchen, Inc. for infringement of the patent-in-suit in the United States District Court for the District of Delaware, Civil Action No. 09-492 (the "Delaware Action"). A copy of the Complaint in the Delaware Action is attached hereto as Exhibit A.

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

21. Upon information and belief, Plaintiffs understand that Anchen may nevertheless contest personal jurisdiction in Delaware. The Hatch-Waxman Act does not address squarely the consequences of the grant of a motion to dismiss for lack of personal jurisdiction in a plaintiff's chosen forum. It is possible that such a dismissal could result in a plaintiff losing the benefit of the 30-month stay of ANDA approval even if the plaintiff refiled the action in another jurisdiction, since the refiling would occur after the 45-day window. Therefore, district courts have countenanced the filing of additional "protective suits" within the 45-day window to ensure a plaintiff will not lose the benefits of the 30-month stay should the court in

the chosen forum dismiss the action for lack of personal jurisdiction. *See e.g., Adams Respiratory Therapeutics, Inc. v. Perrigo Co.*, 2007 WL 4284877 (W.D. Mich. Dec. 3, 2007); *PDL Biopharma, Inc. v. Sun Pharmaceutical Industries, Ltd.*, 2007 WL 2261386 (E.D. Mich. Aug. 6, 2007); *Celgene Corp. v. Abrika Pharmaceuticals, Inc.*, 2007 WL 1456156 (D.N.J. May 17, 2007).

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

FACTS RELEVANT TO ALL CAUSES

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

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

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

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

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

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

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

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

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

32. The Anchen Paragraph IV Notice Letters sent to both Eurand and Cephalon fail to comply with the requirements of 21 U.S.C. § 355 (j)(2)(B)(iv)(II) because, *inter alia*, they contain very limited information about the generic

formulation for which Anchen filed ANDA No. 91-281. For example, the Anchen Paragraph IV Notice Letters do not list any of the ingredients in the proposed generic versions, or the amounts of those ingredients.

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

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

35. Since receiving the Anchen Paragraph IV Notice Letters and the accompanying Anchen Offer, Plaintiffs have negotiated with Anchen to procure a copy of ANDA No. 91-281 under restrictions "as would apply had a protective order been issued." These negotiations have been unsuccessful. For example, Anchen's most recent proposal continues to unreasonably limit the fields of practice and other activities of any person, including outside counsel, who accepts access to the ANDA. Anchen has refused to modify these restrictions despite Judge Robinson's June 23, 2009 Order in the AMRIX® cases pending in the District of Delaware rejecting similar proposals made by the defendants there.

36. Plaintiffs are not aware of any other means of obtaining information regarding the Anchen Generic Products within the 45-day statutory period. In the

absence of such information, Plaintiffs resort to the judicial process and the aid of discovery to obtain, under appropriate judicial safeguards, such information as is required to confirm its allegations of infringement and to present to the Court evidence that the Anchen Generic Products fall within the scope of one or more claims of the '793 patent.

COUNT I

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

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

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

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

COUNT II

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

40. Paragraphs 1 to 39 are incorporated herein as set forth above.

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

42. On information and belief, any commercial manufacture, use, offer for

sale, and/or importation of the Anchen Generic Products prior to patent expiry will infringe the '793 patent.

COUNT III

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

43. Paragraphs 1 to 42 are incorporated herein as set forth above.

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

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

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

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

48. On information and belief, any commercial manufacture, use, offer for sale, and/or importation of generic versions of AMRIX® by the Anchen Defendants prior to patent expiry will directly and/or indirectly infringe, contribute to the infringement of and/or induce infringement of the '793 patent.

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

INJUNCTIVE RELIEF

50. Plaintiffs will be irreparably harmed by the Anchen Defendants' infringing activities unless those activities are enjoined by this Court. Plaintiffs do

not have an adequate remedy at law.

PRAYER FOR RELIEF

Plaintiffs respectfully pray for the following relief:

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

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

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

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

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

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

Anchen Pharmaceuticals, Inc., Anchen, Inc., their officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with any of them or acting on their behalf, engage in the commercial manufacture, use, offer for sale, sale, and/or importation of the Anchen Generic Products prior to patent expiry, it will constitute an act of direct and/or indirect infringement of the '793 patent;

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

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

Dated: July 9, 2009

FISH & RICHARDSON P.C.

By: _____
Jonathan E. Singer (SBN 187908)
Attorneys for Plaintiffs
Eurand, Inc., Cephalon, Inc., and Anesta AG

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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

Plaintiffs,

v.

ANCHEN PHARMACEUTICALS, INC. and ANCHEN, INC.,

Defendants.

Civil Action No. 09-492

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Eurand, Inc., Cephalon, Inc. and Anesta AG (collectively, "Plaintiffs") bring this Complaint against Defendants Anchen Pharmaceuticals, Inc. and Anchen, Inc. (collectively "Anchen" or "Anchen Defendants"), and in support state and allege as follows:

NATURE OF THE ACTION

1. This is an action for patent infringement under the Food and Drug and Patent Laws of the United States, Titles 21 and 35, respectively, arising from Anchen filing an Abbreviated New Drug Application with the United States Food and Drug Administration ("FDA"), seeking approval to commercially market generic versions of the drug product AMRIX® (Cyclobenzaprine HCl extended release capsules) prior to the expiration of United States Patent No. 7,387,793 ("the '793 Patent"), which covers the AMRIX® product.

THE PARTIES

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

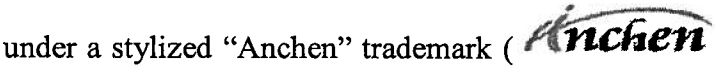
3. Plaintiff Cephalon, Inc. ("Cephalon") is a corporation organized, existing and doing business under and by virtue of the laws of the State of Delaware, with its office and principal place of business located at 41 Moores Road, Frazer, Pennsylvania 19355.

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

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

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

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

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

JURISDICTION AND VENUE

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

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

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

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

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

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

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

FACTS RELEVANT TO ALL CAUSES

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

INJUNCTIVE RELIEF

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

PRAYER FOR RELIEF

Plaintiffs respectfully pray for the following relief:

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

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

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

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

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

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

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

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

FISH & RICHARDSON P.C.

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Dated: July 7, 2009

Exhibit A

US007387793B2

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

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

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

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

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

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

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

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

(65) **Prior Publication Data**

US 2005/0106247 A1 May 19, 2005

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

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

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

(56) **References Cited**

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WO	98/18610		5/1998
WO	98/53802		12/1998
WO	99/12524		3/1999
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Akimoto, M. et al., "Evaluation of sustained-release granules of chlorphenesin carbamate in dogs and humans," *International Journal of Pharmaceutics*, 100, pp. 133-142 (1993).

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

(57) **ABSTRACT**

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

20 Claims, 4 Drawing Sheets

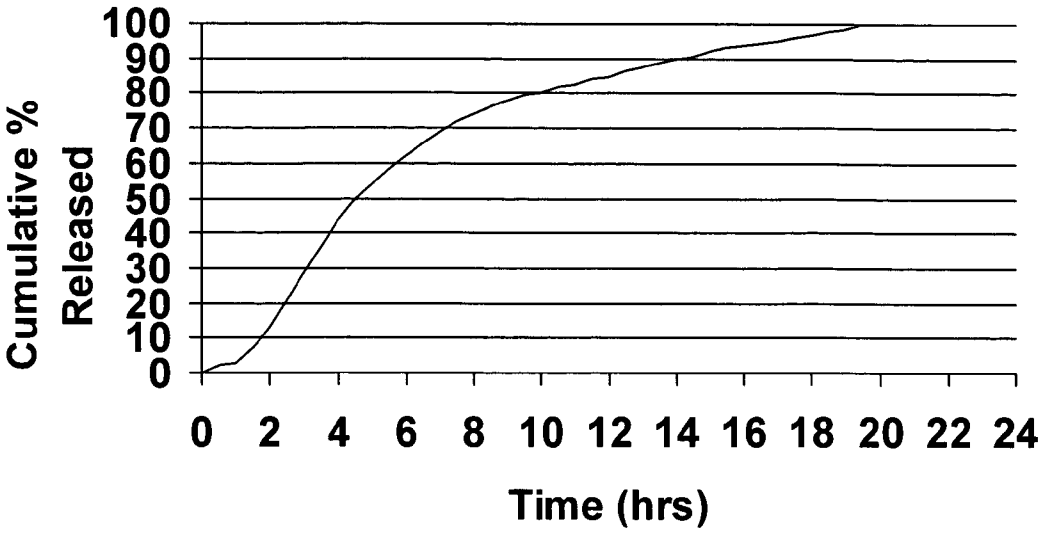

Cumulative % Released
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hrs)

FIG. 1

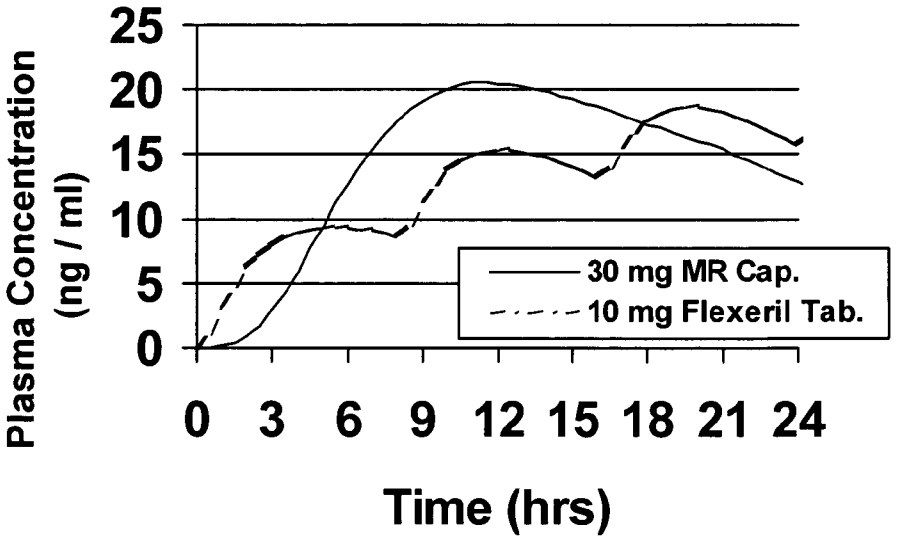

Plasma Concentration (ng / ml)
25
20
15
10
5
0
0 3 6 9 12 15 18 21 24
Time (hrs)
30 mg MR Cap.
10 mg Flexeril Tab.

FIG. 2

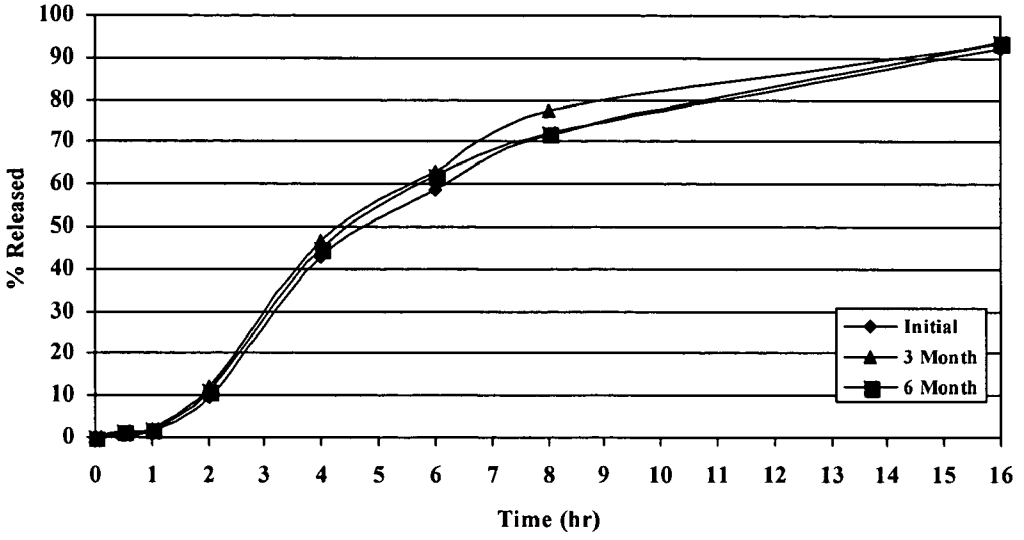

% Released
Time (hr)
Initial
3 Month
6 Month

FIG. 3

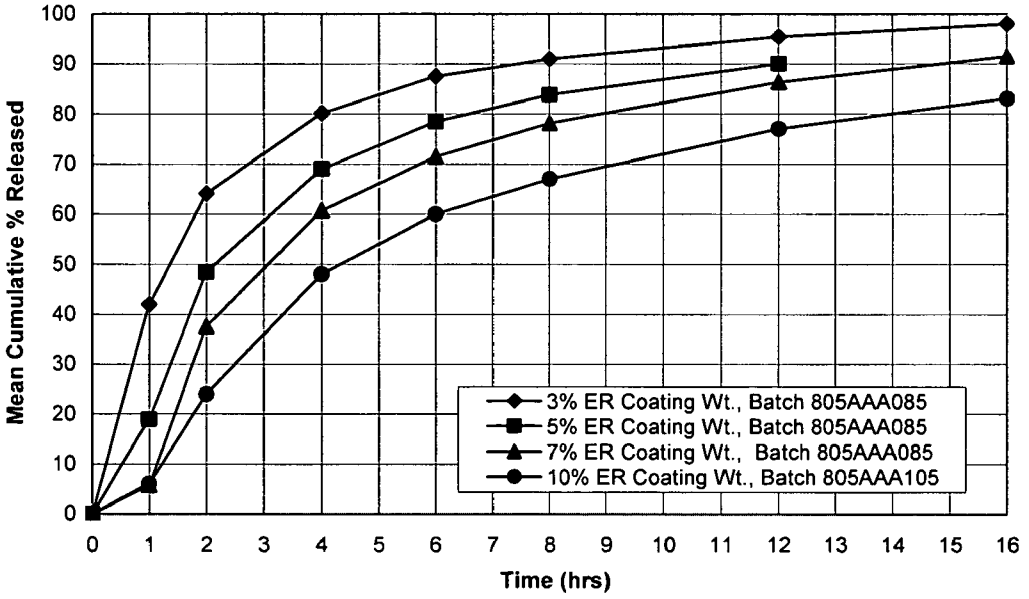

Mean Cumulative % Released
Time (hrs)
3% ER Coating Wt., Batch 805AAA085
5% ER Coating Wt., Batch 805AAA085
7% ER Coating Wt., Batch 805AAA085
10% ER Coating Wt., Batch 805AAA105

FIG. 4

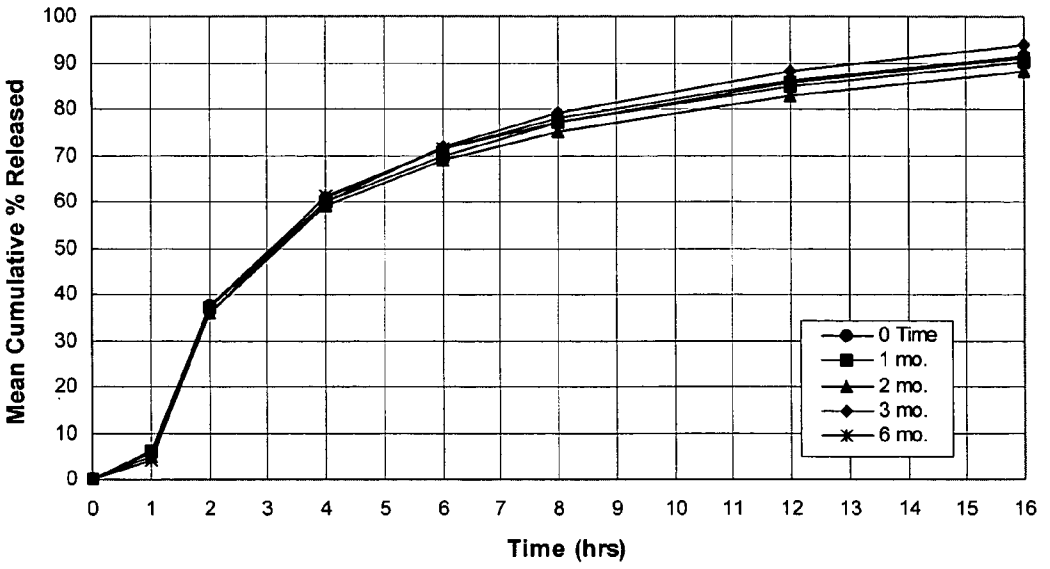

Mean Cumulative % Released
Time (hrs)
0 Time
1 mo.
2 mo.
3 mo.
6 mo.

FIG. 5

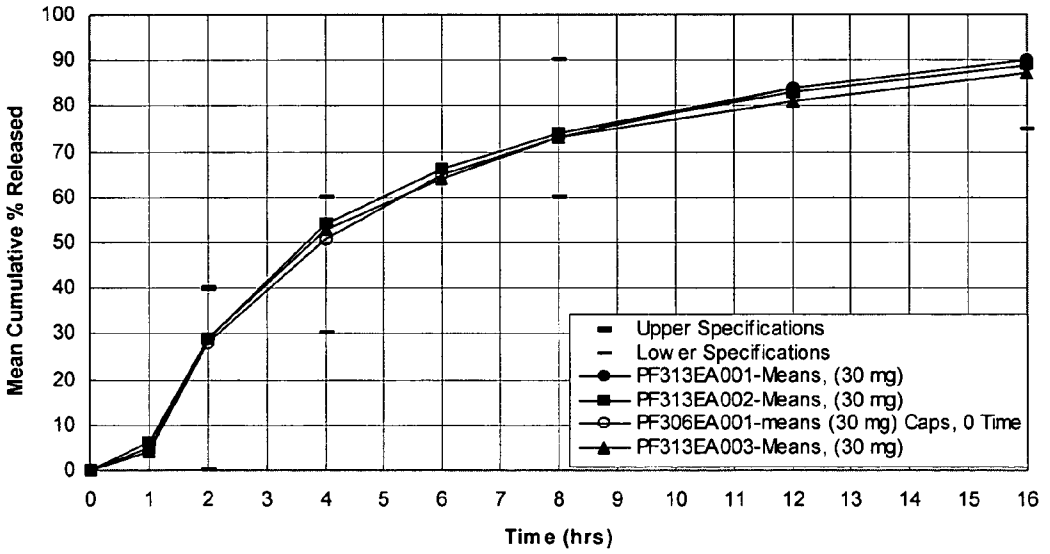

Mean Cumulative % Released
Time (hrs)
Upper Specifications
Lower Specifications
PF313EA001-Means, (30 mg)
PF313EA002-Means, (30 mg)
PF306EA001-means (30 mg) Caps, 0 Time
PF313EA003-Means, (30 mg)

FIG. 6

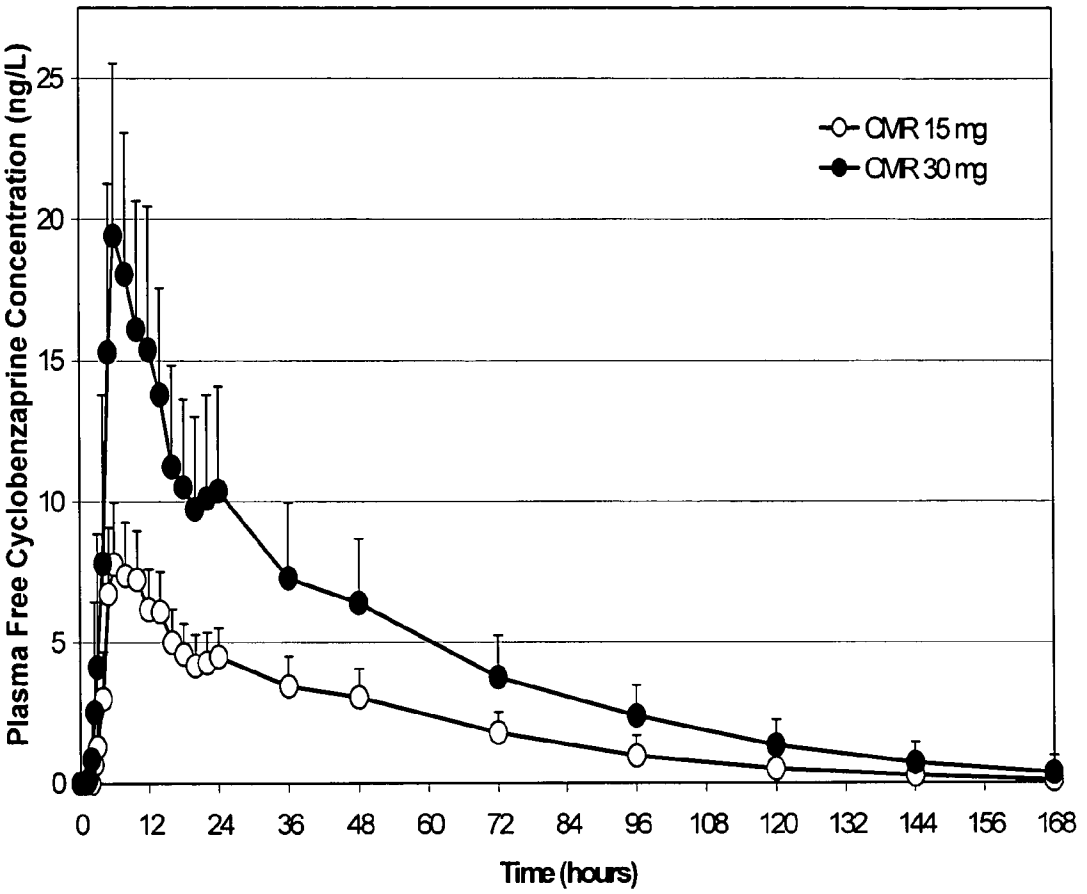

Plasma Free Cyclobenzaprine Concentration (ng/L)
0
5
10
15
20
25
0
12
24
36
48
60
72
84
96
108
120
132
144
156
168
Time (hours)
CMR 15 mg
CMR 30 mg

FIG. 7

MODIFIED RELEASE DOSAGE FORMS OF SKELETAL MUSCLE RELAXANTS

TECHNICAL FIELD

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

BACKGROUND OF THE INVENTION

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

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

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

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

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

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

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

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

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

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

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

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

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

SUMMARY OF THE INVENTION

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

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

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

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

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

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

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

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

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

DETAILED DESCRIPTION OF THE INVENTION

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

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

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

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

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

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

Dissolution Procedure:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

EXAMPLE 1

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

The resulting model parameters are listed below:

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

Theoretical plasma levels were simulated using the pharmacokinetic model given above and the target release rate given in FIG. **1**. FIG. **2** shows the simulated plasma levels for day one following dosing of 1×10 mg Flexeril® Tablet given 3 times a day and the proposed Cyclobenzaprine HCl MR Capsule, 30 mg given once a day.

EXAMPLE 2

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

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

EXAMPLE 3

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

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

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

EXAMPLE 4

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

EXAMPLE 5

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

TABLE 1

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

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

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

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

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

What is claimed is:

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

wherein said extended release beads comprise

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

* * * * *

Exhibit B

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

Anchen Pharmaceuticals, Inc.

BOXED WARNING

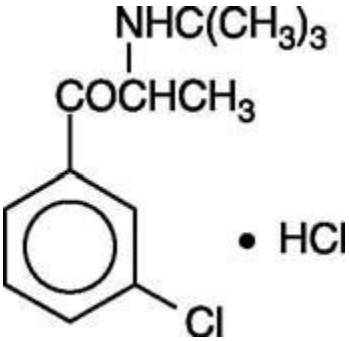
Suicidality and Antidepressant Drugs

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

DESCRIPTION

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

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



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

CLINICAL PHARMACOLOGY

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

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

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

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

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

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

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

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

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

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

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

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

The second study showed no statistically significant differences in the pharmacokinetics of bupropion and its active metabolites in 9 patients with mild to moderate hepatic cirrhosis compared to 8 healthy volunteers. However, more variability was observed in some of the pharmacokinetic parameters for bupropion (AUC, C_{max}, and T_{max}) and its active metabolites (t½) in patients with mild to moderate hepatic cirrhosis. In addition, in patients with severe hepatic cirrhosis, the bupropion C_{max} and AUC were substantially increased (mean difference: by approximately 70% and 3-fold, respectively) and more variable when compared to values in healthy volunteers; the mean bupropion half-life was also longer (29 hours in patients with severe hepatic cirrhosis vs 19 hours in healthy subjects). For the metabolite hydroxybupropion, the mean C_{max} was approximately 69% lower. For the combined amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, the mean C_{max} was approximately 31% lower. The mean AUC increased by about 1½-fold for hydroxybupropion and about 2½-fold for threo/erythrohydrobupropion. The median T_{max} was observed 19 hours later for hydroxybupropion and 31 hours later for threo/erythrohydrobupropion. The mean half-lives for hydroxybupropion and threo/erythrohydrobupropion were increased 5- and 2-fold, respectively, in patients with severe hepatic cirrhosis compared to healthy volunteers (see WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

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

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

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

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

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

CLINICAL TRIALS

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

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

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

INDICATIONS AND USAGE

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

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

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

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

CONTRAINDICATIONS

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

Bupropion hydrochloride extended-release tablets (XL) are contraindicated in patients treated with ZYBAN® (bupropion hydrochloride extended-release tablets (SR), Wellbutrin® (bupropion hydrochloride tablets), the immediate-release formulation, Wellbutrin® SR (bupropion hydrochloride extended-release tablets (SR)), the sustained-release formulation, or any other medications that contain bupropion because the incidence of seizure is dose dependent.
Bupropion hydrochloride extended-release tablets (XL) are contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures noted in patients treated for bulimia with the immediate-release formulation of bupropion.
Bupropion hydrochloride extended-release tablets (XL) are contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines).
The concurrent administration of bupropion hydrochloride extended-release tablets (XL) and a monoamine oxidase (MAO) inhibitor is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with bupropion hydrochloride extended-release tablets (XL).
Bupropion hydrochloride extended-release tablets (XL) are contraindicated in patients who have shown an allergic response to bupropion or the other ingredients that make up bupropion hydrochloride extended-release tablets (XL).

WARNINGS

Clinical Worsening and Suicide Risk:

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.
The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.
Table 1.

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

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.
It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.
All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.
The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal

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

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

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

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

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

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

Bupropion hydrochloride extended-release tablets (XL) should be administered with extreme caution to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or patients treated with other agents (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold.
Hepatic Impairment: Bupropion hydrochloride extended-release tablets (XL) should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients a reduced frequency and/or dose is required, as peak bupropion, as well as AUC, levels are substantially increased and accumulation is likely to occur in such patients to a greater extent than usual. The dose should not exceed 150 mg every other day in these patients (see CLINICAL PHARMACOLOGY, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).
Potential for Hepatotoxicity: In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted.

PRECAUTIONS
General: ***Agitation and Insomnia:*** Increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment, have been associated with treatment with bupropion. Patients in placebo-controlled trials of major depressive disorder with the sustained-release formulation of bupropion, experienced agitation, anxiety, and insomnia as shown in Table 2.
Table 2. Incidence of Agitation, Anxiety, and Insomnia in Placebo-Controlled Trials of Sustained-release Formulation of Bupropion for Major Depressive Disorder

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

In clinical studies of major depressive disorder, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs.
Symptoms in these studies were sufficiently severe to require discontinuation of treatment in 1% and 2.6% of patients treated with 300 and 400 mg/day, respectively, of bupropion sustained-release tablets and 0.8% of patients treated with placebo.
Psychosis, Confusion, and Other Neuropsychiatric Phenomena: Depressed patients treated with bupropion have been reported to show a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment.
Activation of Psychosis and/or Mania: Antidepressants can precipitate manic episodes in bipolar disorder patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Bupropion hydrochloride extended-release tablet (XL) is expected to pose similar risks.
Altered Appetite and Weight: In placebo-controlled studies of major depressive disorder using the sustained-release formulation of bupropion, patients experienced weight gain or weight loss as shown in Table 3.
Table 3. Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials of Sustained-release Formulation of Bupropion for Major Depressive Disorder

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

In studies conducted with the immediate-release formulation of bupropion, 35% of patients receiving tricyclic antidepressants gained weight, compared to 9% of patients treated with the immediate-release formulation of bupropion. If weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight-reducing potential of bupropion hydrochloride extended-release tablets (XL) should be considered.
Allergic Reactions: Anaphylactoid/anaphylactic reactions characterized by symptoms such as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have been reported in clinical trials with bupropion. In addition, there have been rare spontaneous post-marketing reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with bupropion. A patient should stop taking bupropion hydrochloride extended-release tablets (XL) and consult a doctor if experiencing allergic or anaphylactoid/anaphylactic reactions (e.g., skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during treatment. Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity have been reported in association with bupropion. These symptoms may resemble serum sickness.

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

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

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

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

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

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

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

Information for Patients: Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with bupropion hydrochloride extended-release tablets (XL) and should counsel them in its appropriate use. A patient Medication Guide About "Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions" and other important information about using bupropion hydrochloride extended-release tablets (XL) is available for bupropion hydrochloride extended-release tablets (XL). The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guides is reprinted at the end of this document.

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

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

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

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

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

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

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

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

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

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

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

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

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

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

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

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

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

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

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

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

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

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

Pregnancy

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

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

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

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

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

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

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

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

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

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

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

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

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

* Adverse events that occurred in at least 1% of patients treated with either 300 or 400 mg/day of the sustained-release formulation of bupropion, but equally or more frequently in the placebo group, were: abnormal dreams, accidental injury, acne, appetite increased, back pain, bronchitis, dysmenorrhea, dyspepsia, flatulence, flu syndrome, hypertension, neck pain, respiratory disorder, rhinitis, and tooth disorder.

† Incidence based on the number of female patients.

— Hyphen denotes adverse events occurring in greater than 0 but less than 0.5% of patients.

Additional events to those listed in Table 5 that occurred at an incidence of at least 1% in controlled clinical trials of the immediate-release formulation of bupropion (300 to 600 mg/day) and that were numerically more frequent than placebo were: cardiac arrhythmias (5% vs 4%), hypertension (4% vs 2%), hypotension (3% vs 2%), tachycardia (11% vs 9%), appetite increase (4% vs 2%), dyspepsia (3% vs 2%), menstrual complaints (5% vs 1%), akathisia (2% vs 1%), impaired sleep quality (4% vs 2%), sensory disturbance (4% vs 3%), confusion (8% vs 5%), decreased libido (3% vs 2%), hostility (6% vs 4%), auditory disturbance (5% vs 3%), and gustatory disturbance (3% vs 1%).

Incidence of Commonly Observed Adverse Events in Controlled Clinical Trials:

Adverse events from Table 4 occurring in at least 5% of patients treated with the sustained-release formulation of bupropion and at a rate at least twice the placebo rate are listed below for the 300- and 400-mg/day dose groups.

300 mg/day of the Sustained-Release Formulation: Anorexia, dry mouth, rash, sweating, tinnitus, and tremor.

400 mg/day of the Sustained-Release Formulation: Abdominal pain, agitation, anxiety, dizziness, dry mouth, insomnia, myalgia, nausea, palpitation, pharyngitis, sweating, tinnitus, and urinary frequency.

Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion: In addition to the adverse events noted above, the following events have been reported in clinical trials and postmarketing experience with the sustained-release formulation of bupropion in depressed patients and in nondepressed smokers, as well as in clinical trials and postmarketing clinical experience with the immediate-release formulation of bupropion.

Adverse events for which frequencies are provided below occurred in clinical trials with the sustained-release formulation of bupropion. The frequencies represent the proportion of patients who experienced a treatment-emergent adverse event on at least one occasion in placebo-controlled studies for depression (n = 987) or smoking cessation (n = 1,013), or patients who experienced an adverse event requiring discontinuation of treatment in an open-label surveillance study with the sustained-release formulation of bupropion (n = 3,100). All treatment-emergent adverse events are included except those listed in Tables 1 through 4, those events listed in other safety-related sections, those adverse events subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, those events not reasonably associated with the use of the drug, and those events that were not serious and occurred in fewer than 2 patients. Events of major clinical importance are described in the WARNINGS and PRECAUTIONS sections of the labeling.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions of frequency: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients.

Adverse events for which frequencies are not provided occurred in clinical trials or postmarketing experience with bupropion. Only those adverse events not previously listed for sustained-release bupropion are included. The extent to which these events may be associated with bupropion hydrochloride extended-release tablets (XL) is unknown.

Body (General): Infrequent were chills, facial edema, musculoskeletal chest pain, and photosensitivity. Rare was malaise. Also observed were arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness (see PRECAUTIONS).

Cardiovascular: Infrequent were postural hypotension, stroke, tachycardia, and vasodilation. Rare was syncope. Also observed were complete atrioventricular block, extrasystoles, hypotension, hypertension (in some cases severe, see PRECAUTIONS), myocardial infarction, phlebitis, and pulmonary embolism.

Digestive: Infrequent were abnormal liver function, bruxism, gastric reflux, gingivitis, glossitis, increased salivation, jaundice, mouth ulcers, stomatitis, and thirst. Rare was edema of tongue. Also observed were colitis, esophagitis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, intestinal perforation, liver damage, pancreatitis, and stomach ulcer.

Endocrine: Also observed were hyperglycemia, hypoglycemia, and syndrome of inappropriate antidiuretic hormone.

Hemic and Lymphatic: Infrequent was ecchymosis. Also observed were anemia, leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia. Altered PT and/or INR, infrequently associated with hemorrhagic or thrombotic complications, were observed when bupropion was coadministered with warfarin.

Metabolic and Nutritional: Infrequent were edema and peripheral edema. Also observed was glycosuria.

Musculoskeletal: Infrequent were leg cramps. Also observed were muscle rigidity/fever/rhabdomyolysis and muscle weakness.

Nervous System: Infrequent were abnormal coordination, decreased libido, depersonalization, dysphoria, emotional lability, hostility, hyperkinesia, hypertonia, hypesthesia, suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and hypomania. Also observed were abnormal electroencephalogram (EEG), aggression, akinesia, aphasia, coma, delirium, delusions, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hallucinations, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid ideation, restlessness, and unmasking tardive dyskinesia.

Respiratory: Rare was bronchospasm. Also observed was pneumonia.

Skin: Rare was maculopapular rash. Also observed were alopecia, angioedema, exfoliative dermatitis, and hirsutism.
Special Senses: Infrequent were accommodation abnormality and dry eye. Also observed were deafness, diplopia, increased intraocular pressure, and mydriasis.
Urogenital: Infrequent were impotence, polyuria, and prostate disorder. Also observed were abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomastia, menopause, painful erection, salpingitis, urinary incontinence, urinary retention, and vaginitis.
To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals USA at 1-888-493-0857 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: Bupropion is not a controlled substance.
Humans: Controlled clinical studies of bupropion (immediate-release formulation) conducted in normal volunteers, in subjects with a history of multiple drug abuse, and in depressed patients showed some increase in motor activity and agitation/excitement.
In a population of individuals experienced with drugs of abuse, a single dose of 400 mg of bupropion produced mild amphetamine-like activity as compared to placebo on the Morphine-Benzedrine Subscale of the Addiction Research Center Inventories (ARCI), and a score intermediate between placebo and amphetamine on the Liking Scale of the ARCI. These scales measure general feelings of euphoria and drug desirability.
Findings in clinical trials, however, are not known to reliably predict the abuse potential of drugs. Nonetheless, evidence from single-dose studies does suggest that the recommended daily dosage of bupropion when administered in divided doses is not likely to be especially reinforcing to amphetamine or stimulant abusers. However, higher doses that could not be tested because of the risk of seizure might be modestly attractive to those who abuse stimulant drugs.
Animals: Studies in rodents and primates have shown that bupropion exhibits some pharmacologic actions common to psychostimulants. In rodents, it has been shown to increase locomotor activity, elicit a mild stereotyped behavioral response, and increase rates of responding in several schedule-controlled behavior paradigms. In primate models to assess the positive reinforcing effects of psychoactive drugs, bupropion was self-administered intravenously. In rats, bupropion produced amphetamine-like and cocaine-like discriminative stimulus effects in drug discrimination paradigms used to characterize the subjective effects of psychoactive drugs.

OVERDOSAGE

Human Overdose Experience: Overdoses of up to 30 g or more of bupropion have been reported. Seizure was reported in approximately one third of all cases. Other serious reactions reported with overdoses of bupropion alone included hallucinations, loss of consciousness, sinus tachycardia, and ECG changes such as conduction disturbances or arrhythmias. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported mainly when bupropion was part of multiple drug overdoses.
Although most patients recovered without sequelae, deaths associated with overdoses of bupropion alone have been reported in patients ingesting large doses of the drug. Multiple uncontrolled seizures, bradycardia, cardiac failure, and cardiac arrest prior to death were reported in these patients.
Overdosage Management: Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. EEG monitoring is also recommended for the first 48 hours post-ingestion. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients.
Activated charcoal should be administered. There is no experience with the use of forced diuresis, dialysis, hemoperfusion, or exchange transfusion in the management of bupropion overdoses. No specific antidotes for bupropion are known.
Due to the dose-related risk of seizures with bupropion hydrochloride extended-release tablets (XL), hospitalization following suspected overdose should be considered. Based on studies in animals, it is recommended that seizures be treated with intravenous benzodiazepine administration and other supportive measures, as appropriate.
In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION

General Dosing Considerations: It is particularly important to administer bupropion hydrochloride extended-release tablets (XL) in a manner most likely to minimize the risk of seizure (see WARNINGS). Gradual escalation in dosage is also important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these effects may be managed by temporary reduction of dose or the short-term administration of an intermediate to long-acting sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation should be stopped. Bupropion hydrochloride extended-release tablets (XL) should be swallowed whole and not crushed, divided, or chewed. Bupropion hydrochloride extended-release tablets (XL) may be taken without regard to meals.
Major Depressive Disorder: Initial Treatment: The usual adult target dose for bupropion hydrochloride extended-release tablets (XL) is 300 mg/day, given once daily in the morning. Dosing with bupropion hydrochloride extended-release tablets (XL) should

begin at 150 mg/day given as a single daily dose in the morning. If the 150-mg initial dose is adequately tolerated, an increase to the 300-mg/day target dose, given as once daily, may be made as early as day 4 of dosing. There should be an interval of at least 24 hours between successive doses.

Increasing the Dosage Above 300 mg/day: As with other antidepressants, the full antidepressant effect of bupropion hydrochloride extended-release tablets (XL) may not be evident until 4 weeks of treatment or longer. An increase in dosage to the maximum of 450 mg/day, given as a single dose, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day.

Maintenance Treatment: It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacological therapy beyond response to the acute episode. It is unknown whether or not the dose of bupropion hydrochloride extended-release tablets (XL) needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

Switching Patients from Wellbutrin® (bupropion hydrochloride tablets) or from Wellbutrin® SR (bupropion hydrochloride extended-release tablets (SR), revise subsection as follows:

When switching patients from Wellbutrin® (bupropion hydrochloride tablets) to bupropion hydrochloride extended-release tablets (XL) or from Wellbutrin® SR (bupropion hydrochloride extended-release tablets (SR)) to bupropion hydrochloride extended-release tablets (XL), give the same total daily dose when possible. Patients who are currently being treated with Wellbutrin® (bupropion hydrochloride tablets) at 300 mg/day (for example, 100 mg 3 times a day) may be switched to bupropion hydrochloride extended-release tablets (XL) 300 mg once daily. Patients who are currently being treated with Wellbutrin® SR (bupropion hydrochloride extended-release tablets (SR)) at 300 mg/day (for example, 150 mg twice daily) may be switched to bupropion hydrochloride extended-release tablets (XL) 300 mg once daily.

Dosage Adjustment for Patients With Impaired Hepatic Function: Bupropion hydrochloride extended-release tablets (XL) should be used with extreme caution in patients with severe hepatic cirrhosis. The dose should not exceed 150 mg every other day in these patients. Bupropion hydrochloride extended-release tablets (XL) should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and a reduced frequency and/or dose should be considered in patients with mild to moderate hepatic cirrhosis (see CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS).

Dosage Adjustment for Patients With Impaired Renal Function: Bupropion hydrochloride extended-release tablets (XL) should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

HOW SUPPLIED

Bupropion hydrochloride extended-release tablets USP (XL) 150 mg, are white to off-white, round, tablets printed with “A101”. They are supplied as follow:

Bottles of 30 NDC # 10370-101-03
Bottles of 60 NDC # 10370-101-06
Bottles of 90 NDC # 10370-101-09
Bottles of 500 NDC # 10370-101-50
Bottles of 1000 NDC # 10370-101-00

Bupropion hydrochloride extended-release tablets USP (XL) 300 mg, are white to off-white, round, tablets printed with “A102”. They are supplied as follow:

Bottles of 30 NDC # 10370-102-03
Bottles of 60 NDC # 10370-102-06
Bottles of 90 NDC # 10370-102-09
Bottles of 500 NDC # 10370-102-50
Bottles of 1000 NDC # 10370-102-00

Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature]

*The following are registered trademarks of their respective manufacturers: ZYBAN®, WELLBUTRIN®, and WELLBUTRIN SR® / GlaxoSmithKline

Rx Only

Manufactured by:
Anchen Pharmaceuticals, Inc.
Irvine, CA 92618
08/07

Medguide
Medication Guide

Bupropion Hydrochloride Extended-Release Tablets USP (XL)

Read this Medication Guide carefully before you start using bupropion hydrochloride extended-release tablets (XL) and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about bupropion hydrochloride extended-release tablets (XL), ask your doctor or pharmacist.

IMPORTANT: Be sure to read both sections of this Medication Guide. The first section is about the risk of suicidal thoughts and actions with antidepressant medicines; the second section is entitled "What other important information should I know about bupropion hydrochloride extended-release tablets (XL)?"

Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with you or your family member's antidepressant medicine.

This section of the Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.

2.Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.

3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?

- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
- Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
- Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Trouble sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking (mania)
- Other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.

• **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
• **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
• **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.
Bupropion hydrochloride extended-release tablets (XL) have not been studied in children under the age of 18 years and are not approved for use in children and teenagers.

What other important information should I know about bupropion hydrochloride extended-release tablets (XL)?
There is a chance of having a seizure (convulsion, fit) with bupropion hydrochloride extended-release tablets (XL), especially in people:
• with certain medical problems.

• who take certain medicines.

The chance of having seizures increases with higher doses of bupropion hydrochloride extended-release tablets (XL). For more information, see the sections "Who should not take bupropion hydrochloride extended-release tablets (XL)?" and "What should I tell my doctor before using bupropion hydrochloride extended-release tablets (XL)?" Tell your doctor about all of your medical conditions and all the medicines you take. **Do not take any other medicines while you are using bupropion hydrochloride extended-release tablets (XL) unless your doctor has said it is okay to take them**.
If you have a seizure while taking bupropion hydrochloride extended-release tablets (XL), stop taking the tablets and call your doctor right away. Do not take bupropion hydrochloride extended-release tablets (XL) again if you have a seizure.

What are bupropion hydrochloride extended-release tablets (XL)?
Bupropion hydrochloride extended-release tablets (XL) are a prescription medicine used to treat adults with a certain type of depression called major depressive disorder.

Who should not take bupropion hydrochloride extended-release tablets (XL)?
Do not take bupropion hydrochloride extended-release tablets (XL) if you
• have or had a seizure disorder or epilepsy.

• **are taking ZYBAN® (used to help people stop smoking) or any other medicines that contain bupropion hydrochloride, such as bupropion hydrochloride tablets or bupropion hydrochloride sustained-release tablets.** Bupropion is the same active ingredient that is in bupropion hydrochloride extended-release tablets (XL).

• drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these make you sleepy) or benzodiazepines and you stop using them all of a sudden.

• have taken within the last 14 days medicine for depression called a monoamine oxidase inhibitor (MAOI), such as NARDIL® (phenelzine sulfate), PARNATE® (tranylcypromine sulfate), or MARPLAN® (isocarboxazid)*****.

• have or had an eating disorder such as anorexia nervosa or bulimia.

• are allergic to the active ingredient in bupropion hydrochloride extended-release tablets (XL)**,** bupropion, or to any of the inactive ingredients. See the end of this leaflet for a complete list of ingredients in bupropion hydrochloride extended-release tablets (XL).

What should I tell my doctor before using bupropion hydrochloride extended-release tablets (XL)?
• **Tell your doctor about your medical conditions.** Tell your doctor if you

• **are pregnant or plan to become pregnant.** It is not known if bupropion hydrochloride extended-release tablets (XL)can harm your unborn baby.

• **are breastfeeding.** Bupropion hydrochloride extended-release tablets (XL)passes through your milk. It is not known if bupropion hydrochloride extended-release tablets (XL)can harm your baby.

• **have liver problems,** especially cirrhosis of the liver.

• have kidney problems.

• have an eating disorder, such as anorexia nervosa or bulimia.

• have had a head injury.

- have had a seizure (convulsion, fit).
- have a tumor in your nervous system (brain or spine).
- have had a heart attack, heart problems, or high blood pressure.
- are a diabetic taking insulin or other medicines to control your blood sugar.
- drink a lot of alcohol.
- abuse prescription medicines or street drugs.
- **Tell your doctor about all the medicines you take**, including prescription and non-prescription medicines, vitamins and herbal supplements. Many medicines increase your chances of having seizures or other serious side effects if you take them while you are using bupropion hydrochloride extended-release tablets (XL).

How should I take bupropion hydrochloride extended-release tablets (XL)?

- Take bupropion hydrochloride extended-release tablets (XL) exactly as prescribed by your doctor.
- **Do not chew, cut, or crush bupropion hydrochloride extended-release tablets (XL).** You must swallow the tablets whole. **Tell your doctor if you cannot swallow medicine tablets.**
- Take bupropion hydrochloride extended-release tablets (XL) at the same time each day.
- Take your doses of bupropion hydrochloride extended-release tablets (XL)at least 24 hours apart.
- You may take bupropion hydrochloride extended-release tablets (XL)with or without food.
- If you miss a dose, do not take an extra tablet to make up for the dose you forgot. Wait and take your next tablet at the regular time. **This is very important.** Too much bupropion hydrochloride extended-release tablets (XL) can increase your chance of having a seizure.
- If you take too much bupropion hydrochloride extended-release tablets (XL), or overdose, call your local emergency room or poison control center right away.
- The bupropion hydrochloride extended-release tablet (XL) is covered by a shell that slowly releases the medicine inside your body. You may notice something in your stool that looks like a tablet. This is normal. This is the empty shell passing from your body.
- **Do not take any other medicines while using bupropion hydrochloride extended-release tablets (XL) unless your doctor has told you it is okay.**
- If you are taking bupropion hydrochloride extended-release tablets (XL) for the treatment of major depressive disorder, it may take several weeks for you to feel that bupropion hydrochloride extended-release tablets (XL) is working. Once you feel better, it is important to keep taking bupropion hydrochloride extended-release tablets (XL) exactly as directed by your doctor. Call your doctor if you do not feel bupropion hydrochloride extended-release tablets (XL) is working for you.
- Do not change your dose or stop taking bupropion hydrochloride extended-release tablets (XL) without talking with your doctor first.

What should I avoid while taking bupropion hydrochloride extended-release tablets (XL)?

- Do not drink a lot of alcohol while taking bupropion hydrochloride extended-release tablets (XL). If you usually drink a lot of alcohol, talk with your doctor before suddenly stopping. If you suddenly stop drinking alcohol, you may increase your chance of having seizures.
- Do not drive a car or use heavy machinery until you know how bupropion hydrochloride extended-release tablets (XL) affects you. Bupropion hydrochloride extended-release tablets (XL) can impair your ability to perform these tasks.

What are possible side effects of bupropion hydrochloride extended-release tablets (XL)?

- **Seizures.** Some patients get seizures while taking bupropion hydrochloride extended-release tablets (XL). **If you have a seizure while taking bupropion hydrochloride extended-release tablets (XL), stop taking the tablets and call your doctor right away.** Do not take bupropion hydrochloride extended-release tablets (XL) again if you have a seizure.

- **Hypertension (high blood pressure).** Some patients get high blood pressure, sometimes severe, while taking bupropion hydrochloride extended-release tablets (XL). The chance of high blood pressure may be increased if you also use nicotine replacement therapy (for example, a nicotine patch) to help you stop smoking.

- **Severe allergic reactions. Stop bupropion hydrochloride extended-release tablets (XL) and call your doctor right away** if you get a rash, itching, hives, fever, swollen lymph glands, painful sores in the mouth or around the eyes, swelling of the lips or tongue, chest pain, or have trouble breathing. These could be signs of a serious allergic reaction.

- **Unusual thoughts or behaviors.** Some patients have unusual thoughts or behaviors while taking bupropion hydrochloride extended-release tablets (XL), including delusions (believe you are someone else), hallucinations (seeing or hearing things that are not there), paranoia (feeling that people are against you), or feeling confused. If this happens to you, call your doctor.
  Common side effects reported in studies of major depressive disorder include weight loss, loss of appetite, dry mouth, skin rash, sweating, ringing in the ears, shakiness, stomach pain, agitation, anxiety, dizziness, trouble sleeping, muscle pain, nausea, fast heartbeat, sore throat, and urinating more often.
  If you have nausea, take your medicine with food. If you have trouble sleeping, do not take your medicine too close to bedtime.
  Tell your doctor right away about any side effects that bother you.
  These are not all the side effects of bupropion hydrochloride extended-release tablets (XL). For a complete list, ask your doctor or pharmacist.
  How should I store bupropion hydrochloride extended-release tablets (XL)?

- Store bupropion hydrochloride extended-release tablets (XL) at room temperature. Store out of direct sunlight. Keep bupropion hydrochloride extended-release tablets (XL) in its tightly closed bottle.

- Bupropion hydrochloride extended-release tablets (XL) may have an odor.
  General Information about bupropion hydrochloride extended-release tablets (XL).

- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use bupropion hydrochloride extended-release tablets (XL) for a condition for which it was not prescribed. Do not give bupropion hydrochloride extended-release tablets (XL) to other people, even if they have the same symptoms you have. It may harm them. Keep bupropion hydrochloride extended-release tablets (XL)out of the reach of children.

This Medication Guide summarizes important information about bupropion hydrochloride extended-release tablets (XL). For more information, talk with your doctor. You can ask your doctor or pharmacist for information about bupropion hydrochloride extended-release tablets (XL) that is written for health professionals. **To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals USA at 1-888-493-0857 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

What are the ingredients in bupropion hydrochloride extended-release tablets (XL)?

Active ingredient: bupropion hydrochloride.

Inactive ingredients: dehydrated alcohol, ethylcellulose, hydrochloric acid, hydroxypropylcellulose, methacrylic acid copolymer, povidone, silicon dioxide, hydrogenated vegetable oil and ethyl alcohol. The tablets are printed with edible black ink.

*The following are registered trademarks of their respective manufacturers: PROZAC®/Eli Lilly and Company; ZOLOFT®/Pfizer Pharmaceuticals; LUVOX®/Solvay Pharmaceuticals, Inc.; ANAFRANIL®/Mallinckrodt Inc.; NARDIL®/Warner Lambert Company; MARPLAN®/Oxford Pharmaceutical Services, Inc.; PARNATE®/ GlaxoSmithKline.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:

Anchen Pharmaceuticals, Inc.
Irvine, CA 92618
08/08

Exhibit C

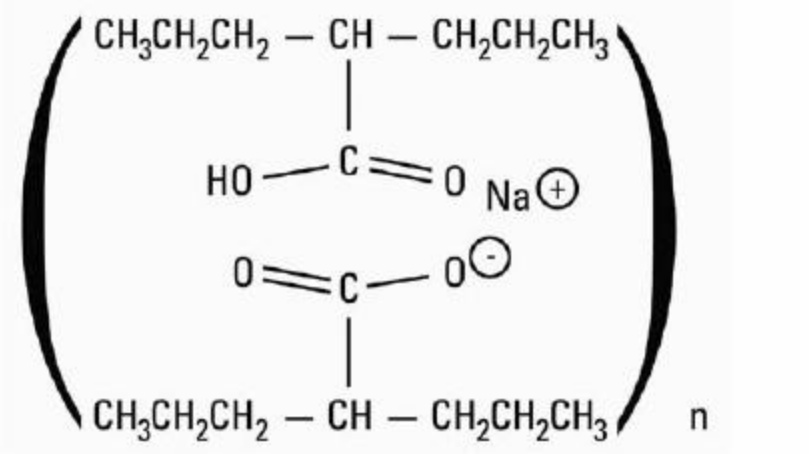
DIVALPROEX SODIUM DELAYED-RELEASE - divalproex sodium tablet, delayed release
Anchen Pharmaceuticals Inc.

Divalproex Sodium Delayed-Release Tablets USP
"Patient Information Leaflet" enclosed.
Rx only

HEPATOTOXICITY

HEPATIC FAILURE RESULTING IN FATALITIES HAS OCCURRED IN PATIENTS RECEIVING VALPROIC ACID AND ITS DERIVATIVES. EXPERIENCE HAS INDICATED THAT CHILDREN UNDER THE AGE OF TWO YEARS ARE AT A CONSIDERABLY INCREASED RISK OF DEVELOPING FATAL HEPATOTOXICITY, ESPECIALLY THOSE ON MULTIPLE ANTICONVULSANTS, THOSE WITH CONGENITAL METABOLIC DISORDERS, THOSE WITH SEVERE SEIZURE DISORDERS ACCOMPANIED BY MENTAL RETARDATION, AND THOSE WITH ORGANIC BRAIN DISEASE. WHEN DIVALPROEX SODIUM DELAYED-RELEASE TABLET IS USED IN THIS PATIENT GROUP, IT SHOULD BE USED WITH EXTREME CAUTION AND AS A SOLE AGENT. THE BENEFITS OF THERAPY SHOULD BE WEIGHED AGAINST THE RISKS. ABOVE THIS AGE GROUP, EXPERIENCE IN EPILEPSY HAS INDICATED THAT THE INCIDENCE OF FATAL HEPATOTOXICITY DECREASES CONSIDERABLY IN PROGRESSIVELY OLDER PATIENT GROUPS.
THESE INCIDENTS USUALLY HAVE OCCURRED DURING THE FIRST SIX MONTHS OF TREATMENT. SERIOUS OR FATAL HEPATOTOXICITY MAY BE PRECEDED BY NON-SPECIFIC SYMPTOMS SUCH AS MALAISE, WEAKNESS, LETHARGY, FACIAL EDEMA, ANOREXIA, AND VOMITING. IN PATIENTS WITH EPILEPSY, A LOSS OF SEIZURE CONTROL MAY ALSO OCCUR. PATIENTS SHOULD BE MONITORED CLOSELY FOR APPEARANCE OF THESE SYMPTOMS. LIVER FUNCTION TESTS SHOULD BE PERFORMED PRIOR TO THERAPY AND AT FREQUENT INTERVALS THEREAFTER, ESPECIALLY DURING THE FIRST SIX MONTHS.
TERATOGENICITY
VALPROATE CAN PRODUCE TERATOGENIC EFFECTS SUCH AS NEURAL TUBE DEFECTS (E.G., SPINA BIFIDA). ACCORDINGLY, THE USE OF DIVALPROEX SODIUM DELAYED-RELEASE TABLETS IN WOMEN OF CHILDBEARING POTENTIAL REQUIRES THAT THE BENEFITS OF ITS USE BE WEIGHED AGAINST THE RISK OF INJURY TO THE FETUS. THIS IS ESPECIALLY IMPORTANT WHEN THE TREATMENT OF A SPONTANEOUSLY REVERSIBLE CONDITION NOT ORDINARILY ASSOCIATED WITH PERMANENT INJURY OR RISK OF DEATH (E.G., MIGRAINE) IS CONTEMPLATED. SEE WARNINGS, INFORMATION FOR PATIENTS.
AN INFORMATION SHEET DESCRIBING THE TERATOGENIC POTENTIAL OF VALPROATE IS AVAILABLE FOR PATIENTS.
PANCREATITIS
CASES OF LIFE-THREATENING PANCREATITIS HAVE BEEN REPORTED IN BOTH CHILDREN AND ADULTS RECEIVING VALPROATE. SOME OF THE CASES HAVE BEEN DESCRIBED AS HEMORRHAGIC WITH A RAPID PROGRESSION FROM INITIAL SYMPTOMS TO DEATH. CASES HAVE BEEN REPORTED SHORTLY AFTER INITIAL USE AS WELL AS AFTER SEVERAL YEARS OF USE. PATIENTS AND GUARDIANS SHOULD BE WARNED THAT ABDOMINAL PAIN, NAUSEA, VOMITING, AND/OR ANOREXIA CAN BE SYMPTOMS OF PANCREATITIS THAT REQUIRE PROMPT MEDICAL EVALUATION. IF PANCREATITIS IS DIAGNOSED, VALPROATE SHOULD ORDINARILY BE DISCONTINUED. ALTERNATIVE TREATMENT FOR THE UNDERLYING MEDICAL CONDITION SHOULD BE INITIATED AS CLINICALLY INDICATED. (See WARNINGS and PRECAUTIONS.)

DESCRIPTION
Divalproex sodium is a stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. Chemically it is designated as sodium hydrogen bis(2-propylpentanoate). Divalproex sodium has the following structure:



Divalproex sodium occurs as a white powder with a characteristic odor.
Divalproex sodium delayed-release tablets are for oral administration. Divalproex sodium delayed-release tablets are supplied as divalproex sodium equivalent to 500 mg of valproic acid.

Inactive Ingredients
Divalproex sodium delayed-release tablets contain the following inactive ingredients: cellacefate, colloidal silicone dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone, talc, titanium dioxide, and triethyl citrate. In addition, the tablets contain: FD&C Yellow No. 5 (see Precautions) and iron oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics
Divalproex sodium dissociates to the valproate ion in the gastrointestinal tract. The mechanisms by which valproate exerts its therapeutic effects have not been established. It has been suggested that its activity in epilepsy is related to increased brain concentrations of gamma-aminobutyric acid (GABA).

Pharmacokinetics

Absorption/Bioavailability
Equivalent oral doses of divalproex sodium delayed-release tablets products and valproic acid capsules deliver equivalent quantities of valproate ion systemically. Although the rate of valproate ion absorption may vary with the formulation administered (liquid, solid, or sprinkle), conditions of use (e.g., fasting or postprandial) and the method of administration (e.g., whether the contents of the capsule are sprinkled on food or the capsule is taken intact), these differences should be of minor clinical importance under the steady state conditions achieved in chronic use in the treatment of epilepsy.

However, it is possible that differences among the various valproate products in T_{max} and C_{max} could be important upon initiation of treatment. For example, in single dose studies, the effect of feeding had a greater influence on the rate of absorption of the tablet (increase in T_{max} from 4 to 8 hours) than on the absorption of the sprinkle capsules (increase in T_{max} from 3.3 to 4.8 hours).

While the absorption rate from the G.I. tract and fluctuation in valproate plasma concentrations vary with dosing regimen and formulation, the efficacy of valproate as an anticonvulsant in chronic use is unlikely to be affected. Experience employing dosing regimens from once-a-day to four-times-a-day, as well as studies in primate epilepsy models involving constant rate infusion, indicate that total daily systemic bioavailability (extent of absorption) is the primary determinant of seizure control and that differences in the ratios of plasma peak to trough concentrations between valproate formulations are inconsequential from a practical clinical standpoint. Whether or not rate of absorption influences the efficacy of valproate as an antimanic or antimigraine agent is unknown.

Co-administration of oral valproate products with food and substitution among the various divalproex sodium delayed-release tablets and valproic acid formulations should cause no clinical problems in the management of patients with epilepsy (see DOSAGE AND ADMINISTRATION). Nonetheless, any changes in dosage administration, or the addition or discontinuance of concomitant drugs should ordinarily be accompanied by close monitoring of clinical status and valproate plasma concentrations.

Distribution
Protein Binding

The plasma protein binding of valproate is concentration dependent and the free fraction increases from approximately 10% at 40 μg/ml to 18.5% at 130 μg/mL. Protein binding of valproate is reduced in the elderly, in patients with chronic hepatic diseases, in patients with renal impairment, and in the presence of other drugs (e.g., aspirin). Conversely, valproate may displace certain protein-bound drugs (e.g., phenytoin, carbamazepine, warfarin, and tolbutamide). (See PRECAUTIONS, Drug Interactions for more detailed information on the pharmacokinetic interactions of valproate with other drugs.)

CNS Distribution

Valproate concentrations in cerebrospinal fluid (CSF) approximate unbound concentrations in plasma (about 10% of total concentration).

Metabolism
Valproate is metabolized almost entirely by the liver. In adult patients on monotherapy, 30-50% of an administered dose appears in urine as a glucuronide conjugate. Mitochondrial β-oxidation is the other major metabolic pathway, typically accounting for over 40% of the dose. Usually, less than 15-20% of the dose is eliminated by other oxidative mechanisms. Less than 3% of an administered dose is excreted unchanged in urine.

The relationship between dose and total valproate concentration is nonlinear; concentration does not increase proportionally with the dose, but rather, increases to a lesser extent due to saturable plasma protein binding. The kinetics of unbound drug are linear.

Elimination
Mean plasma clearance and volume of distribution for total valproate are 0.56 L/hr/1.73 m^2 and 11 L/1.73 m^2, respectively. Mean plasma clearance and volume of distribution for free valproate are 4.6 L/hr/1.73 m^2 and 92 L/1.73 m^2. Mean terminal half-life for valproate monotherapy ranged from 9 to 16 hours following oral dosing regimens of 250 to 1000 mg.

The estimates cited apply primarily to patients who are not taking drugs that affect hepatic metabolizing enzyme systems. For example, patients taking enzyme-inducing antiepileptic drugs (carbamazepine, phenytoin, and phenobarbital) will clear valproate more rapidly. Because of these changes in valproate clearance, monitoring of antiepileptic concentrations should be intensified whenever concomitant antiepileptics are introduced or withdrawn.

Special Populations
Effect of Age

Neonates

Children within the first two months of life have a markedly decreased ability to eliminate valproate compared to older children and adults. This is a result of reduced clearance (perhaps due to delay in development of glucuronosyltransferase and other enzyme systems involved in valproate elimination) as well as increased volume of distribution (in part due to decreased plasma protein binding). For example, in one study, the half-life in children under 10 days ranged from 10 to 67 hours compared to a range of 7 to 13 hours in children greater than 2 months.

Children

Pediatric patients (i.e., between 3 months and 10 years) have 50% higher clearances expressed on weight (i.e., mL/min/kg) than do adults. Over the age of 10 years, children have pharmacokinetic parameters that approximate those of adults.

Elderly

The capacity of elderly patients (age range: 68 to 89 years) to eliminate valproate has been shown to be reduced compared to younger adults (age range: 22 to 26). Intrinsic clearance is reduced by 39%; the free fraction is increased by 44%. Accordingly, the initial dosage should be reduced in the elderly. (See DOSAGE AND ADMISTRATION).

Effect of Gender

There are no differences in the body surface area adjusted unbound clearance between males and females (4.8±0.17 and 4.7±0.07 L/hr per 1.73 m^2, respectively).

Effect of Race

The effects of race on the kinetics of valproate have not been studied.

Effect of Disease

Liver Disease

(See BOXED WARNING, CONTRAINDICATIONS, and WARNINGS). Liver disease impairs the capacity to eliminate valproate. In one study, the clearance of free valproate was decreased by 50% in 7 patients with cirrhosis and by 16% in 4 patients with acute hepatitis, compared with 6 healthy subjects. In that study, the half-life of valproate was increased from 12 to 18 hours. Liver disease is also associated with decreased albumin concentrations and larger unbound fractions (2 to 2.6 fold increase) of valproate. Accordingly, monitoring of total concentrations may be misleading since free concentrations may be substantially elevated in patients with hepatic disease whereas total concentrations may appear to be normal.

Renal Disease

A slight reduction (27%) in the unbound clearance of valproate has been reported in patients with renal failure (creatinine clearance < 10 mL/minute); however, hemodialysis typically reduces valproate concentrations by about 20%. Therefore, no dosage adjustment appears to be necessary in patients with renal failure. Protein binding in these patients is substantially reduced; thus, monitoring total concentrations may be misleading.

Plasma Levels and Clinical Effect
The relationship between plasma concentration and clinical response is not well documented. One contributing factor is the nonlinear, concentration dependent protein binding of valproate which affects the clearance of the drug. Thus, monitoring of total serum valproate cannot provide a reliable index of the bioactive valproate species.

For example, because the plasma protein binding of valproate is concentration dependent, the free fraction increases from approximately 10% at 40 μg/mL to 18.5% at 130 μg/mL. Higher than expected free fractions occur in the elderly, in hyperlipidemic patients, and in patients with hepatic and renal diseases.

Epilepsy

The therapeutic range in epilepsy is commonly considered to be 50 to 100 μg/mL of total valproate, although some patients may be controlled with lower or higher plasma concentrations.

Mania

In placebo-controlled clinical trials of acute mania, patients were dosed to clinical response with trough plasma concentrations between 50 and 125 μg/mL (See DOSAGE AND ADMINISTRATION).

CLINICAL TRIALS

Mania
The effectiveness of divalproex sodium delayed-release tablets for the treatment of acute mania was demonstrated in two 3-week, placebo controlled, parallel group studies.
(1) Study 1: The first study enrolled adult patients who met DSM-III-R criteria for Bipolar Disorder and who were hospitalized for acute mania. In addition, they had a history of failing to respond to or not tolerating previous lithium carbonate treatment. Divalproex sodium delayed-release tablets were initiated at a dose of 250 mg tid and adjusted to achieve serum valproate concentrations in a range of 50-100 μg/mL by day 7. Mean divalproex sodium delayed-release tablets doses for completers in this study were 1118, 1525, and 2402 mg/day at Day 7, 14, and 21, respectively. Patients were assessed on the Young Mania Rating Scale (YMRS; score ranges from 0-60), an augmented Brief Psychiatric Rating Scale (BPRS-A), and the Global Assessment Scale (GAS). Baseline scores and change from baseline in the Week 3 endpoint (last-observation-carry-forward) analysis were as follows:
Study 1

YMRS Total Score

Group	**Baseline[1]**	**BL to Wk 3[2]**	**Difference[3]**
Placebo	28.8	+0.2	
Divalproex Sodium Delayed-Release Tablets	28.5	-9.5	9.7

BPRS-A Total Score

Group	**Baseline[1]**	**BL to Wk 3[2]**	**Difference[3]**
Placebo	76.2	+1.8	
Divalproex Sodium	76.4	-17.0	18.8

Delayed-Release Tablets

	GAS Score		
Group	**Baseline[1]**	**BL to Wk 3[2]**	**Difference[3]**
Placebo	31.8	0.0	
Divalproex Sodium Delayed-Release Tablets	30.3	+18.1	18.1

[1] Mean score at baseline

[2] Change from baseline to Week 3 (LOCF)

[3] Difference in change from baseline to Week 3 endpoint (LOCF) between divalproex sodium delayed-release tablets and placebo

Divalproex sodium delayed-release tablets were statistically significantly superior to placebo on all three measures of outcome.
(2) Study 2: The second study enrolled adult patients who met Research Diagnostic Criteria for manic disorder and who were hospitalized for acute mania. Divalproex sodium delayed-release tablets were initiated at a dose of 250 mg tid and adjusted within a dose range of 750-2500 mg/day to achieve serum valproate concentrations in a range of 40-150 μg/mL. Mean divalproex sodium delayed-release tablets doses for completers in this study were 1116, 1683, and 2006 mg/day at Days 7, 14, and 21, respectively. Study 2 also included a lithium group for which lithium doses for completers were 1312, 1869, and 1984 mg/day at Days 7, 14, and 21, respectively. Patients were assessed on the Manic Rating Scale (MRS; score ranges from 11-63), and the primary outcome measures were the total MRS score, and scores for two subscales of the MRS, i.e., the Manic Syndrome Scale (MSS) and the Behavior and Ideation Scale (BIS). Baseline scores and change from baseline in the Week 3 endpoint (last-observation-carry-forward) analysis were as follows:
Study 2

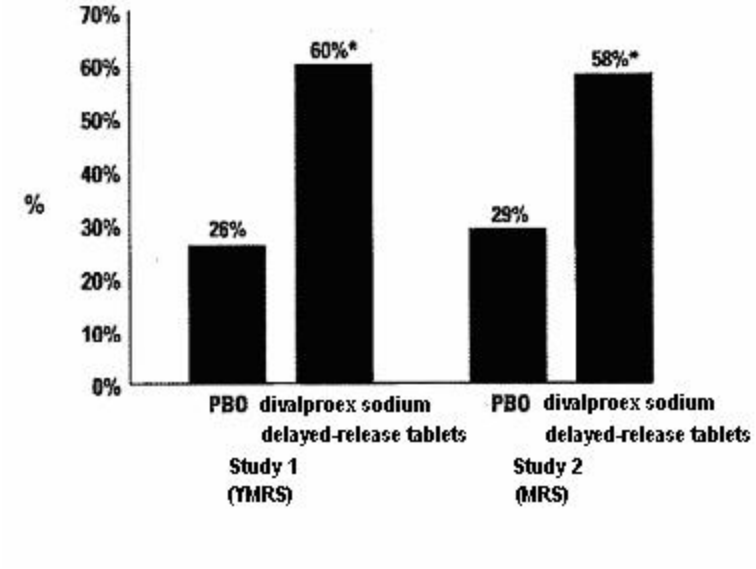
	MRS Total Score		
Group	**Baseline[1]**	**BL to Day 21[2]**	**Difference[3]**
Placebo	38.9	-4.4	
Lithium	37.9	-10.5	6.1
Divalproex Sodium Delayed-Release Tablets	38.1	-9.5	5.1
	MSS Total Score		
Group	**Baseline[1]**	**BL to Day 21[2]**	**Difference[3]**
Placebo	18.9	-2.5	
Lithium	18.5	-6.2	3.7
Divalproex Sodium Delayed-Release Tablets	18.9	-6.0	3.5
	BIS Total Score		
Group	**Baseline[1]**	**BL to Day 21[2]**	**Difference[3]**
Placebo	16.4	-1.4	
Lithium	16.0	-3.8	2.4
Divalproex Sodium Delayed-Release Tablets	15.7	-3.2	1.8

[1] Mean score at baseline

[2] Change from baseline to Day 21 (LOCF)

[3] Difference in change from baseline to Day 21 endpoint (LOCF) between divalproex sodium delayed-release tablets and placebo and lithium and placebo

Divalproex sodium delayed-release tablets were statistically significantly superior to placebo on all three measures of outcome. An exploratory analysis for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or gender.
A comparison of the percentage of patients showing ≥ 30% reduction in the symptom score from baseline in each treatment group, separated by study, is shown in Figure 1.
Figure 1. Percentage of Patients Achieving ≥ 30% Reduction in Symptom Score From Baseline



* $p < 0.05$
PBO = placebo, DVPX = divalproex sodium delayed-release tablets

Migraine

The results of two multicenter, randomized, double-blind, placebo-controlled clinical trials established the effectiveness of divalproex sodium delayed-release tablets in the prophylactic treatment of migraine headache.

Both studies employed essentially identical designs and recruited patients with a history of migraine with or without aura (of at least 6 months in duration) who were experiencing at least 2 migraine headaches a month during the 3 months prior to enrollment. Patients with cluster headaches were excluded. Women of childbearing potential were excluded entirely from one study, but were permitted in the other if they were deemed to be practicing an effective method of contraception.

In each study following a 4-week single-blind placebo baseline period, patients were randomized, under double blind conditions, to divalproex sodium delayed-release tablets or placebo for a 12-week treatment phase, comprised of a 4-week dose titration period followed by an 8-week maintenance period. Treatment outcome was assessed on the basis of 4-week migraine headache rates during the treatment phase.

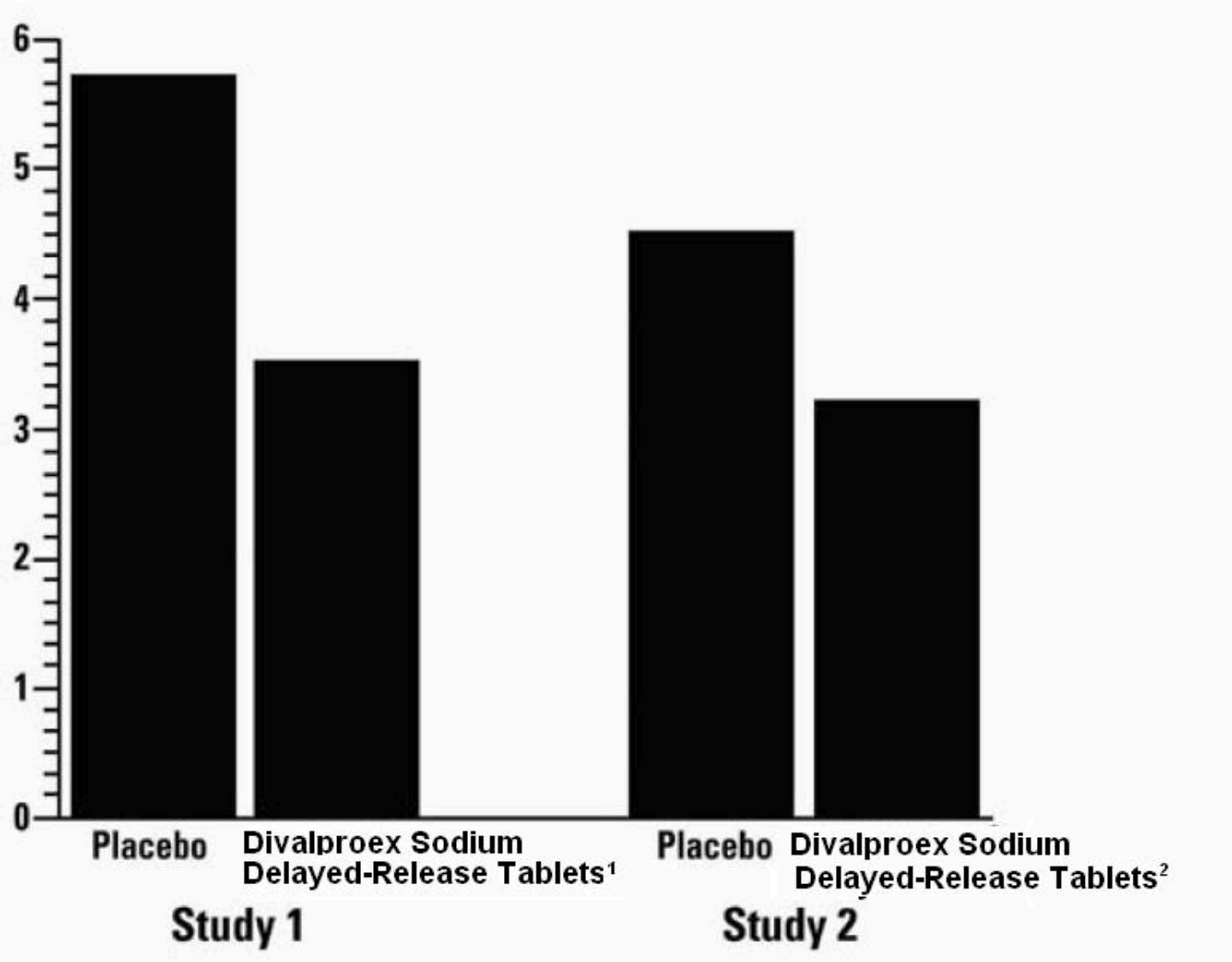
In the first study, a total of 107 patients (24 M, 83 F), ranging in age from 26 to 73 were randomized 2:1, divalproex sodium delayed-release tablets to placebo. Ninety patients completed the 8-week maintenance period. Drug dose titration, using 250 mg tablets, was individualized at the investigator's discretion. Adjustments were guided by actual/sham trough total serum valproate levels in order to maintain the study blind. In patients on divalproex sodium delayed-release tablets dose ranged from 500 to 2500 mg a day. Doses over 500 mg were given in three divided doses (TID). The mean dose during the treatment phase was 1087 mg/day resulting in a mean trough total valproate level of 72.5 μg/mL, with a range of 31 to 133 μg/mL.

The mean 4-week migraine headache rate during the treatment phase was 5.7 in the placebo group compared to 3.5 in the divalproex sodium delayed-release tablets group (see Figure 2). These rates were significantly different.

In the second study, a total of 176 patients (19 males and 157 females), ranging in age from 17 to 76 years, were randomized equally to one of three divalproex sodium delayed-release tablets dose groups (500, 1000, or 1500 mg/day) or placebo. The treatments were given in two divided doses (BID). One hundred thirty-seven patients completed the 8-week maintenance period. Efficacy was to be determined by a comparison of the 4-week migraine headache rate in the combined 1000/1500 mg/day group and placebo group. The initial dose was 250 mg daily. The regimen was advanced by 250 mg every 4 days (8 days for 500 mg/day group), until the randomized dose was achieved. The mean trough total valproate levels during the treatment phase were 39.6, 62.5, and 72.5 μg/mL in the divalproex sodium delayed-release tablets 500, 1000, and 1500 mg/day groups, respectively.

The mean 4-week migraine headache rates during the treatment phase, adjusted for differences in baseline rates, were 4.5 in the placebo group, compared to 3.3, 3.0, and 3.3 in the divalproex sodium delayed-release tablets 500, 1000, and 1500 mg/day groups, respectively, based on intent-to-treat results (see Figure 2). Migraine headache rates in the combined divalproex sodium delayed-release tablets 1000/1500 mg group were significantly lower than in the placebo group.

Figure 2. Mean 4-week Migraine Rates



[1] Mean dose of divalproex sodium delayed-release tablets was 1087 mg/day.

[2] Dose of divalproex sodium delayed-release tablets was 500 or 1000 mg/day.

Epilepsy

The efficacy of divalproex sodium delayed-release tablets in reducing the incidence of complex partial seizures (CPS) that occur in isolation or in association with other seizure types was established in two controlled trials.

In one, multiclinic, placebo controlled study employing an add-on design, (adjunctive therapy) 144 patients who continued to suffer eight or more CPS per 8 weeks during an 8 week period of monotherapy with doses of either carbamazepine or phenytoin sufficient to assure plasma concentrations within the "therapeutic range" were randomized to receive, in addition to their original antiepilepsy drug (AED), either divalproex sodium delayed-release tablets or placebo. Randomized patients were to be followed for a total of 16 weeks. The following table presents the findings.

Adjunctive Therapy Study Median Incidence of CPS per 8 weeks

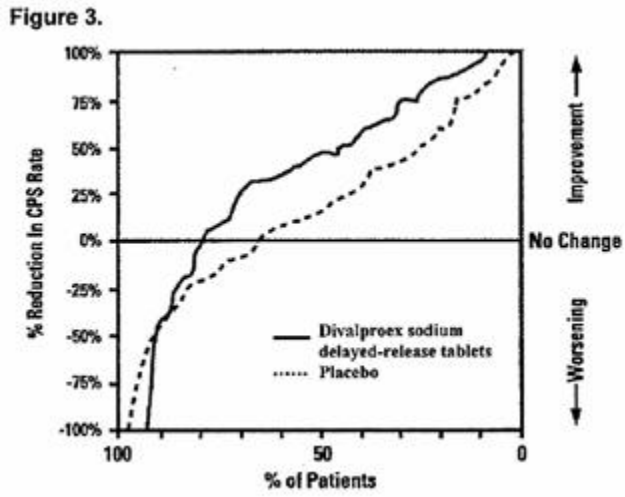
Add-on treatment	Number of Patients	Baseline Incidence	Experimental Incidence
Divalproex Sodium Delayed-Release Tablets	75	16.0	8.9*
Placebo	69	14.5	11.5

*Reduction from baseline statistically significantly greater for divalproex sodium delayed-release tablets than placebo at $p \leq 0.05$ level.

Figure 3 presents the proportion of patients (X axis) whose percentage reduction from baseline in complex partial seizure rates was at least as great as that indicated on the Y axis in the adjunctive therapy study. A positive percent reduction indicates an improvement (i.e., a decrease in seizure frequency), while a negative percent reduction indicates worsening. Thus, in a display of this type, the curve

for an effective treatment is shifted to the left of the curve for placebo. This figure shows that the proportion of patients achieving any particular level of improvement was consistently higher for divalproex sodium delayed-release tablets than for placebo. For example, 45% of patients treated with divalproex sodium delayed-release tablets had a ≥ 50% reduction in complex partial seizure rate compared to 23% of patients treated with placebo.

Figure 3.



The second study assessed the capacity of divalproex sodium delayed-release tablets to reduce the incidence of CPS when administered as the sole AED. The study compared the incidence of CPS among patients randomized to either a high or low dose treatment arm. Patients qualified for entry into the randomized comparison phase of this study only if 1) they continued to experience 2 or more CPS per 4 weeks during an 8 to 12 week long period of monotherapy with adequate doses of an AED (i.e., phenytoin, carbamazepine, phenobarbital, or primidone) and 2) they made a successful transition over a two week interval to divalproex sodium delayed-release tablets. Patients entering the randomized phase were then brought to their assigned target dose, gradually tapered off their concomitant AED and followed for an interval as long as 22 weeks. Less than 50% of the patients randomized, however, completed the study. In patients converted to divalproex sodium delayed-release tablets monotherapy, the mean total valproate concentrations during monotherapy were 71 and 123 μg/mL in the low dose and high dose groups, respectively.

The following table presents the findings for all patients randomized who had at least one post-randomization assessment.

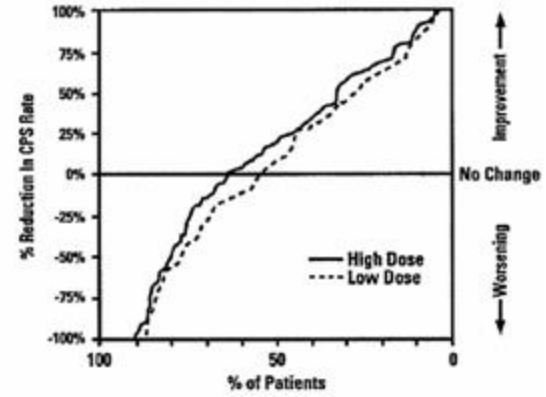
Monotherapy Study Median Incidence of CPS per 8 Weeks

Treatment	Number of Patients	Baseline Incidence	Randomized Phase Incidence
High Dose Divalproex Sodium Delayed-Release Tablets	131	13.2	10.7*
Low Dose Divalproex Sodium Delayed-Release Tablets	134	14.2	13.8

* Reduction from baseline statistically significantly greater for high dose than low dose at $p \leq 0.05$ level.

Figure 4 presents the proportion of patients (X axis) whose percentage reduction from baseline in complex partial seizure rates was at least as great as that indicated on the Y axis in the monotherapy study. A positive percent reduction indicates an improvement (i.e., a decrease in seizure frequency), while a negative percent reduction indicates worsening. Thus, in a display of this type, the curve for a more effective treatment is shifted to the left of the curve for a less effective treatment. This figure shows that the proportion of patients achieving any particular level of reduction was consistently higher for high dose divalproex sodium delayed-release tablets than for low dose divalproex sodium delayed-release tablets. For example, when switching from carbamazepine, phenytoin, phenobarbital or primidone monotherapy to high dose divalproex sodium delayed-release tablets monotherapy, 63% of patients experienced no change or a reduction in complex partial seizure rates compared to 54% of patients receiving low dose divalproex sodium delayed-release tablets.

Figure 4.



INDICATIONS AND USAGE

Mania

Divalproex sodium delayed-release tablets are indicated for the treatment of the manic episodes associated with bipolar disorder. A manic episode is a distinct period of abnormally and persistently elevated, expansive, or irritable mood. Typical symptoms of mania include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, poor judgement, aggressiveness, and possible hostility.

The efficacy of divalproex sodium delayed-release tablets was established in 3-week trials with patients meeting DSM-III-R criteria for bipolar disorder who were hospitalized for acute mania (See Clinical Trials under CLINICAL PHARMACOLOGY).

The safety and effectiveness of divalproex sodium delayed-release tablets for long-term use in mania, i.e., more than 3 weeks, has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use divalproex sodium delayed-release tablets for extended periods should continually reevaluate the long-term usefulness of the drug for the individual patient.

Epilepsy

Divalproex sodium delayed-release tablets are indicated as monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures. Divalproex sodium delayed-release tablets are also indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types that include absence seizures.

Simple absence is defined as very brief clouding of the sensorium or loss of consciousness accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

Migraine

Divalproex sodium delayed-release tablets are indicated for prophylaxis of migraine headaches. There is no evidence that divalproex sodium delayed-release tablets are useful in the acute treatment of migraine headaches. Because valproic acid may be a hazard to the fetus, divalproex sodium delayed-release tablets should be considered for women of childbearing potential only after this risk has been thoroughly discussed with the patient and weighed against the potential benefits of treatment (see WARNINGS - Usage In Pregnancy, PRECAUTIONS - Information for Patients).

SEE WARNINGS FOR STATEMENT REGARDING FATAL HEPATIC DYSFUNCTION.

CONTRAINDICATIONS

DIVALPROEX SODIUM SHOULD NOT BE ADMINISTERED TO PATIENTS WITH HEPATIC DISEASE OR SIGNIFICANT HEPATIC DYSFUNCTION.

Divalproex sodium is contraindicated in patients with known hypersensitivity to the drug.

Divalproex sodium is contraindicated in patients with known urea cycle disorders (see WARNINGS).

WARNINGS

Hepatotoxicity

Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination.

Caution should be observed when administering divalproex sodium delayed-release tablets products to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, children, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk. Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When divalproex sodium delayed-release tablets are used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above this age group, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.
The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug.

Pancreatitis
Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. Some of the cases have been described as hemorrhagic with rapid progression from initial symptoms to death. Some cases have occurred shortly after initial use as well as after several years of use. The rate based upon the reported cases exceeds that expected in the general population and there have been cases in which pancreatitis recurred after rechallenge with valproate. In clinical trials, there were 2 cases of pancreatitis without alternative etiology in 2416 patients, representing 1044 patient-years experience. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated (see BOXED WARNING).

Urea Cycle Disorders (UCD)
Divalproex sodium is contraindicated in patients with known urea cycle disorders.
Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency. Prior to the initiation of valproate therapy, evaluation for UCD should be considered in the following patients: 1) those with a history of unexplained encephalopathy or coma, encephalopathy associated with a protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine; 2) those with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN, or protein avoidance; 3) those with a family history of UCD or a family history of unexplained infant deaths (particularly males); 4) those with other signs or symptoms of UCD. Patients who develop symptoms of unexplained hyperammonemic encephalopathy while receiving valproate therapy should receive prompt treatment (including discontinuation of valproate therapy) and be evaluated for underlying urea cycle disorders (see CONTRAINDICATIONS and PRECAUTIONS).

Somnolence in the Elderly
In a double-blind, multicenter trial of valproate in elderly patients with dementia (mean age = 83 years), doses were increased by 125 mg/day to a target dose of 20 mg/kg/day. A significantly higher proportion of valproate patients had somnolence compared to placebo, and although not statistically significant, there was a higher proportion of patients with dehydration. Discontinuations for somnolence were also significantly higher than with placebo. In some patients with somnolence (approximately one-half), there was associated reduced nutritional intake and weight loss. There was a trend for the patients who experienced these events to have a lower baseline albumin concentration, lower valproate clearance, and a higher BUN. In elderly patients, dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence (see DOSAGE AND ADMINISTRATION).

Thrombocytopenia
The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia [see PRECAUTIONS) may be dose-related. In a clinical trial of divalproex sodium delayed-release tablets as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets $\leq 75 \times 10^9$/L. Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts normalized with continued treatment. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of ≥ 110 μg/mL (females) or ≥ 135 μg/mL (males). The therapeutic benefit which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.

Usage In Pregnancy
VALPROATE CAN PRODUCE TERATOGENIC EFFECTS. DATA SUGGEST THAT THERE IS AN INCREASED INCIDENCE OF CONGENITAL MALFORMATIONS ASSOCIATED WITH THE USE OF VALPROATE BY WOMEN WITH SEIZURE DISORDERS DURING PREGNANCY WHEN COMPARED TO THE INCIDENCE IN WOMEN WITH SEIZURE DISORDERS WHO DO NOT USE ANTIEPILEPTIC DRUGS DURING PREGNANCY, THE INCIDENCE IN WOMEN WITH SEIZURE DISORDERS WHO USE OTHER ANTIEPILEPTIC DRUGS, AND THE BACKGROUND INCIDENCE FOR THE GENERAL

POPULATION. THEREFORE, VALPROATE SHOULD BE CONSIDERED FOR WOMEN OF CHILDBEARING POTENTIAL ONLY AFTER THE RISKS HAVE BEEN THOROUGHLY DISCUSSED WTH THE PATIENT AND WEIGHED AGAINST THE POTENTIAL BENEFITS OF TREATMENT.

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE THAT INDICATE THE USE OF ANTIEPILEPTIC DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF CONGENITAL MALFORMATIONS IN OFFSPRING. ANTIEPILEPTIC DRUGS, INCLUDING VALPROATE, SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR MEDICAL CONDITION.

Antiepileptic drugs should not be discontinued abruptly in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

HUMAN DATA

Congenital Malformations

The North American Antiepileptic Drug Pregnancy Registry reported 16 cases of congenital malformations among the offspring of 149 women with epilepsy who were exposed to valproic acid monotherapy during the first trimester of pregnancy at doses of approximately 1,000 mg per day, for a prevalence rate of 10.7% (95% CI 6.3%-16.9%). Three of the 149 offspring (2%) had neural tube defects and 6 of the 149 (4%) had less severe malformations. Among epileptic women who were exposed to other antiepileptic drug monotherapies during pregnancy (1,048 patients) the malformation rate was 2.9% (95% CI 2.0% to 4.1%). There was a 4-fold increase in congenital malformations among infants with valproic acid-exposed mothers compared with those treated with other antiepileptic monotherapies as a group (Odds Ratio 4.0; 95% CI 2.1 to 7.4). This increased risk does not reflect a comparison versus any specific antiepileptic drug, but the risk versus the heterogeneous group of all other antiepileptic drug monotherapies combined. The increased teratogenic risk from valproic acid in women with epilepsy is expected to be reflected in an increased risk in other indications (e.g., migraine or bipolar disorder).

THE STRONGEST ASSOCIATION OF MATERNAL VALPROATE USAGE WITH CONGENITAL MALFORMATIONS IS WITH NEURAL TUBE DEFECTS (AS DISCUSSED UNDER THE NEXT SUBHEADING). HOWEVER, OTHER CONGENITAL ANOMALIES (E.G. CRANIOFACIAL DEFECTS, CARDIOVASCULAR MALFORMATIONS AND ANOMALIES INVOLVING VARIOUS BODY SYSTEMS), COMPATIBLE AND INCOMPATIBLE WITH LIFE, HAVE BEEN REPORTED. SUFFICIENT DATA TO DETERMINE THE INCIDENCE OF THESE CONGENITAL ANOMALIES IS NOT AVAILABLE.

Neural Tube Defects

THE INCIDENCE OF NEURAL TUBE DEFECTS IN THE FETUS IS INCREASED IN MOTHERS RECEIVING VALPROATE DURING THE FIRST TRIMESTER OF PREGNANCY. THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1 TO 2%. THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG) ESTIMATES THE GENERAL POPULATION RISK FOR CONGENITAL NEURAL TUBE DEFECTS AS 0.14% TO 0.2%.

Tests to detect neural tube and other defects using current accepted procedures should be considered a part of routine prenatal care in pregnant women receiving valproate.

Evidence suggests that pregnant women who receive folic acid supplementation may be at decreased risk for congenital neural tube defects in their offspring compared to pregnant women not receiving folic acid. Whether the risk of neural tube defects in the offspring of women receiving valproate specifically is reduced by folic acid supplementation is unknown. DIETARY FOLIC ACID SUPPLEMENTATION BOTH PRIOR TO AND DURING PREGNANCY SHOULD BE ROUTINELY RECOMMENDED TO PATIENTS CONTEMPLATING PREGNANCY.

Other Adverse Pregnancy Effects

PATIENTS TAKING VALPROATE MAY DEVELOP CLOTTING ABNORMALITIES (SEE PRECAUTIONS - GENERAL AND WARNINGS). A PATIENT WHO HAD LOW FIBRINOGEN WHEN TAKING MULTIPLE ANTICONVULSANTS INCLUDING VALPROATE GAVE BIRTH TO AN INFANT WITH AFIBRINOGENEMIA WHO SUBSEQUENTLY DIED OF HEMORRHAGE. IF VALPROATE IS USED IN PREGNANCY, THE CLOTTING PARAMETERS SHOULD BE MONITORED CAREFULLY.

PATIENTS TAKING VALPROATE MAY DEVELOP HEPATIC FAILURE (SEE WARNINGS - HEPATOTOXICITY AND BOX WARNING). FATAL HEPATIC FAILURES, IN A NEWBORN AND IN AN INFANT, HAVE BEEN REPORTED FOLLOWING THE MATERNAL USE OF VALPROATE DURING PREGNANCY.

ANIMAL DATA

Animal studies have demonstrated valproate-induced teratogenicity. Increased frequencies of malformations, as well as intrauterine growth retardation and death, have been observed in mice, rats, rabbits, and monkeys following prenatal exposure to valproate. Malformations of the skeletal system are the most common structural abnormalities produced in experimental animals, but neural tube closure defects have been seen in mice exposed to maternal plasma valproate concentrations exceeding 230 μg/mL (2.3 times the upper limit of the human therapeutic range) during susceptible periods of embryonic development. Administration of an oral dose of 200 mg/kg/day or greater (50% of the maximum human daily dose or greater on a mg/m^2 basis) to pregnant rats during organogenesis

produced malformations (skeletal, cardiac, and urogenital) and growth retardation in the offspring. These doses resulted in peak maternal plasma valproate levels of approximately 340 μg/mL or greater (3.4 times the upper limit of the human therapeutic range or greater). Behavioral deficits have been reported in the offspring of rats given a dose of 200 mg/kg/day throughout most of pregnancy. An oral dose of 350 mg/kg/day (approximately 2 times the maximum human daily dose on a mg/m^2 basis) produced skeletal and visceral malformations in rabbits exposed during organogenesis. Skeletal malformations, growth retardation, and death were observed in rhesus monkeys following administration of an oral dose of 200 mg/kg/day (equal to the maximum human daily dose on a mg/m^2 basis) during organogenesis. This dose resulted in peak maternal plasma valproate levels of approximately 280 μg/mL (2.8 times the upper limit of the human therapeutic range).

PRECAUTIONS

Hepatic Dysfunction
See BOXED WARNING, CONTRAINDICATIONS and WARNINGS.

Pancreatitis
See BOXED WARNING and WARNINGS.

Hyperammonemia
Hyperammonemia has been reported in association with valproate therapy and may be present despite normal liver function tests. In patients who develop unexplained lethargy and vomiting or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured. If ammonia is increased, valproate therapy should be discontinued. Appropriate interventions for treatment of hyperammonemia should be initiated, and such patients should undergo investigation for underlying urea cycle disorders (see CONTRAINDICATIONS and WARNINGS – Urea Cycle Disorders and PRECAUTIONS- Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use).
Asymptomatic elevations of ammonia are more common and when present, require close monitoring of plasma ammonia levels. If the elevation persists, discontinuation of valproate therapy should be considered. In patients who develop unexplained lethargy, vomiting, or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured. (see CONTRAINDICATIONS and WARNINGS - Urea Cycle Disorders and PRECAUTIONS -Hyperammonemia).

Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use
Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. In most cases, symptoms and signs abated with discontinuation of either drug. This adverse event is not due to a pharmacokinetic interaction. It is not known if topiramate monotherapy is associated with hyperammonemia. Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy. Although not studied, an interaction of topiramate and valproic acid may exacerbate existing defects or unmask deficiencies in susceptible persons. In patients who develop unexplained lethargy, vomiting, or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured. (see CONTRAINDICATIONS and WARNINGS -Urea Cycle Disorders and PRECAUTIONS - Hyperammonemia).

General
This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.
Because of reports of thrombocytopenia (see WARNINGS), inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters, (e.g., low fibrinogen), platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving divalproex sodium delayed-release tablets be monitored for platelet count and coagulation parameters prior to planned surgery. In a clinical trial of divalproex sodium delayed-release tablets as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets ≤ 75×10^9/L. Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts normalized with continued treatment. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of ≥ 110 μg/mL (females) or ≥ 135 μg/mL (males). Evidence of hemorrhage, bruising, or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.
Since divalproex sodium delayed-release tablets may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy. (See PRECAUTIONS- Drug Interactions.)
Valproate is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test. There have been reports of altered thyroid function tests associated with valproate. The clinical significance of these is unknown.

Suicidal ideation may be a manifestation of certain psychiatric disorders, and may persist until significant remission of symptoms occurs. Close supervision of high risk patients should accompany initial drug therapy.
There are *in vitro* studies that suggest valproate stimulates the replication of the HIV and CMV viruses under certain experimental conditions. The clinical consequence, if any, is not known. Additionally, the relevance of these *in vitro* findings is uncertain for patients receiving maximally suppressive antiretroviral therapy. Nevertheless, these data should be borne in mind when interpreting the results from regular monitoring of the viral load in HIV infected patients receiving valproate or when following CMV infected patients clinically.

Multi-organ Hypersensitivity Reaction
Multi-organ hypersensitivity reactions have been rarely reported in close temporal association to the initiation of valproate therapy in adult and pediatric patients (median time to detection 21 days: range 1 to 40 days). Although there have been a limited number of reports, many of these cases resulted in hospitalization and at least one death has been reported. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations may include lymphadenopathy, hepatitis, liver function test abnormalities, hematological abnormalities (e.g., eosinophilia, thrombocytopenia, neutropenia), pruritis, nephritis, oliguria, hepato-renal syndrome, arthralgia, and asthenia. Because the disorder is variable in its expression, other organ system symptoms and signs, not noted here, may occur. If this reaction is suspected, valproate should be discontinued and an alternative treatment started. Although the existence of cross sensitivity with other drugs that produce this syndrome is unclear, the experience amongst drugs associated with multi-organ hypersensitivity would indicate this to be a possibility.

Information for Patients
Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis and, therefore, require further medical evaluation promptly.
Patients should be informed of the signs and symptoms associated with hyperammonemic encephalopathy (see PRECAUTIONS – Hyperammonemia) and be told to inform the prescriber if any of these symptoms occur.
Since divalproex sodium delayed-release tablets products may produce CNS depression, especially when combined with another CNS depressant (eg, alcohol), patients should be advised not to engage in hazardous activities, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.
Since divalproex sodium delayed-release tablets have been associated with certain types of birth defects, female patients of child-bearing age considering the use of divalproex sodium delayed-release tablets should be advised of the risk and of alternative therapeutic options and to read the Patient Information Leaflet, which appears as the last section of the labeling. This is especially important when the treatment of a spontaneously reversible condition not ordinarily associated with permanent injury or risk of death (e.g., migraine) is considered.
Patients should be instructed that a fever associated with other organ system involvement (rash, lymphadenopathy, etc.) may be drug-related and should be reported to the physician immediately (see PRECAUTIONS - Multi-organ Hypersensitivity Reaction).

Drug Interactions

Effects of Co-Administered Drugs on Valproate Clearance
Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronosyltransferases, may increase the clearance of valproate. For example, phenytoin, carbamazepine, and phenobarbital (or primidone) can double the clearance of valproate. Thus, patients on monotherapy will generally have longer half-lives and higher concentrations than patients receiving polytherapy with antiepilepsy drugs.

In contrast, drugs that are inhibitors of cytochrome P450 isozymes, e.g., antidepressants, may be expected to have little effect on valproate clearance because cytochrome P450 microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and beta-oxidation.

Because of these changes in valproate clearance, monitoring of valproate and concomitant drug concentrations should be increased whenever enzyme inducing drugs are introduced or withdrawn.

The following list provides information about the potential for an influence of several commonly prescribed medications on valproate pharmacokinetics. The list is not exhaustive nor could it be, since new interactions are continuously being reported.

Drugs for which a potentially important interaction has been observed
Aspirin

A study involving the co-administration of aspirin at antipyretic doses (11 to 16 mg/kg) with valproate to pediatric patients (n=6) revealed a decrease in protein binding and an inhibition of metabolism of valproate. Valproate free fraction was increased 4-fold in the presence of aspirin compared to valproate alone. The β-oxidation pathway consisting of 2-E-valproic acid, 3-OH-valproic acid,

and 3-keto valproic acid was decreased from 25% of total metabolites excreted on valproate alone to 8.3% in the presence of aspirin. Caution should be observed if valproate and aspirin are to be co-administered.

Felbamate

A study involving the co-administration of 1200 mg/day of felbamate with valproate to patients with epilepsy (n=10) revealed an increase in mean valproate peak concentration by 35% (from 86 to 115 μg/mL) compared to valproate alone. Increasing the felbamate dose to 2400 mg/day increased the mean valproate peak concentration to 133 μg/mL (another 16% increase). A decrease in valproate dosage may be necessary when felbamate therapy is initiated.

Meropenem

Subtherapeutic valproic acid levels have been reported when meropenem was coadministered.

Rifampin

A study involving the administration of a single dose of valproate (7 mg/kg) 36 hours after 5 nights of daily dosing with rifampin (600 mg) revealed a 40% increase in the oral clearance of valproate. Valproate dosage adjustment may be necessary when it is co-administered with rifampin.

Drugs for which either no interaction or a likely clinically unimportant interaction has been observed
Antacids

A study involving the co-administration of valproate 500 mg with commonly administered antacids (Maalox, Trisogel, and Titralac - 160 mEq doses) did not reveal any effect on the extent of absorption of valproate.

Chlorpromazine

A study involving the administration of 100 to 300 mg/day of chlorpromazine to schizophrenic patients already receiving valproate (200 mg BID) revealed a 15% increase in trough plasma levels of valproate.

Haloperidol

A study involving the administration of 6 to 10 mg/day of haloperidol to schizophrenic patients already receiving valproate (200 mg BID) revealed no significant changes in valproate trough plasma levels.

Cimetidine and Ranitidine

Cimetidine and ranitidine do not affect the clearance of valproate.

Effects of Valproate on Other Drugs
Valproate has been found to be a weak inhibitor of some P450 isozymes, epoxide hydrase, and glucuronosyltransferases.

The following list provides information about the potential for an influence of valproate co-administration on the pharmacokinetics or pharmacodynamics of several commonly prescribed medications. The list is not exhaustive, since new interactions are continuously being reported.

Drugs for which a potentially important valproate interaction has been observed
Amitriptyline/Nortriptyline

Administration of a single oral 50 mg dose of amitriptyline to 15 normal volunteers (10 males and 5 females) who received valproate (500 mg BID) resulted in a 21% decrease in plasma clearance of amitriptyline and a 34% decrease in the net clearance of nortriptyline. Rare postmarketing reports of concurrent use of valproate and amitriptyline resulting in an increased amitriptyline level have been received. Concurrent use of valproate and amitriptyline has rarely been associated with toxicity. Monitoring of amitriptyline levels should be considered for patients taking valproate concomitantly with amitriptyline. Consideration should be given to lowering the dose of amitriptyline/nortriptyline in the presence of valproate.

Carbamazepine/carbamazepine-10, 11-Epoxide

Serum levels of carbamazepine (CBZ) decreased 17% while that of carbamazepine- 10, 11-epoxide (CBZ-E) increased by 45% upon co-administration of valproate and CBZ to epileptic patients.

Clonazepam

The concomitant use of valproic acid and clonazepam may induce absence status in patients with a history of absence type seizures.

Diazepam

Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. Co-administration of valproate (1500 mg daily) increased the free fraction of diazepam (10 mg) by 90% in healthy volunteers (n=6). Plasma clearance and volume of distribution for free diazepam were reduced by 25% and 20%, respectively, in the presence of valproate. The elimination half-life of diazepam remained unchanged upon addition of valproate.

Ethosuximide

Valproate inhibits the metabolism of ethosuximide. Administration of a single ethosuximide dose of 500 mg with valproate (800 to 1600 mg/day) to healthy volunteers (n=6) was accompanied by a 25% increase in elimination half-life of ethosuximide and a 15% decrease in its total clearance as compared to ethosuximide alone. Patients receiving valproate and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

Lamotrigine

In a steady-state study involving 10 healthy volunteers, the elimination half-life of lamotrigine increased from 26 to 70 hours with valproate co-administration (a 165% increase). The dose of lamotrigine should be reduced when co-administered with valproate. Serious skin reactions (such as Stevens-Johnson Syndrome and toxic epidermal necrolysis) have been reported with concomitant lamotrigine and valproate administration. See lamotrigine package insert for details on lamotrigine dosing with concomitant valproate administration.

Phenobarbital

Valproate was found to inhibit the metabolism of phenobarbital. Co-administration of valproate (250 mg BID for 14 days) with phenobarbital to normal subjects (n=6) resulted in a 50% increase in half-life and a 30% decrease in plasma clearance of phenobarbital (60 mg single-dose). The fraction of phenobarbital dose excreted unchanged increased by 50% in presence of valproate.

There is evidence for severe CNS depression, with or without significant elevations of barbiturate or valproate serum concentrations. All patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate concentrations should be obtained, if possible, and the barbiturate dosage decreased, if appropriate.

Primidone, which is metabolized to a barbiturate, may be involved in a similar interaction with valproate.

Phenytoin

Valproate displaces phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. Co-administration of valproate (400 mg TID) with phenytoin (250 mg) in normal volunteers (n=7) was associated with a 60% increase in the free fraction of phenytoin. Total plasma clearance and apparent volume of distribution of phenytoin increased 30% in the presence of valproate. Both the clearance and apparent volume of distribution of free phenytoin were reduced by 25%.

In patients with epilepsy, there have been reports of breakthrough seizures occurring with the combination of valproate and phenytoin. The dosage of phenytoin should be adjusted as required by the clinical situation.

Tolbutamide

From *in vitro* experiments, the unbound fraction of tolbutamide was increased from 20% to 50% when added to plasma samples taken from patients treated with valproate. The clinical relevance of this displacement is unknown.

Topiramate

Concomitant administration of valproic acid and topiramate has been associated with hyperammonemia with and without encephalopathy (see CONTRAINDICATIONS and WARNINGS - Urea Cycle Disorders and PRECAUTIONS - Hyperammonemia and - Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use).

Warfarin

In an *in vitro* study, valproate increased the unbound fraction of warfarin by up to 32.6%. The therapeutic relevance of this is unknown; however, coagulation tests should be monitored if divalproex sodium delayed-release tablets therapy is instituted in patients taking anticoagulants.

Zidovudine

In six patients who were seropositive for HIV, the clearance of zidovudine (100 mg q8h) was decreased by 38% after administration of valproate (250 or 500 mg q8h); the half-life of zidovudine was unaffected.

Drugs for which either no interaction or a likely clinically unimportant interaction has been observed
Acetaminophen

Valproate had no effect on any of the pharmacokinetic parameters of acetaminophen when it was concurrently administered to three epileptic patients.

Clozapine

In psychotic patients (n=11), no interaction was observed when valproate was co-administered with clozapine.

Lithium

Co-administration of valproate (500 mg BID) and lithium carbonate (300 mg TID) to normal male volunteers (n=16) had no effect on the steady-state kinetics of lithium.

Lorazepam

Concomitant administration of valproate (500 mg BID) and lorazepam (1 mg BID) in normal male volunteers (n=9) was accompanied by a 17% decrease in the plasma clearance of lorazepam.

Oral Contraceptive Steroids

Administration of a single-dose of ethinyloestradiol (50 μg)/ levonorgestrel (250 μg) to 6 women on valproate (200 mg BID) therapy for 2 months did not reveal any pharmacokinetic interaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Valproic acid was administered orally to Sprague Dawley rats and ICR (HA/ICR) mice at doses of 80 and 170 mg/kg/day (approximately 10 to 50% of the maximum human daily dose on a mg/m^2 basis) for two years. A variety of neoplasms were observed in both species. The chief findings were a statistically significant increase in the incidence of subcutaneous fibrosarcomas in high dose male rats receiving valproic acid and a statistically significant dose-related trend for benign pulmonary adenomas in male mice receiving valproic acid. The significance of these findings for humans is unknown.

Mutagenesis
Valproate was not mutagenic in an *in vitro* bacterial assay (Ames test), did not produce dominant lethal effects in mice, and did not increase chromosome aberration frequency in an *in vivo* cytogenetic study in rats. Increased frequencies of sister chromatid exchange (SCE) have been reported in a study of epileptic children taking valproate, but this association was not observed in another study conducted in adults. There is some evidence that increased SCE frequencies may be associated with epilepsy. The biological significance of an increase in SCE frequency is not known.

Fertility
Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at oral doses of 400 mg/kg/day or greater in rats (approximately equivalent to or greater than the maximum human daily dose on a mg/m^2 basis) and 150 mg/kg/day or greater in dogs (approximately 1.4 times the maximum human daily dose or greater on a mg/m^2 basis). Segment I fertility studies in rats have shown doses up to 350 mg/kg/day (approximately equal to the maximum human daily dose on a mg/m^2 basis) for 60 days to have no effect on fertility. THE EFFECT OF VALPROATE ON TESTICULAR DEVELOPMENT AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

Pregnancy
Pregnancy Category D: See WARNINGS.

Nursing Mothers
Valproate is excreted in breast milk. Concentrations in breast milk have been reported to be 1-10% of serum concentrations. It is not known what effect this would have on a nursing infant. Consideration should be given to discontinuing nursing when divalproex sodium is administered to a nursing woman.

Pediatric Use

Experience has indicated that pediatric patients under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions (see BOXED WARNING). When divalproex sodium delayed-release tablets are used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above the age of 2 years, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

Younger children, especially those receiving enzyme-inducing drugs, will require larger maintenance doses to attain targeted total and unbound valproic acid concentrations.

The variability in free fraction limits the clinical usefulness of monitoring total serum valproic acid concentrations. Interpretation of valproic acid concentrations in children should include consideration of factors that affect hepatic metabolism and protein binding.

The safety and effectiveness of divalproex sodium delayed-release tablets for the treatment of acute mania has not been studied in individuals below the age of 18 years.

The safety and effectiveness of divalproex sodium delayed-release tablets for the prophylaxis of migraines has not been studied in individuals below the age of 16 years.

The basic toxicology and pathologic manifestations of valproate sodium in neonatal (4-day old) and juvenile (14-day old) rats are similar to those seen in young adult rats. However, additional findings, including renal alterations in juvenile rats and renal alterations and retinal dysplasia in neonatal rats, have been reported. These findings occurred at 240 mg/kg/day, a dosage approximately equivalent to the human maximum recommended daily dose on a mg/m^2 basis. They were not seen at 90 mg/kg, or 40% of the maximum human daily dose on a mg/m^2 basis.

Geriatric Use

No patients above the age of 65 years were enrolled in double-blind prospective clinical trials of mania associated with bipolar illness. In a case review study of 583 patients, 72 patients (12%) were greater than 65 years of age. A higher percentage of patients above 65 years of age reported accidental injury, infection, pain, somnolence, and tremor. Discontinuation of valproate was occasionally associated with the latter two events. It is not clear whether these events indicate additional risk or whether they result from preexisting medical illness and concomitant medication use among these patients.

A study of elderly patients with dementia revealed drug related somnolence and discontinuation for somnolence (see WARNINGS - Somnolence in the Elderly). The starting dose should be reduced in these patients, and dosage reductions or discontinuation should be considered in patients with excessive somnolence (see DOSAGE AND ADMINISTRATION).

There is insufficient information available to discern the safety and effectiveness of divalproex sodium delayed-release tablets for the prophylaxis of migraines in patients over 65.

ADVERSE REACTIONS

Mania

The incidence of treatment-emergent events has been ascertained based on combined data from two placebo-controlled clinical trials of divalproex sodium delayed-release tablets in the treatment of manic episodes associated with bipolar disorder. The adverse events were usually mild or moderate in intensity, but sometimes were serious enough to interrupt treatment. In clinical trials, the rates of premature termination due to intolerance were not statistically different between placebo, divalproex sodium delayed-release tablets, and lithium carbonate. A total of 4%, 8% and 11% of patients discontinued therapy due to intolerance in the placebo, divalproex sodium delayed-release tablets, and lithium carbonate groups, respectively.

Table 1 summarizes those adverse events reported for patients in these trials where the incidence rate in the divalproex sodium delayed-release tablet-treated group was greater than 5% and greater than the placebo incidence, or where the incidence in the divalproex sodium delayed-release tablet-treated group was statistically significantly greater than the placebo group. Vomiting was the only event that was reported by significantly ($p \leq 0.05$) more patients receiving divalproex sodium delayed-release tablets compared to placebo.

Table 1. Adverse Events Reported by > 5% of Divalproex Sodium Delayed-Release Tablet-Treated Patients During Placebo-Controlled Trials of Acute Mania[1]

Adverse Event	Divalproex Sodium Delayed-Release Tablets (n=89)	Placebo (n=97)
Nausea	22%	15%
Somnolence	19%	12%
Dizziness	12%	4%
Vomiting	12%	3%
Asthenia	10%	7%
Abdominal pain	9%	8%

Dyspepsia	9%	8%
Rash	6%	3%

[1] The following adverse events occurred at an equal or greater incidence for placebo than for divalproex sodium delayed-release tablets: back pain, headache, constipation, diarrhea, tremor, and pharyngitis.

The following additional adverse events were reported by greater than 1% but not more than 5% of the 89 divalproex sodium-treated patients in controlled clinical trials:

Body as a Whole

Chest pain, chills, chills and fever, fever, neck pain, neck rigidity.

Cardiovascular System

Hypertension, hypotension, palpitations, postural hypotension, tachycardia, vasodilation.

Digestive System

Anorexia, fecal incontinence, flatulence, gastroenteritis, glossitis, periodontal abscess.

Hemic and Lymphatic System

Ecchymosis.

Metabolic and Nutritional Disorders

Edema, peripheral edema.

Musculoskeletal System

Arthralgia, arthrosis, leg cramps, twitching.

Nervous System

Abnormal dreams, abnormal gait, agitation, ataxia, catatonic reaction, confusion, depression, diplopia, dysarthria, hallucinations, hypertonia, hypokinesia, insomnia, paresthesia, reflexes increased, tardive dyskinesia, thinking abnormalities, vertigo.

Respiratory System

Dyspnea, rhinitis.

Skin and Appendages

Alopecia, discoid lupus erythematosis, dry skin, furunculosis, maculopapular rash, seborrhea.

Special Senses

Amblyopia, conjunctivitis, deafness, dry eyes, ear pain, eye pain, tinnitus.

Urogenital System

Dysmenorrhea, dysuria, urinary incontinence.

Migraine

Based on two placebo-controlled clinical trials and their long term extension, divalproex sodium delayed-release tablets were generally well tolerated with most adverse events rated as mild to moderate in severity. Of the 202 patients exposed to divalproex sodium delayed-release tablets in the placebo-controlled trials, 17% discontinued for intolerance. This is compared to a rate of 5% for the 81 placebo patients. Including the long term extension study, the adverse events reported as the primary reason for discontinuation by ≥1% of 248 divalproex sodium delayed-release tablet-treated patients were alopecia (6%), nausea and/or vomiting (5%), weight gain (2%), tremor (2%), somnolence (1%), elevated SGOT and/or SGPT (1%), and depression (1%).

Table 2 includes those adverse events reported for patients in the placebo-controlled trials where the incidence rate in the divalproex sodium delayed-release tablet-treated group was greater than 5% and was greater than that for placebo patients.

Table 2. Adverse Events Reported by >5% of Divalproex Sodium Delayed-Release Tablet-Treated Patients During Migraine Placebo-Controlled Trials with a Greater Incidence Than Patients Taking Placebo[1]

Body System / Event	Divalproex Sodium Delayed-Release Tablets (N=202)	Placebo (N=81)
Gastrointestinal System		
Nausea	31%	10%
Dyspepsia	13%	9%
Diarrhea	12%	7%
Vomiting	11%	1%
Abdominal pain	9%	4%
Increased appetite	6%	4%
Nervous System		
Asthenia	20%	9%
Somnolence	17%	5%
Dizziness	12%	6%

Tremor	9%	0%
Other		
Weight gain	8%	2%
Back pain	8%	6%
Alopecia	7%	1%

[1] The following adverse events occurred in at least 5% of divalproex sodium delayed-release tablet-treated patients and at an equal or greater incidence for placebo than for divalproex sodium delayed-release tablets: flu syndrome and pharyngitis.

The following additional adverse events were reported by greater than 1% but not more than 5% of the 202 divalproex sodium-treated patients in the controlled clinical trials:
Body as a Whole
Chest pain, chills, face edema, fever and malaise.
Cardiovascular System
Vasodilatation.
Digestive System
Anorexia, constipation, dry mouth, flatulence, gastrointestinal disorder (unspecified), and stomatitis.
Hemic and Lymphatic System
Ecchymosis.
Metabolic and Nutritional Disorders
Peripheral edema, SGOT increase, and SGPT increase.
Musculoskeletal System
Leg cramps and myalgia.
Nervous System
Abnormal dreams, amnesia, confusion, depression, emotional lability, insomnia, nervousness, paresthesia, speech disorder, thinking abnormalities, and vertigo.
Respiratory System
Cough increased, dyspnea, rhinitis, and sinusitis.
Skin and Appendages
Pruritus and rash.
Special Senses
Conjunctivitis, ear disorder, taste perversion, and tinnitus.
Urogenital System
Cystitis, metrorrhagia, and vaginal hemorrhage.

Epilepsy
Based on a placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures, divalproex sodium delayed-release tablets were generally well tolerated with most adverse events rated as mild to moderate in severity. Intolerance was the primary reason for discontinuation in the divalproex sodium delayed-release tablet-treated patients (6%), compared to 1% of placebo-treated patients.
Table 3 lists treatment-emergent adverse events which were reported by ≥ 5% of divalproex sodium delayed-release tablet-treated patients and for which the incidence was greater than in the placebo group, in the placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures. Since patients were also treated with other antiepilepsy drugs, it is not possible, in most cases, to determine whether the following adverse events can be ascribed to divalproex sodium delayed-release tablets alone, or the combination of divalproex sodium delayed-release tablets and other antiepilepsy drugs.
Table 3. Adverse Events Reported by ≥ 5% of Patients Treated with Divalproex Sodium Delayed-Release Tablets During Placebo-Controlled Trial of Adjunctive Therapy for Complex Partial Seizures

Body System/ Event	**Divalproex Sodium Delayed-Release Tablets (%) (n=77)**	**Placebo (%) (n=70)**
Body as a Whole		
Headache	31	21
Asthenia	27	7
Fever	6	4
Gastrointestinal System		
Nausea	48	14
Vomiting	27	7
Abdominal Pain	23	6

Diarrhea	13	6
Anorexia	12	0
Dyspepsia	8	4
Constipation	5	1
Nervous System		
Somnolence	27	11
Tremor	25	6
Dizziness	25	13
Diplopia	16	9
Amblyopia/Blurred Vision	12	9
Ataxia	8	1
Nystagmus	8	1
Emotional Lability	6	4
Thinking Abnormal	6	0
Amnesia	5	1
Respiratory System		
Flu Syndrome	12	9
Infection	12	6
Bronchitis	5	1
Rhinitis	5	4
Other		
Alopecia	6	1
Weight Loss	6	0

Table 4 lists treatment-emergent adverse events which were reported by ≥ 5% of patients in the high dose divalproex sodium delayed-release tablets group, and for which the incidence was greater than in the low dose group, in a controlled trial of divalproex sodium delayed-release tablets monotherapy treatment of complex partial seizures. Since patients were being titrated off another antiepilepsy drug during the first portion of the trial, it is not possible, in many cases, to determine whether the following adverse events can be ascribed to divalproex sodium delayed-release tablets alone, or the combination of divalproex sodium delayed-release tablets and other antiepilepsy drugs.

Table 4. Adverse Events Reported by ≥ 5% of Patients in the High Dose Group in the Controlled Trial of Divalproex Sodium Delayed-Release Tablets Monotherapy for Complex Partial Seizures[1]

Body System/ Event	**High Dose (%) (n=131)**	**Low Dose (%) (n=134)**
Body as a Whole		
Asthenia	21	10
Degestive System		
Nausea	34	26
Diarrhea	23	19
Vomiting	23	15
Abdominal Pain	12	9
Anorexia	11	4
Dyspepsia	11	10
Hemic/Lymphatic System		
Thrombocytopenia	24	1
Ecchymosis	5	4
Metabolic/Nutritional		
Weight Gain	9	4
Peripheral Edema	8	3
Nervous System		
Tremor	57	19
Somnolence	30	18

Dizziness	18	13
Insomnia	15	9
Nervousness	11	7
Amnesia	7	4
Nystagmus	7	1
Depression	5	4
Respiratory System		
Infection	20	13
Pharyngitis	8	2
Dyspnea	5	1
Skin and Appendages		
Alopecia	24	13
Special Senses		
Amblyopia/Blurred Vision	8	4
Tinnitus	7	1

[1] Headache was the only adverse event that occurred in ≥ 5% of patients in the high dose group and at an equal or greater incidence in the low dose group.

The following additional adverse events were reported by greater than 1% but less than 5% of the 358 patients treated with divalproex sodium delayed-release tablets in the controlled trials of complex partial seizures:
Body as a Whole
Back pain, chest pain, malaise.
Cardiovascular System
Tachycardia, hypertension, palpitation.
Digestive System
Increased appetite, flatulence, hematemesis, eructation, pancreatitis, periodontal abscess.
Hemic and Lymphatic System
Petechia.
Metabolic and Nutritional Disorders
SGOT increased, SGPT increased.
Musculoskeletal System
Myalgia, twitching, arthralgia, leg cramps, myasthenia.
Nervous System
Anxiety, confusion, abnormal gait, paresthesia, hypertonia, incoordination, abnormal dreams, personality disorder.
Respiratory System
Sinusitis, cough increased, pneumonia, epistaxis.
Skin and Appendages
Rash, pruritus, dry skin.
Special Senses
Taste perversion, abnormal vision, deafness, otitis media.
Urogenital System
Urinary incontinence, vaginitis, dysmenorrhea, amenorrhea, urinary frequency.

Other Patient Populations
Adverse events that have been reported with all dosage forms of valproate from epilepsy trials, spontaneous reports, and other sources are listed below by body system.

Gastrointestinal
The most commonly reported side effects at the initiation of therapy are nausea, vomiting, and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps, and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported. The administration of delayed-release divalproex sodium may result in reduction of gastrointestinal side effects in some patients.

CNS Effects
Sedative effects have occurred in patients receiving valproate alone but occur most often in patients receiving combination therapy. Sedation usually abates upon reduction of other antiepileptic medication. Tremor (may be dose-related), hallucinations, ataxia, headache, nystagmus, diplopia, asterixis, “spots before eyes”, dysarthria, dizziness, confusion, hypesthesia, vertigo, incoordination,

and parkinsonism have been reported with the use of valproate. Rare cases of coma have occurred in patients receiving valproate alone or in conjunction with phenobarbital. In rare instances encephalopathy with or without fever has developed shortly after the introduction of valproate monotherapy without evidence of hepatic dysfunction or inappropriately high plasma valproate levels. Although recovery has been described following drug withdrawal, there have been fatalities in patients with hyperammonemic encephalopathy, particularly in patients with underlying urea cycle disorders (see WARNINGS – Urea Cycle Disorders and PRECAUTIONS).

Several reports have noted reversible cerebral atrophy and dementia in association with valproate therapy.

Dermatologic
Transient hair loss, skin rash, photosensitivity, generalized pruritus, erythema multiforme, and Stevens-Johnson syndrome. Rare cases of toxic epidermal necrolysis have been reported including a fatal case in a 6 month old infant taking valproate and several other concomitant medications. An additional case of toxic epidermal necrosis resulting in death was reported in a 35 year old patient with AIDS taking several concomitant medications and with a history of multiple cutaneous drug reactions. Serious skin reactions have been reported with concomitant administration of lamotrigine and valproate (see PRECAUTIONS - Drug Interactions).

Psychiatric
Emotional upset, depression, psychosis, aggression, hyperactivity, hostility, and behavioral deterioration.

Musculoskeletal
Weakness.

Hematologic
Thrombocytopenia and inhibition of the secondary phase of platelet aggregation may be reflected in altered bleeding time, petechiae, bruising, hematoma formation, epistaxis, and frank hemorrhage (see PRECAUTIONS - General and Drug Interactions). Relative lymphocytosis, macrocytosis, hypofibrinogenemia, leukopenia, eosinophilia, anemia including macrocytic with or without folate deficiency, bone marrow suppression, pancytopenia, aplastic anemia, agranulocytosis, and acute intermittent porphyria.

Hepatic
Minor elevations of transaminases (eg, SGOT and SGPT) and LDH are frequent and appear to be dose-related. Occasionally, laboratory test results include increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity (see WARNINGS).

Endocrine
Irregular menses, secondary amenorrhea, breast enlargement, galactorrhea, and parotid gland swelling. Abnormal thyroid function tests (see PRECAUTIONS).

There have been rare spontaneous reports of polycystic ovary disease. A cause and effect relationship has not been established.

Pancreatic

Acute pancreatitis including fatalities (see WARNINGS).

Metabolic

Hyperammonemia (see PRECAUTIONS), hyponatremia, and inappropriate ADH secretion.

There have been rare reports of Fanconi’s syndrome occurring chiefly in children.

Decreased carnitine concentrations have been reported although the clinical relevance is undetermined.

Hyperglycinemia has occurred and was associated with a fatal outcome in a patient with preexistent nonketotic hyperglycinemia.

Genitourinary

Enuresis and urinary tract infection.

Special Senses

Hearing loss, either reversible or irreversible, has been reported; however, a cause and effect relationship has not been established. Ear pain has also been reported.

Other

Allergic reaction, anaphylaxis, edema of the extremities, lupus erythematosus, bone pain, cough increased, pneumonia, otitis media, bradycardia, cutaneous vasculitis, fever, and hypothermia.

OVERDOSAGE

Overdosage with valproate may result in somnolence, heart block, and deep coma. Fatalities have been reported; however patients have recovered from valproate levels as high as 2120 μg/mL.

In overdose situations, the fraction of drug not bound to protein is high and hemodialysis or tandem hemodialysis plus hemoperfusion may result in significant removal of drug. The benefit of gastric lavage or emesis will vary with the time since ingestion. General supportive measures should be applied with particular attention to the maintenance of adequate urinary output.

Naloxone has been reported to reverse the CNS depressant effects of valproate overdosage. Because naloxone could theoretically also reverse the antiepileptic effects of valproate, it should be used with caution in patients with epilepsy.

DOSAGE AND ADMINISTRATION

Mania

Divalproex sodium delayed-release tablets are administered orally. The recommended initial dose is 750 mg daily in divided doses. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect or the desired range of plasma concentrations. In placebo-controlled clinical trials of acute mania, patients were dosed to a clinical response with a trough plasma concentration between 50 and 125 μg/mL. Maximum concentrations were generally achieved within 14 days. The maximum recommended dosage is 60 mg/kg/day.

There is no body of evidence available from controlled trials to guide a clinician in the longer term management of a patient who improves during divalproex sodium delayed-release tablets treatment of an acute manic episode. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the benefits of divalproex sodium delayed-release tablets in such longer-term treatment. Although there are no efficacy data that specifically address longer-term antimanic treatment with divalproex sodium delayed-release tablets, the safety of divalproex sodium delayed-release tablets in long-term use is supported by data from record reviews involving approximately 360 patients treated with divalproex sodium delayed-release tablets for greater than 3 months.

Epilepsy

Divalproex sodium delayed-release tablets are administered orally. Divalproex sodium delayed-release tablet is indicated as monotherapy and adjunctive therapy in complex partial seizures in adults and pediatric patients down to the age of 10 years, and in simple and complex absence seizures. As the divalproex sodium delayed-release tablets dosage is titrated upward, concentrations of phenobarbital, carbamazepine, and/or phenytoin may be affected (see PRECAUTIONS - Drug Interactions).

Complex Partial Seizures

For adults and children 10 years of age or older.

Monotherapy (Initial Therapy)

Divalproex sodium delayed-release tablets have not been systematically studied as initial therapy. Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 μg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.

The probability of thrombocytopenia increases significantly at total trough valproate plasma concentrations above 110 μg/mL in females and 135 μg/mL in males. The benefit of improved seizure control with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

Conversion to Monotherapy

Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 - 100 μg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. Concomitant antiepilepsy drug (AED) dosage can ordinarily be reduced by approximately 25% every 2 weeks. This reduction may be started at initiation of divalproex sodium delayed-release tablets therapy, or delayed by 1 to 2 weeks if there is a concern that seizures are likely to occur with a reduction. The speed and duration of withdrawal of the concomitant AED can be highly variable, and patients should be monitored closely during this period for increased seizure frequency.

Adjunctive Therapy
Divalproex sodium delayed-release tablets may be added to the patient's regimen at a dosage of 10 to 15 mg/kg/day. The dosage may be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 μg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. If the total daily dose exceeds 250 mg, it should be given in divided doses.

In a study of adjunctive therapy for complex partial seizures in which patients were receiving either carbamazepine or phenytoin in addition to divalproex sodium delayed-release tablets, no adjustment of carbamazepine or phenytoin dosage was needed (see CLINICAL STUDIES). However, since valproate may interact with these or other concurrently administered AEDs as well as other drugs (see Drug Interactions), periodic plasma concentration determinations of concomitant AEDs are recommended during the early course of therapy (see PRECAUTIONS - Drug Interactions).

Simple and Complex Absence Seizures
The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in divided doses.

A good correlation has not been established between daily dose, serum concentrations, and therapeutic effect. However, therapeutic valproate serum concentrations for most patients with absence seizures is considered to range from 50 to 100 μg/mL. Some patients may be controlled with lower or higher serum concentrations (see CLINICAL PHARMACOLOGY).

As the divalproex sodium delayed-release tablets dosage is titrated upward, blood concentrations of phenobarbital and/or phenytoin may be affected (see PRECAUTIONS).

Antiepilepsy drugs should not be abruptly discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life.

In epileptic patients previously receiving valproic acid therapy, divalproex sodium delayed-release tablets should be initiated at the same daily dose and dosing schedule. After the patient is stabilized on divalproex sodium delayed-release tablets, a dosing schedule of two or three times a day may be elected in selected patients.

Migraine
Divalproex sodium delayed-release tablets are administered orally. The recommended starting dose is 250 mg twice daily. Some patients may benefit from doses up to 1000 mg/day. In the clinical trials, there was no evidence that higher doses led to greater efficacy.

General Dosing Advice

Dosing in Elderly Patients
Due to a decrease in unbound clearance of valproate and possibly a greater sensitivity to somnolence in the elderly, the starting dose should be reduced in these patients. Dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence. The ultimate therapeutic dose should be achieved on the basis of both tolerability and clinical response (see WARNINGS).

Dose-Related Adverse Events
The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose-related. The probability of thrombocytopenia appears to increase significantly at total valproate concentrations of ≥ 110 μg/mL (females) or ≥ 135 μg/mL (males) (see PRECAUTIONS). The benefit of improved therapeutic effect with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

G.I. Irritation
Patients who experience G.I. irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

HOW SUPPLIED
Divalproex sodium delayed-release tablets 500 mg, USP are yellow, ovaloid, film-coated tablets with ink printed "A514" on one side. They are supplied as follow:

Bottles of 100 NDC #24979-514-01

Bottles of 500 NDC # 24979-514-05

Recommended storage: **Store tablets at 20-25°C (68-77°F) [see USP controlled room temperature]**

PATIENT INFORMATION LEAFLET

Divalproex Sodium Delayed-Release Tablets USP
Important Information for Women Who Could Become Pregnant About the Use of Divalproex Sodium Delayed-Release Tablets

Please read this leaflet carefully before you take this medication. This leaflet provides a summary of important information about taking this medication to women who could become pregnant. If you have any questions or concerns, or want more information about this medication, contact your doctor or pharmacist.

Information For Women Who Could Become Pregnant
This medication can be obtained only by prescription from your doctor. The decision to use this medication is one that you and your doctor should make together, taking into account your individual needs and medical condition.

Before using this medication, women who can become pregnant should consider the fact that this medication has been associated with birth defects, in particular, with spina bifida and other defects related to failure of the spinal canal to close normally. Approximately 1 to 2% of children born to women with epilepsy taking divalproex sodium delayed-release tablets in the first 12 weeks of pregnancy had these defects (based on data from the Centers for Disease Control, a U.S. agency based in Atlanta). The incidence in the general population is 0.1 to 0.2%.

These medications have also been associated with other birth defects such as defects of the heart, the bones, and other parts of the body. Information suggests that birth defects may be more likely to occur with these medications than some other drugs that treat your medical condition.

Information For Women Who Are Planning to Get Pregnant
- Women taking this medication who are planning to get pregnant should discuss the treatment options with their doctor.

Information For Women Who Become Pregnant
- If you become pregnant while taking this medication you should contact your doctor immediately.

Other Important Information
- Your medication should be taken exactly as prescribed by your doctor to get the most benefits from your medication and reduce the risk of side effects.

- If you have taken more than the prescribed dose of your medication, contact your hospital emergency room or local poison center immediately.

- Your medication was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

Facts About Birth Defects
It is important to know that birth defects may occur even in children of individuals not taking any medications or without any additional risk factors.

This summary provides important information about the use of divalproex sodium delayed-release tablets to women who could become pregnant. If you would like more information about the other potential risks and benefits of this medication, ask your doctor or pharmacist to let you read the professional labeling and then discuss it with them. If you have any questions or concerns about taking this medication, you should discuss them with your doctor.

Rx only

Manufactured by

Anchen Pharmaceuticals (Taiwan), Inc.

No. 3-1, Ziqiang 4th Rd., Zhongli Industrial Zone, Zhongli City, Taoyuan County 320, Taiwan

Revised: 04/08

US007387793B2

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

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

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

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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 470 days.

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

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

(65) **Prior Publication Data**

US 2005/0106247 A1 May 19, 2005

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

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

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

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(57) **ABSTRACT**

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

20 Claims, 4 Drawing Sheets

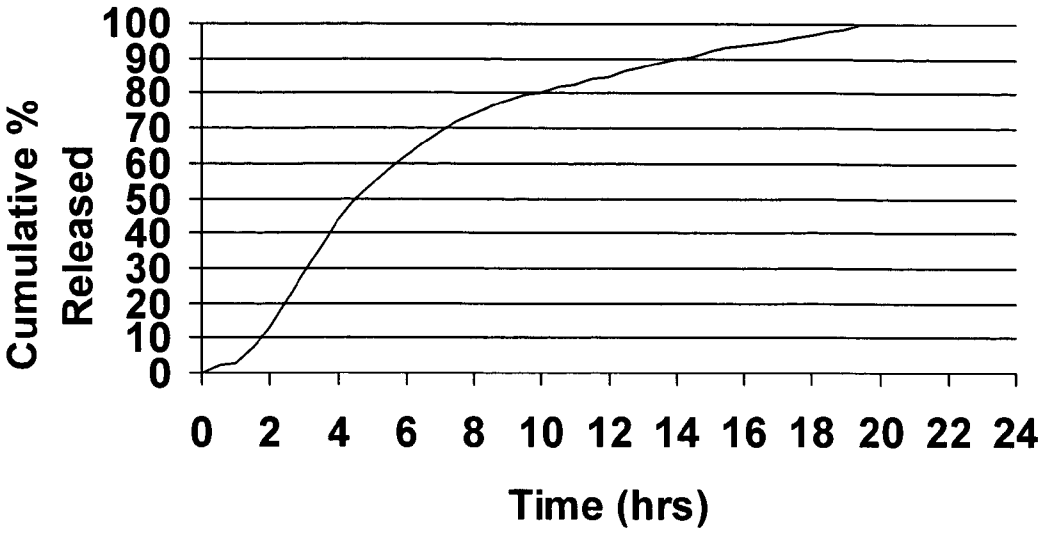

Cumulative % Released
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hrs)

FIG. 1

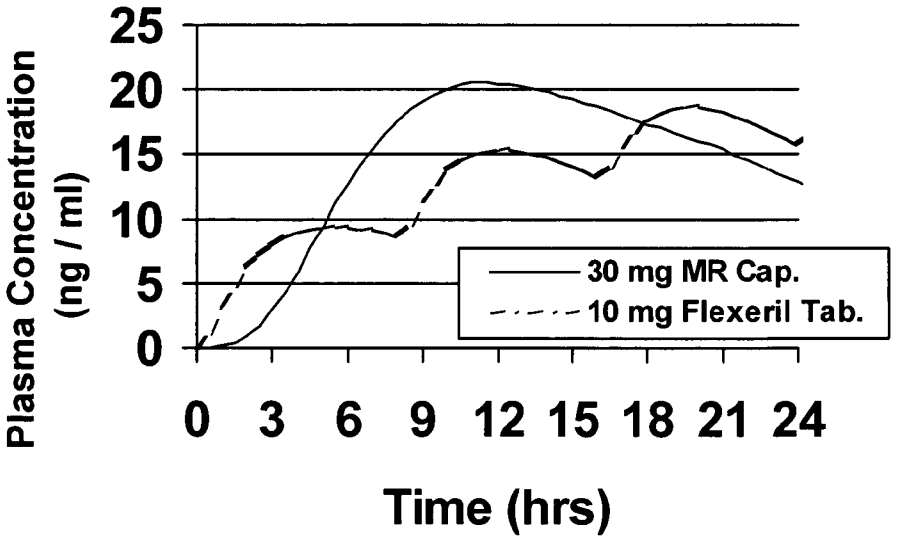

Plasma Concentration (ng / ml)
25
20
15
10
5
0
0 3 6 9 12 15 18 21 24
Time (hrs)
30 mg MR Cap.
10 mg Flexeril Tab.

FIG. 2

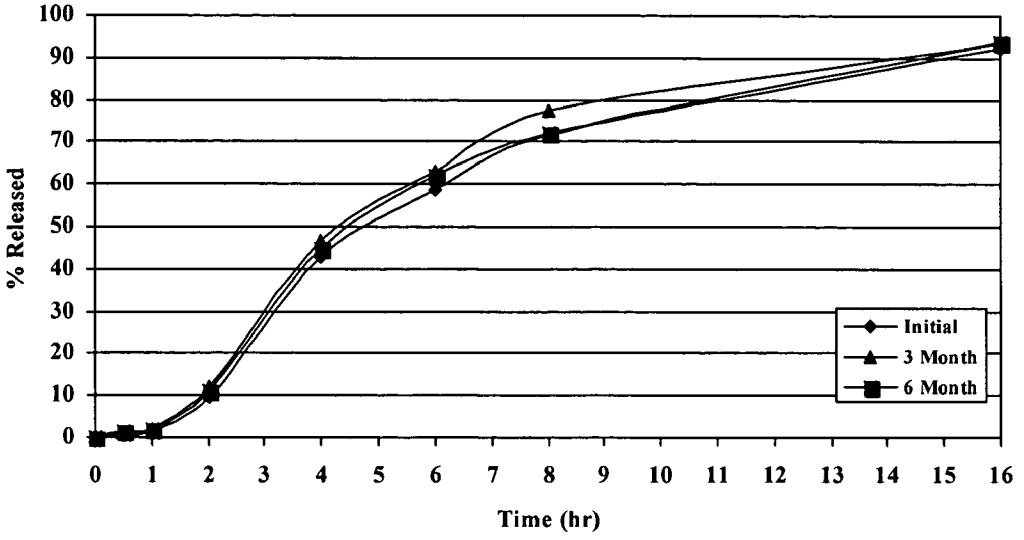

% Released
Time (hr)
Initial
3 Month
6 Month

FIG. 3

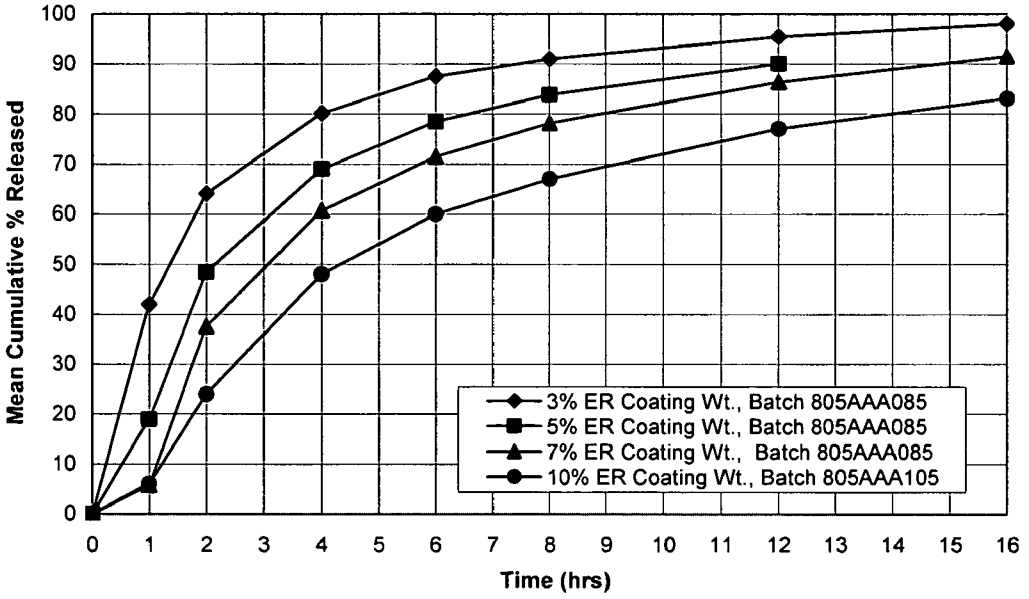

Mean Cumulative % Released
Time (hrs)
3% ER Coating Wt., Batch 805AAA085
5% ER Coating Wt., Batch 805AAA085
7% ER Coating Wt., Batch 805AAA085
10% ER Coating Wt., Batch 805AAA105

FIG. 4

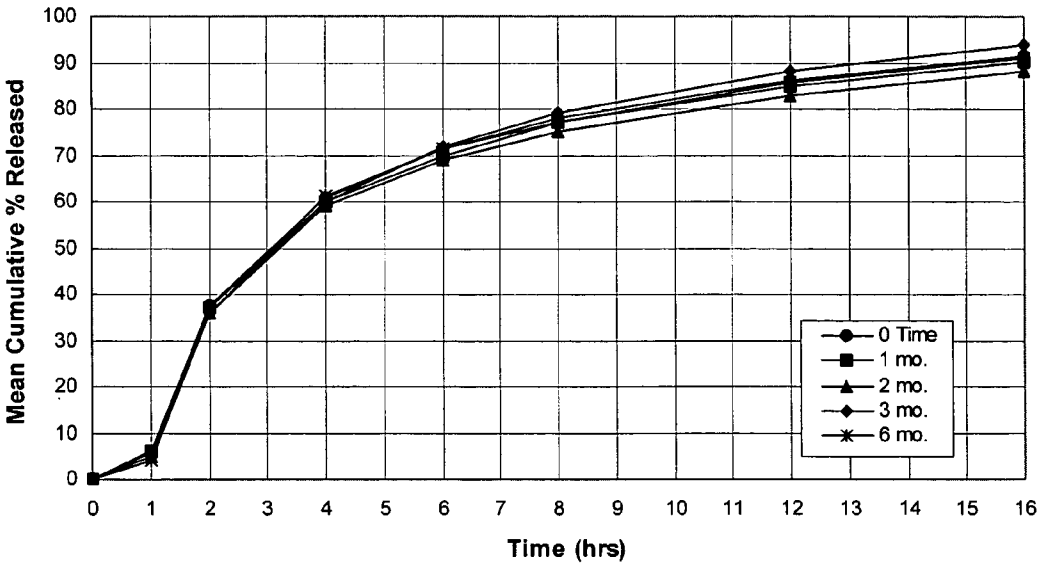

Mean Cumulative % Released
Time (hrs)
0 Time
1 mo.
2 mo.
3 mo.
6 mo.

FIG. 5

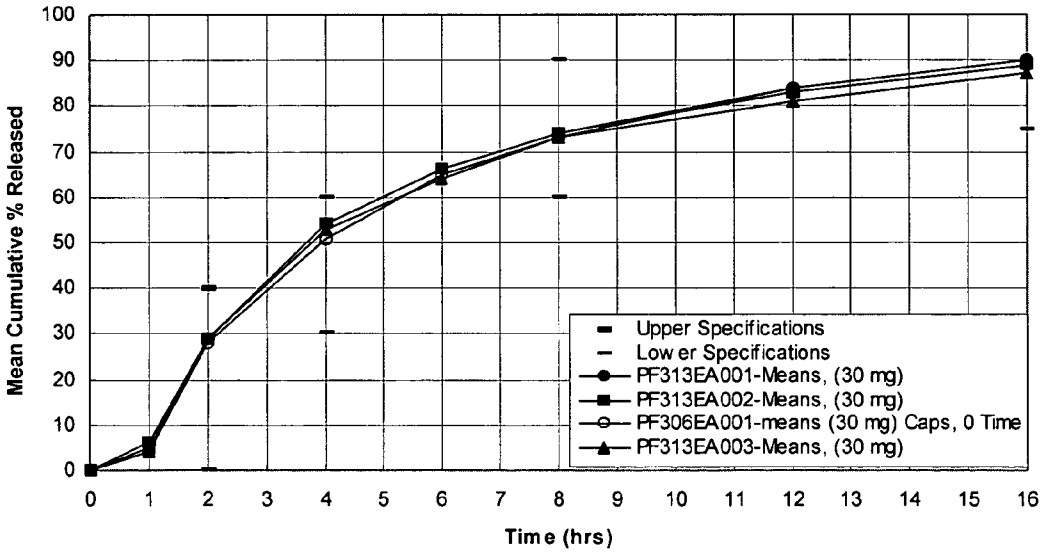

Mean Cumulative % Released
Time (hrs)
Upper Specifications
Lower Specifications
PF313EA001-Means, (30 mg)
PF313EA002-Means, (30 mg)
PF306EA001-means (30 mg) Caps, 0 Time
PF313EA003-Means, (30 mg)

FIG. 6

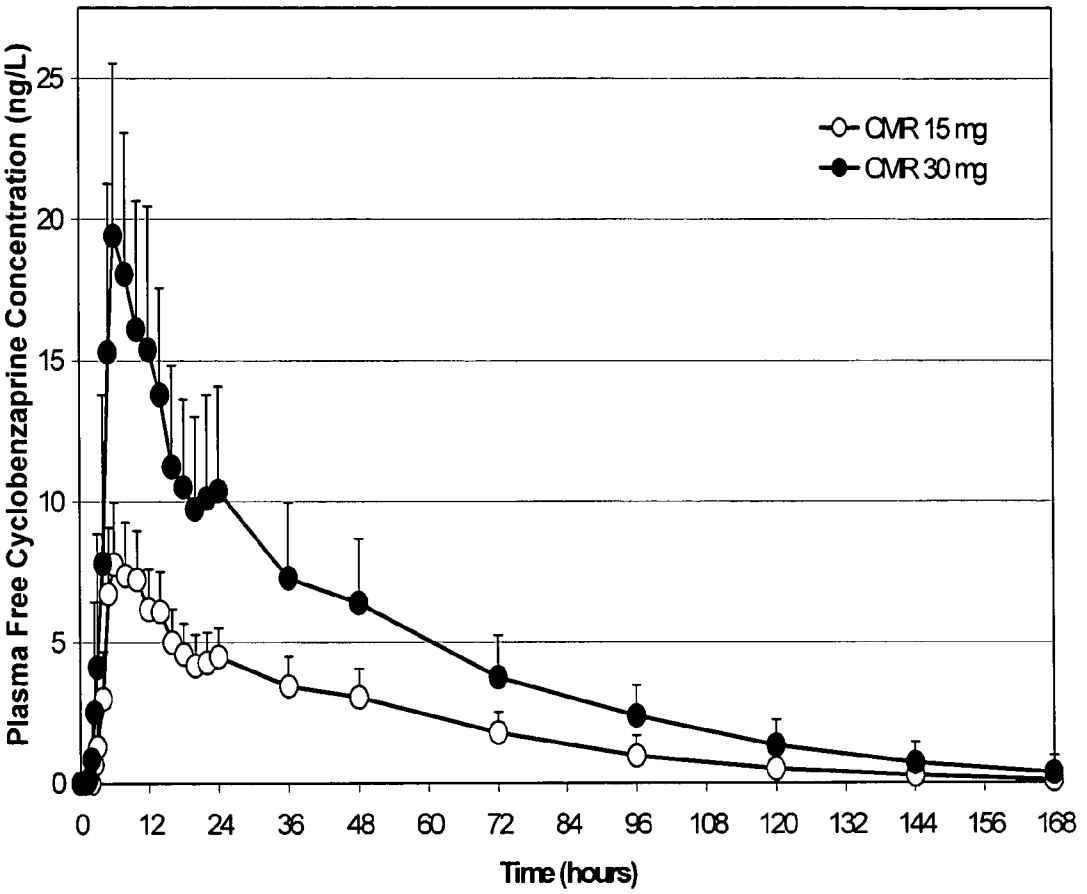

Plasma Free Cyclobenzaprine Concentration (ng/L)
0
5
10
15
20
25
0
12
24
36
48
60
72
84
96
108
120
132
144
156
168
Time (hours)
CMR 15 mg
CMR 30 mg

FIG. 7

MODIFIED RELEASE DOSAGE FORMS OF SKELETAL MUSCLE RELAXANTS

TECHNICAL FIELD

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

BACKGROUND OF THE INVENTION

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

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

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

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

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

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

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

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

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

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

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

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

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

SUMMARY OF THE INVENTION

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

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

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

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

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

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

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

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

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

DETAILED DESCRIPTION OF THE INVENTION

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

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

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

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

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

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

Dissolution Procedure:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

EXAMPLE 1

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

The resulting model parameters are listed below:

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

Theoretical plasma levels were simulated using the pharmacokinetic model given above and the target release rate given in FIG. **1**. FIG. **2** shows the simulated plasma levels for day one following dosing of 1×10 mg Flexeril® Tablet given 3 times a day and the proposed Cyclobenzaprine HCl MR Capsule, 30 mg given once a day.

EXAMPLE 2

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

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

EXAMPLE 3

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

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

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

EXAMPLE 4

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

EXAMPLE 5

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

TABLE 1

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

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

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

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

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

What is claimed is:

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

wherein said extended release beads comprise

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

* * * * *

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

Anchen Pharmaceuticals, Inc.

BOXED WARNING

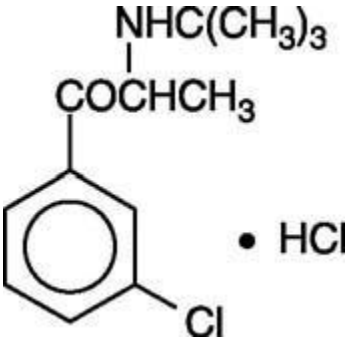
Suicidality and Antidepressant Drugs

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

DESCRIPTION

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

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



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

CLINICAL PHARMACOLOGY

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

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

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

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

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

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

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

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

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

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

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

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

The second study showed no statistically significant differences in the pharmacokinetics of bupropion and its active metabolites in 9 patients with mild to moderate hepatic cirrhosis compared to 8 healthy volunteers. However, more variability was observed in some of the pharmacokinetic parameters for bupropion (AUC, C_{max}, and T_{max}) and its active metabolites (t½) in patients with mild to moderate hepatic cirrhosis. In addition, in patients with severe hepatic cirrhosis, the bupropion C_{max} and AUC were substantially increased (mean difference: by approximately 70% and 3-fold, respectively) and more variable when compared to values in healthy volunteers; the mean bupropion half-life was also longer (29 hours in patients with severe hepatic cirrhosis vs 19 hours in healthy subjects). For the metabolite hydroxybupropion, the mean C_{max} was approximately 69% lower. For the combined amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, the mean C_{max} was approximately 31% lower. The mean AUC increased by about 1½-fold for hydroxybupropion and about 2½-fold for threo/erythrohydrobupropion. The median T_{max} was observed 19 hours later for hydroxybupropion and 31 hours later for threo/erythrohydrobupropion. The mean half-lives for hydroxybupropion and threo/erythrohydrobupropion were increased 5- and 2-fold, respectively, in patients with severe hepatic cirrhosis compared to healthy volunteers (see WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

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

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

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

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

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

CLINICAL TRIALS

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

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

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

INDICATIONS AND USAGE

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

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

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

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

CONTRAINDICATIONS

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

Bupropion hydrochloride extended-release tablets (XL) are contraindicated in patients treated with ZYBAN® (bupropion hydrochloride extended-release tablets (SR), Wellbutrin® (bupropion hydrochloride tablets), the immediate-release formulation, Wellbutrin® SR (bupropion hydrochloride extended-release tablets (SR)), the sustained-release formulation, or any other medications that contain bupropion because the incidence of seizure is dose dependent.
Bupropion hydrochloride extended-release tablets (XL) are contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures noted in patients treated for bulimia with the immediate-release formulation of bupropion.
Bupropion hydrochloride extended-release tablets (XL) are contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines).
The concurrent administration of bupropion hydrochloride extended-release tablets (XL) and a monoamine oxidase (MAO) inhibitor is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with bupropion hydrochloride extended-release tablets (XL).
Bupropion hydrochloride extended-release tablets (XL) are contraindicated in patients who have shown an allergic response to bupropion or the other ingredients that make up bupropion hydrochloride extended-release tablets (XL).

WARNINGS

Clinical Worsening and Suicide Risk:

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.
The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.
Table 1.

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

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.
It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.
All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.
The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal

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

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

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

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

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

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

Bupropion hydrochloride extended-release tablets (XL) should be administered with extreme caution to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or patients treated with other agents (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold.
Hepatic Impairment: Bupropion hydrochloride extended-release tablets (XL) should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients a reduced frequency and/or dose is required, as peak bupropion, as well as AUC, levels are substantially increased and accumulation is likely to occur in such patients to a greater extent than usual. The dose should not exceed 150 mg every other day in these patients (see CLINICAL PHARMACOLOGY, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).
Potential for Hepatotoxicity: In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted.

PRECAUTIONS
General: ***Agitation and Insomnia:*** Increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment, have been associated with treatment with bupropion. Patients in placebo-controlled trials of major depressive disorder with the sustained-release formulation of bupropion, experienced agitation, anxiety, and insomnia as shown in Table 2.
Table 2. Incidence of Agitation, Anxiety, and Insomnia in Placebo-Controlled Trials of Sustained-release Formulation of Bupropion for Major Depressive Disorder

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

In clinical studies of major depressive disorder, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs.
Symptoms in these studies were sufficiently severe to require discontinuation of treatment in 1% and 2.6% of patients treated with 300 and 400 mg/day, respectively, of bupropion sustained-release tablets and 0.8% of patients treated with placebo.
Psychosis, Confusion, and Other Neuropsychiatric Phenomena: Depressed patients treated with bupropion have been reported to show a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment.
Activation of Psychosis and/or Mania: Antidepressants can precipitate manic episodes in bipolar disorder patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Bupropion hydrochloride extended-release tablet (XL) is expected to pose similar risks.
Altered Appetite and Weight: In placebo-controlled studies of major depressive disorder using the sustained-release formulation of bupropion, patients experienced weight gain or weight loss as shown in Table 3.
Table 3. Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials of Sustained-release Formulation of Bupropion for Major Depressive Disorder

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

In studies conducted with the immediate-release formulation of bupropion, 35% of patients receiving tricyclic antidepressants gained weight, compared to 9% of patients treated with the immediate-release formulation of bupropion. If weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight-reducing potential of bupropion hydrochloride extended-release tablets (XL) should be considered.
Allergic Reactions: Anaphylactoid/anaphylactic reactions characterized by symptoms such as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have been reported in clinical trials with bupropion. In addition, there have been rare spontaneous post-marketing reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with bupropion. A patient should stop taking bupropion hydrochloride extended-release tablets (XL) and consult a doctor if experiencing allergic or anaphylactoid/anaphylactic reactions (e.g., skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during treatment. Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity have been reported in association with bupropion. These symptoms may resemble serum sickness.

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

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

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

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

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

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

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

Information for Patients: Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with bupropion hydrochloride extended-release tablets (XL) and should counsel them in its appropriate use. A patient Medication Guide About "Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions" and other important information about using bupropion hydrochloride extended-release tablets (XL) is available for bupropion hydrochloride extended-release tablets (XL). The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guides is reprinted at the end of this document.

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

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

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

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

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

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

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

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

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

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

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

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

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

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

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

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

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

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

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

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

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

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

Pregnancy

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

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

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

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

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

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

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

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

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

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

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

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

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

* Adverse events that occurred in at least 1% of patients treated with either 300 or 400 mg/day of the sustained-release formulation of bupropion, but equally or more frequently in the placebo group, were: abnormal dreams, accidental injury, acne, appetite increased, back pain, bronchitis, dysmenorrhea, dyspepsia, flatulence, flu syndrome, hypertension, neck pain, respiratory disorder, rhinitis, and tooth disorder.

† Incidence based on the number of female patients.

— Hyphen denotes adverse events occurring in greater than 0 but less than 0.5% of patients.

Additional events to those listed in Table 5 that occurred at an incidence of at least 1% in controlled clinical trials of the immediate-release formulation of bupropion (300 to 600 mg/day) and that were numerically more frequent than placebo were: cardiac arrhythmias (5% vs 4%), hypertension (4% vs 2%), hypotension (3% vs 2%), tachycardia (11% vs 9%), appetite increase (4% vs 2%), dyspepsia (3% vs 2%), menstrual complaints (5% vs 1%), akathisia (2% vs 1%), impaired sleep quality (4% vs 2%), sensory disturbance (4% vs 3%), confusion (8% vs 5%), decreased libido (3% vs 2%), hostility (6% vs 4%), auditory disturbance (5% vs 3%), and gustatory disturbance (3% vs 1%).

Incidence of Commonly Observed Adverse Events in Controlled Clinical Trials:

Adverse events from Table 4 occurring in at least 5% of patients treated with the sustained-release formulation of bupropion and at a rate at least twice the placebo rate are listed below for the 300- and 400-mg/day dose groups.

300 mg/day of the Sustained-Release Formulation: Anorexia, dry mouth, rash, sweating, tinnitus, and tremor.

400 mg/day of the Sustained-Release Formulation: Abdominal pain, agitation, anxiety, dizziness, dry mouth, insomnia, myalgia, nausea, palpitation, pharyngitis, sweating, tinnitus, and urinary frequency.

Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion: In addition to the adverse events noted above, the following events have been reported in clinical trials and postmarketing experience with the sustained-release formulation of bupropion in depressed patients and in nondepressed smokers, as well as in clinical trials and postmarketing clinical experience with the immediate-release formulation of bupropion.

Adverse events for which frequencies are provided below occurred in clinical trials with the sustained-release formulation of bupropion. The frequencies represent the proportion of patients who experienced a treatment-emergent adverse event on at least one occasion in placebo-controlled studies for depression (n = 987) or smoking cessation (n = 1,013), or patients who experienced an adverse event requiring discontinuation of treatment in an open-label surveillance study with the sustained-release formulation of bupropion (n = 3,100). All treatment-emergent adverse events are included except those listed in Tables 1 through 4, those events listed in other safety-related sections, those adverse events subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, those events not reasonably associated with the use of the drug, and those events that were not serious and occurred in fewer than 2 patients. Events of major clinical importance are described in the WARNINGS and PRECAUTIONS sections of the labeling.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions of frequency: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients.

Adverse events for which frequencies are not provided occurred in clinical trials or postmarketing experience with bupropion. Only those adverse events not previously listed for sustained-release bupropion are included. The extent to which these events may be associated with bupropion hydrochloride extended-release tablets (XL) is unknown.

Body (General): Infrequent were chills, facial edema, musculoskeletal chest pain, and photosensitivity. Rare was malaise. Also observed were arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness (see PRECAUTIONS).

Cardiovascular: Infrequent were postural hypotension, stroke, tachycardia, and vasodilation. Rare was syncope. Also observed were complete atrioventricular block, extrasystoles, hypotension, hypertension (in some cases severe, see PRECAUTIONS), myocardial infarction, phlebitis, and pulmonary embolism.

Digestive: Infrequent were abnormal liver function, bruxism, gastric reflux, gingivitis, glossitis, increased salivation, jaundice, mouth ulcers, stomatitis, and thirst. Rare was edema of tongue. Also observed were colitis, esophagitis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, intestinal perforation, liver damage, pancreatitis, and stomach ulcer.

Endocrine: Also observed were hyperglycemia, hypoglycemia, and syndrome of inappropriate antidiuretic hormone.

Hemic and Lymphatic: Infrequent was ecchymosis. Also observed were anemia, leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia. Altered PT and/or INR, infrequently associated with hemorrhagic or thrombotic complications, were observed when bupropion was coadministered with warfarin.

Metabolic and Nutritional: Infrequent were edema and peripheral edema. Also observed was glycosuria.

Musculoskeletal: Infrequent were leg cramps. Also observed were muscle rigidity/fever/rhabdomyolysis and muscle weakness.

Nervous System: Infrequent were abnormal coordination, decreased libido, depersonalization, dysphoria, emotional lability, hostility, hyperkinesia, hypertonia, hypesthesia, suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and hypomania. Also observed were abnormal electroencephalogram (EEG), aggression, akinesia, aphasia, coma, delirium, delusions, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hallucinations, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid ideation, restlessness, and unmasking tardive dyskinesia.

Respiratory: Rare was bronchospasm. Also observed was pneumonia.

Skin: Rare was maculopapular rash. Also observed were alopecia, angioedema, exfoliative dermatitis, and hirsutism.
Special Senses: Infrequent were accommodation abnormality and dry eye. Also observed were deafness, diplopia, increased intraocular pressure, and mydriasis.
Urogenital: Infrequent were impotence, polyuria, and prostate disorder. Also observed were abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomastia, menopause, painful erection, salpingitis, urinary incontinence, urinary retention, and vaginitis.
To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals USA at 1-888-493-0857 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: Bupropion is not a controlled substance.
Humans: Controlled clinical studies of bupropion (immediate-release formulation) conducted in normal volunteers, in subjects with a history of multiple drug abuse, and in depressed patients showed some increase in motor activity and agitation/excitement.
In a population of individuals experienced with drugs of abuse, a single dose of 400 mg of bupropion produced mild amphetamine-like activity as compared to placebo on the Morphine-Benzedrine Subscale of the Addiction Research Center Inventories (ARCI), and a score intermediate between placebo and amphetamine on the Liking Scale of the ARCI. These scales measure general feelings of euphoria and drug desirability.
Findings in clinical trials, however, are not known to reliably predict the abuse potential of drugs. Nonetheless, evidence from single-dose studies does suggest that the recommended daily dosage of bupropion when administered in divided doses is not likely to be especially reinforcing to amphetamine or stimulant abusers. However, higher doses that could not be tested because of the risk of seizure might be modestly attractive to those who abuse stimulant drugs.
Animals: Studies in rodents and primates have shown that bupropion exhibits some pharmacologic actions common to psychostimulants. In rodents, it has been shown to increase locomotor activity, elicit a mild stereotyped behavioral response, and increase rates of responding in several schedule-controlled behavior paradigms. In primate models to assess the positive reinforcing effects of psychoactive drugs, bupropion was self-administered intravenously. In rats, bupropion produced amphetamine-like and cocaine-like discriminative stimulus effects in drug discrimination paradigms used to characterize the subjective effects of psychoactive drugs.

OVERDOSAGE

Human Overdose Experience: Overdoses of up to 30 g or more of bupropion have been reported. Seizure was reported in approximately one third of all cases. Other serious reactions reported with overdoses of bupropion alone included hallucinations, loss of consciousness, sinus tachycardia, and ECG changes such as conduction disturbances or arrhythmias. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported mainly when bupropion was part of multiple drug overdoses.
Although most patients recovered without sequelae, deaths associated with overdoses of bupropion alone have been reported in patients ingesting large doses of the drug. Multiple uncontrolled seizures, bradycardia, cardiac failure, and cardiac arrest prior to death were reported in these patients.
Overdosage Management: Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. EEG monitoring is also recommended for the first 48 hours post-ingestion. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients.
Activated charcoal should be administered. There is no experience with the use of forced diuresis, dialysis, hemoperfusion, or exchange transfusion in the management of bupropion overdoses. No specific antidotes for bupropion are known.
Due to the dose-related risk of seizures with bupropion hydrochloride extended-release tablets (XL), hospitalization following suspected overdose should be considered. Based on studies in animals, it is recommended that seizures be treated with intravenous benzodiazepine administration and other supportive measures, as appropriate.
In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION

General Dosing Considerations: It is particularly important to administer bupropion hydrochloride extended-release tablets (XL) in a manner most likely to minimize the risk of seizure (see WARNINGS). Gradual escalation in dosage is also important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these effects may be managed by temporary reduction of dose or the short-term administration of an intermediate to long-acting sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation should be stopped. Bupropion hydrochloride extended-release tablets (XL) should be swallowed whole and not crushed, divided, or chewed. Bupropion hydrochloride extended-release tablets (XL) may be taken without regard to meals.
Major Depressive Disorder: Initial Treatment: The usual adult target dose for bupropion hydrochloride extended-release tablets (XL) is 300 mg/day, given once daily in the morning. Dosing with bupropion hydrochloride extended-release tablets (XL) should

begin at 150 mg/day given as a single daily dose in the morning. If the 150-mg initial dose is adequately tolerated, an increase to the 300-mg/day target dose, given as once daily, may be made as early as day 4 of dosing. There should be an interval of at least 24 hours between successive doses.

Increasing the Dosage Above 300 mg/day: As with other antidepressants, the full antidepressant effect of bupropion hydrochloride extended-release tablets (XL) may not be evident until 4 weeks of treatment or longer. An increase in dosage to the maximum of 450 mg/day, given as a single dose, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day.

Maintenance Treatment: It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacological therapy beyond response to the acute episode. It is unknown whether or not the dose of bupropion hydrochloride extended-release tablets (XL) needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

Switching Patients from Wellbutrin® (bupropion hydrochloride tablets) or from Wellbutrin® SR (bupropion hydrochloride extended-release tablets (SR), revise subsection as follows:

When switching patients from Wellbutrin® (bupropion hydrochloride tablets) to bupropion hydrochloride extended-release tablets (XL) or from Wellbutrin® SR (bupropion hydrochloride extended-release tablets (SR)) to bupropion hydrochloride extended-release tablets (XL), give the same total daily dose when possible. Patients who are currently being treated with Wellbutrin® (bupropion hydrochloride tablets) at 300 mg/day (for example, 100 mg 3 times a day) may be switched to bupropion hydrochloride extended-release tablets (XL) 300 mg once daily. Patients who are currently being treated with Wellbutrin® SR (bupropion hydrochloride extended-release tablets (SR)) at 300 mg/day (for example, 150 mg twice daily) may be switched to bupropion hydrochloride extended-release tablets (XL) 300 mg once daily.

Dosage Adjustment for Patients With Impaired Hepatic Function: Bupropion hydrochloride extended-release tablets (XL) should be used with extreme caution in patients with severe hepatic cirrhosis. The dose should not exceed 150 mg every other day in these patients. Bupropion hydrochloride extended-release tablets (XL) should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and a reduced frequency and/or dose should be considered in patients with mild to moderate hepatic cirrhosis (see CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS).

Dosage Adjustment for Patients With Impaired Renal Function: Bupropion hydrochloride extended-release tablets (XL) should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

HOW SUPPLIED

Bupropion hydrochloride extended-release tablets USP (XL) 150 mg, are white to off-white, round, tablets printed with “A101”. They are supplied as follow:

Bottles of 30 NDC # 10370-101-03
Bottles of 60 NDC # 10370-101-06
Bottles of 90 NDC # 10370-101-09
Bottles of 500 NDC # 10370-101-50
Bottles of 1000 NDC # 10370-101-00

Bupropion hydrochloride extended-release tablets USP (XL) 300 mg, are white to off-white, round, tablets printed with “A102”. They are supplied as follow:

Bottles of 30 NDC # 10370-102-03
Bottles of 60 NDC # 10370-102-06
Bottles of 90 NDC # 10370-102-09
Bottles of 500 NDC # 10370-102-50
Bottles of 1000 NDC # 10370-102-00

Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature]

*The following are registered trademarks of their respective manufacturers: ZYBAN®, WELLBUTRIN®, and WELLBUTRIN SR® / GlaxoSmithKline

Rx Only

Manufactured by:
Anchen Pharmaceuticals, Inc.
Irvine, CA 92618
08/07

Medguide
Medication Guide

Bupropion Hydrochloride Extended-Release Tablets USP (XL)

Read this Medication Guide carefully before you start using bupropion hydrochloride extended-release tablets (XL) and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about bupropion hydrochloride extended-release tablets (XL), ask your doctor or pharmacist.

IMPORTANT: Be sure to read both sections of this Medication Guide. The first section is about the risk of suicidal thoughts and actions with antidepressant medicines; the second section is entitled "What other important information should I know about bupropion hydrochloride extended-release tablets (XL)?"

Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with you or your family member's antidepressant medicine.

This section of the Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.

2.Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.

3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?

- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
- Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
- Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Trouble sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking (mania)
- Other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.

• **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
• **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
• **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.
Bupropion hydrochloride extended-release tablets (XL) have not been studied in children under the age of 18 years and are not approved for use in children and teenagers.

What other important information should I know about bupropion hydrochloride extended-release tablets (XL)?
There is a chance of having a seizure (convulsion, fit) with bupropion hydrochloride extended-release tablets (XL), especially in people:
• with certain medical problems.

• who take certain medicines.

The chance of having seizures increases with higher doses of bupropion hydrochloride extended-release tablets (XL). For more information, see the sections "Who should not take bupropion hydrochloride extended-release tablets (XL)?" and "What should I tell my doctor before using bupropion hydrochloride extended-release tablets (XL)?" Tell your doctor about all of your medical conditions and all the medicines you take. **Do not take any other medicines while you are using bupropion hydrochloride extended-release tablets (XL) unless your doctor has said it is okay to take them**.
If you have a seizure while taking bupropion hydrochloride extended-release tablets (XL), stop taking the tablets and call your doctor right away. Do not take bupropion hydrochloride extended-release tablets (XL) again if you have a seizure.

What are bupropion hydrochloride extended-release tablets (XL)?
Bupropion hydrochloride extended-release tablets (XL) are a prescription medicine used to treat adults with a certain type of depression called major depressive disorder.

Who should not take bupropion hydrochloride extended-release tablets (XL)?
Do not take bupropion hydrochloride extended-release tablets (XL) if you
• have or had a seizure disorder or epilepsy.

• **are taking ZYBAN® (used to help people stop smoking) or any other medicines that contain bupropion hydrochloride, such as bupropion hydrochloride tablets or bupropion hydrochloride sustained-release tablets.** Bupropion is the same active ingredient that is in bupropion hydrochloride extended-release tablets (XL).

• drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these make you sleepy) or benzodiazepines and you stop using them all of a sudden.

• have taken within the last 14 days medicine for depression called a monoamine oxidase inhibitor (MAOI), such as NARDIL® (phenelzine sulfate), PARNATE® (tranylcypromine sulfate), or MARPLAN® (isocarboxazid)*****.

• have or had an eating disorder such as anorexia nervosa or bulimia.

• are allergic to the active ingredient in bupropion hydrochloride extended-release tablets (XL)**,** bupropion, or to any of the inactive ingredients. See the end of this leaflet for a complete list of ingredients in bupropion hydrochloride extended-release tablets (XL).

What should I tell my doctor before using bupropion hydrochloride extended-release tablets (XL)?
• **Tell your doctor about your medical conditions.** Tell your doctor if you

• **are pregnant or plan to become pregnant.** It is not known if bupropion hydrochloride extended-release tablets (XL)can harm your unborn baby.

• **are breastfeeding.** Bupropion hydrochloride extended-release tablets (XL)passes through your milk. It is not known if bupropion hydrochloride extended-release tablets (XL)can harm your baby.

• **have liver problems,** especially cirrhosis of the liver.

• have kidney problems.

• have an eating disorder, such as anorexia nervosa or bulimia.

• have had a head injury.

- have had a seizure (convulsion, fit).
- have a tumor in your nervous system (brain or spine).
- have had a heart attack, heart problems, or high blood pressure.
- are a diabetic taking insulin or other medicines to control your blood sugar.
- drink a lot of alcohol.
- abuse prescription medicines or street drugs.
- **Tell your doctor about all the medicines you take**, including prescription and non-prescription medicines, vitamins and herbal supplements. Many medicines increase your chances of having seizures or other serious side effects if you take them while you are using bupropion hydrochloride extended-release tablets (XL).

How should I take bupropion hydrochloride extended-release tablets (XL)?

- Take bupropion hydrochloride extended-release tablets (XL) exactly as prescribed by your doctor.
- **Do not chew, cut, or crush bupropion hydrochloride extended-release tablets (XL).** You must swallow the tablets whole. **Tell your doctor if you cannot swallow medicine tablets.**
- Take bupropion hydrochloride extended-release tablets (XL) at the same time each day.
- Take your doses of bupropion hydrochloride extended-release tablets (XL)at least 24 hours apart.
- You may take bupropion hydrochloride extended-release tablets (XL)with or without food.
- If you miss a dose, do not take an extra tablet to make up for the dose you forgot. Wait and take your next tablet at the regular time. **This is very important.** Too much bupropion hydrochloride extended-release tablets (XL) can increase your chance of having a seizure.
- If you take too much bupropion hydrochloride extended-release tablets (XL), or overdose, call your local emergency room or poison control center right away.
- The bupropion hydrochloride extended-release tablet (XL) is covered by a shell that slowly releases the medicine inside your body. You may notice something in your stool that looks like a tablet. This is normal. This is the empty shell passing from your body.
- **Do not take any other medicines while using bupropion hydrochloride extended-release tablets (XL) unless your doctor has told you it is okay.**
- If you are taking bupropion hydrochloride extended-release tablets (XL) for the treatment of major depressive disorder, it may take several weeks for you to feel that bupropion hydrochloride extended-release tablets (XL) is working. Once you feel better, it is important to keep taking bupropion hydrochloride extended-release tablets (XL) exactly as directed by your doctor. Call your doctor if you do not feel bupropion hydrochloride extended-release tablets (XL) is working for you.
- Do not change your dose or stop taking bupropion hydrochloride extended-release tablets (XL) without talking with your doctor first.

What should I avoid while taking bupropion hydrochloride extended-release tablets (XL)?

- Do not drink a lot of alcohol while taking bupropion hydrochloride extended-release tablets (XL). If you usually drink a lot of alcohol, talk with your doctor before suddenly stopping. If you suddenly stop drinking alcohol, you may increase your chance of having seizures.
- Do not drive a car or use heavy machinery until you know how bupropion hydrochloride extended-release tablets (XL) affects you. Bupropion hydrochloride extended-release tablets (XL) can impair your ability to perform these tasks.

What are possible side effects of bupropion hydrochloride extended-release tablets (XL)?

- **Seizures.** Some patients get seizures while taking bupropion hydrochloride extended-release tablets (XL). **If you have a seizure while taking bupropion hydrochloride extended-release tablets (XL), stop taking the tablets and call your doctor right away.** Do not take bupropion hydrochloride extended-release tablets (XL) again if you have a seizure.

- **Hypertension (high blood pressure).** Some patients get high blood pressure, sometimes severe, while taking bupropion hydrochloride extended-release tablets (XL). The chance of high blood pressure may be increased if you also use nicotine replacement therapy (for example, a nicotine patch) to help you stop smoking.

- **Severe allergic reactions. Stop bupropion hydrochloride extended-release tablets (XL) and call your doctor right away** if you get a rash, itching, hives, fever, swollen lymph glands, painful sores in the mouth or around the eyes, swelling of the lips or tongue, chest pain, or have trouble breathing. These could be signs of a serious allergic reaction.

- **Unusual thoughts or behaviors.** Some patients have unusual thoughts or behaviors while taking bupropion hydrochloride extended-release tablets (XL), including delusions (believe you are someone else), hallucinations (seeing or hearing things that are not there), paranoia (feeling that people are against you), or feeling confused. If this happens to you, call your doctor.
  Common side effects reported in studies of major depressive disorder include weight loss, loss of appetite, dry mouth, skin rash, sweating, ringing in the ears, shakiness, stomach pain, agitation, anxiety, dizziness, trouble sleeping, muscle pain, nausea, fast heartbeat, sore throat, and urinating more often.
  If you have nausea, take your medicine with food. If you have trouble sleeping, do not take your medicine too close to bedtime.
  Tell your doctor right away about any side effects that bother you.
  These are not all the side effects of bupropion hydrochloride extended-release tablets (XL). For a complete list, ask your doctor or pharmacist.
  How should I store bupropion hydrochloride extended-release tablets (XL)?

- Store bupropion hydrochloride extended-release tablets (XL) at room temperature. Store out of direct sunlight. Keep bupropion hydrochloride extended-release tablets (XL) in its tightly closed bottle.

- Bupropion hydrochloride extended-release tablets (XL) may have an odor.
  General Information about bupropion hydrochloride extended-release tablets (XL).

- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use bupropion hydrochloride extended-release tablets (XL) for a condition for which it was not prescribed. Do not give bupropion hydrochloride extended-release tablets (XL) to other people, even if they have the same symptoms you have. It may harm them. Keep bupropion hydrochloride extended-release tablets (XL)out of the reach of children.

This Medication Guide summarizes important information about bupropion hydrochloride extended-release tablets (XL). For more information, talk with your doctor. You can ask your doctor or pharmacist for information about bupropion hydrochloride extended-release tablets (XL) that is written for health professionals. **To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals USA at 1-888-493-0857 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

What are the ingredients in bupropion hydrochloride extended-release tablets (XL)?

Active ingredient: bupropion hydrochloride.

Inactive ingredients: dehydrated alcohol, ethylcellulose, hydrochloric acid, hydroxypropylcellulose, methacrylic acid copolymer, povidone, silicon dioxide, hydrogenated vegetable oil and ethyl alcohol. The tablets are printed with edible black ink.

*The following are registered trademarks of their respective manufacturers: PROZAC®/Eli Lilly and Company; ZOLOFT®/Pfizer Pharmaceuticals; LUVOX®/Solvay Pharmaceuticals, Inc.; ANAFRANIL®/Mallinckrodt Inc.; NARDIL®/Warner Lambert Company; MARPLAN®/Oxford Pharmaceutical Services, Inc.; PARNATE®/ GlaxoSmithKline.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:

Anchen Pharmaceuticals, Inc.
Irvine, CA 92618
08/08

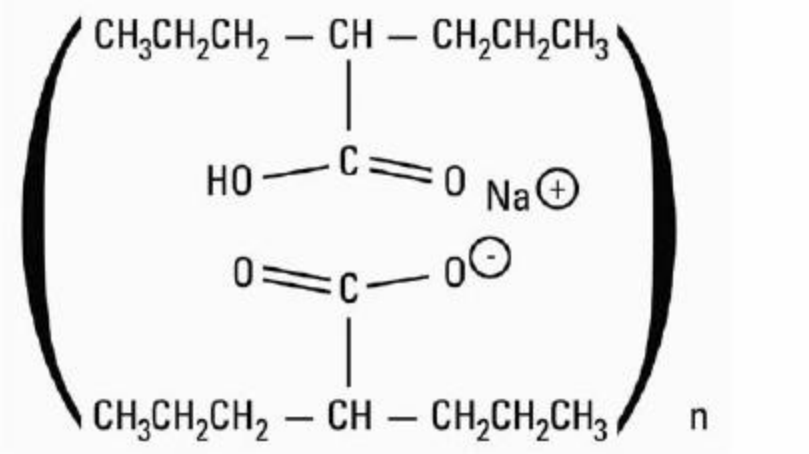
DIVALPROEX SODIUM DELAYED-RELEASE - divalproex sodium tablet, delayed release
Anchen Pharmaceuticals Inc.

Divalproex Sodium Delayed-Release Tablets USP
"Patient Information Leaflet" enclosed.
Rx only

HEPATOTOXICITY

HEPATIC FAILURE RESULTING IN FATALITIES HAS OCCURRED IN PATIENTS RECEIVING VALPROIC ACID AND ITS DERIVATIVES. EXPERIENCE HAS INDICATED THAT CHILDREN UNDER THE AGE OF TWO YEARS ARE AT A CONSIDERABLY INCREASED RISK OF DEVELOPING FATAL HEPATOTOXICITY, ESPECIALLY THOSE ON MULTIPLE ANTICONVULSANTS, THOSE WITH CONGENITAL METABOLIC DISORDERS, THOSE WITH SEVERE SEIZURE DISORDERS ACCOMPANIED BY MENTAL RETARDATION, AND THOSE WITH ORGANIC BRAIN DISEASE. WHEN DIVALPROEX SODIUM DELAYED-RELEASE TABLET IS USED IN THIS PATIENT GROUP, IT SHOULD BE USED WITH EXTREME CAUTION AND AS A SOLE AGENT. THE BENEFITS OF THERAPY SHOULD BE WEIGHED AGAINST THE RISKS. ABOVE THIS AGE GROUP, EXPERIENCE IN EPILEPSY HAS INDICATED THAT THE INCIDENCE OF FATAL HEPATOTOXICITY DECREASES CONSIDERABLY IN PROGRESSIVELY OLDER PATIENT GROUPS.
THESE INCIDENTS USUALLY HAVE OCCURRED DURING THE FIRST SIX MONTHS OF TREATMENT. SERIOUS OR FATAL HEPATOTOXICITY MAY BE PRECEDED BY NON-SPECIFIC SYMPTOMS SUCH AS MALAISE, WEAKNESS, LETHARGY, FACIAL EDEMA, ANOREXIA, AND VOMITING. IN PATIENTS WITH EPILEPSY, A LOSS OF SEIZURE CONTROL MAY ALSO OCCUR. PATIENTS SHOULD BE MONITORED CLOSELY FOR APPEARANCE OF THESE SYMPTOMS. LIVER FUNCTION TESTS SHOULD BE PERFORMED PRIOR TO THERAPY AND AT FREQUENT INTERVALS THEREAFTER, ESPECIALLY DURING THE FIRST SIX MONTHS.
TERATOGENICITY
VALPROATE CAN PRODUCE TERATOGENIC EFFECTS SUCH AS NEURAL TUBE DEFECTS (E.G., SPINA BIFIDA). ACCORDINGLY, THE USE OF DIVALPROEX SODIUM DELAYED-RELEASE TABLETS IN WOMEN OF CHILDBEARING POTENTIAL REQUIRES THAT THE BENEFITS OF ITS USE BE WEIGHED AGAINST THE RISK OF INJURY TO THE FETUS. THIS IS ESPECIALLY IMPORTANT WHEN THE TREATMENT OF A SPONTANEOUSLY REVERSIBLE CONDITION NOT ORDINARILY ASSOCIATED WITH PERMANENT INJURY OR RISK OF DEATH (E.G., MIGRAINE) IS CONTEMPLATED. SEE WARNINGS, INFORMATION FOR PATIENTS.
AN INFORMATION SHEET DESCRIBING THE TERATOGENIC POTENTIAL OF VALPROATE IS AVAILABLE FOR PATIENTS.
PANCREATITIS
CASES OF LIFE-THREATENING PANCREATITIS HAVE BEEN REPORTED IN BOTH CHILDREN AND ADULTS RECEIVING VALPROATE. SOME OF THE CASES HAVE BEEN DESCRIBED AS HEMORRHAGIC WITH A RAPID PROGRESSION FROM INITIAL SYMPTOMS TO DEATH. CASES HAVE BEEN REPORTED SHORTLY AFTER INITIAL USE AS WELL AS AFTER SEVERAL YEARS OF USE. PATIENTS AND GUARDIANS SHOULD BE WARNED THAT ABDOMINAL PAIN, NAUSEA, VOMITING, AND/OR ANOREXIA CAN BE SYMPTOMS OF PANCREATITIS THAT REQUIRE PROMPT MEDICAL EVALUATION. IF PANCREATITIS IS DIAGNOSED, VALPROATE SHOULD ORDINARILY BE DISCONTINUED. ALTERNATIVE TREATMENT FOR THE UNDERLYING MEDICAL CONDITION SHOULD BE INITIATED AS CLINICALLY INDICATED. (See WARNINGS and PRECAUTIONS.)

DESCRIPTION
Divalproex sodium is a stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. Chemically it is designated as sodium hydrogen bis(2-propylpentanoate). Divalproex sodium has the following structure:



Divalproex sodium occurs as a white powder with a characteristic odor.
Divalproex sodium delayed-release tablets are for oral administration. Divalproex sodium delayed-release tablets are supplied as divalproex sodium equivalent to 500 mg of valproic acid.

Inactive Ingredients
Divalproex sodium delayed-release tablets contain the following inactive ingredients: cellacefate, colloidal silicone dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone, talc, titanium dioxide, and triethyl citrate. In addition, the tablets contain: FD&C Yellow No. 5 (see Precautions) and iron oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics
Divalproex sodium dissociates to the valproate ion in the gastrointestinal tract. The mechanisms by which valproate exerts its therapeutic effects have not been established. It has been suggested that its activity in epilepsy is related to increased brain concentrations of gamma-aminobutyric acid (GABA).

Pharmacokinetics

Absorption/Bioavailability
Equivalent oral doses of divalproex sodium delayed-release tablets products and valproic acid capsules deliver equivalent quantities of valproate ion systemically. Although the rate of valproate ion absorption may vary with the formulation administered (liquid, solid, or sprinkle), conditions of use (e.g., fasting or postprandial) and the method of administration (e.g., whether the contents of the capsule are sprinkled on food or the capsule is taken intact), these differences should be of minor clinical importance under the steady state conditions achieved in chronic use in the treatment of epilepsy.

However, it is possible that differences among the various valproate products in T_{max} and C_{max} could be important upon initiation of treatment. For example, in single dose studies, the effect of feeding had a greater influence on the rate of absorption of the tablet (increase in T_{max} from 4 to 8 hours) than on the absorption of the sprinkle capsules (increase in T_{max} from 3.3 to 4.8 hours).

While the absorption rate from the G.I. tract and fluctuation in valproate plasma concentrations vary with dosing regimen and formulation, the efficacy of valproate as an anticonvulsant in chronic use is unlikely to be affected. Experience employing dosing regimens from once-a-day to four-times-a-day, as well as studies in primate epilepsy models involving constant rate infusion, indicate that total daily systemic bioavailability (extent of absorption) is the primary determinant of seizure control and that differences in the ratios of plasma peak to trough concentrations between valproate formulations are inconsequential from a practical clinical standpoint. Whether or not rate of absorption influences the efficacy of valproate as an antimanic or antimigraine agent is unknown.

Co-administration of oral valproate products with food and substitution among the various divalproex sodium delayed-release tablets and valproic acid formulations should cause no clinical problems in the management of patients with epilepsy (see DOSAGE AND ADMINISTRATION). Nonetheless, any changes in dosage administration, or the addition or discontinuance of concomitant drugs should ordinarily be accompanied by close monitoring of clinical status and valproate plasma concentrations.

Distribution
Protein Binding

The plasma protein binding of valproate is concentration dependent and the free fraction increases from approximately 10% at 40 μg/ml to 18.5% at 130 μg/mL. Protein binding of valproate is reduced in the elderly, in patients with chronic hepatic diseases, in patients with renal impairment, and in the presence of other drugs (e.g., aspirin). Conversely, valproate may displace certain protein-bound drugs (e.g., phenytoin, carbamazepine, warfarin, and tolbutamide). (See PRECAUTIONS, Drug Interactions for more detailed information on the pharmacokinetic interactions of valproate with other drugs.)

CNS Distribution

Valproate concentrations in cerebrospinal fluid (CSF) approximate unbound concentrations in plasma (about 10% of total concentration).

Metabolism

Valproate is metabolized almost entirely by the liver. In adult patients on monotherapy, 30-50% of an administered dose appears in urine as a glucuronide conjugate. Mitochondrial β-oxidation is the other major metabolic pathway, typically accounting for over 40% of the dose. Usually, less than 15-20% of the dose is eliminated by other oxidative mechanisms. Less than 3% of an administered dose is excreted unchanged in urine.

The relationship between dose and total valproate concentration is nonlinear; concentration does not increase proportionally with the dose, but rather, increases to a lesser extent due to saturable plasma protein binding. The kinetics of unbound drug are linear.

Elimination

Mean plasma clearance and volume of distribution for total valproate are 0.56 L/hr/1.73 m^2 and 11 L/1.73 m^2, respectively. Mean plasma clearance and volume of distribution for free valproate are 4.6 L/hr/1.73 m^2 and 92 L/1.73 m^2. Mean terminal half-life for valproate monotherapy ranged from 9 to 16 hours following oral dosing regimens of 250 to 1000 mg.

The estimates cited apply primarily to patients who are not taking drugs that affect hepatic metabolizing enzyme systems. For example, patients taking enzyme-inducing antiepileptic drugs (carbamazepine, phenytoin, and phenobarbital) will clear valproate more rapidly. Because of these changes in valproate clearance, monitoring of antiepileptic concentrations should be intensified whenever concomitant antiepileptics are introduced or withdrawn.

Special Populations

Effect of Age

Neonates

Children within the first two months of life have a markedly decreased ability to eliminate valproate compared to older children and adults. This is a result of reduced clearance (perhaps due to delay in development of glucuronosyltransferase and other enzyme systems involved in valproate elimination) as well as increased volume of distribution (in part due to decreased plasma protein binding). For example, in one study, the half-life in children under 10 days ranged from 10 to 67 hours compared to a range of 7 to 13 hours in children greater than 2 months.

Children

Pediatric patients (i.e., between 3 months and 10 years) have 50% higher clearances expressed on weight (i.e., mL/min/kg) than do adults. Over the age of 10 years, children have pharmacokinetic parameters that approximate those of adults.

Elderly

The capacity of elderly patients (age range: 68 to 89 years) to eliminate valproate has been shown to be reduced compared to younger adults (age range: 22 to 26). Intrinsic clearance is reduced by 39%; the free fraction is increased by 44%. Accordingly, the initial dosage should be reduced in the elderly. (See DOSAGE AND ADMISTRATION).

Effect of Gender

There are no differences in the body surface area adjusted unbound clearance between males and females (4.8±0.17 and 4.7±0.07 L/hr per 1.73 m^2, respectively).

Effect of Race

The effects of race on the kinetics of valproate have not been studied.

Effect of Disease

Liver Disease

(See BOXED WARNING, CONTRAINDICATIONS, and WARNINGS). Liver disease impairs the capacity to eliminate valproate. In one study, the clearance of free valproate was decreased by 50% in 7 patients with cirrhosis and by 16% in 4 patients with acute hepatitis, compared with 6 healthy subjects. In that study, the half-life of valproate was increased from 12 to 18 hours. Liver disease is also associated with decreased albumin concentrations and larger unbound fractions (2 to 2.6 fold increase) of valproate. Accordingly, monitoring of total concentrations may be misleading since free concentrations may be substantially elevated in patients with hepatic disease whereas total concentrations may appear to be normal.

Renal Disease

A slight reduction (27%) in the unbound clearance of valproate has been reported in patients with renal failure (creatinine clearance < 10 mL/minute); however, hemodialysis typically reduces valproate concentrations by about 20%. Therefore, no dosage adjustment appears to be necessary in patients with renal failure. Protein binding in these patients is substantially reduced; thus, monitoring total concentrations may be misleading.

Plasma Levels and Clinical Effect
The relationship between plasma concentration and clinical response is not well documented. One contributing factor is the nonlinear, concentration dependent protein binding of valproate which affects the clearance of the drug. Thus, monitoring of total serum valproate cannot provide a reliable index of the bioactive valproate species.

For example, because the plasma protein binding of valproate is concentration dependent, the free fraction increases from approximately 10% at 40 μg/mL to 18.5% at 130 μg/mL. Higher than expected free fractions occur in the elderly, in hyperlipidemic patients, and in patients with hepatic and renal diseases.

Epilepsy

The therapeutic range in epilepsy is commonly considered to be 50 to 100 μg/mL of total valproate, although some patients may be controlled with lower or higher plasma concentrations.

Mania

In placebo-controlled clinical trials of acute mania, patients were dosed to clinical response with trough plasma concentrations between 50 and 125 μg/mL (See DOSAGE AND ADMINISTRATION).

CLINICAL TRIALS

Mania
The effectiveness of divalproex sodium delayed-release tablets for the treatment of acute mania was demonstrated in two 3-week, placebo controlled, parallel group studies.
(1) Study 1: The first study enrolled adult patients who met DSM-III-R criteria for Bipolar Disorder and who were hospitalized for acute mania. In addition, they had a history of failing to respond to or not tolerating previous lithium carbonate treatment. Divalproex sodium delayed-release tablets were initiated at a dose of 250 mg tid and adjusted to achieve serum valproate concentrations in a range of 50-100 μg/mL by day 7. Mean divalproex sodium delayed-release tablets doses for completers in this study were 1118, 1525, and 2402 mg/day at Day 7, 14, and 21, respectively. Patients were assessed on the Young Mania Rating Scale (YMRS; score ranges from 0-60), an augmented Brief Psychiatric Rating Scale (BPRS-A), and the Global Assessment Scale (GAS). Baseline scores and change from baseline in the Week 3 endpoint (last-observation-carry-forward) analysis were as follows:
Study 1

YMRS Total Score

Group	**Baseline[1]**	**BL to Wk 3[2]**	**Difference[3]**
Placebo	28.8	+0.2	
Divalproex Sodium Delayed-Release Tablets	28.5	-9.5	9.7

BPRS-A Total Score

Group	**Baseline[1]**	**BL to Wk 3[2]**	**Difference[3]**
Placebo	76.2	+1.8	
Divalproex Sodium	76.4	-17.0	18.8

Delayed-Release Tablets

	GAS Score		
Group	**Baseline[1]**	**BL to Wk 3[2]**	**Difference[3]**
Placebo	31.8	0.0	
Divalproex Sodium Delayed-Release Tablets	30.3	+18.1	18.1

[1] Mean score at baseline

[2] Change from baseline to Week 3 (LOCF)

[3] Difference in change from baseline to Week 3 endpoint (LOCF) between divalproex sodium delayed-release tablets and placebo

Divalproex sodium delayed-release tablets were statistically significantly superior to placebo on all three measures of outcome.
(2) Study 2: The second study enrolled adult patients who met Research Diagnostic Criteria for manic disorder and who were hospitalized for acute mania. Divalproex sodium delayed-release tablets were initiated at a dose of 250 mg tid and adjusted within a dose range of 750-2500 mg/day to achieve serum valproate concentrations in a range of 40-150 μg/mL. Mean divalproex sodium delayed-release tablets doses for completers in this study were 1116, 1683, and 2006 mg/day at Days 7, 14, and 21, respectively. Study 2 also included a lithium group for which lithium doses for completers were 1312, 1869, and 1984 mg/day at Days 7, 14, and 21, respectively. Patients were assessed on the Manic Rating Scale (MRS; score ranges from 11-63), and the primary outcome measures were the total MRS score, and scores for two subscales of the MRS, i.e., the Manic Syndrome Scale (MSS) and the Behavior and Ideation Scale (BIS). Baseline scores and change from baseline in the Week 3 endpoint (last-observation-carry-forward) analysis were as follows:
Study 2

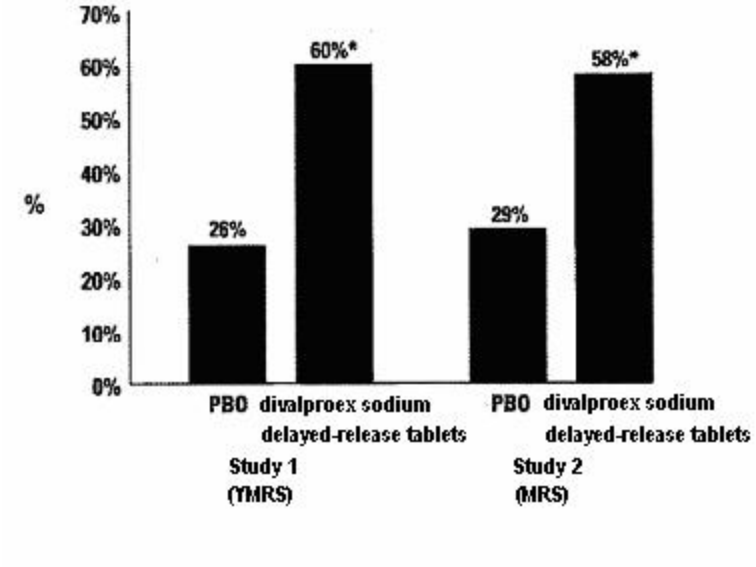
	MRS Total Score		
Group	**Baseline[1]**	**BL to Day 21[2]**	**Difference[3]**
Placebo	38.9	-4.4	
Lithium	37.9	-10.5	6.1
Divalproex Sodium Delayed-Release Tablets	38.1	-9.5	5.1
	MSS Total Score		
Group	**Baseline[1]**	**BL to Day 21[2]**	**Difference[3]**
Placebo	18.9	-2.5	
Lithium	18.5	-6.2	3.7
Divalproex Sodium Delayed-Release Tablets	18.9	-6.0	3.5
	BIS Total Score		
Group	**Baseline[1]**	**BL to Day 21[2]**	**Difference[3]**
Placebo	16.4	-1.4	
Lithium	16.0	-3.8	2.4
Divalproex Sodium Delayed-Release Tablets	15.7	-3.2	1.8

[1] Mean score at baseline

[2] Change from baseline to Day 21 (LOCF)

[3] Difference in change from baseline to Day 21 endpoint (LOCF) between divalproex sodium delayed-release tablets and placebo and lithium and placebo

Divalproex sodium delayed-release tablets were statistically significantly superior to placebo on all three measures of outcome. An exploratory analysis for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or gender.
A comparison of the percentage of patients showing ≥ 30% reduction in the symptom score from baseline in each treatment group, separated by study, is shown in Figure 1.
Figure 1. Percentage of Patients Achieving ≥ 30% Reduction in Symptom Score From Baseline



* $p < 0.05$
PBO = placebo, DVPX = divalproex sodium delayed-release tablets

Migraine

The results of two multicenter, randomized, double-blind, placebo-controlled clinical trials established the effectiveness of divalproex sodium delayed-release tablets in the prophylactic treatment of migraine headache.

Both studies employed essentially identical designs and recruited patients with a history of migraine with or without aura (of at least 6 months in duration) who were experiencing at least 2 migraine headaches a month during the 3 months prior to enrollment. Patients with cluster headaches were excluded. Women of childbearing potential were excluded entirely from one study, but were permitted in the other if they were deemed to be practicing an effective method of contraception.

In each study following a 4-week single-blind placebo baseline period, patients were randomized, under double blind conditions, to divalproex sodium delayed-release tablets or placebo for a 12-week treatment phase, comprised of a 4-week dose titration period followed by an 8-week maintenance period. Treatment outcome was assessed on the basis of 4-week migraine headache rates during the treatment phase.

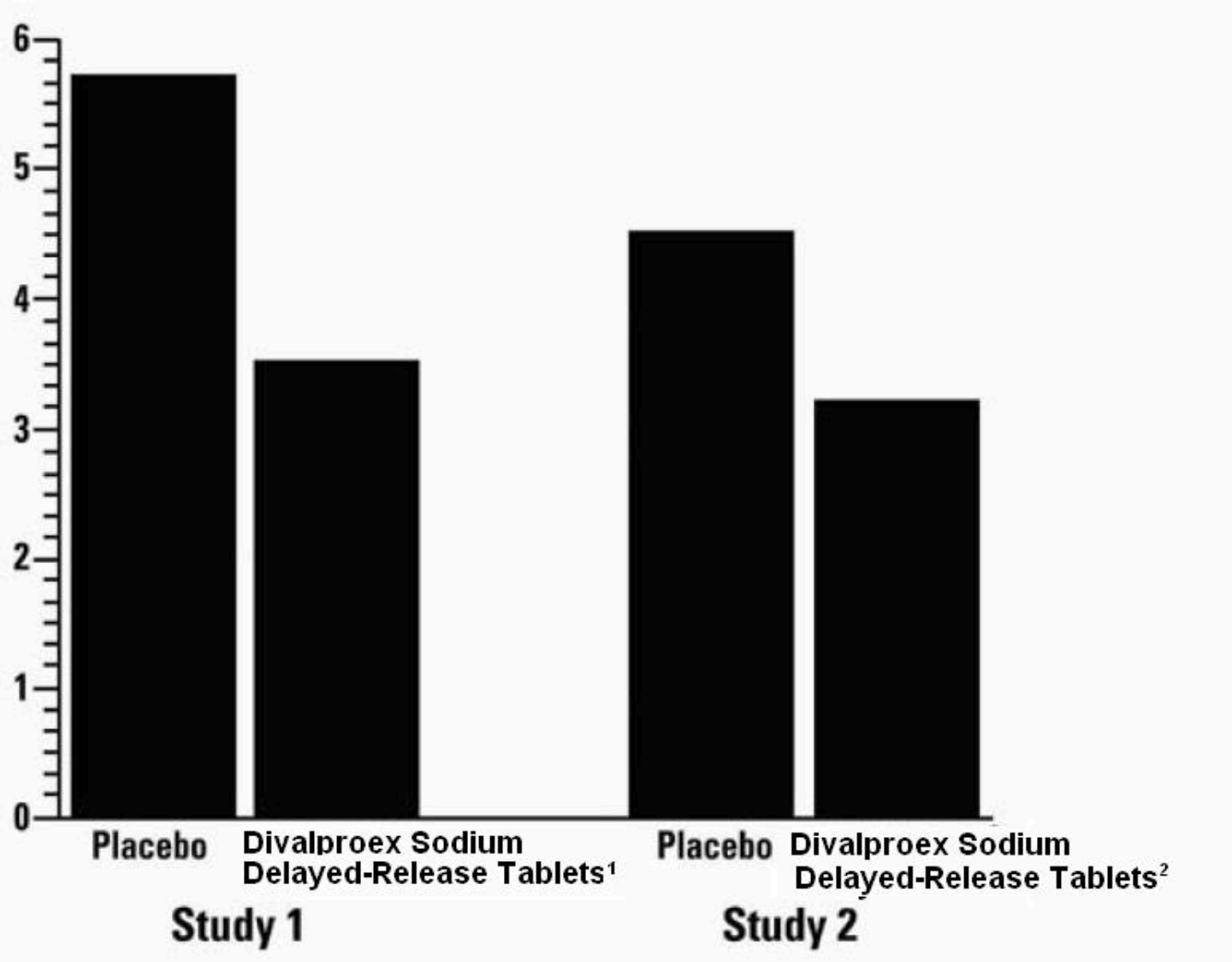
In the first study, a total of 107 patients (24 M, 83 F), ranging in age from 26 to 73 were randomized 2:1, divalproex sodium delayed-release tablets to placebo. Ninety patients completed the 8-week maintenance period. Drug dose titration, using 250 mg tablets, was individualized at the investigator's discretion. Adjustments were guided by actual/sham trough total serum valproate levels in order to maintain the study blind. In patients on divalproex sodium delayed-release tablets dose ranged from 500 to 2500 mg a day. Doses over 500 mg were given in three divided doses (TID). The mean dose during the treatment phase was 1087 mg/day resulting in a mean trough total valproate level of 72.5 μg/mL, with a range of 31 to 133 μg/mL.

The mean 4-week migraine headache rate during the treatment phase was 5.7 in the placebo group compared to 3.5 in the divalproex sodium delayed-release tablets group (see Figure 2). These rates were significantly different.

In the second study, a total of 176 patients (19 males and 157 females), ranging in age from 17 to 76 years, were randomized equally to one of three divalproex sodium delayed-release tablets dose groups (500, 1000, or 1500 mg/day) or placebo. The treatments were given in two divided doses (BID). One hundred thirty-seven patients completed the 8-week maintenance period. Efficacy was to be determined by a comparison of the 4-week migraine headache rate in the combined 1000/1500 mg/day group and placebo group. The initial dose was 250 mg daily. The regimen was advanced by 250 mg every 4 days (8 days for 500 mg/day group), until the randomized dose was achieved. The mean trough total valproate levels during the treatment phase were 39.6, 62.5, and 72.5 μg/mL in the divalproex sodium delayed-release tablets 500, 1000, and 1500 mg/day groups, respectively.

The mean 4-week migraine headache rates during the treatment phase, adjusted for differences in baseline rates, were 4.5 in the placebo group, compared to 3.3, 3.0, and 3.3 in the divalproex sodium delayed-release tablets 500, 1000, and 1500 mg/day groups, respectively, based on intent-to-treat results (see Figure 2). Migraine headache rates in the combined divalproex sodium delayed-release tablets 1000/1500 mg group were significantly lower than in the placebo group.

Figure 2. Mean 4-week Migraine Rates



[1] Mean dose of divalproex sodium delayed-release tablets was 1087 mg/day.

[2] Dose of divalproex sodium delayed-release tablets was 500 or 1000 mg/day.

Epilepsy

The efficacy of divalproex sodium delayed-release tablets in reducing the incidence of complex partial seizures (CPS) that occur in isolation or in association with other seizure types was established in two controlled trials.

In one, multiclinic, placebo controlled study employing an add-on design, (adjunctive therapy) 144 patients who continued to suffer eight or more CPS per 8 weeks during an 8 week period of monotherapy with doses of either carbamazepine or phenytoin sufficient to assure plasma concentrations within the "therapeutic range" were randomized to receive, in addition to their original antiepilepsy drug (AED), either divalproex sodium delayed-release tablets or placebo. Randomized patients were to be followed for a total of 16 weeks. The following table presents the findings.

Adjunctive Therapy Study Median Incidence of CPS per 8 weeks

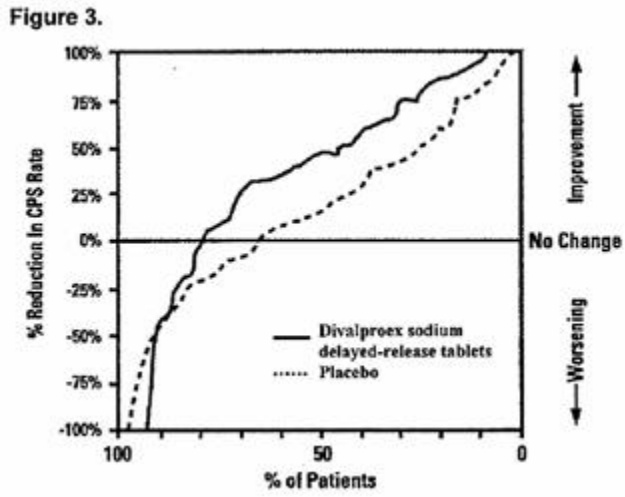
Add-on treatment	Number of Patients	Baseline Incidence	Experimental Incidence
Divalproex Sodium Delayed-Release Tablets	75	16.0	8.9*
Placebo	69	14.5	11.5

*Reduction from baseline statistically significantly greater for divalproex sodium delayed-release tablets than placebo at $p \leq 0.05$ level.

Figure 3 presents the proportion of patients (X axis) whose percentage reduction from baseline in complex partial seizure rates was at least as great as that indicated on the Y axis in the adjunctive therapy study. A positive percent reduction indicates an improvement (i.e., a decrease in seizure frequency), while a negative percent reduction indicates worsening. Thus, in a display of this type, the curve

for an effective treatment is shifted to the left of the curve for placebo. This figure shows that the proportion of patients achieving any particular level of improvement was consistently higher for divalproex sodium delayed-release tablets than for placebo. For example, 45% of patients treated with divalproex sodium delayed-release tablets had a ≥ 50% reduction in complex partial seizure rate compared to 23% of patients treated with placebo.

Figure 3.



The second study assessed the capacity of divalproex sodium delayed-release tablets to reduce the incidence of CPS when administered as the sole AED. The study compared the incidence of CPS among patients randomized to either a high or low dose treatment arm. Patients qualified for entry into the randomized comparison phase of this study only if 1) they continued to experience 2 or more CPS per 4 weeks during an 8 to 12 week long period of monotherapy with adequate doses of an AED (i.e., phenytoin, carbamazepine, phenobarbital, or primidone) and 2) they made a successful transition over a two week interval to divalproex sodium delayed-release tablets. Patients entering the randomized phase were then brought to their assigned target dose, gradually tapered off their concomitant AED and followed for an interval as long as 22 weeks. Less than 50% of the patients randomized, however, completed the study. In patients converted to divalproex sodium delayed-release tablets monotherapy, the mean total valproate concentrations during monotherapy were 71 and 123 μg/mL in the low dose and high dose groups, respectively.

The following table presents the findings for all patients randomized who had at least one post-randomization assessment.

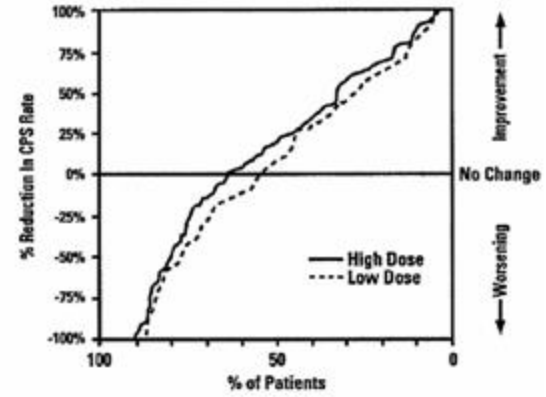
Monotherapy Study Median Incidence of CPS per 8 Weeks

Treatment	Number of Patients	Baseline Incidence	Randomized Phase Incidence
High Dose Divalproex Sodium Delayed-Release Tablets	131	13.2	10.7*
Low Dose Divalproex Sodium Delayed-Release Tablets	134	14.2	13.8

* Reduction from baseline statistically significantly greater for high dose than low dose at $p \leq 0.05$ level.

Figure 4 presents the proportion of patients (X axis) whose percentage reduction from baseline in complex partial seizure rates was at least as great as that indicated on the Y axis in the monotherapy study. A positive percent reduction indicates an improvement (i.e., a decrease in seizure frequency), while a negative percent reduction indicates worsening. Thus, in a display of this type, the curve for a more effective treatment is shifted to the left of the curve for a less effective treatment. This figure shows that the proportion of patients achieving any particular level of reduction was consistently higher for high dose divalproex sodium delayed-release tablets than for low dose divalproex sodium delayed-release tablets. For example, when switching from carbamazepine, phenytoin, phenobarbital or primidone monotherapy to high dose divalproex sodium delayed-release tablets monotherapy, 63% of patients experienced no change or a reduction in complex partial seizure rates compared to 54% of patients receiving low dose divalproex sodium delayed-release tablets.

Figure 4.



INDICATIONS AND USAGE

Mania

Divalproex sodium delayed-release tablets are indicated for the treatment of the manic episodes associated with bipolar disorder. A manic episode is a distinct period of abnormally and persistently elevated, expansive, or irritable mood. Typical symptoms of mania include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, poor judgement, aggressiveness, and possible hostility.

The efficacy of divalproex sodium delayed-release tablets was established in 3-week trials with patients meeting DSM-III-R criteria for bipolar disorder who were hospitalized for acute mania (See Clinical Trials under CLINICAL PHARMACOLOGY).

The safety and effectiveness of divalproex sodium delayed-release tablets for long-term use in mania, i.e., more than 3 weeks, has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use divalproex sodium delayed-release tablets for extended periods should continually reevaluate the long-term usefulness of the drug for the individual patient.

Epilepsy

Divalproex sodium delayed-release tablets are indicated as monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures. Divalproex sodium delayed-release tablets are also indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types that include absence seizures.

Simple absence is defined as very brief clouding of the sensorium or loss of consciousness accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

Migraine

Divalproex sodium delayed-release tablets are indicated for prophylaxis of migraine headaches. There is no evidence that divalproex sodium delayed-release tablets are useful in the acute treatment of migraine headaches. Because valproic acid may be a hazard to the fetus, divalproex sodium delayed-release tablets should be considered for women of childbearing potential only after this risk has been thoroughly discussed with the patient and weighed against the potential benefits of treatment (see WARNINGS - Usage In Pregnancy, PRECAUTIONS - Information for Patients).

SEE WARNINGS FOR STATEMENT REGARDING FATAL HEPATIC DYSFUNCTION.

CONTRAINDICATIONS

DIVALPROEX SODIUM SHOULD NOT BE ADMINISTERED TO PATIENTS WITH HEPATIC DISEASE OR SIGNIFICANT HEPATIC DYSFUNCTION.

Divalproex sodium is contraindicated in patients with known hypersensitivity to the drug.

Divalproex sodium is contraindicated in patients with known urea cycle disorders (see WARNINGS).

WARNINGS

Hepatotoxicity

Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination.

Caution should be observed when administering divalproex sodium delayed-release tablets products to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, children, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk. Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When divalproex sodium delayed-release tablets are used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above this age group, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.
The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug.

Pancreatitis
Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. Some of the cases have been described as hemorrhagic with rapid progression from initial symptoms to death. Some cases have occurred shortly after initial use as well as after several years of use. The rate based upon the reported cases exceeds that expected in the general population and there have been cases in which pancreatitis recurred after rechallenge with valproate. In clinical trials, there were 2 cases of pancreatitis without alternative etiology in 2416 patients, representing 1044 patient-years experience. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated (see BOXED WARNING).

Urea Cycle Disorders (UCD)
Divalproex sodium is contraindicated in patients with known urea cycle disorders.
Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency. Prior to the initiation of valproate therapy, evaluation for UCD should be considered in the following patients: 1) those with a history of unexplained encephalopathy or coma, encephalopathy associated with a protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine; 2) those with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN, or protein avoidance; 3) those with a family history of UCD or a family history of unexplained infant deaths (particularly males); 4) those with other signs or symptoms of UCD. Patients who develop symptoms of unexplained hyperammonemic encephalopathy while receiving valproate therapy should receive prompt treatment (including discontinuation of valproate therapy) and be evaluated for underlying urea cycle disorders (see CONTRAINDICATIONS and PRECAUTIONS).

Somnolence in the Elderly
In a double-blind, multicenter trial of valproate in elderly patients with dementia (mean age = 83 years), doses were increased by 125 mg/day to a target dose of 20 mg/kg/day. A significantly higher proportion of valproate patients had somnolence compared to placebo, and although not statistically significant, there was a higher proportion of patients with dehydration. Discontinuations for somnolence were also significantly higher than with placebo. In some patients with somnolence (approximately one-half), there was associated reduced nutritional intake and weight loss. There was a trend for the patients who experienced these events to have a lower baseline albumin concentration, lower valproate clearance, and a higher BUN. In elderly patients, dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence (see DOSAGE AND ADMINISTRATION).

Thrombocytopenia
The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia [see PRECAUTIONS) may be dose-related. In a clinical trial of divalproex sodium delayed-release tablets as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets $\leq 75 \times 10^9$/L. Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts normalized with continued treatment. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of ≥ 110 μg/mL (females) or ≥ 135 μg/mL (males). The therapeutic benefit which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.

Usage In Pregnancy
VALPROATE CAN PRODUCE TERATOGENIC EFFECTS. DATA SUGGEST THAT THERE IS AN INCREASED INCIDENCE OF CONGENITAL MALFORMATIONS ASSOCIATED WITH THE USE OF VALPROATE BY WOMEN WITH SEIZURE DISORDERS DURING PREGNANCY WHEN COMPARED TO THE INCIDENCE IN WOMEN WITH SEIZURE DISORDERS WHO DO NOT USE ANTIEPILEPTIC DRUGS DURING PREGNANCY, THE INCIDENCE IN WOMEN WITH SEIZURE DISORDERS WHO USE OTHER ANTIEPILEPTIC DRUGS, AND THE BACKGROUND INCIDENCE FOR THE GENERAL

POPULATION. THEREFORE, VALPROATE SHOULD BE CONSIDERED FOR WOMEN OF CHILDBEARING POTENTIAL ONLY AFTER THE RISKS HAVE BEEN THOROUGHLY DISCUSSED WTH THE PATIENT AND WEIGHED AGAINST THE POTENTIAL BENEFITS OF TREATMENT.

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE THAT INDICATE THE USE OF ANTIEPILEPTIC DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF CONGENITAL MALFORMATIONS IN OFFSPRING. ANTIEPILEPTIC DRUGS, INCLUDING VALPROATE, SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR MEDICAL CONDITION.

Antiepileptic drugs should not be discontinued abruptly in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

HUMAN DATA

Congenital Malformations

The North American Antiepileptic Drug Pregnancy Registry reported 16 cases of congenital malformations among the offspring of 149 women with epilepsy who were exposed to valproic acid monotherapy during the first trimester of pregnancy at doses of approximately 1,000 mg per day, for a prevalence rate of 10.7% (95% CI 6.3%-16.9%). Three of the 149 offspring (2%) had neural tube defects and 6 of the 149 (4%) had less severe malformations. Among epileptic women who were exposed to other antiepileptic drug monotherapies during pregnancy (1,048 patients) the malformation rate was 2.9% (95% CI 2.0% to 4.1%). There was a 4-fold increase in congenital malformations among infants with valproic acid-exposed mothers compared with those treated with other antiepileptic monotherapies as a group (Odds Ratio 4.0; 95% CI 2.1 to 7.4). This increased risk does not reflect a comparison versus any specific antiepileptic drug, but the risk versus the heterogeneous group of all other antiepileptic drug monotherapies combined. The increased teratogenic risk from valproic acid in women with epilepsy is expected to be reflected in an increased risk in other indications (e.g., migraine or bipolar disorder).

THE STRONGEST ASSOCIATION OF MATERNAL VALPROATE USAGE WITH CONGENITAL MALFORMATIONS IS WITH NEURAL TUBE DEFECTS (AS DISCUSSED UNDER THE NEXT SUBHEADING). HOWEVER, OTHER CONGENITAL ANOMALIES (E.G. CRANIOFACIAL DEFECTS, CARDIOVASCULAR MALFORMATIONS AND ANOMALIES INVOLVING VARIOUS BODY SYSTEMS), COMPATIBLE AND INCOMPATIBLE WITH LIFE, HAVE BEEN REPORTED. SUFFICIENT DATA TO DETERMINE THE INCIDENCE OF THESE CONGENITAL ANOMALIES IS NOT AVAILABLE.

Neural Tube Defects

THE INCIDENCE OF NEURAL TUBE DEFECTS IN THE FETUS IS INCREASED IN MOTHERS RECEIVING VALPROATE DURING THE FIRST TRIMESTER OF PREGNANCY. THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1 TO 2%. THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG) ESTIMATES THE GENERAL POPULATION RISK FOR CONGENITAL NEURAL TUBE DEFECTS AS 0.14% TO 0.2%.

Tests to detect neural tube and other defects using current accepted procedures should be considered a part of routine prenatal care in pregnant women receiving valproate.

Evidence suggests that pregnant women who receive folic acid supplementation may be at decreased risk for congenital neural tube defects in their offspring compared to pregnant women not receiving folic acid. Whether the risk of neural tube defects in the offspring of women receiving valproate specifically is reduced by folic acid supplementation is unknown. DIETARY FOLIC ACID SUPPLEMENTATION BOTH PRIOR TO AND DURING PREGNANCY SHOULD BE ROUTINELY RECOMMENDED TO PATIENTS CONTEMPLATING PREGNANCY.

Other Adverse Pregnancy Effects

PATIENTS TAKING VALPROATE MAY DEVELOP CLOTTING ABNORMALITIES (SEE PRECAUTIONS - GENERAL AND WARNINGS). A PATIENT WHO HAD LOW FIBRINOGEN WHEN TAKING MULTIPLE ANTICONVULSANTS INCLUDING VALPROATE GAVE BIRTH TO AN INFANT WITH AFIBRINOGENEMIA WHO SUBSEQUENTLY DIED OF HEMORRHAGE. IF VALPROATE IS USED IN PREGNANCY, THE CLOTTING PARAMETERS SHOULD BE MONITORED CAREFULLY.

PATIENTS TAKING VALPROATE MAY DEVELOP HEPATIC FAILURE (SEE WARNINGS - HEPATOTOXICITY AND BOX WARNING). FATAL HEPATIC FAILURES, IN A NEWBORN AND IN AN INFANT, HAVE BEEN REPORTED FOLLOWING THE MATERNAL USE OF VALPROATE DURING PREGNANCY.

ANIMAL DATA

Animal studies have demonstrated valproate-induced teratogenicity. Increased frequencies of malformations, as well as intrauterine growth retardation and death, have been observed in mice, rats, rabbits, and monkeys following prenatal exposure to valproate. Malformations of the skeletal system are the most common structural abnormalities produced in experimental animals, but neural tube closure defects have been seen in mice exposed to maternal plasma valproate concentrations exceeding 230 μg/mL (2.3 times the upper limit of the human therapeutic range) during susceptible periods of embryonic development. Administration of an oral dose of 200 mg/kg/day or greater (50% of the maximum human daily dose or greater on a mg/m^2 basis) to pregnant rats during organogenesis

produced malformations (skeletal, cardiac, and urogenital) and growth retardation in the offspring. These doses resulted in peak maternal plasma valproate levels of approximately 340 μg/mL or greater (3.4 times the upper limit of the human therapeutic range or greater). Behavioral deficits have been reported in the offspring of rats given a dose of 200 mg/kg/day throughout most of pregnancy. An oral dose of 350 mg/kg/day (approximately 2 times the maximum human daily dose on a mg/m^2 basis) produced skeletal and visceral malformations in rabbits exposed during organogenesis. Skeletal malformations, growth retardation, and death were observed in rhesus monkeys following administration of an oral dose of 200 mg/kg/day (equal to the maximum human daily dose on a mg/m^2 basis) during organogenesis. This dose resulted in peak maternal plasma valproate levels of approximately 280 μg/mL (2.8 times the upper limit of the human therapeutic range).

PRECAUTIONS

Hepatic Dysfunction
See BOXED WARNING, CONTRAINDICATIONS and WARNINGS.

Pancreatitis
See BOXED WARNING and WARNINGS.

Hyperammonemia
Hyperammonemia has been reported in association with valproate therapy and may be present despite normal liver function tests. In patients who develop unexplained lethargy and vomiting or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured. If ammonia is increased, valproate therapy should be discontinued. Appropriate interventions for treatment of hyperammonemia should be initiated, and such patients should undergo investigation for underlying urea cycle disorders (see CONTRAINDICATIONS and WARNINGS – Urea Cycle Disorders and PRECAUTIONS- Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use).
Asymptomatic elevations of ammonia are more common and when present, require close monitoring of plasma ammonia levels. If the elevation persists, discontinuation of valproate therapy should be considered. In patients who develop unexplained lethargy, vomiting, or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured. (see CONTRAINDICATIONS and WARNINGS - Urea Cycle Disorders and PRECAUTIONS -Hyperammonemia).

Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use
Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. In most cases, symptoms and signs abated with discontinuation of either drug. This adverse event is not due to a pharmacokinetic interaction. It is not known if topiramate monotherapy is associated with hyperammonemia. Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy. Although not studied, an interaction of topiramate and valproic acid may exacerbate existing defects or unmask deficiencies in susceptible persons. In patients who develop unexplained lethargy, vomiting, or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured. (see CONTRAINDICATIONS and WARNINGS -Urea Cycle Disorders and PRECAUTIONS - Hyperammonemia).

General
This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.
Because of reports of thrombocytopenia (see WARNINGS), inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters, (e.g., low fibrinogen), platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving divalproex sodium delayed-release tablets be monitored for platelet count and coagulation parameters prior to planned surgery. In a clinical trial of divalproex sodium delayed-release tablets as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets ≤ 75×10^9/L. Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts normalized with continued treatment. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of ≥ 110 μg/mL (females) or ≥ 135 μg/mL (males). Evidence of hemorrhage, bruising, or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.
Since divalproex sodium delayed-release tablets may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy. (See PRECAUTIONS- Drug Interactions.)
Valproate is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test. There have been reports of altered thyroid function tests associated with valproate. The clinical significance of these is unknown.

Suicidal ideation may be a manifestation of certain psychiatric disorders, and may persist until significant remission of symptoms occurs. Close supervision of high risk patients should accompany initial drug therapy.
There are *in vitro* studies that suggest valproate stimulates the replication of the HIV and CMV viruses under certain experimental conditions. The clinical consequence, if any, is not known. Additionally, the relevance of these *in vitro* findings is uncertain for patients receiving maximally suppressive antiretroviral therapy. Nevertheless, these data should be borne in mind when interpreting the results from regular monitoring of the viral load in HIV infected patients receiving valproate or when following CMV infected patients clinically.

Multi-organ Hypersensitivity Reaction
Multi-organ hypersensitivity reactions have been rarely reported in close temporal association to the initiation of valproate therapy in adult and pediatric patients (median time to detection 21 days: range 1 to 40 days). Although there have been a limited number of reports, many of these cases resulted in hospitalization and at least one death has been reported. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations may include lymphadenopathy, hepatitis, liver function test abnormalities, hematological abnormalities (e.g., eosinophilia, thrombocytopenia, neutropenia), pruritis, nephritis, oliguria, hepato-renal syndrome, arthralgia, and asthenia. Because the disorder is variable in its expression, other organ system symptoms and signs, not noted here, may occur. If this reaction is suspected, valproate should be discontinued and an alternative treatment started. Although the existence of cross sensitivity with other drugs that produce this syndrome is unclear, the experience amongst drugs associated with multi-organ hypersensitivity would indicate this to be a possibility.

Information for Patients
Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis and, therefore, require further medical evaluation promptly.
Patients should be informed of the signs and symptoms associated with hyperammonemic encephalopathy (see PRECAUTIONS – Hyperammonemia) and be told to inform the prescriber if any of these symptoms occur.
Since divalproex sodium delayed-release tablets products may produce CNS depression, especially when combined with another CNS depressant (eg, alcohol), patients should be advised not to engage in hazardous activities, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.
Since divalproex sodium delayed-release tablets have been associated with certain types of birth defects, female patients of child-bearing age considering the use of divalproex sodium delayed-release tablets should be advised of the risk and of alternative therapeutic options and to read the Patient Information Leaflet, which appears as the last section of the labeling. This is especially important when the treatment of a spontaneously reversible condition not ordinarily associated with permanent injury or risk of death (e.g., migraine) is considered.
Patients should be instructed that a fever associated with other organ system involvement (rash, lymphadenopathy, etc.) may be drug-related and should be reported to the physician immediately (see PRECAUTIONS - Multi-organ Hypersensitivity Reaction).

Drug Interactions

Effects of Co-Administered Drugs on Valproate Clearance
Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronosyltransferases, may increase the clearance of valproate. For example, phenytoin, carbamazepine, and phenobarbital (or primidone) can double the clearance of valproate. Thus, patients on monotherapy will generally have longer half-lives and higher concentrations than patients receiving polytherapy with antiepilepsy drugs.

In contrast, drugs that are inhibitors of cytochrome P450 isozymes, e.g., antidepressants, may be expected to have little effect on valproate clearance because cytochrome P450 microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and beta-oxidation.

Because of these changes in valproate clearance, monitoring of valproate and concomitant drug concentrations should be increased whenever enzyme inducing drugs are introduced or withdrawn.

The following list provides information about the potential for an influence of several commonly prescribed medications on valproate pharmacokinetics. The list is not exhaustive nor could it be, since new interactions are continuously being reported.

Drugs for which a potentially important interaction has been observed
Aspirin

A study involving the co-administration of aspirin at antipyretic doses (11 to 16 mg/kg) with valproate to pediatric patients (n=6) revealed a decrease in protein binding and an inhibition of metabolism of valproate. Valproate free fraction was increased 4-fold in the presence of aspirin compared to valproate alone. The β-oxidation pathway consisting of 2-E-valproic acid, 3-OH-valproic acid,

and 3-keto valproic acid was decreased from 25% of total metabolites excreted on valproate alone to 8.3% in the presence of aspirin. Caution should be observed if valproate and aspirin are to be co-administered.

Felbamate

A study involving the co-administration of 1200 mg/day of felbamate with valproate to patients with epilepsy (n=10) revealed an increase in mean valproate peak concentration by 35% (from 86 to 115 μg/mL) compared to valproate alone. Increasing the felbamate dose to 2400 mg/day increased the mean valproate peak concentration to 133 μg/mL (another 16% increase). A decrease in valproate dosage may be necessary when felbamate therapy is initiated.

Meropenem

Subtherapeutic valproic acid levels have been reported when meropenem was coadministered.

Rifampin

A study involving the administration of a single dose of valproate (7 mg/kg) 36 hours after 5 nights of daily dosing with rifampin (600 mg) revealed a 40% increase in the oral clearance of valproate. Valproate dosage adjustment may be necessary when it is co-administered with rifampin.

Drugs for which either no interaction or a likely clinically unimportant interaction has been observed
Antacids

A study involving the co-administration of valproate 500 mg with commonly administered antacids (Maalox, Trisogel, and Titralac - 160 mEq doses) did not reveal any effect on the extent of absorption of valproate.

Chlorpromazine

A study involving the administration of 100 to 300 mg/day of chlorpromazine to schizophrenic patients already receiving valproate (200 mg BID) revealed a 15% increase in trough plasma levels of valproate.

Haloperidol

A study involving the administration of 6 to 10 mg/day of haloperidol to schizophrenic patients already receiving valproate (200 mg BID) revealed no significant changes in valproate trough plasma levels.

Cimetidine and Ranitidine

Cimetidine and ranitidine do not affect the clearance of valproate.

Effects of Valproate on Other Drugs
Valproate has been found to be a weak inhibitor of some P450 isozymes, epoxide hydrase, and glucuronosyltransferases.

The following list provides information about the potential for an influence of valproate co-administration on the pharmacokinetics or pharmacodynamics of several commonly prescribed medications. The list is not exhaustive, since new interactions are continuously being reported.

Drugs for which a potentially important valproate interaction has been observed
Amitriptyline/Nortriptyline

Administration of a single oral 50 mg dose of amitriptyline to 15 normal volunteers (10 males and 5 females) who received valproate (500 mg BID) resulted in a 21% decrease in plasma clearance of amitriptyline and a 34% decrease in the net clearance of nortriptyline. Rare postmarketing reports of concurrent use of valproate and amitriptyline resulting in an increased amitriptyline level have been received. Concurrent use of valproate and amitriptyline has rarely been associated with toxicity. Monitoring of amitriptyline levels should be considered for patients taking valproate concomitantly with amitriptyline. Consideration should be given to lowering the dose of amitriptyline/nortriptyline in the presence of valproate.

Carbamazepine/carbamazepine-10, 11-Epoxide

Serum levels of carbamazepine (CBZ) decreased 17% while that of carbamazepine- 10, 11-epoxide (CBZ-E) increased by 45% upon co-administration of valproate and CBZ to epileptic patients.

Clonazepam

The concomitant use of valproic acid and clonazepam may induce absence status in patients with a history of absence type seizures.

Diazepam

Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. Co-administration of valproate (1500 mg daily) increased the free fraction of diazepam (10 mg) by 90% in healthy volunteers (n=6). Plasma clearance and volume of distribution for free diazepam were reduced by 25% and 20%, respectively, in the presence of valproate. The elimination half-life of diazepam remained unchanged upon addition of valproate.

Ethosuximide

Valproate inhibits the metabolism of ethosuximide. Administration of a single ethosuximide dose of 500 mg with valproate (800 to 1600 mg/day) to healthy volunteers (n=6) was accompanied by a 25% increase in elimination half-life of ethosuximide and a 15% decrease in its total clearance as compared to ethosuximide alone. Patients receiving valproate and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

Lamotrigine

In a steady-state study involving 10 healthy volunteers, the elimination half-life of lamotrigine increased from 26 to 70 hours with valproate co-administration (a 165% increase). The dose of lamotrigine should be reduced when co-administered with valproate. Serious skin reactions (such as Stevens-Johnson Syndrome and toxic epidermal necrolysis) have been reported with concomitant lamotrigine and valproate administration. See lamotrigine package insert for details on lamotrigine dosing with concomitant valproate administration.

Phenobarbital

Valproate was found to inhibit the metabolism of phenobarbital. Co-administration of valproate (250 mg BID for 14 days) with phenobarbital to normal subjects (n=6) resulted in a 50% increase in half-life and a 30% decrease in plasma clearance of phenobarbital (60 mg single-dose). The fraction of phenobarbital dose excreted unchanged increased by 50% in presence of valproate.

There is evidence for severe CNS depression, with or without significant elevations of barbiturate or valproate serum concentrations. All patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate concentrations should be obtained, if possible, and the barbiturate dosage decreased, if appropriate.

Primidone, which is metabolized to a barbiturate, may be involved in a similar interaction with valproate.

Phenytoin

Valproate displaces phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. Co-administration of valproate (400 mg TID) with phenytoin (250 mg) in normal volunteers (n=7) was associated with a 60% increase in the free fraction of phenytoin. Total plasma clearance and apparent volume of distribution of phenytoin increased 30% in the presence of valproate. Both the clearance and apparent volume of distribution of free phenytoin were reduced by 25%.

In patients with epilepsy, there have been reports of breakthrough seizures occurring with the combination of valproate and phenytoin. The dosage of phenytoin should be adjusted as required by the clinical situation.

Tolbutamide

From *in vitro* experiments, the unbound fraction of tolbutamide was increased from 20% to 50% when added to plasma samples taken from patients treated with valproate. The clinical relevance of this displacement is unknown.

Topiramate

Concomitant administration of valproic acid and topiramate has been associated with hyperammonemia with and without encephalopathy (see CONTRAINDICATIONS and WARNINGS - Urea Cycle Disorders and PRECAUTIONS - Hyperammonemia and - Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use).

Warfarin

In an *in vitro* study, valproate increased the unbound fraction of warfarin by up to 32.6%. The therapeutic relevance of this is unknown; however, coagulation tests should be monitored if divalproex sodium delayed-release tablets therapy is instituted in patients taking anticoagulants.

Zidovudine

In six patients who were seropositive for HIV, the clearance of zidovudine (100 mg q8h) was decreased by 38% after administration of valproate (250 or 500 mg q8h); the half-life of zidovudine was unaffected.

Drugs for which either no interaction or a likely clinically unimportant interaction has been observed
Acetaminophen

Valproate had no effect on any of the pharmacokinetic parameters of acetaminophen when it was concurrently administered to three epileptic patients.

Clozapine

In psychotic patients (n=11), no interaction was observed when valproate was co-administered with clozapine.

Lithium

Co-administration of valproate (500 mg BID) and lithium carbonate (300 mg TID) to normal male volunteers (n=16) had no effect on the steady-state kinetics of lithium.

Lorazepam

Concomitant administration of valproate (500 mg BID) and lorazepam (1 mg BID) in normal male volunteers (n=9) was accompanied by a 17% decrease in the plasma clearance of lorazepam.

Oral Contraceptive Steroids

Administration of a single-dose of ethinyloestradiol (50 μg)/ levonorgestrel (250 μg) to 6 women on valproate (200 mg BID) therapy for 2 months did not reveal any pharmacokinetic interaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Valproic acid was administered orally to Sprague Dawley rats and ICR (HA/ICR) mice at doses of 80 and 170 mg/kg/day (approximately 10 to 50% of the maximum human daily dose on a mg/m^2 basis) for two years. A variety of neoplasms were observed in both species. The chief findings were a statistically significant increase in the incidence of subcutaneous fibrosarcomas in high dose male rats receiving valproic acid and a statistically significant dose-related trend for benign pulmonary adenomas in male mice receiving valproic acid. The significance of these findings for humans is unknown.

Mutagenesis
Valproate was not mutagenic in an *in vitro* bacterial assay (Ames test), did not produce dominant lethal effects in mice, and did not increase chromosome aberration frequency in an *in vivo* cytogenetic study in rats. Increased frequencies of sister chromatid exchange (SCE) have been reported in a study of epileptic children taking valproate, but this association was not observed in another study conducted in adults. There is some evidence that increased SCE frequencies may be associated with epilepsy. The biological significance of an increase in SCE frequency is not known.

Fertility
Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at oral doses of 400 mg/kg/day or greater in rats (approximately equivalent to or greater than the maximum human daily dose on a mg/m^2 basis) and 150 mg/kg/day or greater in dogs (approximately 1.4 times the maximum human daily dose or greater on a mg/m^2 basis). Segment I fertility studies in rats have shown doses up to 350 mg/kg/day (approximately equal to the maximum human daily dose on a mg/m^2 basis) for 60 days to have no effect on fertility. THE EFFECT OF VALPROATE ON TESTICULAR DEVELOPMENT AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

Pregnancy
Pregnancy Category D: See WARNINGS.

Nursing Mothers
Valproate is excreted in breast milk. Concentrations in breast milk have been reported to be 1-10% of serum concentrations. It is not known what effect this would have on a nursing infant. Consideration should be given to discontinuing nursing when divalproex sodium is administered to a nursing woman.

Pediatric Use

Experience has indicated that pediatric patients under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions (see BOXED WARNING). When divalproex sodium delayed-release tablets are used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above the age of 2 years, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

Younger children, especially those receiving enzyme-inducing drugs, will require larger maintenance doses to attain targeted total and unbound valproic acid concentrations.

The variability in free fraction limits the clinical usefulness of monitoring total serum valproic acid concentrations. Interpretation of valproic acid concentrations in children should include consideration of factors that affect hepatic metabolism and protein binding.

The safety and effectiveness of divalproex sodium delayed-release tablets for the treatment of acute mania has not been studied in individuals below the age of 18 years.

The safety and effectiveness of divalproex sodium delayed-release tablets for the prophylaxis of migraines has not been studied in individuals below the age of 16 years.

The basic toxicology and pathologic manifestations of valproate sodium in neonatal (4-day old) and juvenile (14-day old) rats are similar to those seen in young adult rats. However, additional findings, including renal alterations in juvenile rats and renal alterations and retinal dysplasia in neonatal rats, have been reported. These findings occurred at 240 mg/kg/day, a dosage approximately equivalent to the human maximum recommended daily dose on a mg/m^2 basis. They were not seen at 90 mg/kg, or 40% of the maximum human daily dose on a mg/m^2 basis.

Geriatric Use

No patients above the age of 65 years were enrolled in double-blind prospective clinical trials of mania associated with bipolar illness. In a case review study of 583 patients, 72 patients (12%) were greater than 65 years of age. A higher percentage of patients above 65 years of age reported accidental injury, infection, pain, somnolence, and tremor. Discontinuation of valproate was occasionally associated with the latter two events. It is not clear whether these events indicate additional risk or whether they result from preexisting medical illness and concomitant medication use among these patients.

A study of elderly patients with dementia revealed drug related somnolence and discontinuation for somnolence (see WARNINGS - Somnolence in the Elderly). The starting dose should be reduced in these patients, and dosage reductions or discontinuation should be considered in patients with excessive somnolence (see DOSAGE AND ADMINISTRATION).

There is insufficient information available to discern the safety and effectiveness of divalproex sodium delayed-release tablets for the prophylaxis of migraines in patients over 65.

ADVERSE REACTIONS

Mania

The incidence of treatment-emergent events has been ascertained based on combined data from two placebo-controlled clinical trials of divalproex sodium delayed-release tablets in the treatment of manic episodes associated with bipolar disorder. The adverse events were usually mild or moderate in intensity, but sometimes were serious enough to interrupt treatment. In clinical trials, the rates of premature termination due to intolerance were not statistically different between placebo, divalproex sodium delayed-release tablets, and lithium carbonate. A total of 4%, 8% and 11% of patients discontinued therapy due to intolerance in the placebo, divalproex sodium delayed-release tablets, and lithium carbonate groups, respectively.

Table 1 summarizes those adverse events reported for patients in these trials where the incidence rate in the divalproex sodium delayed-release tablet-treated group was greater than 5% and greater than the placebo incidence, or where the incidence in the divalproex sodium delayed-release tablet-treated group was statistically significantly greater than the placebo group. Vomiting was the only event that was reported by significantly ($p \leq 0.05$) more patients receiving divalproex sodium delayed-release tablets compared to placebo.

Table 1. Adverse Events Reported by > 5% of Divalproex Sodium Delayed-Release Tablet-Treated Patients During Placebo-Controlled Trials of Acute Mania[1]

Adverse Event	Divalproex Sodium Delayed-Release Tablets (n=89)	Placebo (n=97)
Nausea	22%	15%
Somnolence	19%	12%
Dizziness	12%	4%
Vomiting	12%	3%
Asthenia	10%	7%
Abdominal pain	9%	8%

Dyspepsia	9%	8%
Rash	6%	3%

[1] The following adverse events occurred at an equal or greater incidence for placebo than for divalproex sodium delayed-release tablets: back pain, headache, constipation, diarrhea, tremor, and pharyngitis.

The following additional adverse events were reported by greater than 1% but not more than 5% of the 89 divalproex sodium-treated patients in controlled clinical trials:

Body as a Whole

Chest pain, chills, chills and fever, fever, neck pain, neck rigidity.

Cardiovascular System

Hypertension, hypotension, palpitations, postural hypotension, tachycardia, vasodilation.

Digestive System

Anorexia, fecal incontinence, flatulence, gastroenteritis, glossitis, periodontal abscess.

Hemic and Lymphatic System

Ecchymosis.

Metabolic and Nutritional Disorders

Edema, peripheral edema.

Musculoskeletal System

Arthralgia, arthrosis, leg cramps, twitching.

Nervous System

Abnormal dreams, abnormal gait, agitation, ataxia, catatonic reaction, confusion, depression, diplopia, dysarthria, hallucinations, hypertonia, hypokinesia, insomnia, paresthesia, reflexes increased, tardive dyskinesia, thinking abnormalities, vertigo.

Respiratory System

Dyspnea, rhinitis.

Skin and Appendages

Alopecia, discoid lupus erythematosis, dry skin, furunculosis, maculopapular rash, seborrhea.

Special Senses

Amblyopia, conjunctivitis, deafness, dry eyes, ear pain, eye pain, tinnitus.

Urogenital System

Dysmenorrhea, dysuria, urinary incontinence.

Migraine

Based on two placebo-controlled clinical trials and their long term extension, divalproex sodium delayed-release tablets were generally well tolerated with most adverse events rated as mild to moderate in severity. Of the 202 patients exposed to divalproex sodium delayed-release tablets in the placebo-controlled trials, 17% discontinued for intolerance. This is compared to a rate of 5% for the 81 placebo patients. Including the long term extension study, the adverse events reported as the primary reason for discontinuation by ≥1% of 248 divalproex sodium delayed-release tablet-treated patients were alopecia (6%), nausea and/or vomiting (5%), weight gain (2%), tremor (2%), somnolence (1%), elevated SGOT and/or SGPT (1%), and depression (1%).

Table 2 includes those adverse events reported for patients in the placebo-controlled trials where the incidence rate in the divalproex sodium delayed-release tablet-treated group was greater than 5% and was greater than that for placebo patients.

Table 2. Adverse Events Reported by >5% of Divalproex Sodium Delayed-Release Tablet-Treated Patients During Migraine Placebo-Controlled Trials with a Greater Incidence Than Patients Taking Placebo[1]

Body System / Event	Divalproex Sodium Delayed-Release Tablets (N=202)	Placebo (N=81)
Gastrointestinal System		
Nausea	31%	10%
Dyspepsia	13%	9%
Diarrhea	12%	7%
Vomiting	11%	1%
Abdominal pain	9%	4%
Increased appetite	6%	4%
Nervous System		
Asthenia	20%	9%
Somnolence	17%	5%
Dizziness	12%	6%

Tremor	9%	0%
Other		
Weight gain	8%	2%
Back pain	8%	6%
Alopecia	7%	1%

[1] The following adverse events occurred in at least 5% of divalproex sodium delayed-release tablet-treated patients and at an equal or greater incidence for placebo than for divalproex sodium delayed-release tablets: flu syndrome and pharyngitis.

The following additional adverse events were reported by greater than 1% but not more than 5% of the 202 divalproex sodium-treated patients in the controlled clinical trials:
Body as a Whole
Chest pain, chills, face edema, fever and malaise.
Cardiovascular System
Vasodilatation.
Digestive System
Anorexia, constipation, dry mouth, flatulence, gastrointestinal disorder (unspecified), and stomatitis.
Hemic and Lymphatic System
Ecchymosis.
Metabolic and Nutritional Disorders
Peripheral edema, SGOT increase, and SGPT increase.
Musculoskeletal System
Leg cramps and myalgia.
Nervous System
Abnormal dreams, amnesia, confusion, depression, emotional lability, insomnia, nervousness, paresthesia, speech disorder, thinking abnormalities, and vertigo.
Respiratory System
Cough increased, dyspnea, rhinitis, and sinusitis.
Skin and Appendages
Pruritus and rash.
Special Senses
Conjunctivitis, ear disorder, taste perversion, and tinnitus.
Urogenital System
Cystitis, metrorrhagia, and vaginal hemorrhage.

Epilepsy
Based on a placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures, divalproex sodium delayed-release tablets were generally well tolerated with most adverse events rated as mild to moderate in severity. Intolerance was the primary reason for discontinuation in the divalproex sodium delayed-release tablet-treated patients (6%), compared to 1% of placebo-treated patients.
Table 3 lists treatment-emergent adverse events which were reported by ≥ 5% of divalproex sodium delayed-release tablet-treated patients and for which the incidence was greater than in the placebo group, in the placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures. Since patients were also treated with other antiepilepsy drugs, it is not possible, in most cases, to determine whether the following adverse events can be ascribed to divalproex sodium delayed-release tablets alone, or the combination of divalproex sodium delayed-release tablets and other antiepilepsy drugs.
Table 3. Adverse Events Reported by ≥ 5% of Patients Treated with Divalproex Sodium Delayed-Release Tablets During Placebo-Controlled Trial of Adjunctive Therapy for Complex Partial Seizures

Body System/ Event	**Divalproex Sodium Delayed-Release Tablets (%) (n=77)**	**Placebo (%) (n=70)**
Body as a Whole		
Headache	31	21
Asthenia	27	7
Fever	6	4
Gastrointestinal System		
Nausea	48	14
Vomiting	27	7
Abdominal Pain	23	6

Diarrhea	13	6
Anorexia	12	0
Dyspepsia	8	4
Constipation	5	1
Nervous System		
Somnolence	27	11
Tremor	25	6
Dizziness	25	13
Diplopia	16	9
Amblyopia/Blurred Vision	12	9
Ataxia	8	1
Nystagmus	8	1
Emotional Lability	6	4
Thinking Abnormal	6	0
Amnesia	5	1
Respiratory System		
Flu Syndrome	12	9
Infection	12	6
Bronchitis	5	1
Rhinitis	5	4
Other		
Alopecia	6	1
Weight Loss	6	0

Table 4 lists treatment-emergent adverse events which were reported by ≥ 5% of patients in the high dose divalproex sodium delayed-release tablets group, and for which the incidence was greater than in the low dose group, in a controlled trial of divalproex sodium delayed-release tablets monotherapy treatment of complex partial seizures. Since patients were being titrated off another antiepilepsy drug during the first portion of the trial, it is not possible, in many cases, to determine whether the following adverse events can be ascribed to divalproex sodium delayed-release tablets alone, or the combination of divalproex sodium delayed-release tablets and other antiepilepsy drugs.

Table 4. Adverse Events Reported by ≥ 5% of Patients in the High Dose Group in the Controlled Trial of Divalproex Sodium Delayed-Release Tablets Monotherapy for Complex Partial Seizures[1]

Body System/ Event	**High Dose (%) (n=131)**	**Low Dose (%) (n=134)**
Body as a Whole		
Asthenia	21	10
Degestive System		
Nausea	34	26
Diarrhea	23	19
Vomiting	23	15
Abdominal Pain	12	9
Anorexia	11	4
Dyspepsia	11	10
Hemic/Lymphatic System		
Thrombocytopenia	24	1
Ecchymosis	5	4
Metabolic/Nutritional		
Weight Gain	9	4
Peripheral Edema	8	3
Nervous System		
Tremor	57	19
Somnolence	30	18

Dizziness	18	13
Insomnia	15	9
Nervousness	11	7
Amnesia	7	4
Nystagmus	7	1
Depression	5	4
Respiratory System		
Infection	20	13
Pharyngitis	8	2
Dyspnea	5	1
Skin and Appendages		
Alopecia	24	13
Special Senses		
Amblyopia/Blurred Vision	8	4
Tinnitus	7	1

[1] Headache was the only adverse event that occurred in ≥ 5% of patients in the high dose group and at an equal or greater incidence in the low dose group.

The following additional adverse events were reported by greater than 1% but less than 5% of the 358 patients treated with divalproex sodium delayed-release tablets in the controlled trials of complex partial seizures:
Body as a Whole
Back pain, chest pain, malaise.
Cardiovascular System
Tachycardia, hypertension, palpitation.
Digestive System
Increased appetite, flatulence, hematemesis, eructation, pancreatitis, periodontal abscess.
Hemic and Lymphatic System
Petechia.
Metabolic and Nutritional Disorders
SGOT increased, SGPT increased.
Musculoskeletal System
Myalgia, twitching, arthralgia, leg cramps, myasthenia.
Nervous System
Anxiety, confusion, abnormal gait, paresthesia, hypertonia, incoordination, abnormal dreams, personality disorder.
Respiratory System
Sinusitis, cough increased, pneumonia, epistaxis.
Skin and Appendages
Rash, pruritus, dry skin.
Special Senses
Taste perversion, abnormal vision, deafness, otitis media.
Urogenital System
Urinary incontinence, vaginitis, dysmenorrhea, amenorrhea, urinary frequency.

Other Patient Populations
Adverse events that have been reported with all dosage forms of valproate from epilepsy trials, spontaneous reports, and other sources are listed below by body system.

Gastrointestinal
The most commonly reported side effects at the initiation of therapy are nausea, vomiting, and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps, and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported. The administration of delayed-release divalproex sodium may result in reduction of gastrointestinal side effects in some patients.

CNS Effects
Sedative effects have occurred in patients receiving valproate alone but occur most often in patients receiving combination therapy. Sedation usually abates upon reduction of other antiepileptic medication. Tremor (may be dose-related), hallucinations, ataxia, headache, nystagmus, diplopia, asterixis, “spots before eyes”, dysarthria, dizziness, confusion, hypesthesia, vertigo, incoordination,

and parkinsonism have been reported with the use of valproate. Rare cases of coma have occurred in patients receiving valproate alone or in conjunction with phenobarbital. In rare instances encephalopathy with or without fever has developed shortly after the introduction of valproate monotherapy without evidence of hepatic dysfunction or inappropriately high plasma valproate levels. Although recovery has been described following drug withdrawal, there have been fatalities in patients with hyperammonemic encephalopathy, particularly in patients with underlying urea cycle disorders (see WARNINGS – Urea Cycle Disorders and PRECAUTIONS).

Several reports have noted reversible cerebral atrophy and dementia in association with valproate therapy.

Dermatologic
Transient hair loss, skin rash, photosensitivity, generalized pruritus, erythema multiforme, and Stevens-Johnson syndrome. Rare cases of toxic epidermal necrolysis have been reported including a fatal case in a 6 month old infant taking valproate and several other concomitant medications. An additional case of toxic epidermal necrosis resulting in death was reported in a 35 year old patient with AIDS taking several concomitant medications and with a history of multiple cutaneous drug reactions. Serious skin reactions have been reported with concomitant administration of lamotrigine and valproate (see PRECAUTIONS - Drug Interactions).

Psychiatric
Emotional upset, depression, psychosis, aggression, hyperactivity, hostility, and behavioral deterioration.

Musculoskeletal
Weakness.

Hematologic
Thrombocytopenia and inhibition of the secondary phase of platelet aggregation may be reflected in altered bleeding time, petechiae, bruising, hematoma formation, epistaxis, and frank hemorrhage (see PRECAUTIONS - General and Drug Interactions). Relative lymphocytosis, macrocytosis, hypofibrinogenemia, leukopenia, eosinophilia, anemia including macrocytic with or without folate deficiency, bone marrow suppression, pancytopenia, aplastic anemia, agranulocytosis, and acute intermittent porphyria.

Hepatic
Minor elevations of transaminases (eg, SGOT and SGPT) and LDH are frequent and appear to be dose-related. Occasionally, laboratory test results include increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity (see WARNINGS).

Endocrine
Irregular menses, secondary amenorrhea, breast enlargement, galactorrhea, and parotid gland swelling. Abnormal thyroid function tests (see PRECAUTIONS).

There have been rare spontaneous reports of polycystic ovary disease. A cause and effect relationship has not been established.

Pancreatic

Acute pancreatitis including fatalities (see WARNINGS).

Metabolic

Hyperammonemia (see PRECAUTIONS), hyponatremia, and inappropriate ADH secretion.

There have been rare reports of Fanconi’s syndrome occurring chiefly in children.

Decreased carnitine concentrations have been reported although the clinical relevance is undetermined.

Hyperglycinemia has occurred and was associated with a fatal outcome in a patient with preexistent nonketotic hyperglycinemia.

Genitourinary

Enuresis and urinary tract infection.

Special Senses

Hearing loss, either reversible or irreversible, has been reported; however, a cause and effect relationship has not been established. Ear pain has also been reported.

Other

Allergic reaction, anaphylaxis, edema of the extremities, lupus erythematosus, bone pain, cough increased, pneumonia, otitis media, bradycardia, cutaneous vasculitis, fever, and hypothermia.

OVERDOSAGE

Overdosage with valproate may result in somnolence, heart block, and deep coma. Fatalities have been reported; however patients have recovered from valproate levels as high as 2120 μg/mL.

In overdose situations, the fraction of drug not bound to protein is high and hemodialysis or tandem hemodialysis plus hemoperfusion may result in significant removal of drug. The benefit of gastric lavage or emesis will vary with the time since ingestion. General supportive measures should be applied with particular attention to the maintenance of adequate urinary output.

Naloxone has been reported to reverse the CNS depressant effects of valproate overdosage. Because naloxone could theoretically also reverse the antiepileptic effects of valproate, it should be used with caution in patients with epilepsy.

DOSAGE AND ADMINISTRATION

Mania

Divalproex sodium delayed-release tablets are administered orally. The recommended initial dose is 750 mg daily in divided doses. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect or the desired range of plasma concentrations. In placebo-controlled clinical trials of acute mania, patients were dosed to a clinical response with a trough plasma concentration between 50 and 125 μg/mL. Maximum concentrations were generally achieved within 14 days. The maximum recommended dosage is 60 mg/kg/day.

There is no body of evidence available from controlled trials to guide a clinician in the longer term management of a patient who improves during divalproex sodium delayed-release tablets treatment of an acute manic episode. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the benefits of divalproex sodium delayed-release tablets in such longer-term treatment. Although there are no efficacy data that specifically address longer-term antimanic treatment with divalproex sodium delayed-release tablets, the safety of divalproex sodium delayed-release tablets in long-term use is supported by data from record reviews involving approximately 360 patients treated with divalproex sodium delayed-release tablets for greater than 3 months.

Epilepsy

Divalproex sodium delayed-release tablets are administered orally. Divalproex sodium delayed-release tablet is indicated as monotherapy and adjunctive therapy in complex partial seizures in adults and pediatric patients down to the age of 10 years, and in simple and complex absence seizures. As the divalproex sodium delayed-release tablets dosage is titrated upward, concentrations of phenobarbital, carbamazepine, and/or phenytoin may be affected (see PRECAUTIONS - Drug Interactions).

Complex Partial Seizures

For adults and children 10 years of age or older.

Monotherapy (Initial Therapy)

Divalproex sodium delayed-release tablets have not been systematically studied as initial therapy. Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 μg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.

The probability of thrombocytopenia increases significantly at total trough valproate plasma concentrations above 110 μg/mL in females and 135 μg/mL in males. The benefit of improved seizure control with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

Conversion to Monotherapy

Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 - 100 μg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. Concomitant antiepilepsy drug (AED) dosage can ordinarily be reduced by approximately 25% every 2 weeks. This reduction may be started at initiation of divalproex sodium delayed-release tablets therapy, or delayed by 1 to 2 weeks if there is a concern that seizures are likely to occur with a reduction. The speed and duration of withdrawal of the concomitant AED can be highly variable, and patients should be monitored closely during this period for increased seizure frequency.

Adjunctive Therapy
Divalproex sodium delayed-release tablets may be added to the patient's regimen at a dosage of 10 to 15 mg/kg/day. The dosage may be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 μg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. If the total daily dose exceeds 250 mg, it should be given in divided doses.

In a study of adjunctive therapy for complex partial seizures in which patients were receiving either carbamazepine or phenytoin in addition to divalproex sodium delayed-release tablets, no adjustment of carbamazepine or phenytoin dosage was needed (see CLINICAL STUDIES). However, since valproate may interact with these or other concurrently administered AEDs as well as other drugs (see Drug Interactions), periodic plasma concentration determinations of concomitant AEDs are recommended during the early course of therapy (see PRECAUTIONS - Drug Interactions).

Simple and Complex Absence Seizures
The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in divided doses.

A good correlation has not been established between daily dose, serum concentrations, and therapeutic effect. However, therapeutic valproate serum concentrations for most patients with absence seizures is considered to range from 50 to 100 μg/mL. Some patients may be controlled with lower or higher serum concentrations (see CLINICAL PHARMACOLOGY).

As the divalproex sodium delayed-release tablets dosage is titrated upward, blood concentrations of phenobarbital and/or phenytoin may be affected (see PRECAUTIONS).

Antiepilepsy drugs should not be abruptly discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life.

In epileptic patients previously receiving valproic acid therapy, divalproex sodium delayed-release tablets should be initiated at the same daily dose and dosing schedule. After the patient is stabilized on divalproex sodium delayed-release tablets, a dosing schedule of two or three times a day may be elected in selected patients.

Migraine
Divalproex sodium delayed-release tablets are administered orally. The recommended starting dose is 250 mg twice daily. Some patients may benefit from doses up to 1000 mg/day. In the clinical trials, there was no evidence that higher doses led to greater efficacy.

General Dosing Advice

Dosing in Elderly Patients
Due to a decrease in unbound clearance of valproate and possibly a greater sensitivity to somnolence in the elderly, the starting dose should be reduced in these patients. Dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence. The ultimate therapeutic dose should be achieved on the basis of both tolerability and clinical response (see WARNINGS).

Dose-Related Adverse Events
The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose-related. The probability of thrombocytopenia appears to increase significantly at total valproate concentrations of ≥ 110 μg/mL (females) or ≥ 135 μg/mL (males) (see PRECAUTIONS). The benefit of improved therapeutic effect with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

G.I. Irritation
Patients who experience G.I. irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

HOW SUPPLIED
Divalproex sodium delayed-release tablets 500 mg, USP are yellow, ovaloid, film-coated tablets with ink printed "A514" on one side. They are supplied as follow:

Bottles of 100 NDC #24979-514-01

Bottles of 500 NDC # 24979-514-05

Recommended storage: **Store tablets at 20-25°C (68-77°F) [see USP controlled room temperature]**

PATIENT INFORMATION LEAFLET

Divalproex Sodium Delayed-Release Tablets USP
Important Information for Women Who Could Become Pregnant About the Use of Divalproex Sodium Delayed-Release Tablets

Please read this leaflet carefully before you take this medication. This leaflet provides a summary of important information about taking this medication to women who could become pregnant. If you have any questions or concerns, or want more information about this medication, contact your doctor or pharmacist.

Information For Women Who Could Become Pregnant
This medication can be obtained only by prescription from your doctor. The decision to use this medication is one that you and your doctor should make together, taking into account your individual needs and medical condition.

Before using this medication, women who can become pregnant should consider the fact that this medication has been associated with birth defects, in particular, with spina bifida and other defects related to failure of the spinal canal to close normally. Approximately 1 to 2% of children born to women with epilepsy taking divalproex sodium delayed-release tablets in the first 12 weeks of pregnancy had these defects (based on data from the Centers for Disease Control, a U.S. agency based in Atlanta). The incidence in the general population is 0.1 to 0.2%.

These medications have also been associated with other birth defects such as defects of the heart, the bones, and other parts of the body. Information suggests that birth defects may be more likely to occur with these medications than some other drugs that treat your medical condition.

Information For Women Who Are Planning to Get Pregnant
- Women taking this medication who are planning to get pregnant should discuss the treatment options with their doctor.

Information For Women Who Become Pregnant
- If you become pregnant while taking this medication you should contact your doctor immediately.

Other Important Information
- Your medication should be taken exactly as prescribed by your doctor to get the most benefits from your medication and reduce the risk of side effects.

- If you have taken more than the prescribed dose of your medication, contact your hospital emergency room or local poison center immediately.

- Your medication was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

Facts About Birth Defects
It is important to know that birth defects may occur even in children of individuals not taking any medications or without any additional risk factors.

This summary provides important information about the use of divalproex sodium delayed-release tablets to women who could become pregnant. If you would like more information about the other potential risks and benefits of this medication, ask your doctor or pharmacist to let you read the professional labeling and then discuss it with them. If you have any questions or concerns about taking this medication, you should discuss them with your doctor.

Rx only

Manufactured by

Anchen Pharmaceuticals (Taiwan), Inc.

No. 3-1, Ziqiang 4th Rd., Zhongli Industrial Zone, Zhongli City, Taoyuan County 320, Taiwan

Revised: 04/08

UNITED STATES DISTRICT COURT, CENTRAL DISTRICT OF CALIFORNIA
CIVIL COVER SHEET

I. (a) PLAINTIFFS (Check box if you are representing yourself ☐)

EURAND, INC., CEPHALON, INC., AND ANESTA AG

DEFENDANTS

ANCHEN PHARMACEUTICALS, INC. and ANCHEN, INC.

(b) Attorneys (Firm Name, Address and Telephone Number. If you are representing yourself, provide same.)

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Attorneys (If Known)

II. BASIS OF JURISDICTION (Place an "X" in one box only.)

- ☐ 1. U.S. Government Plaintiff
- ☒ 3. Federal Question (U.S. Government Not a Party)
- ☐ 2. U.S. Government Defendant
- ☐ 4. Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES - For Diversity Cases Only
(Place an "X" in one box for plaintiff and one for defendant.)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	of Business In this State Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. ORIGIN (Place "X" in One Box Only)

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from another district (specify): ☐ 6 Multidistrict Litigation ☐ 7 Appeal to District Magistrate Judgment

V. REQUESTED IN COMPLAINT: JURY DEMAND: ☐ Yes ☒ No (Check 'Yes' only if demanded in complaint.)

CLASS ACTION under F.R.C.P. 23: ☐ Yes ☒ No ☐ **MONEY DEMANDED IN COMPLAINT: $** _____

VI. CAUSE OF ACTION (Cite the U.S. Civil Statute under which you are filing and write a brief statement of cause. Do not cite jurisdictional statutes unless diversity.)

Brief description of cause: Patent Infringement under 35 U.S.C. § 271 and 28 U.S.C. §§ 2201-02

VII. NATURE OF SUIT (Place an "X" in one box only)

OTHER STATUTES
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce/ICC Rates/etc.
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 480 Consumer Credit
- ☐ 490 Cable/Sat TV
- ☐ 810 Selective Service
- ☐ 850 Securities/ Commodities / Exchange
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- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Act
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Info. Act
- ☐ 900 Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes

CONTRACT
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- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excl. Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
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TORTS

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- ☐ 315 Airplane Product Liability
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- ☐ 555 Prison Condition

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- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs.
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor/Mgmt. Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl. Ret. Inc. Security Act

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS – Third Party 26 USC 7609

For office use only: Case Number: **CV09-4931 CBM(MLGX)**

AFTER COMPLETING THE FRONT SIDE OF FORM CV-71, COMPLETE THE INFORMATION REQUESTED BELOW.

UNITED STATES DISTRICT COURT, CENTRAL DISTRICT OF CALIFORNIA
CIVIL COVER SHEET

VIII(a) IDENTICAL CASES. Has this action been previously filed in this court and dismissed, remanded or closed? ☒ No ☐ Yes
If yes, list case numbers(s):
See related cases filed in other districts indicated in Notice of Pendency of Other Actions or Proceedings [L.R. RULE 83.1-4]

VIII(b) RELATED CASES: Have any cases been previously filed in this court that are related to the present case? ☒ No ☐ Yes
If yes, list case numbers(s):
See related cases filed in other districts indicated in Notice of Pendency of Other Actions or Proceedings [L.R. RULE 83.1-4]

Civil cases are deemed related if a previously filed case and the present case:
(Check all boxes that apply)
- ☐ A. Arise from the same or closely related transactions, happening, or events; or
- ☐ B. Call for determination of the same or substantially related to similar questions of law and fact; or
- ☐ C. For other reasons would entail substantial duplication of labor if heard by different judges; or
- ☐ D. Involve the same patent, trademark or copyright, and one of the factors identified above in a, b or c also is present

IX. VENUE: (When completing the following information, use an additional sheet if necessary.)

(a) List the County in this District; California County outside of this District; State if other than California; or Foreign Country, in which **EACH** named plaintiff resides.
☐ Check here if the government, its agencies or employees is a named plaintiff. If this box is checked, go to item (b).

County in this District:*	California County outside of this District, State, if other than California, or Foreign County
	Eurand, Inc. - Ohio **Cephalon, Inc. - Pennsylvania** **Anesta AG - Switzerland**

(b) List the County in this District; California County outside of this District; State if other than California; or Foreign Country, in which **EACH** named defendant resides.
☐ Check here if the government, its agencies or employees is a named plaintiff. If this box is checked, go to item (c).

County in this District:*	California County outside of this District, State, if other than California, or Foreign County
Anchen Pharmaceuticals, Inc. – Orange County **Anchen, Inc. – Orange County**	

(c) List the County in this District; California County outside of this District; State if other than California; or Foreign Country, in which **EACH** claim arose.
Note: In land condemnation cases, use the location of the tract of land involved.

County in this District:*	California County outside of this District, State, if other than California, or Foreign County
	Delaware

***Los Angeles, Orange, San Bernardino, Riverside, Ventura, Santa Barbara, or San Luis Obispo Counties**
Note: In land condemnation cases, use the location of the tract of land involved

X. SIGNATURE OF ATTORNEY (OR PRO PER): _____ Date 7/9/09

Notice to Counsel/Parties: The CV-71 (JS-44) Civil Cover Sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law. This form, approved by the Judicial Conference of the United States in September 1974, is required pursuant to Local Rule 3-1 is not filed but is used by the Clerk of the Court for the purpose of statistics, venue and initiating the civil docket sheet. (For more detailed instructions, see separate instruction sheet.)

Key to Statistical codes relating to Social Security Cases:

861	HIA	All claims for health insurance benefits (Medicare) under Title 18, Part A, of the Social Security Act, as amended. Also, include claims by hospitals, skilled nursing facilities, etc., for certification as providers of services under the program (42 U.S.C. 1935FF(b))
862	BL	All claims for "Black Lung" benefits under Title 4, Part B, of the Federal Coal Mine Health and Safety Act of 1969. (30 U.S.C. 923)
863	DIWC	All claims filed by insured workers for disability insurance benefits under Title 2 of the Social Security Act, as amended, plus all claims filed for child's insurance benefits based on disability. (42 U.S.C. 405(g))
863	DIWW	All claims filed for widows or widowers insurance benefits based on disability under Title 2 of the Social Security Act, as amended. (42 U.S.C. 405(g))
864	SSID	All claims for supplemental security income payments based upon disability filed under Title 16 of the Social Security Act, as amended.
865	RSI	All claims for retirement (old age) and survivors benefits under Title 2 of the Social Security Act, as amended. (42 U.S.C.(g))

UNITED STATES DISTRICT COURT
CENTRAL DISTRICT OF CALIFORNIA

NOTICE OF ASSIGNMENT TO UNITED STATES MAGISTRATE JUDGE FOR DISCOVERY

This case has been assigned to District Judge Consuelo B. Marshall and the assigned discovery Magistrate Judge is Marc Goldman.

The case number on all documents filed with the Court should read as follows:

CV09- 4931 CBM (MLGx)

Pursuant to General Order 05-07 of the United States District Court for the Central District of California, the Magistrate Judge has been designated to hear discovery related motions.

All discovery related motions should be noticed on the calendar of the Magistrate Judge

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NOTICE TO COUNSEL

A copy of this notice must be served with the summons and complaint on all defendants (if a removal action is filed, a copy of this notice must be served on all plaintiffs).

Subsequent documents must be filed at the following location:

[X] Western Division
312 N. Spring St., Rm. G-8
Los Angeles, CA 90012

[ ] Southern Division
411 West Fourth St., Rm. 1-053
Santa Ana, CA 92701-4516

[ ] Eastern Division
3470 Twelfth St., Rm. 134
Riverside, CA 92501

Failure to file at the proper location will result in your documents being returned to you.

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

UNITED STATES DISTRICT COURT
CENTRAL DISTRICT OF CALIFORNIA

EURAND, INC., CEPHALON, INC., and ANESTA AG, PLAINTIFF(S) v. ANCHEN PHARMACEUTICALS, INC. and ANCHEN, INC., DEFENDANT(S).	CASE NUMBER **CV09-4931 CBM(MLGX)** **SUMMONS**

TO: DEFENDANT(S): _____

_____

A lawsuit has been filed against you.

Within 20 days after service of this summons on you (not counting the day you received it), you must serve on the plaintiff an answer to the attached ☑ complaint ☐ _____ amended complaint ☐ counterclaim ☐ cross-claim or a motion under Rule 12 of the Federal Rules of Civil Procedure. The answer or motion must be served on the plaintiff's attorney, Todd G. Miller, whose address is Fish & Richardson P.C., 12390 El Camino Real, San Diego, CA 92130. If you fail to do so, judgment by default will be entered against you for the relief demanded in the complaint. You also must file your answer or motion with the court.

Clerk, U.S. District Court

Dated: JUL - 9 2009

By: Nancy Castro
Deputy Clerk

SEAL

(Seal of the Court)

[Use 60 days if the defendant is the United States or a United States agency, or is an officer or employee of the United States. Allowed 60 days by Rule 12(a)(3)].