CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-360

Name:	Gabapentin Capsules, 100 mg, 300 mg and 400 mg
Sponsor:	Apotex
Approval Date:	April 6, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-360

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-360

APPROVAL LETTER

ANDA 75-360

APR 6 2005

Apotex Corp.
Attention: Marcy Macdonald
U.S. Agent for: Apotex Inc.
616 Heathrow Drive
Lincolnshire, IL 60069

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated April 17, 1998, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Gabapentin Capsules, 100 mg, 300 mg, and 400 mg.

Reference is made to our approvable letter dated December 6, 2002, and to our tentative approval letter dated January 29, 2003, as revised on February 26, 2003. Reference is also made to your amendments dated July 15, 1998; July 22, 2004; and January 7, February 1, and March 3, 2005. We also refer to our letter dated January 28, 2003, addressing issues associated with 180-day generic drug exclusivity for this drug product.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Gabapentin Capsules, 100 mg, 300 mg, and 400 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Neurontin Capsules, 100 mg, 300 mg, and 400 mg, respectively, of Pfizer Pharmaceuticals Ltd. (Pfizer). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

The listed drug product (RLD) referenced in your application, Pfizer's Neurontin Capsules, is subject to periods of patent protection and exclusivity. As noted in the agency's publication entitled Approved Drug Products with Therapeutic

Equivalence Evaluations (the "Orange Book"), U.S. Patent No. 4,894,476 (the '476 patent) is scheduled to expire on November 2, 2008, and U.S. Patent No. 6,054,482 (the '482 patent) is scheduled to expire on October 25, 2017. Your application contains paragraph IV certifications to each of these patents under section 505(j)(2)(A)(vii)(IV) of the Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of the drug product. As discussed in our tentative approval letter of February, 26, 2003, the 30-month period identified in section 505(j)(5)(B)(iii) of the Act has expired; during the 30-month period FDA was precluded from approving your application because of ongoing litigation with respect to the '482 patent. The agency also recognizes that the 180-day generic drug exclusivity previously held by Purepac Pharmaceutical Company with respect to Gabapentin Capsules 100 mg, 300 mg, and 400 mg, expired on April 6, 2005. Therefore, there is no longer any bar to approval of your ANDA.

Under section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-42
5600 Fishers Lane
Rockville, MD 20857

We call your attention to 21 CFR 314.81(b)(3) which requires that all materials for any subsequent advertising or promotional campaign be submitted to the Division of Drug Marketing, Advertising, and Communications (HFD-42) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 4/6/05
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-360
Division File
Field Copy
HFD-610/R. West
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-640/D.Skanchy/3/9/05 3/11/05
HFD-640/N.Ya for S.Rosencrance/3/9/05 3/11/05
HFD-617/T.Hinchliffe/3/9/05 3/11/05
HFD-617/M.Dillahunt/3/9/05 3/10/05
HFD-613/L.Golson/3/9/05 3/10/05

CMC OK
RCA
3/18/05

Robert Lyet
3/21/2005

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F/T by TOH/3/9/05

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-360

TENTATIVE APPROVAL LETTER(S)

ANDA 75-360

FEB 26 2003

Apotex Corp.
Attention: Marcy Macdonald
U.S. Agent for: TorPharm
50 Lakeview Parkway, Suite #127
Vernon Hills, NJ 60061

Dear Madam:

This letter is a correction to our January 29, 2003, Tentative Approval letter. Reference is made to your abbreviated new drug application (ANDA) dated April 17, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Gabapentin Capsules, 100 mg, 300 mg, and 400 mg.

Reference is also made to the approvable letter from this office dated December 6, 2002, and to your amendment dated December 13, 2002.

We have completed the review of this abbreviated application as amended and have concluded that based upon the information you have presented to date, the drug product is safe and effective for use as recommended in the submitted labeling. Although we are unable to grant final approval at this time due to 180-day generic drug exclusivity issues described below, the application is **tentatively approved**. This determination is based upon information available to the agency at this time, (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). The determination is subject to change on the basis of new information that may come to our attention.

The listed drug product (RLD) referenced in your application, Neurontin® Capsules of Pfizer, Inc., is subject to periods of patent protection and exclusivity. As noted in the Agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", the patents expire on November 2, 2008 (U.S. Patent No. 4,894,476, the '476 patent), and October 25, 2017 (U.S. Patent No. 6,054,482, the '482 patent). Your application contains paragraph IV

certifications to each of these patents under Section 505(j)(2)(A)(vii)(IV) of the Act stating that the patents will not be infringed by your manufacture, use, or sale of the drug product. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA may be made effective immediately, unless an action is brought against TorPharm for infringement of one or more of the patents that are the subject of the certifications. This action must be brought against TorPharm prior to the expiration of 45 days from the date the notice you provided to the NDA/patent holder(s) under paragraph (2)(B)(i) was received.

You have notified the agency that Torpharm has complied with the requirements of Section 505(j)(2)(B) of the Act. In addition, you have informed the agency that litigation concerning the '476 patent has been completed. You have also informed the agency that litigation is ongoing in the United States District Court for the Northern District of Illinois Eastern Division (Pfizer Inc., Warner-Lambert Company and Godecke Aktiengesellschaft v. Apotex Corp., Apotex, Inc. and Torpharm, Inc., Civil Action No. 00 C 4398) involving your challenge to the '482 patent. With respect to the litigation on the '482 patent, the Agency recognizes that the 30-month period identified in Section 505(j)(5)(B)(iii) of the Act, during which time FDA was precluded from approving your application, has expired.

However, we are unable to grant final approval to your application at this time. Our letter dated January 28, 2003, addressed to both TorPharm and Purepac Pharmaceutical Company, discussed the withdrawal of U.S. Patent No. 5,084,479 (the '479 patent) from the Orange Book. The letter also stated the agency's decision that, under the provisions of section 505(j) of the Act and related FDA regulations, TorPharm is not eligible for 180-day exclusivity as to the '479 patent. Furthermore, with respect to the '476 and '482 patents, the Act provides that approval of an ANDA that contains a certification described in section 505(j)(2)(A)(vii)(IV), a paragraph IV certification, and that provides for approval of the same drug product as that for which another ANDA containing a paragraph IV certification to the same patent was previously received, shall be made effective not earlier than one hundred and eighty (180) days after:

1. the date the Secretary receives notice from the applicant of the previous application that commercial marketing of the drug product approved in that application was initiated, or

2. the date of a decision of a court holding the patent which was the subject of the paragraph IV certification to be invalid or not infringed,

whichever occurs first [section 505(j)(5)(B)(iv)].

In this instance, the Office of Generic Drugs received and filed an ANDA containing paragraph IV certifications to the '476 and '482 patents listed for Neurontin® Capsules prior to the filing of your application. Accordingly, your application will not be eligible for full approval until the first applicant's 180-day exclusivity as to both the '476 and the '482 patent has expired. Exclusivity as to the '476 patent was triggered with the unappealed district court decision and has expired. Exclusivity as to the '482 patent will be triggered either by commercial marketing or a court decision finding the '482 patent invalid or not infringed, whichever comes first. We refer you to the agency's guidance document "180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments" (June 1998), for additional information.

The Orange Book also notes that certain portions of the labeling for Neurontin® Capsules are subject to periods of exclusivity; i.e. Code I-311. Section 11 of the Best Pharmaceuticals for Children Act (BPCA), signed into law in January 2002, allows certain portions of the NDA holder's labeling which is the subject of pediatric exclusivity protection to be omitted from the labeling of products approved under section 505(j). The BPCA also permits the addition of language to the labeling of products approved under section 505(j) that informs health care practitioners that the NDA holder's product has been approved for pediatric use and that that informationis protected by exclusivity. The agency has determined that the final printed labeling you have submitted is in compliance with the BPCA with respect to pediatric use information protected by exclusivity.

In order to reactivate your application prior to final approval, please submit a MINOR AMENDMENT - FINAL APPROVAL REQUESTED between 60 to 90 days prior to the date you believe that your application will be eligible for final approval. This amendment should provide a justification for the reasons you believe the ANDA is eligible for final approval, and it should also identify changes, if any, in the conditions under which the product was tentatively approved; i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in

your cover letter that it represents a MINOR AMENDMENT - FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the agency may request at any time prior to the final date of approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to agency review before final approval of the application will be made. Such changes should be submitted as an amendment to the application and categorized as representing either "major" or "minor" changes. The amendment will be reviewed according to OGD policy in effect at the time of receipt. Your submission of multiple amendments prior to final approval may lead to a delay in the issuance of the final approval letter.

Please note that this drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 501 of the Act and 21 U.S.C. 331(d). Also, until the agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355, and will not be listed in the Orange Book.

For further information on the status of this application, or prior to submitting additional amendments, please contact Thomas Hinchliffe, R.Ph., Project Manager, at (301) 827-5849.

Sincerely yours,

2/26/03

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-360
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205

Endorsements:
HFD-640/T.Wang/12/16/02;12/17/02
HFD-640/S.Rosencrance/12/16/02;12/17/02
HFD-617/T.Hinchliffe/12/16/0212/17/02
HFD-617/M.Dillahunt/12/16/02
HFD-613/L.Golson/12/16/02

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F/T by TOH\12/16/02; Revised to Tentative Approval letter
From Approval letter:RLWest/1/29/03. Refer to letter dated 1/28/03 as basis for change to T/A status.
2/25/03 edited by P. Rickman
2/26/03 edited by L. Dickinson

CORRECTION TO TENTATIVE APPROVAL!

ANDA 75-360

JAN 29 2003

Apotex Corp.
Attention: Marcy Macdonald
U.S. Agent for: TorPharm
50 Lakeview Parkway, Suite #127
Vernon Hills, NJ 60061

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated April 17, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Gabapentin Capsules, 100 mg, 300 mg, and 400 mg.

Reference is also made to the approvable letter from this office dated December 6, 2002, and to your amendment dated December 13, 2002.

We have completed the review of this abbreviated application as amended and have concluded that based upon the information you have presented to date, the drug product is safe and effective for use as recommended in the submitted labeling. Although we are unable to grant final approval at this time due to 180-day generic drug exclusivity issues described below, the application is **tentatively approved.** This determination is based upon information available to the agency at this time, (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). The determination is subject to change on the basis of new information that may come to our attention.

The listed drug product (RLD) referenced in your application, Neurontin® Capsules of Pfizer, Inc., is subject to periods of patent protection and exclusivity. As noted in the Agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", the patents expire on November 2, 2008 (U.S. Patent No. 4,894,476, the '476 patent), and October 25, 2017 (U.S. Patent No. 6,054,482, the '482 patent). Your application contains Paragraph IV

Certifications to each of these patents under Section 505(j)(2)(A)(vii)(IV) of the Act stating that the patents will not be infringed by your manufacture, use, or sale of the drug product. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA may be made effective immediately, unless an action is brought against TorPharm for infringement of one or more of the patents that are the subject of the certifications. This action must be brought against TorPharm prior to the expiration of 45 days from the date the notice you provided to the NDA/patent holder(s) under paragraph (2)(B)(i) was received. You have notified the agency that Torpharm has complied with the requirements of Section 505(j)(2)(B) of the Act. In addition, you have informed the agency that litigation concerning the '476 patent remains ongoing in the United States District Court for the Northern District of Illinois Eastern Division (Warner-Lambert Company v. Apotex Corp., Apotex, Inc. and Torpharm, Inc., Civil Action No. 98 C 4293). You have also informed the agency that litigation is ongoing in the same district court involving your challenge to the '482 patent (Pfizer Inc., Warner-Lambert Company and Godecke Aktiengesellschaft v. Apotex Corp., Apotex, Inc. and Torpharm, Inc., Civil Action No. 00 C 4398). With respect to both litigations, the Agency recognizes that the 30-month period identified in Section 505(j)(5)(B)(iii) of the Act, during which time FDA was precluded from approving your application, has expired.

However, we are unable to grant final approval to your application at this time. Our letter dated January 28, 2003, addressed to both TorPharm and Purepac Pharmaceutical Company, discussed the withdrawal of the '479 patent from the Orange Book. The letter also stated the agency's decision that, under the provisions of section 505(j) of the Act and related FDA regulations, TorPharm is not eligible for 180-day exclusivity as to the '479 patent. Furthermore, with respect to the '476 and '482 patents, the Act provides that approval of an ANDA that contains a certification described in section 505(j)(2)(A)(vii)(IV), a paragraph IV certification, and that provides for approval of the same drug product as that for which another ANDA containing a paragraph IV certification was previously received, shall be made effective not earlier than one hundred and eighty (180) days after:

1. the date the Secretary receives notice from the applicant of the previous application that commercial marketing of the drug product approved in that application was initiated, or

2. the date of as decision of a court holding one or more of patents which were the subject of the paragraph IV certifications (the '476 and '482 patents) to be invalid or not infringed; whichever option occurs first [section 505(j)(5)(B)(iv)].

In this instance, the Office of Generic Drugs received and filed an ANDA containing paragraph IV certifications to the '476 and '482 patents listed for Neurontin® Capsules prior to the filing of your application. Accordingly, your application will not be eligible for full approval until 180-days following the earlier of event 1. Or 2. Stated above. We refer you to the agency's guidance document "180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments" (June 1998), for additional information.

The Orange Book also notes that certain portions of the labeling for Neurontin® Capsules are subject to periods of exclusivity; i.e. Code I-311. Section 11 of the Best Pharmaceuticals for Children Act (BPCA), signed into law in January 2002, allows certain portions of the NDA holder's labeling which is the subject of pediatric exclusivity protection to be omitted from the labeling of products approved under section 505(j). The BPCA also permits the addition of language to the labeling of products approved under section 505(j) that informs health care practitioners that the NDA holder's product has been approved for pediatric use. The agency has determined that the final printed labeling you have submitted is in compliance with the BPCA with respect to pediatric use information protected by exclusivity.

In order to reactivate your application prior to final approval, please submit a MINOR AMENDMENT - FINAL APPROVAL REQUESTED between 60 to 90 days prior to the date you believe that your application will be eligible for final approval. This amendment should provide a justification for the reasons you believe the ANDA is eligible for final approval, and it should also identify changes, if any, in the conditions under which the product was tentatively approved; i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter that it represents a MINOR AMENDMENT - FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the agency may request at any time prior to the final date of approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to agency review before final approval of the application will be made. Such changes should be submitted as an amendment to the application and categorized as representing either "major" or "minor" changes. The amendment will be reviewed according to OGD policy in effect at the time of receipt. Your submission of multiple amendments prior to final approval may lead to a delay in the issuance of the final approval letter.

Please note that this drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 501 of the Act and 21 U.S.C. 331(d). Also, until the agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355, and will not be listed in the Orange Book.

For further information on the status of this application, or prior to submitting additional amendments, please contact Thomas Hinchliffe, R.Ph., Project Manager, at (301) 827-5849.

Sincerely yours,

Robert Lee for 1/29/2003

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-360
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205

Endorsements:
HFD-640/T.Wang/12/16/02 T.C.Wang 12/17/02
HFD-640/S.Rosencrance/12/16/02 12/17/02
HFD-617/T.Hinchliffe/12/16/02 12/17/02
HFD-617/M.Dillahunt/12/16/02 M.Dillahunt 12/16/02
HFD-613/L.Golson/12/16/02 12/16/02

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F/T by TOH\12/16/02

~~APPROVAL~~

TENTATIVE APPROVAL

Robert Lyn West
1/29/2003

core satisfactory
12/17/02

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-360

APPROVABLE LETTER(S)

ANDA 75-360

DEC 6 2002

Apotex Corp.
Attention: Marcy Macdonald
U.S. Agent for: TorPharm
50 Lakeview Parkway, Suite #127
Vernon Hills, NJ 60061

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated April 17, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act) for Gabapentin Capsules, 100 mg, 300 mg, and 400 mg.

Reference is also made to your amendments dated July 22, and October 18, 2002. We also acknowledge receipt of your correspondence dated June 3, 1998, February 26, 1999, August 17, 2000, and June 13, 2002 addressing various patent and/or exclusivity issues.

We have completed the review of this ANDA as submitted, and have concluded that the application is APPROVABLE pending satisfactory resolution of the outstanding labeling issues described below. Should that process be completed prior to the expiration of the 30-month litigation period identified in Section 505(j)(5)(iii) of the Act, your application will be eligible for tentative approval status. Final approval must await the satisfactory resolution of (1) the labeling issues, and (2) resolution of the civil litigation discussed below, or the expiration of the 30-month statutory period of litigation. This letter does not address notice issues related to the 180-day exclusivity provisions under Section 505(j)(5)(B)(iv) of the Act.

With regard to the labeling for the drug product, exclusivity issues related to the recently approved pediatric labeling for the reference listed drug product, Neurontin® Capsules of Pfizer, Inc., as described in

21 CFR 314.108(b)(5) require further agency resolution. FDA is authorized to approve an ANDA that omits an indication or other aspect of labeling of the listed drug that is protected by patent or exclusivity [21 CFR 314.94(a)(8)(iv)]. In addition, Section 11 of the Best Pharmaceuticals for Children Act (BPCA), signed into law in January 2002, allows incorporation of language in the labeling of generic products that informs health care practitioners that the reference listed drug has been approved for pediatric use. The agency is currently evaluating the content and format of package insert labeling which generic applicants may utilize to omit the pediatric indication or any other aspect of labeling pertaining to pediatric use. Such an evaluation is necessary in order to assure that any such omission does not render the drug product less safe or effective for the remaining conditions of use. The agency expects to complete its review of the labeling issues as promptly as possible. All ANDA applicants for this drug product will be advised of the outcome. Please note that with regard to pediatric labeling for this drug product, there are no additional materials you should submit to FDA at this time.

In addition, we are unable to grant final approval at this time because the listed drug product (RLD) referenced in your application, Neurontin® Capsules of Pfizer, Inc., is subject to periods of patent protection. As noted in the Agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", the patents expire on November 2, 2008 (U.S. Patent No. 4,894,476, the '476 patent), July 2, 2010 (U.S. Patent No. 5,084,479, the '479 patent), and October 25, 2017 (U.S. Patent No. 6,054,482, the '482 patent). Your application contains Paragraph IV Certifications to each of these patents under Section 505(j)(2)(A)(vii)(IV) of the Act stating that the patents will not be infringed by your manufacture, use, or sale of the drug product. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA may be made effective immediately, unless an action is brought against TorPharm for infringement of one or more of the patents that are the subject of the certifications. This action must be brought against TorPharm prior to the expiration of 45 days from the date the notice you provided to the NDA/patent holder(s) under paragraph (2)(B)(i) was received. You have notified the agency that Torpharm has complied with the requirements of Section 505(j)(2)(B) of the Act. You have informed the agency that litigation

concerning the '479 patent is continuing in the United States District Court for the Northern District of Illinois Eastern Division (Warner-Lambert Company v. Apotex Corp., Apotex, Inc. and Torpharm, Inc., Civil Action No. 98 C 4293). You have also informed the agency that litigation is ongoing in the same district court involving your challenge to the '482 patent (Pfizer Inc., Warner-Lambert Company and Godecke Aktiengesellschaft v. Apotex Corp., Apotex, Inc. and Torpharm, Inc., Civil Action No. 00 C 4398).

Accordingly, please note that final approval of this application cannot be granted until the labeling issues referred to earlier in this letter are satisfactorily resolved and:

1. the expiration of the 30-month period provided for in Section 505(j)(5)(B)(iii) beginning with the date of receipt of the 45-day notice required for the '482 patent under Section 505(j)(2)(B)(i), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,

2. the date of a court decision [505(j)(5)(B)(iii)(I), (II), or (III)], which has been interpreted by the agency to mean the date of the final order or judgement of that court from which no appeal can be or has been taken, or

3. all listed patents have expired, and

4. the agency is assured that there is no new information that would affect whether final approval should be granted.

The agency will provide you with a template for the package insert labeling which it believes will be consistent with BPCA. Please follow the instructions accompanying the labeling in preparing and submitting your printed labeling. Your amendment containing this labeling will reactivate your application prior to tentative approval, and should be clearly identified as a MINOR AMENDMENT - TENTATIVE APPROVAL REQUESTED in your cover letter. This amendment may also be used to notify the agency of the legal/regulatory events that have occurred to permit

approval of the application. If applicable, a copy of a final order or judgement from which no appeal may be taken (which may not be the decision of the district court), or a settlement or licensing agreement between the parties should be included. This amendment should also contain data or information necessary to update the application to provide for changes implemented since the date of this approvable letter. Such information should include final-printed labeling, chemistry, manufacturing and controls data, or any other significant change in the conditions already outlined in the ANDA. Alternatively, a statement should be made confirming that none of these changes were made since the date of this letter.

Any significant changes in the conditions outlined in your ANDA should be categorized and submitted as amendments to the ANDA according to established office policy. Such changes as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to agency review before final approval of the application will be made.

This is not an approval letter. This drug product may not be marketed without final agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 301(d) of the Act. Also, until the agency issues the final approval letter, this drug product will not be deemed approved for marketing under Section 505 of the Act and will not be listed in "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), published by the agency.

Should the pediatric labeling issue be satisfactorily resolved prior to the resolution of the patent issue noted above, the office will issue a tentative approval letter.

A copy of the recently approved package insert for Gabapentin Capsules is available on the FDA Website at http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html.

Please contact Thomas Hinchliffe, Project Manager at (301) 827-5771 if you have further questions about the status of this application.

Sincerely yours,

Robert Lee Sett for 12/6/2002

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-360
Division File
Field Copy
GCF-1 Liz Dickinson
GCF-1 Kim Dettelbach
HFD-610/R.West
HFD-92
HFD-330
HFD-205/F.O.I.

Endorsements:
HFD-640/TCWang/ TCCWang 11/5/02
HFD-645/SRosencrance/ 11/6/02
HFD-617/THinchliffe/ 11/8/02
HFD-613/MDillahunt 11/18/02
HFD-613/LGolson 11/8/02
V:\firmsnz\torpharm\ltrs&rev\75360aef2.doc
F/t by: TOH/11/6/02 ; Revised:RLWest/

APPROVABLE

core satisfactory
Wayne Kaywell
11/20/02

Satisfactory to issue approvable letter at Torpharm's request.
Robert L. West
12/6/2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

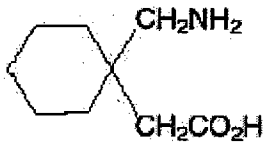
ANDA 75-360

APPROVED LABELING

GABAPENTIN CAPSULES
100 mg, 300 mg and 400 mg
℞ only

DESCRIPTION

Gabapentin is described as 1-(aminomethyl)cyclohexaneacetic acid with a molecular formula of $C_9H_{17}NO_2$ and a molecular weight of 171.24. Gabapentin is a white to off-white crystalline solid with a pK_{a1} of 3.7 and a pK_{a2} of 10.7. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is –1.25. It has the following structural formula:



Each capsule for oral administration contains 100 mg, 300 mg and 400 mg of gabapentin. In addition, each capsule contains the following inactive ingredients: crosscarmellose sodium and magnesium stearate. The 100 mg, 300 mg and 400 mg capsule imprinting ink black SW-9008/SW-9009 contains the following inactive ingredients: ammonium hydroxide; black iron oxide, bacteria controlled EEC No.172; n-butyl; ethyl alcohol, anhydrous, 200 proof; isopropyl alcohol USP; potassium hydroxide; propylene glycol; purified water and shellac.

The 100 mg capsule shell contains gelatin and titanium dioxide.

The 300 mg capsule shell contains gelatin, yellow iron oxide and titanium dioxide.

The 400 mg capsule shell contains gelatin, red iron oxide, yellow iron oxide and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism by which gabapentin exerts its anticonvulsant action is unknown, but in animal test systems designed to detect anticonvulsant activity, gabapentin prevents seizures as do other marketed anticonvulsants. Gabapentin exhibits antiseizure activity in mice and rats in both the maximal electroshock and pentylenetetrazole seizure models and other preclinical models (e.g., strains with genetic epilepsy, etc.). The relevance of these models to human epilepsy is not known.

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but it does not modify $GABA_A$ or $GABA_B$ radioligand binding, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation. Gabapentin was tested in radioligand binding assays at concentrations up to 100 mcM and did not exhibit affinity for a number of other common receptor sites, including benzodiazepine, glutamate, N-methyl-D-aspartate (NMDA), quisqualate, kainate, strychnine-insensitive or strychnine-sensitive glycine, alpha 1, alpha 2, or beta adrenergic, adenosine A1 or A2, cholinergic muscarinic or nicotinic, dopamine D1 or D2, histamine H1, serotonin S1 or S2, opiate mu, delta or kappa, cannabinoid 1, voltage-sensitive calcium channel sites labeled with nitrendipine or diltiazem, or at voltage-sensitive sodium channel sites labeled with batrachotoxinin A 20-alpha-benzoate. Furthermore, gabapentin did not alter the cellular uptake of dopamine, noradrenaline, or serotonin.

In vitro studies with radiolabeled gabapentin have revealed a gabapentin binding site in areas of rat brain including neocortex and hippocampus. A high-affinity binding protein in animal brain tissue has been identified as an auxiliary subunit of voltage-activated calcium channels. However, functional correlates of gabapentin binding, if any, remain to be elucidated.

Pharmacokinetics and Drug Metabolism

All pharmacological actions following gabapentin administration are due to the activity of the parent compound; gabapentin is not appreciably metabolized in humans.

Oral Bioavailability: Gabapentin bioavailability is not dose proportional; i.e., as dose is increased, bioavailability decreases. Bioavailability of gabapentin is approximately 60%, 47%, 34%, 33%, and 27% following 900, 1200, 2400, 3600, and 4800 mg/day given in 3 divided doses, respectively. Food has only a slight effect on the rate and extent of absorption of gabapentin (14% increase in AUC and C_{max}).

Distribution: Less than 3% of gabapentin circulates bound to plasma protein. The apparent volume of distribution of gabapentin after 150 mg intravenous administration is 58±6 L (Mean ±SD). In patients with epilepsy, steady-state predose (C_{min}) concentrations of gabapentin in cerebrospinal fluid were approximately 20% of the corresponding plasma concentrations.

Elimination: Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug. Gabapentin is not appreciably metabolized in humans.

Gabapentin elimination half-life is 5 to 7 hours and is unaltered by dose or following multiple dosing. Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance (see **Special Populations**: *Adult Patients With Renal Insufficiency*, below). In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin can be removed from plasma by hemodialysis.

Dosage adjustment in patients with compromised renal function or undergoing hemodialysis is recommended (see **DOSAGE AND ADMINISTRATION**, Table 3).

Special Populations: *Adult Patients With Renal Insufficiency:* Subjects (N=60) with renal insufficiency (mean creatinine clearance ranging from 13-114 mL/min) were administered single 400 mg oral doses of gabapentin. The mean gabapentin half-life ranged from about 6.5 hours (patients with creatinine clearance >60 mL/min) to 52 hours (creatinine clearance <30 mL/min) and gabapentin renal clearance from about 90 mL/min (>60 mL/min group) to about 10 mL/min (<30 mL/min). Mean plasma clearance (CL/F) decreased from approximately 190 mL/min to 20 mL/min.

Dosage adjustment in adult patients with compromised renal function is necessary (see **DOSAGE AND ADMINISTRATION**). Pediatric patients with renal insufficiency have not been studied.

Hemodialysis: In a study in anuric adult subjects (N=11), the apparent elimination half-life of gabapentin on nondialysis days was about 132 hours; during dialysis the apparent half-life of gabapentin was reduced to 3.8 hours. Hemodialysis thus has a significant effect on gabapentin elimination in anuric subjects.

Dosage adjustment in patients undergoing hemodialysis is necessary (see **DOSAGE AND ADMINISTRATION).**

Hepatic disease: Because gabapentin is not metabolized, no study was performed in patients with hepatic impairment.

Age: The effect of age was studied in subjects 20-80 years of age. Apparent oral clearance (CL/F) of gabapentin decreased as age increased, from about 225 mL/min in those under 30 years of age to about 125 mL/min in those over 70 years of age. Renal clearance (CLr) and CLr adjusted for body surface area also declined with age; however, the decline in the renal clearance of gabapentin with age can largely be explained by the decline in renal function. Reduction of gabapentin dose may be required in patients who have age related compromised renal function. (See **PRECAUTIONS, Geriatric Use**, and **DOSAGE AND ADMINISTRATION.**)

Pediatric: Gabapentin pharmacokinetics were determined in 48 pediatric subjects between the ages of 1 month and 12 years following a dose of approximately 10 mg/kg. Peak plasma concentrations were similar across the entire age group and occurred 2 to 3 hours postdose. In general, pediatric subjects between 1 month and <5 years of age achieved approximately 30% lower exposure (AUC) than that observed in those 5 years of age and older. Accordingly, oral clearance normalized per body weight was higher in the younger children. Apparent oral clearance of gabapentin was directly proportional to creatinine clearance. Gabapentin elimination half-life averaged 4.7 hours and was similar across the age groups studied.

A population pharmacokinetic analysis was performed in 253 pediatric subjects between 1 month and 13 years of age. Patients received 10 to 65 mg/kg/day given T.I.D. Apparent oral clearance (CL/F) was directly proportional to creatinine clearance and this relationship was similar following a single dose and at steady state. Higher oral clearance values were observed in children <5 years of age compared to those observed in children 5 years of age and older, when normalized per body weight. The clearance was highly variable in infants <1 year of age. The normalized CL/F values observed in pediatric patients 5 years of age and older were consistent with values observed in adults after a single dose. The oral volume of distribution normalized per body weight was constant across the age range.

These pharmacokinetic data indicate that the effective daily dose in pediatric patients with epilepsy ages 3 and 4 years should be 40 mg/kg/day to achieve average plasma concentrations similar to those achieved in patients 5 years of age and older receiving gabapentin at 30 mg/kg/day (see **DOSAGE AND ADMINISTRATION**).

Gender: Although no formal study has been conducted to compare the pharmacokinetics of gabapentin in men and women, it appears that the pharmacokinetic parameters for males and females are similar and there are no significant gender differences.

Race: Pharmacokinetic differences due to race have not been studied. Because gabapentin is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

Clinical Studies

Epilepsy

The effectiveness of gabapentin as adjunctive therapy (added to other antiepileptic drugs) was established in multicenter placebo-controlled, double-blind, parallel-group clinical trials in adult and pediatric patients (3 years and older) with refractory partial seizures.

Evidence of the effectiveness was obtained in three trials conducted in 705 patients (age 12 years and above) and one trial conducted in 247 pediatric patients (3 to 12 years of age). The patients enrolled had a history of at least 4 partial seizures per month in spite of receiving one or more antiepileptic drugs at therapeutic levels and were observed on their established antiepileptic drug regimen during a 12-week baseline period (6 weeks in the study of pediatric patients). In patients continuing to have at least 2 (or 4 in some studies) seizures per month, gabapentin or placebo was then added on to the existing therapy during a 12-week treatment period. Effectiveness was assessed primarily on the basis of the percent of patients with a 50% or greater reduction in seizure frequency from baseline to treatment (the "responder rate") and a derived measure called response ratio, a measure of change defined as (T - B)/(T + B), where B is the patient's baseline seizure frequency and T is the patient's seizure frequency during treatment. Response ratio is distributed within the range -1 to +1. A zero value indicates no change while complete elimination of seizures would give a value of -1; increased seizure rates would give positive values. A response ratio of -0.33 corresponds to a 50% reduction in seizure frequency. The results

given below are for all partial seizures in the intent-to-treat (all patients who received any doses of treatment) population in each study, unless otherwise indicated.

One study compared gabapentin 1200 mg/day divided T.I.D. with placebo. Responder rate was 23% (14/61) in the gabapentin group and 9% (6/66) in the placebo group; the difference between groups was statistically significant. Response ratio was also better in the gabapentin group (-0.199) than in the placebo group (-0.044), a difference that also achieved statistical significance.

A second study compared primarily 1200 mg/day divided T.I.D. gabapentin (N=101) with placebo (N=98). Additional smaller gabapentin dosage groups (600 mg/day, N=53; 1800 mg/day, N=54) were also studied for information regarding dose response. Responder rate was higher in the gabapentin 1200 mg/day group (16%) than in the placebo group (8%), but the difference was not statistically significant. The responder rate at 600 mg (17%) was also not significantly higher than in the placebo, but the responder rate in the 1800 mg group (26%) was statistically significantly superior to the placebo rate. Response ratio was better in the gabapentin 1200 mg/day group (-0.103) than in the placebo group (-0.022); but this difference was also not statistically significant ($p = 0.224$). A better response was seen in the gabapentin 600 mg/day group (-0.105) and 1800 mg/day group (-0.222) than in the 1200 mg/day group, with the 1800 mg/day group achieving statistical significance compared to the placebo group.

A third study compared gabapentin 900 mg/day divided T.I.D. (N=111) and placebo (N=109). An additional gabapentin 1200 mg/day dosage group (N=52) provided dose-response data. A statistically significant difference in responder rate was seen in the gabapentin 900 mg/day group (22%) compared to that in the placebo group (10%). Response ratio was also statistically significantly superior in the gabapentin 900 mg/day group (-0.119) compared to that in the placebo group (-0.027), as was response ratio in 1200 mg/day gabapentin (-0.184) compared to placebo.

Analyses were also performed in each study to examine the effect of gabapentin on preventing secondarily generalized tonic-clonic seizures. Patients who experienced a secondarily generalized tonic-clonic seizure in either the baseline or in the treatment period in all three placebo-controlled studies were included in these analyses. There were several response ratio comparisons that showed a statistically significant advantage for gabapentin compared to placebo and favorable trends for almost all comparisons.

Analysis of responder rate using combined data from all three studies and all doses (N=162, gabapentin; N=89, placebo) also showed a significant advantage for gabapentin over placebo in reducing the frequency of secondarily generalized tonic-clonic seizures.

In two of the three controlled studies, more than one dose of gabapentin was used. Within each study the results did not show a consistently increased response to dose. However, looking across studies, a trend toward increasing efficacy with increasing dose is evident (see Figure 1).

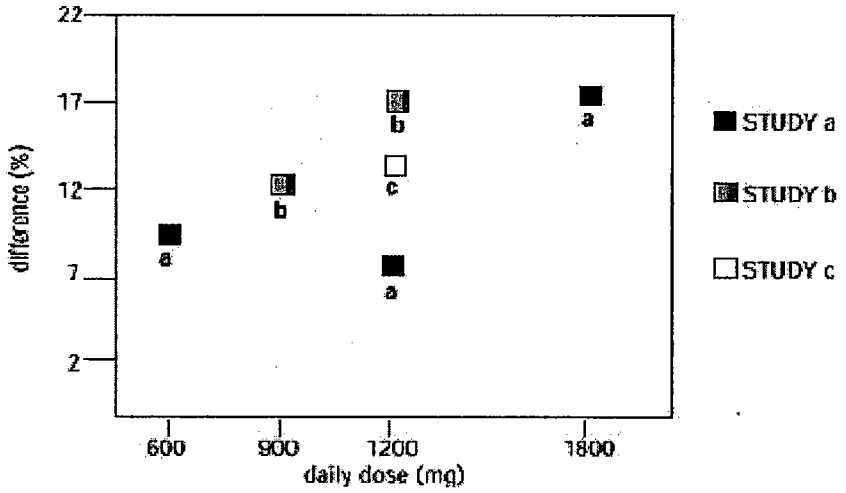


Figure 1. Responder Rate in Patients Receiving Gabapentin Expressed as a Difference From Placebo by Dose and Study: Adjunctive Therapy Studies in Patients ≥12 Years of Age with Partial Seizures.

In the figure, treatment effect magnitude, measured on the Y axis in terms of the difference in the proportion of gabapentin and placebo assigned patients attaining a 50% or greater reduction in seizure frequency from baseline, is plotted against the daily dose of gabapentin administered (X axis).

Although no formal analysis by gender has been performed, estimates of response (Response Ratio) derived from clinical trials (398 men, 307 women) indicate no important gender differences exist. There was no consistent pattern indicating that age had any effect on the response to gabapentin. There were insufficient numbers of patients of races other than Caucasian to permit a comparison of efficacy among racial groups.

A fourth study in pediatric patients age 3 to 12 years compared 25 – 35 mg/kg/day gabapentin (N=118) with placebo (N=127). For all partial seizures in the intent-to-treat population, the response ratio was statistically significantly better for the gabapentin group (-0.146) than for the placebo group (-0.079). For the same population, the responder rate for gabapentin (21%) was not significantly different from placebo (18%).

A study in pediatric patients age 1 month to 3 years compared 40 mg/kg/day gabapentin (N=38) with placebo (N=38) in patients who were receiving at least one marketed antiepileptic drug and had at least one partial seizure during the screening period (within 2 weeks prior to baseline). Patients had up to 48 hours of baseline and up to 72 hours of double-blind video EEG monitoring to record and count the occurrence of seizures. There were no statistically significant differences between treatments in either the response ratio or responder rate.

INDICATIONS AND USAGE

Epilepsy

Gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy. Gabapentin is also indicated as adjunctive therapy in the treatment of partial seizures in pediatric patients age 3 – 12 years.

CONTRAINDICATIONS

Gabapentin is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS

Neuropsychiatric Adverse Events—Pediatric Patients 3-12 Years of Age

Gabapentin use in pediatric patients with epilepsy 3–12 years of age is associated with the occurrence of central nervous system related adverse events. The most significant of these can be classified into the following categories: 1) emotional lability (primarily behavioral problems), 2) hostility, including aggressive behaviors, 3) thought disorder, including concentration problems and change in school performance, and 4) hyperkinesia (primarily restlessness and hyperactivity). Among the gabapentin-treated patients, most of the events were mild to moderate in intensity.

In controlled trials in pediatric patients 3–12 years of age, the incidence of these adverse events was: emotional lability 6% (gabapentin-treated patients) vs 1.3% (placebo-treated patients); hostility 5.2% vs 1.3%; hyperkinesia 4.7% vs 2.9%; and thought disorder 1.7% vs 0%. One of these events, a report of hostility, was considered serious. Discontinuation of gabapentin treatment occurred in 1.3% of patients reporting emotional lability and hyperkinesia and 0.9% of gabapentin-treated patients reporting hostility and thought disorder. One placebo-treated patient (0.4%) withdrew due to emotional lability.

Withdrawal Precipitated Seizure, Status Epilepticus

Antiepileptic drugs should not be abruptly discontinued because of the possibility of increasing seizure frequency.

In the placebo-controlled studies in patients >12 years of age, the incidence of status epilepticus in patients receiving gabapentin was 0.6% (3 of 543) versus 0.5% in patients receiving placebo (2 of 378). Among the 2074 patients >12 years of age treated with gabapentin across all studies (controlled and uncontrolled) 31 (1.5%) had status epilepticus. Of these, 14 patients had no prior history of status epilepticus either before treatment or while on other medications. Because adequate historical data are not available, it is impossible to say whether or not treatment with gabapentin is associated with a higher or lower rate of status epilepticus than would be expected to occur in a similar population not treated with gabapentin.

Tumorigenic Potential

In standard preclinical *in vivo* lifetime carcinogenicity studies, an unexpectedly high incidence of pancreatic acinar adenocarcinomas was identified in male, but not female, rats (see **PRECAUTIONS**: **Carcinogenesis, Mutagenesis, Impairment of Fertility**). The clinical significance of this finding is unknown. Clinical experience during gabapentin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies in adjunctive therapy in epilepsy comprising 2085 patient-years of exposure in patients >12 years of age, new tumors were reported in 10 patients (2 breast, 3 brain, 2 lung, 1 adrenal, 1 non-Hodgkin's lymphoma, 1 endometrial carcinoma *in situ*), and preexisting tumors worsened in 11 patients (9 brain, 1 breast, 1 prostate) during or up to 2 years following discontinuation of gabapentin. Without knowledge of the background incidence and recurrence in a similar population not treated with gabapentin, it is impossible to know whether the incidence seen in this cohort is or is not affected by treatment.

Sudden and Unexplained Death in Patients With Epilepsy

During the course of premarketing development of gabapentin 8 sudden and unexplained deaths were recorded among a cohort of 2203 patients treated (2103 patient-years of exposure).

Some of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. This represents an incidence of 0.0038 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving gabapentin (ranging from 0.0005 for the general population of epileptics to 0.003 for a clinical trial population similar to that in the gabapentin program, to 0.005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or raise further concern depends on comparability of the populations reported upon to the gabapentin cohort and the accuracy of the estimates provided.

PRECAUTIONS

Information for Patients

Patients should be instructed to take gabapentin only as prescribed.

Patients should be advised that gabapentin may cause dizziness, somnolence and other symptoms and signs of CNS depression. Accordingly, they should be advised neither to drive a car nor to operate other complex machinery until they have gained sufficient experience on gabapentin to gauge whether or not it affects their mental and/or motor performance adversely.

Patients who require concomitant treatment with morphine may experience increases in gabapentin concentrations. Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately (see **Drug Interactions**).

Laboratory Tests

Clinical trials data do not indicate that routine monitoring of clinical laboratory parameters is necessary for the safe use of gabapentin. The value of monitoring gabapentin blood concentrations has not been established. Gabapentin may be used in combination with other antiepileptic drugs without concern for alteration of the blood concentrations of gabapentin or of other antiepileptic drugs.

Drug Interactions

In vitro studies were conducted to investigate the potential of gabapentin to inhibit the major cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) that mediate drug and xenobiotic metabolism using isoform selective marker substrates and human liver microsomal preparations. Only at the highest concentration tested (171 mcg/mL; 1 mM) was a slight degree of inhibition (14%-30%) of isoform CYP2A6 observed. No inhibition of any of the other isoforms tested was observed at gabapentin concentrations up to 171 mcg/mL (approximately 15 times the C_{max} at 3600 mg/day).

Gabapentin is not appreciably metabolized nor does it interfere with the metabolism of commonly coadministered antiepileptic drugs.

The drug interaction data described in this section were obtained from studies involving healthy adults and adult patients with epilepsy.

Phenytoin: In a single (400 mg) and multiple dose (400 mg T.I.D.) study of gabapentin in epileptic patients (N=8) maintained on phenytoin monotherapy for at least 2 months, gabapentin had no effect on the steady-state trough plasma concentrations of phenytoin and phenytoin had no effect on gabapentin pharmacokinetics.

Carbamazepine: Steady-state trough plasma carbamazepine and carbamazepine 10, 11 epoxide concentrations were not affected by concomitant gabapentin (400 mg T.I.D.; N=12) administration. Likewise, gabapentin pharmacokinetics were unaltered by carbamazepine administration.

Valproic Acid: The mean steady-state trough serum valproic acid concentrations prior to and during concomitant gabapentin administration (400 mg T.I.D.; N=17) were not different and neither were gabapentin pharmacokinetic parameters affected by valproic acid.

Phenobarbital: Estimates of steady-state pharmacokinetic parameters for phenobarbital or gabapentin (300 mg T.I.D.; N=12) are identical whether the drugs are administered alone or together.

Naproxen: Coadministration (N=18) of naproxen sodium capsules (250 mg) with gabapentin (125 mg) appears to increase the amount of gabapentin absorbed by 12% to 15%. Gabapentin had no effect on naproxen pharmacokinetic parameters. These doses are lower than the therapeutic doses for both drugs. The magnitude of interaction within the recommended dose ranges of either drug is not known.

Hydrocodone: Coadministration of gabapentin (125 to 500 mg; N=48) decreases hydrocodone (10 mg; N=50) C_{max} and AUC values in a dose-dependent manner relative to administration of hydrocodone alone; C_{max} and AUC values are 3% to 4% lower, respectively, after administration of 125 mg gabapentin and 21% to 22% lower, respectively, after administration of 500 mg gabapentin. The mechanism for this interaction is unknown. Hydrocodone increases gabapentin AUC values by 14%. The magnitude of interaction at other doses is not known.

Morphine: A literature article reported that when a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule (N=12), mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine (see **PRECAUTIONS**). Morphine pharmacokinetic parameter values were not affected by administration of gabapentin 2 hours after morphine. The magnitude of interaction at other doses is not known.

Cimetidine: In the presence of cimetidine at 300 mg Q.I.D. (N=12) the mean apparent oral clearance of gabapentin fell by 14% and creatinine clearance fell by 10%. Thus cimetidine appeared to alter the renal excretion of both gabapentin and creatinine, an endogenous marker of renal function. This small decrease in excretion of gabapentin by cimetidine is not expected to be of clinical importance. The effect of gabapentin on cimetidine was not evaluated.

Oral Contraceptive: Based on AUC and half-life, multiple-dose pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of tablets containing 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol were similar with and without coadministration of gabapentin (400 mg T.I.D.; N=13). The C_{max} of norethindrone was 13% higher when it was coadministered with gabapentin; this interaction is not expected to be of clinical importance.

Antacid (Maalox®*): Maalox® reduced the bioavailability of gabapentin (N=16) by about 20%. This decrease in bioavailability was about 5% when gabapentin was administered 2 hours after Maalox®. It is recommended that gabapentin be taken at least 2 hours following Maalox® administration.

Effect of Probenecid: Probenecid is a blocker of renal tubular secretion. Gabapentin pharmacokinetic parameters without and with probenecid were comparable. This indicates that gabapentin does not undergo renal tubular secretion by the pathway that is blocked by probenecid.

Drug/Laboratory Tests Interactions

Because false positive readings were reported with the Ames N-Multistix SG® dipstick test for urinary protein when gabapentin was added to other antiepileptic drugs, the more specific sulfosalicylic acid precipitation procedure is recommended to determine the presence of urine protein.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for 2 years. A statistically significant increase in the incidence of pancreatic acinar cell adenomas and carcinomas was found in male rats receiving the high dose; the no-effect dose for the occurrence of carcinomas was 1000 mg/kg/day. Peak plasma concentrations of gabapentin in rats receiving the high dose of 2000 mg/kg were 10 times higher than plasma concentrations in humans receiving 3600 mg/day, and in rats receiving 1000 mg/kg/day peak plasma concentrations were 6.5 times higher than in humans receiving 3600 mg/day. The pancreatic acinar cell carcinomas did not affect survival, did not metastasize and were not locally invasive. The relevance of this finding to carcinogenic risk in humans is unclear.

Studies designed to investigate the mechanism of gabapentin-induced pancreatic carcinogenesis in rats indicate that gabapentin stimulates DNA synthesis in rat pancreatic acinar cells *in vitro* and, thus, may be acting as a tumor promoter by enhancing mitogenic activity. It is not known whether gabapentin has the ability to increase cell proliferation in other cell types or in other species, including humans.

Gabapentin did not demonstrate mutagenic or genotoxic potential in three *in vitro* and four *in vivo* assays. It was negative in the Ames test and the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay; it was negative in the *in vivo* chromosomal aberration assay and in the *in vivo* micronucleus test in Chinese hamster bone marrow; it was negative in the *in vivo* mouse micronucleus assay; and it did not induce unscheduled DNA synthesis in hepatocytes from rats given gabapentin.

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately 5 times the maximum recommended human dose on a mg/m^2 basis).

Pregnancy

Pregnancy Category C: Gabapentin has been shown to be fetotoxic in rodents, causing delayed ossification of several bones in the skull, vertebrae, forelimbs, and hindlimbs. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during the period of organogenesis, or approximately 1 to 4 times the maximum dose of 3600 mg/day given to epileptic patients on a mg/m^2 basis. The no-effect level was 500 mg/kg/day or approximately ½ of the human dose on a mg/m^2 basis.

When rats were dosed prior to and during mating, and throughout gestation, pups from all dose groups (500, 1000 and 2000 mg/kg/day) were affected. These doses are equivalent to less than approximately 1 to 5 times the maximum human dose on a mg/m^2 basis. There was an increased incidence of hydroureter and/or hydronephrosis in rats in a study of fertility and general reproductive performance at 2000 mg/kg/day with no effect at 1000 mg/kg/day, in a teratology study at 1500 mg/kg/day with no effect at 300 mg/kg/day, and in a perinatal and postnatal study at all doses studied (500, 1000 and 2000 mg/kg/day). The doses at which the effects occurred are approximately 1 to 5 times the maximum human dose of 3600 mg/day on a mg/m^2 basis; the no-effect doses were approximately 3 times (Fertility and General Reproductive Performance study) and approximately equal to (Teratogenicity study) the maximum human dose on a mg/m^2 basis. Other than hydroureter and hydronephrosis, the etiologies of which are unclear, the incidence of malformations was not increased compared to controls in offspring of mice, rats, or rabbits given doses up to 50 times (mice), 30 times (rats), and 25 times (rabbits) the human daily dose on a mg/kg basis, or 4 times (mice), 5 times (rats), or 8 times (rabbits) the human daily dose on a mg/m^2 basis.

In a teratology study in rabbits, an increased incidence of postimplantation fetal loss occurred in dams exposed to 60, 300 and 1500 mg/kg/day, or less than approximately ¼ to 8 times the maximum human dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Nursing Mothers

Gabapentin is secreted into human milk following oral administration. A nursed infant could be exposed to a maximum dose of approximately 1 mg/kg/day of gabapentin. Because the effect on the nursing infant is unknown, gabapentin should be used in women who are nursing only if the benefits clearly outweigh the risks.

Pediatric Use

Effectiveness as adjunctive therapy in the treatment of partial seizures in pediatric patients below the age of 3 years has not been established (see **CLINICAL PHARMACOLOGY, Clinical Studies**).

Geriatric Use

Clinical studies of gabapentin in epilepsy did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions 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 dose should be adjusted based on creatinine clearance values in these patients (see **CLINICAL PHARMACOLOGY**, **ADVERSE REACTIONS**, and **DOSAGE AND ADMINISTRATION** sections).

ADVERSE REACTIONS

Epilepsy

The most commonly observed adverse events associated with the use of gabapentin in combination with other antiepileptic drugs in patients >12 years of age, not seen at an equivalent frequency among placebo-treated patients, were somnolence, dizziness, ataxia, fatigue, and nystagmus. The most commonly observed adverse events reported with the use of gabapentin in combination with other antiepileptic drugs in pediatric patients 3 to 12 years of age, not seen at an equal frequency among placebo-treated patients, were viral infection, fever, nausea and/or vomiting, somnolence, and hostility (see **WARNINGS, Neuropsychiatric Adverse Events**).

Approximately 7% of the 2074 patients >12 years of age and approximately 7% of the 449 pediatric patients 3 to 12 years of age who received gabapentin in premarketing clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal in patients >12 years of age were somnolence (1.2%), ataxia (0.8%), fatigue (0.6%), nausea and/or vomiting (0.6%), and dizziness (0.6%). The adverse events most commonly associated with withdrawal in pediatric patients were emotional lability (1.6%), hostility (1.3%), and hyperkinesia (1.1%).

Incidence in Controlled Clinical Trials

Table 1 lists treatment-emergent signs and symptoms that occurred in at least 1% of gabapentin-treated patients >12 years of age with epilepsy participating in placebo-controlled trials and were numerically more common in the gabapentin group. In these studies, either gabapentin or placebo was added to the patient's current antiepileptic drug therapy. Adverse events were usually mild to moderate in intensity.

The prescriber should be aware that these figures, obtained when gabapentin was added to concurrent antiepileptic drug therapy, cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescribing physician with one basis to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

TABLE 1. Treatment-Emergent Adverse Event Incidence in Controlled Add-On Trials in Patients >12 years of age (Events in at Least 1% of Gabapentin Patients and Numerically More Frequent Than in the Placebo Group)

Body System/ Adverse Event	Gabapentin[a] N=543 %	Placebo[a] N=378 %
Body As A Whole		
Fatigue	11.0	5.0
Weight Increase	2.9	1.6
Back Pain	1.8	0.5
Peripheral Edema	1.7	0.5
Cardiovascular		
Vasodilatation	1.1	0.3
Digestive System		
Dyspepsia	2.2	0.5
Mouth or Throat Dry	1.7	0.5
Constipation	1.5	0.8
Dental Abnormalities	1.5	0.3
Increased Appetite	1.1	0.8
Hematologic and Lymphatic Systems		
Leukopenia	1.1	0.5
Musculoskeletal System		
Myalgia	2.0	1.9
Fracture	1.1	0.8
Nervous System		
Somnolence	19.3	8.7
Dizziness	17.1	6.9
Ataxia	12.5	5.6
Nystagmus	8.3	4.0
Tremor	6.8	3.2
Nervousness	2.4	1.9
Dysarthria	2.4	0.5
Amnesia	2.2	0.0
Depression	1.8	1.1
Thinking Abnormal	1.7	1.3
Twitching	1.3	0.5
Coordination Abnormal	1.1	0.3
Respiratory System		
Rhinitis	4.1	3.7
Pharyngitis	2.8	1.6
Coughing	1.8	1.3

Skin and Appendages		
Abrasion	1.3	0.0
Pruritus	1.3	0.5
Urogenital System		
Impotence	1.5	1.1
Special Senses		
Diplopia	5.9	1.9
Amblyopia[b]	4.2	1.1
Laboratory Deviations		
WBC Decreased	1.1	0.5

[a] Plus background antiepileptic drug therapy

[b] Amblyopia was often described as blurred vision.

Other events in more than 1% of patients >12 years of age but equally or more frequent in the placebo group included: headache, viral infection, fever, nausea and/or vomiting, abdominal pain, diarrhea, convulsions, confusion, insomnia, emotional lability, rash, acne.

Among the treatment-emergent adverse events occurring at an incidence of at least 10% of gabapentin-treated patients, somnolence and ataxia appeared to exhibit a positive dose-response relationship.

The overall incidence of adverse events and the types of adverse events seen were similar among men and women treated with gabapentin. The incidence of adverse events increased slightly with increasing age in patients treated with either gabapentin or placebo. Because only 3% of patients (28/921) in placebo-controlled studies were identified as nonwhite (black or other), there are insufficient data to support a statement regarding the distribution of adverse events by race.

Table 2 lists treatment-emergent signs and symptoms that occurred in at least 2% of gabapentin-treated patients age 3 to 12 years of age with epilepsy participating in placebo-controlled trials and were numerically more common in the gabapentin group. Adverse events were usually mild to moderate in intensity.

TABLE 2. Treatment-Emergent Adverse Event Incidence in Pediatric Patients Age 3 to 12 Years in a Controlled Add-On Trial (Events in at Least 2% of Gabapentin Patients and Numerically More Frequent Than in the Placebo Group)

Body System/ Adverse Event	Gabapentin[a] N=119 %	Placebo[a] N=128 %
Body as a Whole		
Viral Infection	10.9	3.1
Fever	10.1	3.1
Weight Increase	3.4	0.8

Fatigue	3.4	1.6
Digestive System		
Nausea and/or Vomiting	8.4	7.0
Nervous System		
Somnolence	8.4	4.7
Hostility	7.6	2.3
Emotional Lability	4.2	1.6
Dizziness	2.5	1.6
Hyperkinesia	2.5	0.8
Respiratory System		
Bronchitis	3.4	0.8
Respiratory Infection	2.5	0.8

[a] Plus background antiepileptic drug therapy

Other events in more than 2% of pediatric patients 3 to 12 years of age but equally or more frequent in the placebo group included: pharyngitis, upper respiratory infection, headache, rhinitis, convulsions, diarrhea, anorexia, coughing, and otitis media.

Other Adverse Events Observed During All Clinical Trials

Clinical Trials in Adults and Adolescents (Except Clinical Trials in Neuropathic Pain)

Gabapentin has been administered to 2074 patients >12 years of age during all adjunctive therapy clinical trials (except clinical trials in patients with neuropathic pain), only some of which were placebo-controlled. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. These categories are used in the listing below. The frequencies presented represent the proportion of the 2074 patients >12 years of age exposed to gabapentin who experienced an event of the type cited on at least one occasion while receiving gabapentin. All reported events are included except those already listed in Table 1, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body As A Whole: *Frequent:* asthenia, malaise, face edema; *Infrequent:* allergy, generalized edema, weight decrease, chill; *Rare:* strange feelings, lassitude, alcohol intolerance, hangover effect.

Cardiovascular System: *Frequent:* hypertension; *Infrequent:* hypotension, angina pectoris, peripheral vascular disorder, palpitation, tachycardia, migraine, murmur; *Rare:* atrial fibrillation, heart failure, thrombophlebitis, deep thrombophlebitis, myocardial infarction, cerebrovascular accident, pulmonary thrombosis, ventricular extrasystoles, bradycardia, premature atrial contraction, pericardial rub, heart block, pulmonary embolus, hyperlipidemia, hypercholesterolemia, pericardial effusion, pericarditis.

Digestive System: *Frequent:* anorexia, flatulence, gingivitis; *Infrequent:* glossitis, gum hemorrhage, thirst, stomatitis, increased salivation, gastroenteritis, hemorrhoids, bloody stools, fecal incontinence, hepatomegaly; *Rare:* dysphagia, eructation, pancreatitis, peptic ulcer, colitis, blisters in mouth, tooth discolor, perlèche, salivary gland enlarged, lip hemorrhage, esophagitis, hiatal hernia, hematemesis, proctitis, irritable bowel syndrome, rectal hemorrhage, esophageal spasm.

Endocrine System: *Rare:* hyperthyroid, hypothyroid, goiter, hypoestrogen, ovarian failure, epididymitis, swollen testicle, cushingoid appearance.

Hematologic and Lymphatic System: *Frequent:* purpura most often described as bruises resulting from physical trauma; *Infrequent:* anemia, thrombocytopenia, lymphadenopathy; *Rare:* WBC count increased, lymphocytosis, non-Hodgkin's lymphoma, bleeding time increased.

Musculoskeletal System: *Frequent:* arthralgia; *Infrequent:* tendinitis, arthritis, joint stiffness, joint swelling, positive Romberg test; *Rare:* costochondritis, osteoporosis, bursitis, contracture.

Nervous System: *Frequent:* vertigo, hyperkinesia, paresthesia, decreased or absent reflexes, increased reflexes, anxiety, hostility; *Infrequent:* CNS tumors, syncope, dreaming abnormal, aphasia, hypesthesia, intracranial hemorrhage, hypotonia, dysesthesia, paresis, dystonia, hemiplegia, facial paralysis, stupor, cerebellar dysfunction, positive Babinski sign, decreased position sense, subdural hematoma, apathy, hallucination, decrease or loss of libido, agitation, paranoia, depersonalization, euphoria, feeling high, doped-up sensation, suicidal, psychosis; *Rare:* choreoathetosis, orofacial dyskinesia, encephalopathy, nerve palsy, personality disorder, increased libido, subdued temperament, apraxia, fine motor control disorder, meningismus, local myoclonus, hyperesthesia, hypokinesia, mania, neurosis, hysteria, antisocial reaction, suicide gesture.

Respiratory System: *Frequent:* pneumonia; *Infrequent:* epistaxis, dyspnea, apnea; *Rare:* mucositis, aspiration pneumonia, hyperventilation, hiccup, laryngitis, nasal obstruction, snoring, bronchospasm, hypoventilation, lung edema.

Dermatological: *Infrequent:* alopecia, eczema, dry skin, increased sweating, urticaria, hirsutism, seborrhea, cyst, herpes simplex; *Rare:* herpes zoster, skin discolor, skin papules, photosensitive reaction, leg ulcer, scalp seborrhea, psoriasis, desquamation, maceration, skin nodules, subcutaneous nodule, melanosis, skin necrosis, local swelling.

Urogenital System: *Infrequent:* hematuria, dysuria, urination frequency, cystitis, urinary retention, urinary incontinence, vaginal hemorrhage, amenorrhea, dysmenorrhea, menorrhagia, breast cancer, unable to climax, ejaculation abnormal; *Rare:* kidney pain, leukorrhea, pruritus genital, renal stone, acute renal failure, anuria, glycosuria, nephrosis, nocturia, pyuria, urination urgency, vaginal pain, breast pain, testicle pain.

Special Senses: *Frequent:* abnormal vision; *Infrequent:* cataract, conjunctivitis, eyes dry, eye pain, visual field defect, photophobia, bilateral or unilateral ptosis, eye hemorrhage, hordeolum, hearing loss, earache, tinnitus, inner ear infection, otitis, taste loss, unusual taste, eye twitching, ear fullness; *Rare:* eye itching, abnormal accommodation, perforated ear drum, sensitivity to noise, eye focusing problem, watery eyes, retinopathy, glaucoma, iritis, corneal disorders, lacrimal dysfunction, degenerative eye changes, blindness, retinal degeneration, miosis, chorioretinitis, strabismus, eustachian tube dysfunction, labyrinthitis, otitis externa, odd smell.

Clinical Trials in Pediatric Patients With Epilepsy

Adverse events occurring during epilepsy clinical trials in 449 pediatric patients 3 to 12 years of age treated with gabapentin that were not reported in adjunctive trials in adults are:

Body as a Whole: dehydration, infectious mononucleosis

Digestive System: hepatitis

Hemic and Lymphatic System: coagulation defect

Nervous System: aura disappeared, occipital neuralgia

Psychobiologic Function: sleepwalking

Respiratory System: pseudocroup, hoarseness

Postmarketing and Other Experience

In addition to the adverse experiences reported during clinical testing of gabapentin, the following adverse experiences have been reported in patients receiving marketed gabapentin. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: angioedema, blood glucose fluctuation, erythema multiforme, elevated liver function tests, fever, hyponatremia, jaundice, movement disorder such as dyskinesia, Stevens-Johnson syndrome.

Adverse events following the abrupt discontinuation of gabapentin have also been reported. The most frequently reported events were anxiety, insomnia, nausea, pain and sweating.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of gabapentin has not been evaluated in human studies.

OVERDOSAGE

A lethal dose of gabapentin was not identified in mice and rats receiving single oral doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, sedation, hypoactivity, or excitation.

Acute oral overdoses of gabapentin up to 49 grams have been reported. In these cases, double vision, slurred speech, drowsiness, lethargy and diarrhea were observed. All patients recovered with supportive care.

Gabapentin can be removed by hemodialysis. Although hemodialysis has not been performed in the few overdose cases reported, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

DOSAGE AND ADMINISTRATION

Gabapentin is given orally with or without food.

If gabapentin dose is reduced, discontinued or substituted with an alternative medication, this should be done gradually over a minimum of 1 week.

Epilepsy

Gabapentin is recommended for add-on therapy in patients 3 years of age and older. Effectiveness in pediatric patients below the age of 3 years has not been established.

Patients >12 Years of Age: The effective dose of gabapentin is 900 to 1800 mg/day and given in divided doses (three times a day) using 300 or 400 mg capsules. The starting dose is 300 mg three times a day. If necessary, the dose may be increased using 300 mg or 400 mg capsules three times a day up to 1800 mg/day. Dosages up to 2400 mg/day have been well tolerated in long-term clinical studies. Doses of 3600 mg/day have also been administered to a small number of patients for a relatively short duration, and have been well tolerated. The maximum time between doses in the T.I.D. schedule should not exceed 12 hours.

Pediatric Patients Age 3–12 Years: The starting dose should range from 10-15 mg/kg/day in 3 divided doses, and the effective dose reached by upward titration over a period of approximately 3 days. The effective dose of gabapentin in patients 5 years of age and older is 25–35 mg/kg/day and given in divided doses (three times a day). The effective dose in pediatric patients ages 3 and 4 years is 40 mg/kg/day and given in divided doses (three times a day) (See **CLINICAL PHARMACOLOGY, Pediatrics**).

Dosages up to 50 mg/kg/day have been well tolerated in a long-term clinical study. The maximum time interval between doses should not exceed 12 hours.

It is not necessary to monitor gabapentin plasma concentrations to optimize gabapentin therapy. Further, because there are no significant pharmacokinetic interactions among gabapentin and other commonly used antiepileptic drugs, the addition of gabapentin does not alter the plasma levels of these drugs appreciably.

If gabapentin is discontinued and/or an alternate anticonvulsant medication is added to the therapy, this should be done gradually over a minimum of 1 week.

Dosage in Renal Impairment

Creatinine clearance is difficult to measure in outpatients. In patients with stable renal function, creatinine clearance (CCr) can be reasonably well estimated using the equation of Cockcroft and Gault:

for females $C_{Cr} = (0.85)(140\text{-age})(\text{weight})/[(72)(S_{cr})]$

for males $C_{Cr} = (140\text{-age})(\text{weight})/[(72)(S_{cr})]$

where age is in years, weight is in kilograms and S_{cr} is serum creatinine in mg/dL.

Dosage adjustment in patients ≥ 12 years of age with compromised renal function or undergoing hemodialysis is recommended as follows (see dosing recommendations above for effective doses in each indication).

TABLE 3. Gabapentin Dosage Based on Renal Function

Renal Function Creatinine Clearance (mL/min)	Total Daily Dose Range (mg/day)	Dosage Regimen (mg)				
≥ 60	900-3600	300 TID	400 TID	600 TID	800 TID	1200TID
> 30-59	400-1400	200 BID	300 BID	400 BID	500 BID	700 BID
> 15-29	200-700	200 QD	300 QD	400 QD	500 QD	700 QD
< 15[a]	100-300	100 QD	125 QD	150 QD	200 QD	300 QD
		Post-Hemodialysis Supplemental Dose (mg)[b]				
Hemodialysis		125[b]	150[b]	200[b]	250[b]	350[b]

[a]For patients with creatinine clerance <15 mL/min, reduce daily dose in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 mL/min should receive one-half the daily dose that patients with a creatinine clearance of 15 mL/min receive).

[b]Patients on hemodialysis should receive maintenance doses based on estimates of creatinine clearance as indicated in the upper portion of the table and a supplemental post-hemodialysis dose administered after each 4 hours of hemodialysis as indicated in the lower portion of the table.

The use of gabapentin in patients <12 years of age with compromised renal function has not been studied.

Dosage in Elderly

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and dose should be adjusted based on creatinine clearance values in these patients.

HOW SUPPLIED

Gabapentin Capsules 100 mg are available for oral administration as hard gelatin capsules with a white opaque body and a white opaque cap. "APO 112" is imprinted on each capsule in black ink; supplied in bottles of 100 (NDC 60505-0112-1).

Gabapentin Capsules 300 mg are available for oral administration as hard gelatin capsules with a white opaque body and a yellow opaque cap. "APO 113" is imprinted on each capsule in black ink; supplied in bottles of 100 (NDC 60505-0113-1).

Gabapentin Capsules 400 mg are available for oral administration as hard gelatin capsules with a white opaque body and an orange opaque cap." APO 114" is imprinted on each capsule in black ink; supplied in bottles of 100 (NDC 60505-0114-1).

Storage

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86° F)[see USP Controlled Room Temperature]. Dispense in a tight, light-resistant container [see USP].

* Maalox® is a registered trademark of Novartis Consumer Health, Inc.

APOTEX INC.
GABAPENTIN CAPSULES 100 mg, 300 mg and 400 mg

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, Florida
33326

(GAB/C-RO3-51X138MM-LFLT-090104)

Revised: December 2004

Rev. 1

Each capsule contains 100 mg gabapentin.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Dispense in a tight, light-resistant container [see USP].

Usual Dosage: See package insert.

214309

APOTEX CORP.

Gabapentin Capsules

100 mg

100 Capsules

℞ Only

NDC 60505-0112-1

N 3 60505-0112-1 6

Manufactured by:
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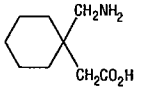
Manufactured for:
Apotex Corp.
Weston, Florida 33326

GABAPENTIN CAPSULES
100 mg, 300 mg and 400 mg

℞ only

DESCRIPTION

Gabapentin is described as 1-(aminomethyl) cyclohexaneacetic acid with a molecular formula of $C_9H_{17}NO_2$ and a molecular weight of 171.24. Gabapentin is a white to off-white crystalline solid with a pK_{a1} of 3.7 and a pK_{a2} of 10.7. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is -1.25. It has the following structural formula:



Each capsule for oral administration contains 100 mg, 300 mg, and 400 mg of gabapentin. In addition, each capsule contains the following inactive ingredients: croscarmellose sodium and magnesium stearate. The 100 mg, 300 mg and 400 mg

NON PRINTING AREA (GLUE PANEL)

Open Here

N 3 60505-0112-1 6

Manufactured by:
Apotex Inc.
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Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, Florida 33326

NDC 60505-0112-1

Gabapentin Capsules

100 mg

100 Capsules

℞ Only

APOTEX CORP.

Each capsule contains 100 mg gabapentin.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Dispense in a tight, light-resistant container [see USP].

Usual Dosage: See package insert.

214309

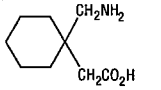
concentrations in humans receiving 3600 mg/day, and in rats receiving 1000 mg/kg/day peak plasma concentrations were 6.5 times higher than in humans receiving 3600 mg/day. The pancreatic acinar cell carcinomas did not affect survival, did not metastasize and were not locally invasive. The relevance of this finding to carcinogenic risk in humans is unclear.

Studies designed to investigate the mechanism of gabapentin-induced pancreatic carcinogenesis in rats indicate that gabapentin stimulates DNA synthesis in rat pancreatic acinar cells *in vitro* and, thus, may be acting as a tumor promoter by enhancing mitogenic activity. It is not known whether gabapentin has the ability to increase cell proliferation in other cell types or in other species, including humans.

Gabapentin did not demonstrate mutagenic or genotoxic potential in three *in vitro* and four *in vivo* assays. It was negative in the Ames test and the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay; it was negative in the *in vivo* chromosomal aberration assay and in the *in vivo* micronucleus test in Chinese hamster bone marrow; it was negative in the *in vivo* mouse micronucleus assay; and it did not include unscheduled DNA synthesis in hepatocytes from rats given gabapentin.

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately 5 times the maximum recommended human dose on a mg/m^2 basis).

a white to off-white crystalline solid with a pK_{a1} of 3.7 and a pK_{a2} of 10.7. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is -1.25. It has the following structural formula:



Each capsule for oral administration contains 100 mg, 300 mg, and 400 mg of gabapentin. In addition, each capsule contains the following inactive ingredients: croscarmellose sodium and magnesium stearate. The 100 mg, 300 mg and 400 mg capsule imprinting ink black SW-9008/SW-9009 contains the following inactive ingredients: ammonium hydroxide; black iron oxide, bacteria controlled EEC No. 172; n-butyl; ethyl alcohol, anhydrous, 200 proof; isopropyl alcohol USP; potassium hydroxide; propylene glycol; purified water and shellac.

The 100 mg capsule shell contains gelatin and titanium dioxide.

The 300 mg capsule shell contains gelatin, yellow iron oxide and titanium dioxide.

The 400 mg capsule shell contains gelatin, red iron oxide, yellow iron oxide and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action
The mechanism by which gabapentin exerts its anticonvulsant action is unknown, but in animal test systems designed to detect anticonvulsant activity, gabapentin prevents seizures as do other marketed anticonvulsants. Gabapentin exhibits antiseizure activity in mice and rats in both the maximal electroshock and pentylenetetrazole seizure models and other preclinical models (e.g., strains with genetic epilepsy, etc.). The relevance of these models to human epilepsy is not known.

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but it does not modify $GABA_A$ or $GABA_B$ radioligand binding. It is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation. Gabapentin was tested in radioligand binding assays at concentrations up to 100 mcM and did not exhibit affinity for a number of other common receptor sites, including benzodiazepine, glutamate, N-methyl-D-aspartate (**NMDA**), quisqualate, kainate, strychnine-insensitive or strychnine-sensitive glycine, alpha 1, alpha 2, or beta adrenergic, adenosine A1 or A2, cholinergic muscarinic or nicotinic, dopamine D1 or D2, histamine H1, serotonin S1 or S2, opiate mu, delta or kappa, cannabinoid 1, voltage-sensitive calcium channel sites labeled with nitrendipine or diltiazem, or at voltage-sensitive sodium channel sites labeled with batrachotoxin A 20-alpha-benzoate. Furthermore, gabapentin did not alter the cellular uptake of dopamine, noradrenaline, or serotonin.

In vitro studies with radiolabeled gabapentin have revealed a gabapentin binding site in areas of rat brain including neocortex and hippocampus. A high-affinity binding protein in animal brain tissue has been identified as an auxiliary subunit of voltage-activated calcium channels. However, functional correlates of gabapentin binding, if any, remain to be elucidated.

Pharmacokinetics and Drug Metabolism
All pharmacological actions following gabapentin administration are due to the activity of the parent compound; gabapentin is not appreciably metabolized in humans.

Oral Bioavailability: Gabapentin bioavailability is not dose proportional; i.e., as dose is increased, bioavailability decreases. Bioavailability of gabapentin is approximately 60%, 47%, 34%, 33%, and 27% following 900, 1200, 2400, 3600, and 4800 mg/day given in 3 divided doses, respectively. Food has only a slight effect on the rate and extent of absorption of gabapentin (14% increase in AUC and C_{max}).

Distribution: Less than 3% of gabapentin circulates bound to plasma protein. The apparent volume of distribution of gabapentin after 150 mg intravenous administration is 58 ± 6 L (Mean ± SD). In patients with epilepsy, steady-state predose (C_{min}) concentrations of gabapentin in cerebrospinal fluid were approximately 20% of the corresponding plasma concentrations.

Elimination: Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug. Gabapentin is not appreciably metabolized in humans.

Gabapentin elimination half-life is 5 to 7 hours and is unaltered by dose or following multiple dosing. Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance (see **Special Populations:** *Adult Patients With Renal Insufficiency*, below). In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin can be removed from plasma by hemodialysis.

Dosage adjustment in patients with compromised renal function or undergoing hemodialysis is recommended (see **DOSAGE AND ADMINISTRATION**, Table 3).

Special Populations: *Adult Patients With Renal Insufficiency:* Subjects (N = 60) with renal insufficiency (mean creatinine clearance ranging from 13-114 mL/min) were administered single 400 mg oral doses of gabapentin. The mean gabapentin half-life ranged from about 6.5 hours (patients with creatinine clearance >60 mL/min) to 52 hours (creatinine clearance <30 mL/min) and gabapentin renal clearance from about 90 mL/min (>60 mL/min group) to about 10 mL/min (<30 mL/min). Mean plasma clearance (CL/F) decreased from approximately 190 mL/min to 20 mL/min.

Dosage adjustment in adult patients with compromised renal function is necessary (see **DOSAGE AND ADMINISTRATION**). Pediatric patients with renal insufficiency have not been studied.

Hemodialysis: In a study in anuric adult subjects (N = 11), the apparent elimination half-life of gabapentin on nondialysis days was about 132 hours; during dialysis the apparent half-life of gabapentin was reduced to 3.8 hours. Hemodialysis thus has a significant effect on gabapentin elimination in anuric subjects.

Dosage adjustment in patients undergoing hemodialysis is necessary (see **DOSAGE AND ADMINISTRATION**).

Hepatic Disease: Because gabapentin is not metabolized, no study was performed in patients with hepatic impairment.

Age: The effect of age was studied in subjects 20-80 years of age. Apparent oral clearance (CL/F) of gabapentin decreased as age increased, from about 225 mL/min in those under 30 years of age to about 125 mL/min in those over 70 years of age. Renal clearance (CLr) and CLr adjusted for body surface area also declined with age; however, the decline in the renal clearance of gabapentin with age can largely be explained by the decline in renal function. Reduction of gabapentin dose may be required in patients who have age related compromised renal function (see **PRECAUTIONS**, **Geriatric Use**, and **DOSAGE AND ADMINISTRATION**).

Pediatric: Gabapentin pharmacokinetics were determined in 48 pediatric subjects between the ages of 1 month and 12 years following a dose of approximately 10 mg/kg. Peak plasma concentrations were similar across the entire age group and occurred 2 to 3 hours postdose. In general, pediatric subjects between 1 month and <5 years of age achieved approximately 30% lower exposure (AUC) than that observed in those 5 years of age and older. Accordingly, oral clearance normalized per body weight was higher in the younger children. Apparent oral clearance of gabapentin was directly proportional to creatinine clearance. Gabapentin elimination half-life averaged 4.7 hours and was similar across the age groups studied.

A population pharmacokinetic analysis was performed in 253 pediatric subjects between 1 month and 13 years of age. Patients received 10 to 65 mg/kg/day give T.I.D. Apparent oral clearance (CL/F) was directly proportional to creatinine clearance and this relationship was similar following a single dose and at steady state. Higher oral clearance values were observed in children <5 years of age compared to those observed in children 5 years of age and older, when normalized per body weight. The clearance was highly variable in infants <1 year of age. The normalized CL/F values observed in pediatric patients 5 years of age and older were consistent with values observed in adults after a single dose. The oral volume of distribution normalized per body weight was constant across the age range.

These pharmacokinetic data indicate that the effective daily dose in pediatric patients with epilepsy ages 3 and 4 years should be 40 mg/kg/day to achieve average plasma concentrations similar to those achieved in patients 5 years of age and older receiving gabapentin at 30 mg/kg/day. (See **DOSAGE AND ADMINISTRATION**.)

Gender: Although no formal study has been conducted to compare the pharmacokinetics of gabapentin in men and women, it appears that the pharmacokinetic parameters for males and females are similar and there are no significant gender differences.

Race: Pharmacokinetic differences due to race have not been studied. Because gabapentin is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

Clinical Studies

Epilepsy
The effectiveness of gabapentin as adjunctive therapy (added to other enhancing mitogenic activity. It is not known whether gabapentin has the ability to increase cell proliferation in other cell types or in other species, including humans.

Gabapentin did not demonstrate mutagenic or genotoxic potential in three *in vitro* and four *in vivo* assays. It was negative in the Ames test and the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay; it was negative in the *in vivo* chromosomal aberration assay and in the *in vivo* micronucleus test in Chinese hamster bone marrow; it was negative in the *in vivo* mouse micronucleus assay, and it did not include unscheduled DNA synthesis in hepatocytes from rats given gabapentin.

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately 5 times the maximum recommended human dose on a mg/m^2 basis).

Pregnancy
Pregnancy Category C: Gabapentin has been shown to be fetotoxic in rodents, causing delayed ossification of several bones in the skull, vertebrae, forelimbs, and hindlimbs. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during the period of organogenesis, or approximately 1 to 4 times the maximum dose of 3600 mg/day given to epileptic patients on a mg/m^2 basis. The no-effect level was 500 mg/kg/day or approximately 1/2 of the human dose on a mg/m^2 basis.

When rats were dosed prior to and during mating, and throughout gestation, pups from all dose groups (500, 1000 and 2000 mg/kg/day) were affected. These doses are equivalent to less than approximately 1 to 5 times the maximum human dose on a mg/m^2 basis. There was an increased incidence of hydroureter and/or hydronephrosis in rats in a study of fertility and general reproductive performance at 2000 mg/kg/day with no effect at 1000 mg/kg/day, in a teratology study at 1500 mg/kg/day with no effect at 300 mg/kg/day, and in a perinatal and postnatal study at all doses studied (500, 1000 and 2000 mg/kg/day). The doses at which the effects occurred are approximately 1 to 5 times the maximum human dose of 3600 mg/day on a mg/m^2 basis; the no-effect doses were approximately 3 times (Fertility and General Reproductive Performance study) and approximately equal to (Teratogenicity study) the maximum human dose on a mg/m^2 basis. Other than hydroureter and hydronephrosis, the etiologies of which are unclear, the incidence of malformations was not increased compared to controls in offspring of mice, rats, or rabbits given doses up to 50 times (mice), 30 times (rats), and 25 times (rabbits) the human daily dose on a mg/kg basis, or 4 times (mice), 5 times (rats), or 8 times (rabbits) the human daily dose on a mg/m^2 basis.

In a teratology study in rabbits, an increased incidence of postimplantation fetal loss occurred in dams exposed to 60, 300 and 1500 mg/kg/day, or less than approximately 1/4 to 8 times the maximum human dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Nursing Mothers
Gabapentin is secreted into human milk following oral administration. A nursed infant could be exposed to a maximum dose of approximately 1 mg/kg/day of gabapentin. Because the effect on the nursing infant is unknown, gabapentin should be used in women who are nursing only if the benefits clearly outweigh the risks.

Pediatric Use
Effectiveness as adjunctive therapy in the treatment of partial seizures in pediatric patients below the age of 3 years has not been established (see **CLINICAL PHARMACOLOGY, Clinical Studies**).

Geriatric Use
Clinical studies of gabapentin in epilepsy did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions 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 dose should be adjusted based on creatinine clearance values in these patients (see **CLINICAL PHARMACOLOGY, ADVERSE REACTIONS,** and **DOSAGE AND ADMINISTRATION** sections).

ADVERSE REACTIONS

Epilepsy
The most commonly observed adverse events associated with the use of gabapentin in combination with other antiepileptic drugs in patients >12 years of age, not seen at an equivalent frequency among placebo-treated patients, were somnolence, dizziness, ataxia, fatigue, and nystagmus. The most commonly observed adverse events reported with the use of gabapentin in combination with other antiepileptic drugs in pediatric patients 3 to 12 years of age, not seen at an equal frequency among placebo-treated patients, were viral infection, fever, nausea and/or vomiting, somnolence, and hostility (see **WARNINGS, Neuropsychiatric Adverse Events**).

Approximately 7% of the 2074 patients >12 years of age and approximately 7% of the 449 pediatric patients 3 to 12 years of age who received gabapentin in premarketing clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal in patients >12 years of age were somnolence (1.2%), ataxia (0.8%), fatigue (0.6%), nausea and/or vomiting (0.6%), and dizziness (0.6%). The adverse events most commonly associated with withdrawal in pediatric patients were emotional lability (1.6%), hostility (1.3%), and hyperkinesia (1.1%).

Incidence in Controlled Clinical Trials
Table 1 lists treatment-emergent signs and symptoms that occurred in at least 1% of gabapentin-treated patients >12 years of age with epilepsy participating in placebo-controlled trials and were numerically more common in the gabapentin group. In these studies, either gabapentin or placebo was added to the patient's current antiepileptic drug therapy. Adverse events were usually mild to moderate in intensity.

The prescriber should be aware that these figures, obtained when gabapentin was added to concurrent antiepileptic drug therapy, cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescribing physician with one basis to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

TABLE 1. Treatment - Emergent Adverse Event Incidence in Controlled Add-On Trials in Patients >12 years of age (Events in at Least 1% of Gabapentin Patients and Numerically More Frequent Than in the Placebo Group)

Body System/ Adverse Event	Gabapentin[a] N = 543 %	Placebo[a] N = 378 %
Body As A Whole		
Fatigue	11.0	5.0
Weight Increase	2.9	1.6
Back Pain	1.8	0.5
Peripheral Edema	1.7	0.5
Cardiovascular		
Vasodilatation	1.1	0.3
Digestive System		
Dyspepsia	2.2	0.5
Mouth or Throat Dry	1.7	0.5
Constipation	1.5	0.8
Dental Abnormalities	1.5	0.3
Increased Appetite	1.1	0.8
Hematologic and Lymphatic Systems		
Leukopenia	1.1	0.5
Musculoskeletal System		
Myalgia	2.0	1.9
Fracture	1.1	0.8
Nervous System		
Somnolence	19.3	8.7
Dizziness	17.1	6.9
Ataxia	12.5	5.6
Nystagmus	8.3	4.0
Tremor	6.8	3.2
Nervousness	2.4	1.9
Dysarthria	2.4	0.5
Amnesia	2.2	0.0
Depression	1.8	1.1
Thinking Abnormal	1.7	1.3
Twitching	1.3	0.5
Coordination Abnormal	1.1	0.3
Respiratory System		
Rhinitis	4.1	3.7

ISTRATION.)

Gender: Although no formal study has been conducted to compare the pharmacokinetics of gabapentin in men and women, it appears that the pharmacokinetic parameters for males and females are similar and there are no significant gender differences.

Race: Pharmacokinetic differences due to race have not been studied. Because gabapentin is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

Clinical Studies

Epilepsy
The effectiveness of gabapentin as adjunctive therapy (added to other antiepileptic drugs) was established in multicenter placebo-controlled, double-blind, parallel-group clinical trials in adult and pediatric patients (3 years and older) with refractory partial seizures.

Evidence of the effectiveness was obtained in three trials conducted in 705 patients (age 12 years and above) and one trial conducted in 247 pediatric patients (3 to 12 years of age). The patients enrolled had a history of at least 4 partial seizures per month in spite of receiving one or more antiepileptic drugs at therapeutic levels and were observed on their established antiepileptic drug regimen during a 12-week baseline period (6 weeks in the study of pediatric patients). In patients continuing to have at least 2 (or 4 in some studies) seizures per month, gabapentin or placebo was then added on to the existing therapy during a 12-week treatment period. Effectiveness was assessed primarily on the basis of the percent of patients with a 50% or greater reduction in seizure frequency from baseline to treatment (the "responder rate") and a derived measure called response ratio, a measure of change defined as (T - B)/(T + B), where B is the patient's baseline seizure frequency and T is the patient's seizure frequency during treatment. Response ratio is distributed within the range -1 to +1. A zero value indicates no change while complete elimination of seizures would give a value of -1; increased seizure rates would give positive values. A response ratio of -0.33 corresponds to a 50% reduction in seizure frequency. The results given below are for all partial seizures in the intent-to-treat (all patients who received any doses of treatment) population in each study, unless otherwise indicated.

One study compared gabapentin 1200 mg/day divided T.I.D. with placebo. Responder rate was 23% (14/61) in the gabapentin group and 9% (6/66) in the placebo group; the difference between groups was statistically significant. Response ratio was also better in the gabapentin group (-0.199) than in the placebo group (-0.044), a difference that also achieved statistical significance.

A second study compared primarily 1200 mg/day divided T.I.D. gabapentin (N = 101) with placebo (N = 98). Additional smaller gabapentin dosage groups (600 mg/day, N = 53; 1800 mg/day, N = 54) were also studied for information regarding dose response. Responder rate was higher in the gabapentin 1200 mg/day group (16%) than in the placebo group (8%), but the difference was not statistically significant. The responder rate at 600 mg (17%) was also not significantly higher than in the placebo, but the responder rate in the 1800 mg group (26%) was statistically significantly superior to the placebo rate. Response ratio was better in the gabapentin 1200 mg/day group (-0.103) than in the placebo group (-0.022); but this difference was also not statistically significant ($p = 0.224$). A better response was seen in the gabapentin 600 mg/day group (-0.105) and 1800 mg/day group (-0.222) than in the 1200 mg/day group, with the 1800 mg/day group achieving statistical significance compared to the placebo group.

A third study compared gabapentin 900 mg/day divided T.I.D. (N = 111) and placebo (N = 109). An additional gabapentin 1200 mg/day dosage group (N = 52) provided dose-response data. A statistically significant difference in responder rate was seen in the gabapentin 900 mg/day group (22%) compared to that in the placebo group (10%). Response ratio was also statistically significantly superior in the gabapentin 900 mg/day group (-0.119) compared to that in the placebo group (-0.027), as was response ratio in 1200 mg/day gabapentin (-0.184) compared to placebo.

Analyses were also performed in each study to examine the effect of gabapentin on preventing secondarily generalized tonic-clonic seizures. Patients who experienced a secondarily generalized tonic-clonic seizure in either the baseline or in the treatment period in all three placebo-controlled studies were included in these analyses. There were several response ratio comparisons that showed a statistically significant advantage for gabapentin compared to placebo and favorable trends for almost all comparisons.

Analysis of responder rate using combined data from all three studies and all doses (N = 162, gabapentin; N = 89, placebo) also showed a significant advantage for gabapentin over placebo in reducing the frequency of secondarily generalized tonic-clonic seizures.

In two of the three controlled studies, more than one dose of gabapentin was used. Within each study the results did not show a consistently increased response to dose. However, looking across studies, a trend toward increasing efficacy with increasing dose is evident (see Figure 1).

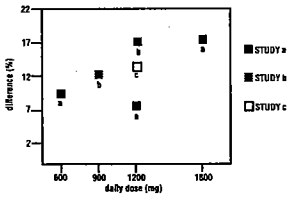


FIGURE 1. Responder Rate in Patients Receiving Gabapentin Expressed as a Difference From Placebo by Dose and Study: Adjunctive Therapy Studies in Patients ≥12 Years of Age With Partial Seizures.

In the figure, treatment effect magnitude, measured on the Y axis in terms of the difference in the proportion of gabapentin and placebo assigned patients attaining a 50% or greater reduction in seizure frequency from baseline, is plotted against the daily dose of gabapentin administered (X axis).

Although no formal analysis by gender has been performed, estimates of response (Response Ratio) derived from clinical trials (398 men, 307 women) indicate no important gender differences exist. There was no consistent pattern indicating that age had any effect on the response to gabapentin. There were insufficient numbers of patients of races other than Caucasian to permit a comparison of efficacy among racial groups.

A fourth study in pediatric patients age 3 to 12 years compared 25-35 mg/kg/day gabapentin (N=118) with placebo (N=127). For all partial seizures in the intent-to-treat population, the response ratio was statistically significantly better for the gabapentin group (-0.146) than for the placebo group (-0.079). For the same population, the responder rate for gabapentin (21%) was not significantly different from placebo (18%).

A study in pediatric patients age 1 month to 3 years compared 40 mg/kg/day gabapentin (N=38) with placebo (N=38) in patients who were receiving at least one marketed antiepileptic drug and had at least one partial seizure during the screening period (within 2 weeks prior to baseline). Patients had up to 48 hours of baseline and up to 72 hours of double-blind video EEG monitoring to record and count the occurrence of seizures. There were no statistically significant differences between treatments in either the response ratio or responder rate.

INDICATIONS AND USAGE

Epilepsy
Gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy. Gabapentin is also indicated as adjunctive therapy in the treatment of partial seizures in pediatric patients age 3-12 years.

CONTRAINDICATIONS

Gabapentin is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS

Neuropsychiatric Adverse Events - Pediatric Patients 3-12 years of age
Gabapentin use in pediatric patients with epilepsy 3-12 years of age is associated with the occurrence of central nervous system related adverse events. The most significant of these can be classified into the following categories: 1) emotional lability (primarily behavioral problems), 2) hostility, including aggressive behaviors, 3) thought disorder, including concentration problems and change in school performance, and 4) hyperkinesia (primarily restlessness and hyperactivity). Among the gabapentin-treated patients, most of the events were mild to moderate in intensity.

In controlled trials in pediatric patients 3-12 years of age, the incidence of these adverse events was: emotional lability 6% (gabapentin-treated patients) vs 1.3% (placebo-treated patients); hostility 5.2% vs 1.3%; hyperkinesia 4.7% vs 2.9%; and thought disorder 1.7% vs 0%. One of these events, a report of hostility, was considered serious. Discontinuation of gabapentin treatment occurred in 1.3% of patients reporting emotional lability and hyperkinesia and 0.9% of gabapentin-

Dizziness	17.1	6.9
Ataxia	12.5	5.6
Nystagmus	8.3	4.0
Tremor	6.8	3.2
Nervousness	2.4	1.9
Dysarthria	2.4	0.5
Amnesia	2.2	0.0
Depression	1.8	1.1
Thinking Abnormal	1.7	1.3
Twitching	1.3	0.5
Coordination Abnormal	1.1	0.3
Respiratory System		
Rhinitis	4.1	3.7
Pharyngitis	2.8	1.6
Coughing	1.8	1.3
Skin and Appendages		
Abrasion	1.3	0.0
Pruritus	1.3	0.5
Urogenital System		
Impotence	1.5	1.1
Special Senses		
Diplopia	5.9	1.9
Amblyopia[b]	4.2	1.1
Laboratory Deviations		
WBC Decreased	1.1	0.5

[a]Plus background antiepileptic drug therapy
[b]Amblyopia was often described as blurred vision.

Other events in more than 1% of patients >12 years of age but equally or more frequent in the placebo group included: headache, viral infection, fever, nausea and/or vomiting, abdominal pain, diarrhea, convulsions, confusion, insomnia, emotional lability, rash, acne.

Among the treatment-emergent adverse events occurring at an incidence of at least 10% of gabapentin-treated patients, somnolence and ataxia appeared to exhibit a positive dose-response relationship.

The overall incidence of adverse events and the types of adverse events seen were similar among men and women treated with gabapentin. The incidence of adverse events increased slightly with increasing age in patients treated with either gabapentin or placebo. Because only 3% of patients (28/921) in placebo-controlled studies were identified as nonwhite (black or other), there are insufficient data to support a statement regarding the distribution of adverse events by race.

Table 2 lists treatment-emergent signs and symptoms that occurred in at least 2% of gabapentin-treated patients age 3 to 12 years of age with epilepsy participating in placebo-controlled trials and were numerically more common in the gabapentin group. Adverse events were usually mild to moderate in intensity.

TABLE 2. Treatment-Emergent Adverse Event Incidence in Pediatric Patients Age 3 to 12 Years in a Controlled Add-On Trial (Events in at Least 2% of Gabapentin Patients and Numerically More Frequent Than in the Placebo Group)

Body System/ Adverse Event	Gabapentin[a] N=119 %	Placebo[a] N=128 %
Body As A Whole		
Viral Infection	10.9	3.1
Fever	10.1	3.1
Weight Increase	3.4	0.8
Fatigue	3.4	1.6
Digestive System		
Nausea and/or Vomiting	8.4	7.0
Nervous System		
Somnolence	8.4	4.7
Hostility	7.6	2.3
Emotional Lability	4.2	1.6
Dizziness	2.5	1.6
Hyperkinesia	2.5	0.8
Respiratory System		
Bronchitis	3.4	0.8
Respiratory Infection	2.5	0.8

[a]Plus background antiepileptic drug therapy

Other events in more than 2% of pediatric patients 3 to 12 years of age but equally or more frequent in the placebo group included: pharyngitis, upper respiratory infection, headache, rhinitis, convulsions, diarrhea, anorexia, coughing, and otitis media.

Other Adverse Events Observed During All Clinical Trials

Clinical Trials in Adults and Adolescents (Except Clinical Trials in Neuropathic Pain)
Gabapentin has been administered to 2074 patients >12 years of age during all adjunctive therapy clinical trials (except clinical trials in patients with neuropathic pain), only some of which were placebo-controlled. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. These categories are used in the listing below. The frequencies presented represent the proportion of the 2074 patients >12 years of age exposed to gabapentin who experienced an event of the type cited on at least one occasion while receiving gabapentin. All reported events are included except those already listed in Table 1, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body As A Whole: *Frequent :* asthenia, malaise, face edema; *Infrequent :* allergy, generalized edema, weight decrease, chill; *Rare :* strange feelings, lassitude, alcohol intolerance, hangover effect.

Cardiovascular System: *Frequent :* hypertension; *Infrequent :* hypotension, angina pectoris, peripheral vascular disorder, palpitation, tachycardia, migraine, murmur; *Rare :* atrial fibrillation, heart failure, thrombophlebitis, deep thrombophlebitis, myocardial infarction, cerebrovascular accident, pulmonary thrombosis, ventricular extrasystoles, bradycardia, premature atrial contraction, pericardial rub, heart block, pulmonary embolus, hyperlipidemia, hypercholesterolemia, pericardial effusion, pericarditis.

Digestive System: *Frequent :* anorexia, flatulence, gingivitis; *Infrequent :* glossitis, gum hemorrhage, thirst, stomatitis, increased salivation, gastroenteritis, hemorrhoids, bloody stools, fecal incontinence, hepatomegaly; *Rare :* dysphagia, eructation, pancreatitis, peptic ulcer, colitis, blisters in mouth, tooth discolor, perlèche, salivary gland enlarged, lip hemorrhage, esophagitis, hiatal hernia, hematemesis, proctitis, irritable bowel syndrome, rectal hemorrhage, esophageal spasm.

Endocrine System: *Rare :* hyperthyroid, hypothyroid, goiter, hypoestrogen, ovarian failure, epididymitis, swollen testicle, cushingoid appearance.

Hematologic and Lymphatic System: *Frequent :* purpura most often described as bruises resulting from physical trauma; *Infrequent :* anemia, thrombocytopenia, lymphadenopathy; *Rare :* WBC count increased, lymphocytosis, non-Hodgkin's lymphoma, bleeding time increased.

Musculoskeletal System: *Frequent :* arthralgia; *Infrequent :* tendinitis, arthritis, joint stiffness, joint swelling, positive Romberg test; *Rare :* costochondritis, osteoporosis, bursitis, contracture.

Nervous System: *Frequent :* vertigo, hyperkinesia, paresthesia, decreased or absent reflexes, increased reflexes, anxiety, hostility; *Infrequent :* CNS tumors, syncope, dreaming abnormal, aphasia, hypesthesia, intracranial hemorrhage, hypotonia, dysesthesia, paresis, dystonia, hemiplegia, facial paralysis, stupor, cerebellar dysfunction, positive Babinski sign, decreased position sense, subdural hematoma, apathy, hallucination, decrease or loss of libido, agitation, paranoia, depersonalization, euphoria, feeling high, doped-up sensation, suicidal, psychosis; *Rare :* choreoathetosis, orofacial dyskinesia, encephalopathy, nerve palsy, personality disorder, increased libido, subdued temperament, aprazia, fine motor control disorder, meningismus, local myoclonus, hyperesthesia, hypokinesia, mania, neurosis, hysteria, antisocial reaction, suicide gesture.

Respiratory System: *Frequent :* pneumonia; *Infrequent :* epistaxis, dyspnea, apnea; *Rare :* mucositis, aspiration pneumonia, hyperventilation, hiccup, laryngitis, nasal obstruction, snoring, bronchospasm, hyperventilation, lung edema.

Dermatological: *Infrequent :* alopecia, eczema, dry skin, increased sweating, urticaria, hirsutism, seborrhea, cyst, herpes simplex; *Rare :* herpes zoster, skin discolor, skin papules, photosensitive reaction, leg ulcer, scalp seborrhea, psoriasis, desquamation, maceration, skin nodules, subcutaneous nodule, melanosis, skin necrosis, local swelling.

Adverse Events Leading to Discontinuation of Therapy in Patients 3-12 Years of Age

Gabapentin use in pediatric patients with epilepsy 3-12 years of age is associated with the occurrence of central nervous system related adverse events. The most significant of these can be classified into the following categories: 1) emotional lability (primarily behavioral problems), 2) hostility, including aggressive behaviors, 3) thought disorder, including concentration problems and change in school performance, and 4) hyperkinesia (primarily restlessness and hyperactivity). Among the gabapentin-treated patients, most of the events were mild to moderate in intensity.

In controlled trials in pediatric patients 3-12 years of age, the incidence of these adverse events was: emotional lability 6% (gabapentin-treated patients) vs 1.3% (placebo-treated patients); hostility 5.2% vs 1.3%; hyperkinesia 4.7% vs 2.9%; and thought disorder 1.7% vs 0%. One of these events, a report of hostility, was considered serious. Discontinuation of gabapentin treatment occurred in 1.3% of patients reporting emotional lability and hyperkinesia and 0.5% of gabapentin-treated patients reporting hostility and thought disorder. One placebo-treated patient (0.4%) withdrew due to emotional lability.

Withdrawal Precipitated Seizure, Status Epilepticus

Antiepileptic drugs should not be abruptly discontinued because of the possibility of increasing seizure frequency.

In the placebo-controlled studies in patients >12 years of age, the incidence of status epilepticus in patients receiving gabapentin was 0.6% (3 of 543) versus 0.5% in patients receiving placebo (2 of 378). Among the 2074 patients >12 years of age treated with gabapentin across all studies (controlled and uncontrolled) 31 (1.5%) had status epilepticus. Of these, 14 patients had no prior history of status epilepticus either before treatment or while on other medications. Because adequate historical data are not available, it is impossible to say whether or not treatment with gabapentin is associated with a higher or lower rate of status epilepticus than would be expected to occur in a similar population not treated with gabapentin.

Tumorigenic Potential

In standard preclinical *in vivo* lifetime carcinogenicity studies, an unexpectedly high incidence of pancreatic acinar adenocarcinomas was identified in male, but not female, rats (see **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility**). The clinical significance of this finding is unknown. Clinical experience during gabapentin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies in adjunctive therapy in epilepsy comprising 2085 patient-years of exposure in patients >12 years of age, new tumors were reported in 10 patients (2 breast, 3 brain, 2 lung, 1 adrenal, 1 non-Hodgkin's lymphoma, 1 endometrial carcinoma *in situ*), and pre-existing tumors worsened in 11 patients (9 brain, 1 breast, 1 prostate) during or up to 2 years following discontinuation of gabapentin. Without knowledge of the background incidence and recurrence in a similar population not treated with gabapentin, it is impossible to know whether the incidence seen in this cohort is or is not affected by treatment.

Sudden and Unexplained Death in Patients With Epilepsy

During the course of premarketing development of gabapentin 8 sudden and unexplained deaths were recorded among a cohort of 2203 patients treated (2103 patient-years of exposure).

Some of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. This represents an incidence of 0.0038 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving gabapentin (ranging from 0.0005 for the general population of epileptics to 0.003 for a clinical trial population similar to that in the gabapentin program, to 0.005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or raise further concern depends on comparability of the populations reported upon to the gabapentin cohort and the accuracy of the estimates provided.

PRECAUTIONS

Information for Patients

Patients should be instructed to take gabapentin only as prescribed.

Patients should be advised that gabapentin may cause dizziness, somnolence and other symptoms and signs of CNS depression. Accordingly, they should be advised neither to drive a car nor to operate other complex machinery until they have gained sufficient experience on gabapentin to gauge whether or not it affects their mental and/or motor performance adversely.

Patients who require concomitant treatment with morphine may experience increases in gabapentin concentrations. Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately (see **Drug Interactions**).

Laboratory Tests

Clinical trials data do not indicate that routine monitoring of clinical laboratory parameters is necessary for the safe use of gabapentin. The value of monitoring gabapentin blood concentrations has not been established. Gabapentin may be used in combination with other antiepileptic drugs without concern for alteration of the blood concentrations of gabapentin or of other antiepileptic drugs.

Drug Interactions

In vitro studies were conducted to investigate the potential of gabapentin to inhibit the major cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) that mediate drug and xenobiotic metabolism using isoform selective marker substrates and human liver microsomal preparations. Only at the highest concentration tested (171 mcg/mL; 1 mM) was a slight degree of inhibition (14%-30%) of isoform CYP2A6 observed. No inhibition of any of the other isoforms tested was observed at gabapentin concentrations up to 171 mcg/mL (approximately 15 times the C_{max} at 3600 mg/day).

Gabapentin is not appreciably metabolized nor does it interfere with the metabolism of commonly coadministered antiepileptic drugs.

The drug interaction data described in this section were obtained from studies involving healthy adults and adult patients with epilepsy.

Phenytoin: In a single (400 mg) and multiple dose (400 mg T.I.D.) study of gabapentin in epileptic patients (N = 8) maintained on phenytoin monotherapy for at least 2 months, gabapentin had no effect on the steady-state trough plasma concentrations of phenytoin and phenytoin had no effect on gabapentin pharmacokinetics.

Carbamazepine: Steady-state trough plasma carbamazepine and carbamazepine 10, 11 epoxide concentrations were not affected by concomitant gabapentin (400 mg T.I.D.; N = 12) administration. Likewise, gabapentin pharmacokinetics were unaltered by carbamazepine administration.

Valproic Acid: The mean steady-state trough serum valproic acid concentrations prior to and during concomitant gabapentin administration (400 mg T.I.D.; N = 17) were not different and neither were gabapentin pharmacokinetic parameters affected by valproic acid.

Phenobarbital: Estimates of steady-state pharmacokinetic parameters for phenobarbital or gabapentin (300 mg T.I.D.; N = 12) are identical whether the drugs are administered alone or together.

Naproxen: Coadministration (N = 18) of naproxen sodium capsules (250 mg) with gabapentin (125 mg) appears to increase the amount of gabapentin absorbed by 12% to 15%. Gabapentin had no effect on naproxen pharmacokinetic parameters. These doses are lower than the therapeutic doses for both drugs. The magnitude of interaction within the recommended dose ranges of either drug is not known.

Hydrocodone: Coadministration of gabapentin (125 to 500 mg; N = 48) decreases hydrocodone (10 mg; N = 50) C_{max} and AUC values in a dose-dependent manner relative to administration of hydrocodone alone; C_{max} and AUC values are 3% to 4% lower, respectively, after administration of 125 mg gabapentin and 21% to 22% lower, respectively, after administration of 500 mg gabapentin. The mechanism for this interaction is unknown. Hydrocodone increases gabapentin AUC values by 14%. The magnitude of interaction at other doses is not known.

Morphine: A literature article reported that when a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule (N = 12), mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine (see **PRECAUTIONS**). Morphine pharmacokinetic parameter values were not affected by administration of gabapentin 2 hours after morphine. The magnitude of interaction at other doses is not known.

Cimetidine: In the presence of cimetidine at 300 mg Q.I.D. (N = 12) the mean apparent oral clearance of gabapentin fell by 14% and creatinine clearance fell by 10%. Thus cimetidine appeared to alter the renal excretion of both gabapentin and creatinine, an endogenous marker of renal function. This small decrease in excretion of gabapentin by cimetidine is not expected to be of clinical importance. The effect of gabapentin on cimetidine was not evaluated.

Oral Contraceptive: Based on AUC and half-life, multiple-dose pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of tablets containing 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol were similar with and without coadministration of gabapentin (400 mg T.I.D.; N = 13). The C_{max} of norethindrone was 13% higher when it was coadministered with gabapentin; this interaction is not expected to be of clinical importance.

Antacid (Maalox®†): Maalox® reduced the bioavailability of gabapentin (N = 18) by about 20%. This decrease in bioavailability was about 5% when gabapentin was administered 2 hours after Maalox®. It is recommended that gabapentin be taken at least 2 hours following Maalox® administration.

depersonalization, euphoria, feeling high, doped-up sensation, suicidal, psychosis; *Rare :* choreoathetosis, orofacial dyskinesia, encephalopathy, nerve palsy, personality disorder, increased libido, subdued temperament, apraxia, fine motor control disorder, meningismus, focal myoclonus, hyperesthesia, hypokinesia, mania, neurosis, hysteria, antisocial reaction, suicide gesture.

Respiratory System: *Frequent :* pneumonia; *Infrequent :* epistaxis, dyspnea, apnea; *Rare :* mucositis, aspiration pneumonia, hyperventilation, hiccup, laryngitis, nasal obstruction, snoring, bronchospasm, hypoventilation, lung edema.

Dermatological: *Infrequent :* alopecia, eczema, dry skin, increased sweating, urticaria, hirsutism, seborrhea, cyst, herpes simplex; *Rare :* herpes zoster, skin discolor, skin papules, photosensitive reaction, leg ulcer, scalp seborrhea, psoriasis, desquamation, maceration, skin nodules, subcutaneous nodule, melanosis, skin necrosis, local swelling.

Urogenital System: *Infrequent :* hematuria, dysuria, urination frequency, cystitis, urinary retention, urinary incontinence, vaginal hemorrhage, amenorrhea, dysmenorrhea, menorrhagia, breast cancer, unable to climax, ejaculation abnormal; *Rare :* kidney pain, leukorrhea, pruritus genital, renal stone, acute renal failure, anuria, glycosuria, nephrosis, nocturia, pyuria, urination urgency, vaginal pain, breast pain, testicle pain.

Special Senses: *Frequent :* abnormal vision; *Infrequent :* cataract, conjunctivitis, eyes dry, eye pain, visual field defect, photophobia, bilateral or unilateral ptosis, eye hemorrhage, hordeolum, hearing loss, earache, tinnitus, inner ear infection, otitis, taste loss, unusual taste, eye twitching, ear fullness; *Rare :* eye itching, abnormal accommodation, perforated ear drum, sensitivity to noise, eye focusing problem, watery eyes, retinopathy, glaucoma, iritis, corneal disorders, lacrimal dysfunction, degenerative eye changes, blindness, retinal degeneration, miosis, chorioretinitis, strabismus, eustachian tube dysfunction, labyrinthitis, otitis externa, odd smell.

Clinical Trials in Pediatric Patients With Epilepsy

Adverse events occurring during epilepsy clinical trials in 449 pediatric patients 3 to 12 years of age treated with gabapentin that were not reported in adjunctive trials in adults are:

Body as a Whole: dehydration, infectious mononucleosis

Digestive System: hepatitis

Hemic and Lymphatic System: coagulation defect

Nervous System: aura disappeared, occipital neuralgia

Psychobiologic Function: sleepwalking

Respiratory System: pseudocroup, hoarseness

Postmarketing and Other Experience

In addition to the adverse experiences reported during clinical testing of gabapentin, the following adverse experiences have been reported in patients receiving marketed gabapentin. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: angioedema, blood glucose fluctuation, erythema multiforme, elevated liver function tests, fever, hyponatremia, jaundice, movement disorder such as dyskinesia, Stevens-Johnson syndrome.

Adverse events following the abrupt discontinuation of gabapentin have also been reported. The most frequently reported events were anxiety, insomnia, nausea, pain and sweating.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of gabapentin has not been evaluated in human studies.

OVERDOSAGE

A lethal dose of gabapentin was not identified in mice and rats receiving single oral doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, sedation, hypoactivity, or excitation.

Acute oral overdoses of gabapentin up to 49 grams have been reported. In these cases, double vision, slurred speech, drowsiness, lethargy and diarrhea were observed. All patients recovered with supportive care.

Gabapentin can be removed by hemodialysis. Although hemodialysis has not been performed in the few overdose cases reported, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

DOSAGE AND ADMINISTRATION

Gabapentin is given orally with or without food.

If gabapentin dose is reduced, discontinued or substituted with an alternative medication, this should be done gradually over a minimum of 1 week.

Epilepsy

Gabapentin is recommended for add-on therapy in patients 3 years of age and older. Effectiveness in pediatric patients below the age of 3 years has not been established.

Patients >12 years of age: The effective dose of gabapentin is 900 to 1800 mg/day and given in divided doses (three times a day) using 300 or 400 mg capsules. The starting dose is 300 mg three times a day. If necessary, the dose may be increased using 300 mg or 400 mg capsules three times a day up to 1800 mg/day. Dosages up to 2400 mg/day have been well tolerated in long-term clinical studies. Doses of 3600 mg/day have also been administered to a small number of patients for a relatively short duration, and have been well tolerated. The maximum time between doses in the T.I.D. schedule should not exceed 12 hours.

Pediatric Patients Age 3-12 years: The starting dose should range from 10-15 mg/kg/day in 3 divided doses, and the effective dose reached by upward titration over a period of approximately 3 days. The effective dose of gabapentin in patients 5 years of age and older is 25-35 mg/kg/day and given in divided doses (three times a day). The effective dose in pediatric patients ages 3 and 4 years is 40 mg/kg/day and given in divided doses (three times a day) (See **CLINICAL PHARMACOLOGY, Pediatrics**). Dosages up to 50 mg/kg/day have been well tolerated in a long-term clinical study. The maximum time interval between doses should not exceed 12 hours.

It is not necessary to monitor gabapentin plasma concentrations to optimize gabapentin therapy. Further, because there are no significant pharmacokinetic interactions among gabapentin and other commonly used antiepileptic drugs, the addition of gabapentin does not alter the plasma levels of these drugs appreciably.

If gabapentin is discontinued and/or an alternate anticonvulsant medication is added to the therapy, this should be done gradually over a minimum of 1 week.

Dosage in Renal Impairment

Creatinine clearance is difficult to measure in outpatients. In patients with stable renal function, creatinine clearance (C_{Cr}) can be reasonably well estimated using the equation of Cockcroft and Gault:

for females: $C_{Cr} = (0.85)(140\text{-age})(\text{weight})/[(72)(S_{Cr})]$

for males: $C_{Cr} = (140\text{-age})(\text{weight})/[(72)(S_{Cr})]$

where age is in years, weight is in kilograms and S_{Cr} is serum creatinine in mg/dL.

Dosage adjustment in patients ≥12 years of age with compromised renal function or undergoing hemodialysis is recommended as follows (see dosing recommendations above for effective doses in each indication).

TABLE 3. Gabapentin Dosage Based on Renal Function

Renal Function Creatinine Clearance (mL/min)	Total Daily Dose Range (mg/day)	Dose Regimen (mg)				
≥60	900-3600	300 TID	400 TID	600 TID	800 TID	1200 TID
>30-59	400-1400	200 BID	300 BID	400 BID	500 BID	700 BID
>15-29	200-700	200 QD	300 QD	400 QD	500 QD	700 QD
<15[a]	100-300	100 QD	125 QD	150 QD	200 QD	300 QD

	Post-Hemodialysis Supplemental Dose (mg)[b]				
Hemodialysis	125[b]	150[b]	200[b]	250[b]	350[b]

[a]For patients with creatinine clearance <15 mL/min, reduce daily dose in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 mL/min should receive one-half the daily dose that patients with a creatinine clearance of 15 mL/min receive).

[b]Patients on hemodialysis should receive maintenance doses based on estimates of creatinine clearance as indicated in the upper portion of the table and a supplemental post-hemodialysis dose administered after each 4 hours of hemodialysis as indicated in the lower portion of the table.

The use of gabapentin in patients <12 years of age with compromised renal function has not been studied.

Dosage in Elderly

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and dose should be adjusted based on creatinine clearance values in these patients.

HOW SUPPLIED

Gabapentin Capsules 100 mg are available for oral administration as hard gelatin capsules with a white opaque body and a white opaque cap. "APO 112" is imprinted on each capsule in black ink; supplied in bottles of 100 (NDC 60505-0112-1).

Gabapentin Capsules 300 mg are available for oral administration as hard gelatin capsules with a white opaque body and a yellow opaque cap. "APO 113" is imprinted on each capsule in black ink; supplied in bottles of 100 (NDC 60505-0113-1).

Gabapentin Capsules 400 mg are available for oral administration as hard gelatin capsules with a white opaque body and an orange opaque cap. "APO 114" is imprinted on each capsule in black ink; supplied in bottles of

10%. This decrease appeared to alter the renal excretion of both gabapentin and creatinine, an endogenous marker of renal function. This small decrease in excretion of gabapentin by cimetidine is not expected to be of clinical importance. The effect of gabapentin on cimetidine was not evaluated.

Oral Contraceptive: Based on AUC and half-life, multiple-dose pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of tablets containing 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol were similar with and without coadministration of gabapentin (400 mg T.I.D.; N = 13). The C_{max} of norethindrone was 13% higher when it was coadministered with gabapentin; this interaction is not expected to be of clinical importance.

Antacid (Maalox®*): Maalox® reduced the bioavailability of gabapentin (N = 16) by about 20%. This decrease in bioavailability was about 5% when gabapentin was administered 2 hours after Maalox®. It is recommended that gabapentin be taken at least 2 hours following Maalox® administration.

Effect of Probenecid: Probenecid is a blocker of renal tubular secretion. Gabapentin pharmacokinetic parameters without and with probenecid were comparable. This indicates that gabapentin does not undergo renal tubular secretion by the pathway that is blocked by probenecid.

Drug/Laboratory Tests Interactions
Because false positive readings were reported with the Ames N-Multistix SG® dipstick test for urinary protein when gabapentin was added to other antiepileptic drugs, the more specific sulfosalicylic acid precipitation procedure is recommended to determine the presence of urine protein.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for 2 years. A statistically significant increase in the incidence of pancreatic acinar cell adenomas and carcinomas was found in male rats receiving the high dose; the no-effect dose for the occurrence of carcinomas was 1000 mg/kg/day. Peak plasma concentrations of gabapentin in rats receiving the high dose of 2000 mg/kg were 10 times higher than plasma

should be taken in dose selection, and dose should be adjusted based on creatinine clearance values in these patients.

HOW SUPPLIED

Gabapentin Capsules 100 mg are available for oral administration as hard gelatin capsules with a white opaque body and a white opaque cap. "APO 112" is imprinted on each capsule in black ink; supplied in bottles of 100 (NDC 60505-0112-1).

Gabapentin Capsules 300 mg are available for oral administration as hard gelatin capsules with a white opaque body and a yellow opaque cap. "APO 113" is imprinted on each capsule in black ink; supplied in bottles of 100 (NDC 60505-0113-1).

Gabapentin Capsules 400 mg are available for oral administration as hard gelatin capsules with a white opaque body and an orange opaque cap. "APO 114" is imprinted on each capsule in black ink; supplied in bottles of 100 (NDC 60505-0114-1).

Storage

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant container [see USP].

*Maalox® is a registered trademark of Novartis Consumer Health, Inc.

APOTEX INC.
GABAPENTIN CAPSULES 100 mg, 300 mg and 400 mg

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, Florida
33326

(GABC-R03-51X138MM-LFLT-090104)

Revised: December 2004

Rev. 1

Each capsule contains 300 mg gabapentin.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant container [see USP].

Usual Dosage: See package insert.

214311

APOTEX CORP.

NDC 60505-0113-1

Gabapentin Capsules

300 mg

100 Capsules

℞ Only

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, Florida 33326

N 3 60505-0113-1 5

GABAPENTIN CAPSULES
100 mg, 300 mg and 400 mg

℞ only

DESCRIPTION

Gabapentin is described as 1-(aminomethyl) cyclohexaneacetic acid with a molecular formula of $C_9H_{17}NO_2$ and a molecular weight of 171.24. Gabapentin is a white to off-white crystalline solid with a pK_1 of 3.7 and a pK_2 of 10.7. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is -1.25. It has the following structural formula:

Each capsule for oral administration contains 100 mg, 300 mg, and 400 mg of gabapentin. In addition, each capsule contains the following inactive ingredients: croscarmellose sodium and magnesium stearate. The 100 mg, 300 mg and 400 mg capsule imprinting ink black SW-9008/SW-9009 contains the following inactive ingredients: ammonium hydroxide; black iron oxide, bacteria controlled EEC No. 172; n-butyl; ethyl alcohol, anhydrous, 200 proof; isopropyl alcohol USP;

NON PRINTING AREA (GLUE PANEL)

Open Here

N 3 60505-0113-1 5

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Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, Florida 33326

NDC 60505-0113-1

Gabapentin Capsules

300 mg

100 Capsules

℞ Only

APOTEX CORP.

Each capsule contains 300 mg gabapentin.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant container [see USP].

Usual Dosage: See package insert.

214311

concentrations in humans receiving 3600 mg/day, and in rats receiving 1000 mg/kg/day peak plasma concentrations were 6.5 times higher than in humans receiving 3600 mg/day. The pancreatic acinar cell carcinomas did not affect survival, did not metastasize and were not locally invasive. The relevance of this finding to carcinogenic risk in humans is unclear.

Studies designed to investigate the mechanism of gabapentin-induced pancreatic carcinogenesis in rats indicate that gabapentin stimulates DNA synthesis in rat pancreatic acinar cells *in vitro* and, thus, may be acting as a tumor promotor by enhancing mitogenic activity. It is not known whether gabapentin has the ability to increase cell proliferation in other cell types or in other species, including humans.

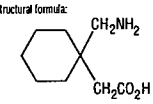
Gabapentin did not demonstrate mutagenic or genotoxic potential in three *in vitro* and four *in vivo* assays. It was negative in the Ames test and the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay; it was negative in the *in vivo* chromosomal aberration assay and in the *in vivo* micronucleus test in Chinese hamster bone marrow; it was negative in the *in vivo* mouse micronucleus assay; and it did not include unscheduled DNA synthesis in hepatocytes from rats given gabapentin.

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately 5 times the maximum recommended human dose on a mg/m^2 basis).

Pregnancy

Pregnancy Category C: Gabapentin has been shown to be fetotoxic in rodents, causing delayed ossification of several bones in the skull, vertebrae, forelimbs,

has the following structural formula:



Each capsule for oral administration contains 100 mg, 300 mg, and 400 mg of gabapentin. In addition, each capsule contains the following inactive ingredients: croscarmellosa sodium and magnesium stearate. The 100 mg, 300 mg and 400 mg capsule imprinting ink black SW-9008/SW-9009 contains the following inactive ingredients: ammonium hydroxide; black iron oxide, bacteria controlled EEC No. 172; n-butyl; ethyl alcohol, anhydrous, 200 proof; isopropyl alcohol USP; potassium hydroxide; propylene glycol; purified water and shellac.

The 100 mg capsule shell contains gelatin and titanium dioxide.

The 300 mg capsule shell contains gelatin, yellow iron oxide and titanium dioxide.

The 400 mg capsule shell contains gelatin, red iron oxide, yellow iron oxide and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action
The mechanism by which gabapentin exerts its anticonvulsant action is unknown, but in animal test systems designed to detect anticonvulsant activity, gabapentin prevents seizures as do other marketed anticonvulsants. Gabapentin exhibits antiseizure activity in mice and rats in both the maximal electroshock and pentylenetetrazole seizure models and other preclinical models (e.g., strains with genetic epilepsy, etc.). The relevance of these models to human epilepsy is not known.

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but it does not modify $GABA_A$ or $GABA_B$ radioligand binding, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation. Gabapentin was tested in radioligand binding assays at concentrations up to 100 mcM and did not exhibit affinity for a number of other common receptor sites, including benzodiazepine, glutamate, N-methyl-D-aspartate (NMDA), quisqualate, kainate, strychnine-insensitive or strychnine-sensitive glycine, alpha 1, alpha 2, or beta adrenergic, adenosine A1 or A2, cholinergic muscarinic or nicotinic, dopamine D1 or D2, histamine H1, serotonin S1 or S2, opiate mu, delta or kappa, cannabinoid 1, voltage-sensitive calcium channel sites labeled with nitrendipine or diltiazem, or at voltage-sensitive sodium channel sites labeled with batrachotoxinin A 20-alpha-benzoate. Furthermore, gabapentin did not alter the cellular uptake of dopamine, noradrenaline, or serotonin.

In vitro studies with radiolabeled gabapentin have revealed a gabapentin binding site in areas of rat brain including neocortex and hippocampus. A high-affinity binding protein in animal brain tissue has been identified as an auxiliary subunit of voltage-activated calcium channels. However, functional correlates of gabapentin binding, if any, remain to be elucidated.

Pharmacokinetics and Drug Metabolism
All pharmacological actions following gabapentin administration are due to the activity of the parent compound; gabapentin is not appreciably metabolized in humans.

Oral Bioavailability: Gabapentin bioavailability is not dose proportional; i.e., as dose is increased, bioavailability decreases. Bioavailability of gabapentin is approximately 60%, 47%, 34%, 33%, and 27% following 900, 1200, 2400, 3600, and 4800 mg/day given in 3 divided doses, respectively. Food has only a slight effect on the rate and extent of absorption of gabapentin (14% increase in AUC and C_{max}).

Distribution: Less than 3% of gabapentin circulates bound to plasma protein. The apparent volume of distribution of gabapentin after 150 mg intravenous administration is 58 ± 6 L (Mean ± SD). In patients with epilepsy, steady-state predose (C_{min}) concentrations of gabapentin in cerebrospinal fluid were approximately 20% of the corresponding plasma concentrations.

Elimination: Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug. Gabapentin is not appreciably metabolized in humans.

Gabapentin elimination half-life is 5 to 7 hours and is unaltered by dose or following multiple dosing. Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance (see **Special Populations:** *Adult Patients With Renal Insufficiency*, below). In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin can be removed from plasma by hemodialysis.

Dosage adjustment in patients with compromised renal function or undergoing hemodialysis is recommended (see **DOSAGE AND ADMINISTRATION**, Table 3).

Special Populations: *Adult Patients With Renal Insufficiency:* Subjects (N = 60) with renal insufficiency (mean creatinine clearance ranging from 13-114 mL/min) were administered single 400 mg oral doses of gabapentin. The mean gabapentin half-life ranged from about 6.5 hours (patients with creatinine clearance >60 mL/min) to 52 hours (creatinine clearance <30 mL/min) and gabapentin renal clearance from about 90 mL/min (>60 mL/min group) to about 10 mL/min (<30 mL/min). Mean plasma clearance (CL/F) decreased from approximately 190 mL/min to 20 mL/min.

Dosage adjustment in adult patients with compromised renal function is necessary (see **DOSAGE AND ADMINISTRATION**). Pediatric patients with renal insufficiency have not been studied.

Hemodialysis: In a study in anuric adult subjects (N = 11), the apparent elimination half-life of gabapentin on nondialysis days was about 132 hours; during dialysis the apparent half-life of gabapentin was reduced to 3.8 hours. Hemodialysis thus has a significant effect on gabapentin elimination in anuric subjects.

Dosage adjustment in patients undergoing hemodialysis is necessary (see **DOSAGE AND ADMINISTRATION**).

Hepatic Disease: Because gabapentin is not metabolized, no study was performed in patients with hepatic impairment.

Age: The effect of age was studied in subjects 20-80 years of age. Apparent oral clearance (CL/F) of gabapentin decreased as age increased, from about 225 mL/min in those under 30 years of age to about 125 mL/min in those over 70 years of age. Renal clearance (CLr) and CLr adjusted for body surface area also declined with age; however, the decline in the renal clearance of gabapentin with age can largely be explained by the decline in renal function. Reduction of gabapentin dose may be required in patients who have age related compromised renal function (see **PRECAUTIONS, Geriatric Use**, and **DOSAGE AND ADMINISTRATION**).

Pediatric: Gabapentin pharmacokinetics were determined in 48 pediatric subjects between the ages of 1 month and 12 years following a dose of approximately 10 mg/kg. Peak plasma concentrations were similar across the entire age group and occurred 2 to 3 hours postdose. In general, pediatric subjects between 1 month and <5 years of age achieved approximately 30% lower exposure (AUC) than that observed in those 5 years of age and older. Accordingly, oral clearance normalized per body weight was higher in the younger children. Apparent oral clearance of gabapentin was directly proportional to creatinine clearance. Gabapentin elimination half-life averaged 4.7 hours and was similar across the age groups studied.

A population pharmacokinetic analysis was performed in 253 pediatric subjects between 1 month and 13 years of age. Patients received 10 to 65 mg/kg/day give T.I.D. Apparent oral clearance (CL/F) was directly proportional to creatinine clearance and this relationship was similar following a single dose and at steady state. Higher oral clearance values were observed in children <5 years of age compared to those observed in children 5 years of age and older, when normalized per body weight. The clearance was highly variable in infants <1 year of age. The normalized CL/F values observed in pediatric patients 5 years of age and older were consistent with values observed in adults after a single dose. The oral volume of distribution normalized per body weight was constant across the age range.

These pharmacokinetic data indicate that the effective daily dose in pediatric patients with epilepsy ages 3 and 4 years should be 40 mg/kg/day to achieve average plasma concentrations similar to those achieved in patients 5 years of age and older receiving gabapentin at 30 mg/kg/day. (See **DOSAGE AND ADMINISTRATION.**)

Gender: Although no formal study has been conducted to compare the pharmacokinetics of gabapentin in men and women, it appears that the pharmacokinetic parameters for males and females are similar and there are no significant gender differences.

Race: Pharmacokinetic differences due to race have not been studied. Because gabapentin is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

Clinical Studies

Epilepsy
The effectiveness of gabapentin as adjunctive therapy (added to other antiepileptic drugs) was established in multicenter placebo-controlled, double-blind, parallel-group clinical trials in adult and pediatric patients (3 years and older) with refractory partial seizures.

Gabapentin did not demonstrate mutagenic or genotoxic potential in tests *in vitro* and four *in vivo* assays. It was negative in the Ames test and the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay; it was negative in the *in vivo* chromosomal aberration assay and in the *in vivo* micronucleus test in Chinese hamster bone marrow; it was negative in the *in vivo* mouse micronucleus assay; and it did not include unscheduled DNA synthesis in hepatocytes from rats given gabapentin.

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately 5 times the maximum recommended human dose on a mg/m^2 basis).

Pregnancy
Pregnancy Category C: Gabapentin has been shown to be fetotoxic in rodents, causing delayed ossification of several bones in the skull, vertebrae, forelimbs, and hindlimbs. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during the period of organogenesis, or approximately 1 to 4 times the maximum dose of 3600 mg/day given to epileptic patients on a mg/m^2 basis. The no-effect level was 500 mg/kg/day or approximately 1/2 of the human dose on a mg/m^2 basis.

When rats were dosed prior to and during mating, and throughout gestation, pups from all dose groups (500, 1000 and 2000 mg/kg/day) were affected. These doses are equivalent to less than approximately 1 to 5 times the maximum human dose on a mg/m^2 basis. There was an increased incidence of hydroureter and/or hydronephrosis in rats in a study of fertility and general reproductive performance at 2000 mg/kg/day with no effect at 1000 mg/kg/day, in a teratology study at 1500 mg/kg/day with no effect at 300 mg/kg/day, and in a perinatal and postnatal study at all doses studied (500, 1000 and 2000 mg/kg/day). The doses at which the effects occurred are approximately 1 to 5 times the maximum human dose of 3600 mg/day on a mg/m^2 basis; the no-effect doses were approximately 3 times (Fertility and General Reproductive Performance study) and approximately equal to (Teratogenicity study) the maximum human dose on a mg/m^2 basis. Other than hydroureter and hydronephrosis, the etiologies of which are unclear, the incidence of malformations was not increased compared to controls in offspring of mice, rats, or rabbits given doses up to 50 times (mice), 30 times (rats), and 25 times (rabbits) the human daily dose on a mg/kg basis, or 4 times (mice), 5 times (rats), or 8 times (rabbits) the human daily dose on a mg/m^2 basis.

In a teratology study in rabbits, an increased incidence of postimplantation fetal loss occurred in dams exposed to 60, 300 and 1500 mg/kg/day, or less than approximately 1/4 to 8 times the maximum human dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Nursing Mothers
Gabapentin is secreted into human milk following oral administration. A nursed infant could be exposed to a maximum dose of approximately 1 mg/kg/day of gabapentin. Because the effect on the nursing infant is unknown, gabapentin should be used in women who are nursing only if the benefits clearly outweigh the risks.

Pediatric Use
Effectiveness as adjunctive therapy in the treatment of partial seizures in pediatric patients below the age of 3 years has not been established (see **CLINICAL PHARMACOLOGY, Clinical Studies**).

Geriatric Use
Clinical studies of gabapentin in epilepsy did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions 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 dose should be adjusted based on creatinine clearance values in these patients (see **CLINICAL PHARMACOLOGY, ADVERSE REACTIONS,** and **DOSAGE AND ADMINISTRATION** sections).

ADVERSE REACTIONS

Epilepsy
The most commonly observed adverse events associated with the use of gabapentin in combination with other antiepileptic drugs in patients >12 years of age, not seen at an equivalent frequency among placebo-treated patients, were somnolence, dizziness, ataxia, fatigue, and nystagmus. The most commonly observed adverse events reported with the use of gabapentin in combination with other antiepileptic drugs in pediatric patients 3 to 12 years of age, not seen at an equal frequency among placebo-treated patients, were viral infection, fever, nausea and/or vomiting, somnolence, and hostility (see **WARNINGS, Neuropsychiatric Adverse Events**).

Approximately 7% of the 2074 patients >12 years of age and approximately 7% of the 449 pediatric patients 3 to 12 years of age who received gabapentin in premarketing clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal in patients >12 years of age were somnolence (1.2%), ataxia (0.8%), fatigue (0.6%), nausea and/or vomiting (0.6%), and dizziness (0.6%). The adverse events most commonly associated with withdrawal in pediatric patients were emotional lability (1.6%), hostility (1.3%), and hyperkinesia (1.1%).

Incidence in Controlled Clinical Trials
Table 1 lists treatment-emergent signs and symptoms that occurred in at least 1% of gabapentin-treated patients >12 years of age with epilepsy participating in placebo-controlled trials and were numerically more common in the gabapentin group. In these studies, either gabapentin or placebo was added to the patient's current antiepileptic drug therapy. Adverse events were usually mild to moderate in intensity.

The prescriber should be aware that these figures, obtained when gabapentin was added to concurrent antiepileptic drug therapy, cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescribing physician with one basis to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

TABLE 1. Treatment - Emergent Adverse Event Incidence in Controlled Add-On Trials in Patients >12 years of age (Events in at Least 1% of Gabapentin Patients and Numerically More Frequent Than in the Placebo Group)

Body System/ Adverse Event	Gabapentin[a] N = 543 %	Placebo[a] N = 378 %
Body As A Whole		
Fatigue	11.0	5.0
Weight Increase	2.9	1.6
Back Pain	1.8	0.5
Peripheral Edema	1.7	0.5
Cardiovascular		
Vasodilatation	1.1	0.3
Digestive System		
Dyspepsia	2.2	0.5
Mouth or Throat Dry	1.7	0.5
Constipation	1.5	0.8
Dental Abnormalities	1.5	0.3
Increased Appetite	1.1	0.8
Hematologic and Lymphatic Systems		
Leukopenia	1.1	0.5
Musculoskeletal System		
Myalgia	2.0	1.9
Fracture	1.1	0.8
Nervous System		
Somnolence	19.3	8.7
Dizziness	17.1	6.9
Ataxia	12.5	5.6
Nystagmus	8.3	4.0
Tremor	6.8	3.2
Nervousness	2.4	1.9
Dysarthria	2.4	0.5
Amnesia	2.2	0.0
Depression	1.8	1.1
Thinking Abnormal	1.7	1.3
Twitching	1.3	0.5
Coordination Abnormal	1.1	0.3
Respiratory System		
Rhinitis	4.1	3.7
Pharyngitis	2.8	1.6
Coughing	1.8	1.3

pharmacokinetics of gabapentin in men and women, it appears that the pharmacokinetic parameters for males and females are similar and there are no significant gender differences.

Race: Pharmacokinetic differences due to race have not been studied. Because gabapentin is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

Clinical Studies

Epilepsy
The effectiveness of gabapentin as adjunctive therapy (added to other antiepileptic drugs) was established in multicenter placebo-controlled, double-blind, parallel-group clinical trials in adult and pediatric patients (3 years and older) with refractory partial seizures.

Evidence of the effectiveness was obtained in three trials conducted in 705 patients (age 12 years and above) and one trial conducted in 247 pediatric patients (3 to 12 years of age). The patients enrolled had a history of at least 4 partial seizures per month in spite of receiving one or more antiepileptic drugs at therapeutic levels and were observed on their established antiepileptic drug regimen during a 12-week baseline period (6 weeks in the study of pediatric patients). In patients continuing to have at least 2 (or 4 in some studies) seizures per month, gabapentin or placebo was then added on to the existing therapy during a 12-week treatment period. Effectiveness was assessed primarily on the basis of the percent of patients with a 50% or greater reduction in seizure frequency from baseline to treatment (the "responder rate") and a derived measure called response ratio, a measure of change defined as (T - B)/(T + B), where B is the patient's baseline seizure frequency and T is the patient's seizure frequency during treatment. Response ratio is distributed within the range -1 to +1. A zero value indicates no change while complete elimination of seizures would give a value of -1; increased seizure rates would give positive values. A response ratio of -0.33 corresponds to a 50% reduction in seizure frequency. The results given below are for all partial seizures in the intent-to-treat (all patients who received any doses of treatment) population in each study, unless otherwise indicated.

One study compared gabapentin 1200 mg/day divided T.I.D. with placebo. Responder rate was 23% (14/61) in the gabapentin group and 9% (6/66) in the placebo group; the difference between groups was statistically significant. Response ratio was also better in the gabapentin group (-0.199) than in the placebo group (-0.044), a difference that also achieved statistical significance.

A second study compared primarily 1200 mg/day divided T.I.D. gabapentin (N = 101) with placebo (N = 98). Additional smaller gabapentin dosage groups (600 mg/day, N = 53; 1800 mg/day, N = 54) were also studied for information regarding dose response. Responder rate was higher in the gabapentin 1200 mg/day group (16%) than in the placebo group (8%), but the difference was not statistically significant. The responder rate at 600 mg (17%) was also not significantly higher than in the placebo, but the responder rate in the 1800 mg group (26%) was statistically significantly superior to the placebo rate. Response ratio was better in the gabapentin 1200 mg/day group (-0.103) than in the placebo group (-0.022); but this difference was also not statistically significant (p = 0.224). A better response was seen in the gabapentin 600 mg/day group (-0.105) and 1800 mg/day group (-0.222) than in the 1200 mg/day group, with the 1800 mg/day group achieving statistical significance compared to the placebo group.

A third study compared gabapentin 900 mg/day divided T.I.D. (N = 111) and placebo (N = 109). An additional gabapentin 1200 mg/day dosage group (N = 52) provided dose-response data. A statistically significant difference in responder rate was seen in the gabapentin 900 mg/day group (22%) compared to that in the placebo group (10%). Response ratio was also statistically significantly superior in the gabapentin 900 mg/day group (-0.119) compared to that in the placebo group (-0.027), as was response ratio in 1200 mg/day gabapentin (-0.184) compared to placebo.

Analyses were also performed in each study to examine the effect of gabapentin on preventing secondarily generalized tonic-clonic seizures. Patients who experienced a secondarily generalized tonic-clonic seizure in either the baseline or in the treatment period in all three placebo-controlled studies were included in these analyses. There were several response ratio comparisons that showed a statistically significant advantage for gabapentin compared to placebo and favorable trends for almost all comparisons.

Analysis of responder rate using combined data from all three studies and all doses (N = 192, gabapentin; N = 89, placebo) also showed a significant advantage for gabapentin over placebo in reducing the frequency of secondarily generalized tonic-clonic seizures.

In two of the three controlled studies, more than one dose of gabapentin was used. Within each study the results did not show a consistently increased response to dose. However, looking across studies, a trend toward increasing efficacy with increasing dose is evident (see Figure 1).

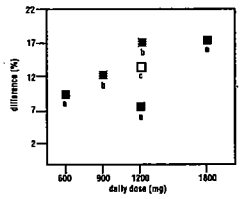


FIGURE 1. Responder Rate in Patients Receiving Gabapentin Expressed as a Difference From Placebo by Dose and Study: Adjunctive Therapy Studies in Patients ≥12 Years of Age With Partial Seizures.

In the figure, treatment effect magnitude, measured on the Y axis in terms of the difference in the proportion of gabapentin and placebo assigned patients attaining a 50% or greater reduction in seizure frequency from baseline, is plotted against the daily dose of gabapentin administered (X axis).

Although no formal analysis by gender has been performed, estimates of response (Response Ratio) derived from clinical trials (398 men, 307 women) indicate no important gender differences exist. There was no consistent pattern indicating that age had any effect on the response to gabapentin. There were insufficient numbers of patients of races other than Caucasian to permit a comparison of efficacy among racial groups.

A fourth study in pediatric patients age 3 to 12 years compared 25-35 mg/kg/day gabapentin (N=118) with placebo (N=127). For all partial seizures in the intent-to-treat population, the response ratio was statistically significantly better for the gabapentin group (-0.146) than for the placebo group (-0.079). For the same population, the responder rate for gabapentin (21%) was not significantly different from placebo (18%).

A study in pediatric patients age 1 month to 3 years compared 40 mg/kg/day gabapentin (N=38) with placebo (N=38) in patients who were receiving at least one marketed antiepileptic drug and had at least one partial seizure during the screening period (within 2 weeks prior to baseline). Patients had up to 48 hours of baseline and up to 72 hours of double-blind video EEG monitoring to record and count the occurrence of seizures. There were no statistically significant differences between treatments in either the response ratio or responder rate.

INDICATIONS AND USAGE

Epilepsy
Gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy. Gabapentin is also indicated as adjunctive therapy in the treatment of partial seizures in pediatric patients age 3-12 years.

CONTRAINDICATIONS

Gabapentin is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS

Neuropsychiatric Adverse Events - Pediatric Patients 3-12 years of age
Gabapentin use in pediatric patients with epilepsy 3-12 years of age is associated with the occurrence of central nervous system related adverse events. The most significant of these can be classified into the following categories: 1) emotional lability (primarily behavioral problems), 2) hostility, including aggressive behaviors, 3) thought disorder, including concentration problems and change in school performance, and 4) hyperkinesia (primarily restlessness and hyperactivity). Among the gabapentin-treated patients, most of the events were mild to moderate in intensity.

In controlled trials in pediatric patients 3-12 years of age, the incidence of these adverse events was: emotional lability 6% (gabapentin-treated patients) vs 1.3% (placebo-treated patients); hostility 5.2% vs 1.3%; hyperkinesia 4.7% vs 2.9%; and thought disorder 1.7% vs 0%. One of these events, a report of hostility, was considered serious. Discontinuation of gabapentin treatment occurred in 1.3% of patients reporting emotional lability and hyperkinesia and 0.9% of gabapentin-treated patients reporting hostility and thought disorder. One placebo-treated patient (0.4%) withdrew due to emotional lability.

Tremor	6.8	3.2
Nervousness	2.4	1.9
Dysarthria	2.4	0.5
Amnesia	2.2	0.0
Depression	1.8	1.1
Thinking Abnormal	1.7	1.3
Twitching	1.3	0.5
Coordination Abnormal	1.1	0.3
Respiratory System		
Rhinitis	4.1	3.7
Pharyngitis	2.8	1.6
Coughing	1.8	1.3
Skin and Appendages		
Abrasion	1.3	0.0
Pruritus	1.3	0.5
Urogenital System		
Impotence	1.5	1.1
Special Senses		
Diplopia	5.9	1.9
Amblyopia[b]	4.2	1.1
Laboratory Deviations		
WBC Decreased	1.1	0.5

[a]Plus background antiepileptic drug therapy
[b]Amblyopia was often described as blurred vision.

Other events in more than 1% of patients >12 years of age but equally or more frequent in the placebo group included: headache, viral infection, fever, nausea and/or vomiting, abdominal pain, diarrhea, convulsions, confusion, insomnia, emotional lability, rash, acne.

Among the treatment-emergent adverse events occurring at an incidence of at least 10% of gabapentin-treated patients, somnolence and ataxia appeared to exhibit a positive dose-response relationship.

The overall incidence of adverse events and the types of adverse events seen were similar among men and women treated with gabapentin. The incidence of adverse events increased slightly with increasing age in patients treated with either gabapentin or placebo. Because only 3% of patients (28/921) in placebo-controlled studies were identified as nonwhite (black or other), there are insufficient data to support a statement regarding the distribution of adverse events by race.

Table 2 lists treatment-emergent signs and symptoms that occurred in at least 2% of gabapentin-treated patients age 3 to 12 years of age with epilepsy participating in placebo-controlled trials and were numerically more common in the gabapentin group. Adverse events were usually mild to moderate in intensity.

TABLE 2. Treatment-Emergent Adverse Event Incidence in Pediatric Patients Age 3 to 12 Years in a Controlled Add-On Trial (Events in at Least 2% of Gabapentin Patients and Numerically More Frequent Than in the Placebo Group)

Body System/ Adverse Event	Gabapentin[a] N=119 %	Placebo[a] N=128 %
Body As A Whole		
Viral Infection	10.9	3.1
Fever	10.1	3.1
Weight Increase	3.4	0.8
Fatigue	3.4	1.6
Digestive System		
Nausea and/or Vomiting	8.4	7.0
Nervous System		
Somnolence	8.4	4.7
Hostility	7.6	2.3
Emotional Lability	4.2	1.6
Dizziness	2.5	1.6
Hyperkinesia	2.5	0.8
Respiratory System		
Bronchitis	3.4	0.8
Respiratory Infection	2.5	0.8

[a] Plus background antiepileptic drug therapy

Other events in more than 2% of pediatric patients 3 to 12 years of age but equally or more frequent in the placebo group included: pharyngitis, upper respiratory infection, headache, rhinitis, convulsions, diarrhea, anorexia, coughing, and otitis media.

Other Adverse Events Observed During All Clinical Trials

Clinical Trials in Adults and Adolescents (Except Clinical Trials in Neuropathic Pain)
Gabapentin has been administered to 2074 patients >12 years of age during all adjunctive therapy clinical trials (except clinical trials in patients with neuropathic pain), only some of which were placebo-controlled. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. These categories are used in the listing below. The frequencies presented represent the proportion of the 2074 patients >12 years of age exposed to gabapentin who experienced an event of the type cited on at least one occasion while receiving gabapentin. All reported events are included except those already listed in Table 1, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body As A Whole: *Frequent :* asthenia, malaise, face edema; *Infrequent :* allergy, generalized edema, weight decrease, chill; *Rare :* strange feelings, lassitude, alcohol intolerance, hangover effect.

Cardiovascular System: *Frequent :* hypertension; *Infrequent :* hypotension, angina pectoris, peripheral vascular disorder, palpitation, tachycardia, migraine, murmur; *Rare :* atrial fibrillation, heart failure, thrombophlebitis, deep thrombophlebitis, myocardial infarction, cerebrovascular accident, pulmonary thrombosis, ventricular extrasystoles, bradycardia, premature atrial contraction, pericardial rub, heart block, pulmonary embolus, hyperlipidemia, hypercholesterolemia, pericardial effusion, pericarditis.

Digestive System: *Frequent :* anorexia, flatulence, gingivitis; *Infrequent :* glossitis, gum hemorrhage, thirst, stomatitis, increased salivation, gastroenteritis, hemorrhoids, bloody stools, fecal incontinence, hepatomegaly; *Rare :* dysphagia, eructation, pancreatitis, peptic ulcer, colitis, blisters in mouth, tooth discolor, perfeche, salivary gland enlarged, lip hemorrhage, esophagitis, hiatal hernia, hematemesis, proctitis, irritable bowel syndrome, rectal hemorrhage, esophageal spasm.

Endocrine System: *Rare :* hyperthyroid, hypothyroid, goiter, hypoestrogen, ovarian failure, epididymitis, swollen testicle, cushingoid appearance.

Hematologic and Lymphatic System: *Frequent :* purpura most often described as bruises resulting from physical trauma; *Infrequent :* anemia, thrombocytopenia, lymphadenopathy; *Rare :* WBC count increased, lymphocytosis, non-Hodgkin's lymphoma, bleeding time increased.

Musculoskeletal System: *Frequent :* arthralgia; *Infrequent :* tendinitis, arthritis, joint stiffness, joint swelling, positive Romberg test; *Rare :* costochondritis, osteoporosis, bursitis, contracture.

Nervous System: *Frequent :* vertigo, hyperkinesia, paresthesia, decreased or absent reflexes, increased reflexes, anxiety, hostility; *Infrequent :* CNS tumors, syncope, dreaming abnormal, aphasia, hypesthesia, intracranial hemorrhage, hypotonia, dysesthesia, paresis, dystonia, hemiplegia, facial paralysis, stupor, cerebellar dysfunction, positive Babinski sign, decreased position sense, subdural hematoma, apathy, hallucination, decrease or loss of libido, agitation, paranoia, depersonalization, euphoria, feeling high, doped-up sensation, suicidal, psychosis; *Rare :* choreoathetosis, orofacial dyskinesia, encephalopathy, nerve palsy, personality disorder, increased libido, subdued temperament, aprazia, fine motor control disorder, meningismus, local myoclonus, hyperesthesia, hypokinesia, mania, neurosis, hysteria, antisocial reaction, suicide gesture.

Respiratory System: *Frequent :* pneumonia; *Infrequent :* epistaxis, dyspnea, apnea; *Rare :* mucositis, aspiration pneumonia, hyperventilation, hiccup, laryngitis, nasal obstruction, snoring, bronchospasm, hypoventilation, lung edema.

Dermatological: *Infrequent :* alopecia, eczema, dry skin, increased sweating, urticaria, hirsutism, seborrhea, cyst, herpes simplex; *Rare :* herpes zoster, skin discolor, skin papules, photosensitive reaction, leg ulcer, scalp seborrhea, psoriasis, desquamation, maceration, skin nodules, subcutaneous nodule, melanosis, skin necrosis, local swelling.

Urogenital System: *Infrequent :* hematuria, dysuria, urination frequency, cystitis, urinary retention, urinary incontinence, vaginal hemorrhage, amenorrhea,

agonism of brain cells of children with the identifying categories: 1) emotional lability (primarily behavioral problems), 2) hostility, including aggressive behaviors, 3) thought disorder, including concentration problems and change in school performance, and 4) hyperkinesia (primarily restlessness and hyperactivity). Among the gabapentin-treated patients, most of the events were mild to moderate in intensity.

In controlled trials in pediatric patients 3-12 years of age, the incidence of these adverse events was: emotional lability 6% (gabapentin-treated patients) vs 1.3% (placebo-treated patients); hostility 5.2% vs 1.3%; hyperkinesia 4.7% vs 2.9%; and thought disorder 1.7% vs 0%. One of these events, a report of hostility, was considered serious. Discontinuation of gabapentin treatment occurred in 1.3% of patients reporting emotional lability and hyperkinesia and 0.9% of gabapentin-treated patients reporting hostility and thought disorder. One placebo-treated patient (0.4%) withdrew due to emotional lability.

Withdrawal Precipitated Seizure, Status Epilepticus
Antiepileptic drugs should not be abruptly discontinued because of the possibility of increasing seizure frequency.

In the placebo-controlled studies in patients >12 years of age, the incidence of status epilepticus in patients receiving gabapentin was 0.6% (3 of 543) versus 0.5% in patients receiving placebo (2 of 378). Among the 2074 patients >12 years of age treated with gabapentin across all studies (controlled and uncontrolled) 31 (1.5%) had status epilepticus. Of these, 14 patients had no prior history of status epilepticus either before treatment or while on other medications. Because adequate historical data are not available, it is impossible to say whether or not treatment with gabapentin is associated with a higher or lower rate of status epilepticus than would be expected to occur in a similar population not treated with gabapentin.

Tumorigenic Potential
In standard preclinical *in vivo* lifetime carcinogenicity studies, an unexpectedly high incidence of pancreatic acinar adenocarcinomas was identified in male, but not female, rats (see **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility**). The clinical significance of this finding is unknown. Clinical experience during gabapentin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies in adjunctive therapy in epilepsy comprising 2085 patient-years of exposure in patients >12 years of age, new tumors were reported in 10 patients (2 breast, 3 brain, 2 lung, 1 adrenal, 1 non-Hodgkin's lymphoma, 1 endometrial carcinoma *in situ*), and pre-existing tumors worsened in 11 patients (9 brain, 1 breast, 1 prostate) during or up to 2 years following discontinuation of gabapentin. Without knowledge of the background incidence and recurrence in a similar population not treated with gabapentin, it is impossible to know whether the incidence seen in this cohort is or is not affected by treatment.

Sudden and Unexplained Death in Patients With Epilepsy
During the course of premarketing development of gabapentin 8 sudden and unexplained deaths were recorded among a cohort of 2203 patients treated (2103 patient-years of exposure).

Some of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. This represents an incidence of 0.0038 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving gabapentin (ranging from 0.0005 for the general population of epileptics to 0.003 for a clinical trial population similar to that in the gabapentin program, to 0.005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or raise further concern depends on comparability of the populations reported upon to the gabapentin cohort and the accuracy of the estimates provided.

PRECAUTIONS

Information for Patients
Patients should be instructed to take gabapentin only as prescribed.

Patients should be advised that gabapentin may cause dizziness, somnolence and other symptoms and signs of CNS depression. Accordingly, they should be advised neither to drive a car nor to operate other complex machinery until they have gained sufficient experience on gabapentin to gauge whether or not it affects their mental and/or motor performance adversely.

Patients who require concomitant treatment with morphine may experience increases in gabapentin concentrations. Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately (see **Drug Interactions**).

Laboratory Tests
Clinical trials data do not indicate that routine monitoring of clinical laboratory parameters is necessary for the safe use of gabapentin. The value of monitoring gabapentin blood concentrations has not been established. Gabapentin may be used in combination with other antiepileptic drugs without concern for alteration of the blood concentrations of gabapentin or of other antiepileptic drugs.

Drug Interactions
In vitro studies were conducted to investigate the potential of gabapentin to inhibit the major cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) that mediate drug and xenobiotic metabolism using isoform selective marker substrates and human liver microsomal preparations. Only at the highest concentration tested (171 mcg/mL; 1 mM) was a slight degree of inhibition (14%-30%) of isoform CYP2A6 observed. No inhibition of any of the other isoforms tested was observed at gabapentin concentrations up to 171 mcg/mL (approximately 15 times the C_{max} at 3600 mg/day).

Gabapentin is not appreciably metabolized nor does it interfere with the metabolism of commonly coadministered antiepileptic drugs.

The drug interaction data described in this section were obtained from studies involving healthy adults and adult patients with epilepsy.

Phenytoin: In a single (400 mg) and multiple dose (400 mg T.I.D.) study of gabapentin in epileptic patients (N = 8) maintained on phenytoin monotherapy for at least 2 months, gabapentin had no effect on the steady-state trough plasma concentrations of phenytoin and phenytoin had no effect on gabapentin pharmacokinetics.

Carbamazepine: Steady-state trough plasma carbamazepine and carbamazepine 10, 11 epoxide concentrations were not affected by concomitant gabapentin (400 mg T.I.D.; N = 12) administration. Likewise, gabapentin pharmacokinetics were unaltered by carbamazepine administration.

Valproic Acid: The mean steady-state trough serum valproic acid concentrations prior to and during concomitant gabapentin administration (400 mg T.I.D.; N = 17) were not different and neither were gabapentin pharmacokinetic parameters affected by valproic acid.

Phenobarbital: Estimates of steady-state pharmacokinetic parameters for phenobarbital or gabapentin (300 mg T.I.D.; N = 12) are identical whether the drugs are administered alone or together.

Naproxen: Coadministration (N = 18) of naproxen sodium capsules (250 mg) with gabapentin (125 mg) appears to increase the amount of gabapentin absorbed by 12% to 15%. Gabapentin had no effect on naproxen pharmacokinetic parameters. These doses are lower than the therapeutic doses for both drugs. The magnitude of interaction within the recommended dose ranges of either drug is not known.

Hydrocodone: Coadministration of gabapentin (125 to 500 mg; N = 48) decreases hydrocodone (10 mg; N = 50) C_{max} and AUC values in a dose-dependent manner relative to administration of hydrocodone alone; C_{max} and AUC values are 3% to 4% lower, respectively, after administration of 125 mg gabapentin and 21% to 22% lower, respectively, after administration of 500 mg gabapentin. The mechanism for this interaction is unknown. Hydrocodone increases gabapentin AUC values by 14%. The magnitude of interaction at other doses is not known.

Morphine: A literature article reported that when a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule (N = 12), mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine (see **PRECAUTIONS**). Morphine pharmacokinetic parameter values were not affected by administration of gabapentin 2 hours after morphine. The magnitude of interaction at other doses is not known.

Cimetidine: In the presence of cimetidine at 300 mg Q.I.D. (N = 12) the mean apparent oral clearance of gabapentin fell by 14% and creatinine clearance fell by 10%. Thus cimetidine appeared to alter the renal excretion of both gabapentin and creatinine, an endogenous marker of renal function. This small decrease in excretion of gabapentin by cimetidine is not expected to be of clinical importance. The effect of gabapentin on cimetidine was not evaluated.

Oral Contraceptive: Based on AUC and half-life, multiple-dose pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of tablets containing 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol were similar with and without coadministration of gabapentin (400 mg T.I.D.; N = 13). The C_{max} of norethindrone was 13% higher when it was coadministered with gabapentin; this interaction is not expected to be of clinical importance.

Antacid (Maalox®): Maalox® reduced the bioavailability of gabapentin (N = 16) by about 20%. This decrease in bioavailability was about 5% when gabapentin was administered 2 hours after Maalox®. It is recommended that gabapentin be taken at least 2 hours following Maalox® administration.

Effect of Probenecid: Probenecid is a blocker of renal tubular secretion. Gabapentin pharmacokinetic parameters without and with probenecid were comparable. This indicates that gabapentin does not undergo renal tubular

motor control disorder, meningismus, focal myoclonus, hyperesthesia, hypokinesia, mania, neurosis, hysteria, antisocial reaction, suicide gesture.

Respiratory System: *Frequent :* pneumonia; *Infrequent :* epistaxis, dyspnea, apnea; *Rare :* mucositis, aspiration pneumonia, hyperventilation, hiccup, laryngitis, nasal obstruction, snoring, bronchospasm, hypoventilation, lung edema.

Dermatological: *Infrequent :* alopecia, eczema, dry skin, increased sweating, urticaria, hirsutism, seborrhea, cyst, herpes simplex; *Rare :* herpes zoster, skin discolor, skin papules, photosensitive reaction, leg ulcer, scalp seborrhea, psoriasis, desquamation, maceration, skin nodules, subcutaneous nodule, melanosis, skin necrosis, focal swelling.

Urogenital System: *Infrequent :* hematuria, dysuria, urination frequency, cystitis, urinary retention, urinary incontinence, vaginal hemorrhage, amenorrhea, dysmenorrhea, menorrhagia, breast cancer, unable to climax, ejaculation abnormal; *Rare :* kidney pain, leukorrhea, pruritus genital, renal stone, acute renal failure, anuria, glycosuria, nephrosis, nocturia, pyuria, urination urgency, vaginal pain, breast pain, testicle pain.

Special Senses: *Frequent :* abnormal vision; *Infrequent :* cataract, conjunctivitis, eyes dry, eye pain, visual field defect, photophobia, bilateral or unilateral ptosis, eye hemorrhage, hordeolum, hearing loss, earache, tinnitus, inner ear infection, otitis, taste loss, unusual taste, eye twitching, ear fullness; *Rare :* eye itching, abnormal accommodation, perforated ear drum, sensitivity to noise, eye focusing problem, watery eyes, retinopathy, glaucoma, iritis, corneal disorders, lacrimal dysfunction, degenerative eye changes, blindness, retinal degeneration, miosis, chororetinitis, strabismus, eustachian tube dysfunction, labyrinthitis, otitis externa, odd smell.

Clinical Trials in Pediatric Patients With Epilepsy
Adverse events occurring during epilepsy clinical trials in 449 pediatric patients 3 to 12 years of age treated with gabapentin that were not reported in adjunctive trials in adults are:

Body as a Whole: dehydration, infectious mononucleosis

Digestive System: hepatitis

Hemic and Lymphatic System: coagulation defect

Nervous System: aura disappeared, occipital neuralgia

Psychobiologic Function: sleepwalking

Respiratory System: pseudocroup, hoarseness

Postmarketing and Other Experience
In addition to the adverse experiences reported during clinical testing of gabapentin, the following adverse experiences have been reported in patients receiving marketed gabapentin. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: angioedema, blood glucose fluctuation, erythema multiforme, elevated liver function tests, fever, hyponatremia, jaundice, movement disorder such as dyskinesia, Stevens-Johnson syndrome.

Adverse events following the abrupt discontinuation of gabapentin have also been reported. The most frequently reported events were anxiety, insomnia, nausea, pain and sweating.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of gabapentin has not been evaluated in human studies.

OVERDOSAGE

A lethal dose of gabapentin was not identified in mice and rats receiving single oral doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, sedation, hypoactivity, or excitation.

Acute oral overdoses of gabapentin up to 49 grams have been reported. In these cases, double vision, slurred speech, drowsiness, lethargy and diarrhea were observed. All patients recovered with supportive care.

Gabapentin can be removed by hemodialysis. Although hemodialysis has not been performed in the few overdose cases reported, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

DOSAGE AND ADMINISTRATION

Gabapentin is given orally with or without food.

If gabapentin dose is reduced, discontinued or substituted with an alternative medication, this should be done gradually over a minimum of 1 week.

Epilepsy
Gabapentin is recommended for add-on therapy in patients 3 years of age and older. Effectiveness in pediatric patients below the age of 3 years has not been established.

Patients >12 years of age: The effective dose of gabapentin is 900 to 1800 mg/day and given in divided doses (three times a day) using 300 or 400 mg capsules. The starting dose is 300 mg three times a day. If necessary, the dose may be increased using 300 mg or 400 mg capsules three times a day up to 1800 mg/day. Dosages up to 2400 mg/day have been well tolerated in long-term clinical studies. Doses of 3600 mg/day have also been administered to a small number of patients for a relatively short duration, and have been well tolerated. The maximum time between doses in the T.I.D. schedule should not exceed 12 hours.

Pediatric Patients Age 3-12 years: The starting dose should range from 10-15 mg/kg/day in 3 divided doses, and the effective dose reached by upward titration over a period of approximately 3 days. The effective dose of gabapentin in patients 5 years of age and older is 25-35 mg/kg/day and given in divided doses (three times a day). The effective dose in pediatric patients ages 3 and 4 years is 40 mg/kg/day and given in divided doses (three times a day) (See **CLINICAL PHARMACOLOGY, Pediatrics**). Dosages up to 50 mg/kg/day have been well tolerated in a long-term clinical study. The maximum time interval between doses should not exceed 12 hours.

It is not necessary to monitor gabapentin plasma concentrations to optimize gabapentin therapy. Further, because there are no significant pharmacokinetic interactions among gabapentin and other commonly used antiepileptic drugs, the addition of gabapentin does not alter the plasma levels of these drugs appreciably.

If gabapentin is discontinued and/or an alternate anticonvulsant medication is added to the therapy, this should be done gradually over a minimum of 1 week.

Dosage in Renal Impairment
Creatinine clearance is difficult to measure in outpatients. In patients with stable renal function, creatinine clearance (C_{Cr}) can be reasonably well estimated using the equation of Cockcroft and Gault:

for females: $C_{Cr} = (0.85)(140\text{-age})(\text{weight})/[(72)(S_{Cr})]$
for males: $C_{Cr} = (140\text{-age})(\text{weight})/[(72)(S_{Cr})]$

where age is in years, weight is in kilograms and S_{Cr} is serum creatinine in mg/dL.

Dosage adjustment in patients ≥12 years of age with compromised renal function or undergoing hemodialysis is recommended as follows (see dosing recommendations above for effective doses in each indication).

TABLE 3. Gabapentin Dosage Based on Renal Function

Renal Function Creatinine Clearance (mL/min)	Total Daily Dose Range (mg/day)	Dose Regimen (mg)				
≥60	900-3600	300 TID	400 TID	600 TID	800 TID	1200 TID
≥30-59	400-1400	200 BID	300 BID	400 BID	500 BID	700 BID
≥15-29	200-700	200 QD	300 QD	400 QD	500 QD	700 QD
<15[a]	100-300	100 QD	125 QD	150 QD	200 QD	300 QD
		Post-Hemodialysis Supplemental Dose (mg)[b]				
Hemodialysis		125[b]	150[b]	200[b]	250[b]	350[b]

[a]For patients with creatinine clearance <15 mL/min, reduce daily dose in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 mL/min should receive one-half the daily dose that patients with a creatinine clearance of 15 mL/min receive).

[b]Patients on hemodialysis should receive maintenance doses based on estimates of creatinine clearance as indicated in the upper portion of the table and a supplemental post-hemodialysis dose administered after each 4 hours of hemodialysis as indicated in the lower portion of the table.

The use of gabapentin in patients <12 years of age with compromised renal function has not been studied.

Dosage in Elderly
Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and dose should be adjusted based on creatinine clearance values in these patients.

HOW SUPPLIED

Gabapentin Capsules 100 mg are available for oral administration as hard gelatin capsules with a white opaque body and a white opaque cap. "APO 112" is imprinted on each capsule in black ink; supplied in bottles of 100 (NDC 60505-0112-1).

Gabapentin Capsules 300 mg are available for oral administration as hard gelatin capsules with a white opaque body and a yellow opaque cap. "APO 132" is imprinted on each capsule in black ink; supplied in bottles of 100 (NDC 60505-0113-1).

Gabapentin Capsules 400 mg are available for oral administration as hard gelatin capsules with a white opaque body and an orange opaque cap. "APO 114" is imprinted on each capsule in black ink; supplied in bottles of 100 (NDC 60505-0114-1).

Storage

The effect of gabapentin on cimetidine was not evaluated.

Oral Contraceptive: Based on AUC and half-life, multiple-dose pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of tablets containing 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol were similar with and without coadministration of gabapentin (400 mg T.I.D.; N = 13). The C_{max} of norethindrone was 13% higher when it was coadministered with gabapentin; this interaction is not expected to be of clinical importance.

Antacid (Maalox®*): Maalox® reduced the bioavailability of gabapentin (N = 16) by about 20%. This decrease in bioavailability was about 5% when gabapentin was administered 2 hours after Maalox®. It is recommended that gabapentin be taken at least 2 hours following Maalox® administration.

Effect of Probenecid: Probenecid is a blocker of renal tubular secretion. Gabapentin pharmacokinetic parameters without and with probenecid were comparable. This indicates that gabapentin does not undergo renal tubular secretion by the pathway that is blocked by probenecid.

Drug/Laboratory Tests Interactions
Because false positive readings were reported with the Ames N-Multistix SG® dipstick test for urinary protein when gabapentin was added to other antiepileptic drugs, the more specific sulfosalicylic acid precipitation procedure is recommended to determine the presence of urine protein.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for 2 years. A statistically significant increase in the incidence of pancreatic acinar cell adenomas and carcinomas was found in male rats receiving the high dose; the no-effect dose for the occurrence of carcinomas was 1000 mg/kg/day. Peak plasma concentrations of gabapentin in rats receiving the high dose of 2000 mg/kg were 10 times higher than plasma

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Gabapentin Capsules 300 mg are available for oral administration as hard gelatin capsules with a white opaque body and a yellow opaque cap. "APO 113" is imprinted on each capsule in black ink; supplied in bottles of 100 (NDC 60505-0113-1).

Gabapentin Capsules 400 mg are available for oral administration as hard gelatin capsules with a white opaque body and an orange opaque cap. "APO 114" is imprinted on each capsule in black ink; supplied in bottles of 100 (NDC 60505-0114-1).

Storage

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant container [see USP].

*Maalox® is a registered trademark of Novartis Consumer Health, Inc.

APOTEX INC.
GABAPENTIN CAPSULES 100 mg, 300 mg and 400 mg

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, Florida
33326

(GAB/C-R03-51X138MM-LFLT-090104)

Revised: December 2004

Rev. 1

Each capsule contains 400 mg gabapentin.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Dispense in a tight, light-resistant container [see USP].

Usual Dosage: See package insert.

214313

APOTEX CORP.

Gabapentin Capsules

400 mg

100 Capsules

℞ Only

NDC 60505-0114-1

Manufactured by:
Apotex Inc.
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Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, Florida 33326

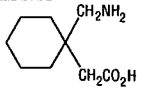
NDC 60505-0114-1 4

GABAPENTIN CAPSULES
100 mg, 300 mg and 400 mg

℞ only

DESCRIPTION

Gabapentin is described as 1-(aminomethyl) cyclohexaneacetic acid with a molecular formula of $C_9H_{17}NO_2$ and a molecular weight of 171.24. Gabapentin is a white to off-white crystalline solid with a pK_{a1} of 3.7 and a pK_{a2} of 10.7. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is -1.25. It has the following structural formula:



Each capsule for oral administration contains 100 mg, 300 mg, and 400 mg of gabapentin. In addition, each capsule contains the following inactive ingredients: croscarmellose sodium and magnesium stearate. The 100 mg, 300 mg and 400 mg capsule imprinting ink black SW-9008/SW-9009 contains the following inactive ingredients: ammonium hydroxide; black iron oxide, bacteria controlled

NON PRINTING AREA (GLUE PANEL)

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Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, Florida 33326

60505-0114-1 4

NDC 60505-0114-1

Gabapentin Capsules

400 mg

100 Capsules

℞ Only

APOTEX CORP.

Each capsule contains 400 mg gabapentin.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Dispense in a tight, light-resistant container [see USP].

Usual Dosage: See package insert.

214313

concentrations in humans receiving 3600 mg/day, and in rats receiving 1000 mg/kg/day peak plasma concentrations were 6.5 times higher than in humans receiving 3600 mg/day. The pancreatic acinar cell carcinomas did not affect survival, did not metastasize and were not locally invasive. The relevance of this finding to carcinogenic risk in humans is unclear.

Studies designed to investigate the mechanism of gabapentin-induced pancreatic carcinogenesis in rats indicate that gabapentin stimulates DNA synthesis in rat pancreatic acinar cells *in vitro* and, thus, may be acting as a tumor promoter by enhancing mitogenic activity. It is not known whether gabapentin has the ability to increase cell proliferation in other cell types or in other species, including humans.

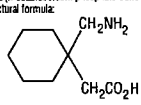
Gabapentin did not demonstrate mutagenic or genotoxic potential in three *in vitro* and four *in vivo* assays. It was negative in the Ames test and the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay; it was negative in the *in vivo* chromosomal aberration assay and in the *in vivo* micronucleus test in Chinese hamster bone marrow; it was negative in the *in vivo* mouse micronucleus assay; and it did not include unscheduled DNA synthesis in hepatocytes from rats given gabapentin.

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately 5 times the maximum recommended human dose on a mg/m^2 basis).

Pregnancy

Pregnancy Category C: Gabapentin has been shown to be fetotoxic in rodents,

the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is ~1.25. It has the following structural formula:



Each capsule for oral administration contains 100 mg, 300 mg, and 400 mg of gabapentin. In addition, each capsule contains the following inactive ingredients: croscarmellose sodium and magnesium stearate. The 100 mg, 300 mg and 400 mg capsule imprinting ink black SW-9008/SW-9009 contains the following inactive ingredients: ammonium hydroxide; black iron oxide, bacteria controlled EEC No. 172; n-butyl; ethyl alcohol, anhydrous, 200 proof; isopropyl alcohol USP; potassium hydroxide; propylene glycol; purified water and shellac.

The 100 mg capsule shell contains gelatin and titanium dioxide.

The 300 mg capsule shell contains gelatin, yellow iron oxide and titanium dioxide.

The 400 mg capsule shell contains gelatin, red iron oxide, yellow iron oxide and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism by which gabapentin exerts its anticonvulsant action is unknown, but in animal test systems designed to detect anticonvulsant activity, gabapentin prevents seizures as do other marketed anticonvulsants. Gabapentin exhibits antiseizure activity in mice and rats in both the maximal electroshock and pentylenetetrazole seizure models and other preclinical models (e.g., strains with genetic epilepsy, etc.). The relevance of these models to human epilepsy is not known.

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but it does not modify $GABA_A$ or $GABA_B$ radioligand binding, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation. Gabapentin was tested in radioligand binding assays at concentrations up to 100 mcM and did not exhibit affinity for a number of other common receptor sites, including benzodiazepine, glutamate, N-methyl-D-aspartate (NMDA), quisqualate, kainate, strychnine-insensitive or strychnine-sensitive glycine, alpha 1, alpha 2, or beta adrenergic, adenosine A1 or A2, cholinergic muscarinic or nicotinic, dopamine D1 or D2, histamine H1, serotonin S1 or S2, opiate mu, delta or kappa, cannabinoid 1, voltage-sensitive calcium channel sites labeled with nifendipine or diltiazem, or at voltage-sensitive sodium channel sites labeled with batrachotoxin A 20-alpha-benzoate. Furthermore, gabapentin did not alter the cellular uptake of dopamine, noradrenaline, or serotonin.

In vitro studies with radiolabeled gabapentin have revealed a gabapentin binding site in areas of rat brain including neocortex and hippocampus. A high-affinity binding protein in animal brain tissue has been identified as an auxiliary subunit of voltage-activated calcium channels. However, functional correlates of gabapentin binding, if any, remain to be elucidated.

Pharmacokinetics and Drug Metabolism

All pharmacological actions following gabapentin administration are due to the activity of the parent compound; gabapentin is not appreciably metabolized in humans.

Oral Bioavailability: Gabapentin bioavailability is not dose proportional; i.e., as dose is increased, bioavailability decreases. Bioavailability of gabapentin is approximately 60%, 47%, 34%, 33%, and 27% following 900, 1200, 2400, 3600, and 4800 mg/day given in 3 divided doses, respectively. Food has only a slight effect on the rate and extent of absorption of gabapentin (14% increase in AUC and C_{max}).

Distribution: Less than 3% of gabapentin circulates bound to plasma protein. The apparent volume of distribution of gabapentin after 150 mg intravenous administration is 58 ± 6 L (Mean ± SD). In patients with epilepsy, steady-state predose (C_{min}) concentrations of gabapentin in cerebrospinal fluid were approximately 20% of the corresponding plasma concentrations.

Elimination: Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug. Gabapentin is not appreciably metabolized in humans.

Gabapentin elimination half-life is 5 to 7 hours and is unaltered by dose or following multiple dosing. Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance (see **Special Populations:** *Adult Patients With Renal Insufficiency*, below). In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin can be removed from plasma by hemodialysis.

Dosage adjustment in patients with compromised renal function or undergoing hemodialysis is recommended (see **DOSAGE AND ADMINISTRATION**, Table 3).

Special Populations: *Adult Patients With Renal Insufficiency:* Subjects (N = 60) with renal insufficiency (mean creatinine clearance ranging from 13-114 mL/min) were administered single 400 mg oral doses of gabapentin. The mean gabapentin half-life ranged from about 6.5 hours (patients with creatinine clearance >60 mL/min) to 52 hours (creatinine clearance <30 mL/min) and gabapentin renal clearance from about 90 mL/min (>60 mL/min group) to about 10 mL/min (<30 mL/min). Mean plasma clearance (CL/F) decreased from approximately 190 mL/min to 20 mL/min.

Dosage adjustment in adult patients with compromised renal function is necessary (see **DOSAGE AND ADMINISTRATION**). Pediatric patients with renal insufficiency have not been studied.

Hemodialysis: In a study in anuric adult subjects (N = 11), the apparent elimination half-life of gabapentin on nondialysis days was about 132 hours; during dialysis the apparent half-life of gabapentin was reduced to 3.8 hours. Hemodialysis thus has a significant effect on gabapentin elimination in anuric subjects.

Dosage adjustment in patients undergoing hemodialysis is necessary (see **DOSAGE AND ADMINISTRATION**).

Hepatic Disease: Because gabapentin is not metabolized, no study was performed in patients with hepatic impairment.

Age: The effect of age was studied in subjects 20-80 years of age. Apparent oral clearance (CL/F) of gabapentin decreased as age increased, from about 225 mL/min in those under 30 years of age to about 125 mL/min in those over 70 years of age. Renal clearance (CLr) and CLr adjusted for body surface area also declined with age; however, the decline in the renal clearance of gabapentin with age can largely be explained by the decline in renal function. Reduction of gabapentin dose may be required in patients who have age related compromised renal function (see **PRECAUTIONS, Geriatric Use,** and **DOSAGE AND ADMINISTRATION**).

Pediatric: Gabapentin pharmacokinetics were determined in 48 pediatric subjects between the ages of 1 month and 12 years following a dose of approximately 10 mg/kg. Peak plasma concentrations were similar across the entire age group and occurred 2 to 3 hours postdose. In general, pediatric subjects between 1 month and <5 years of age achieved approximately 30% lower exposure (AUC) than that observed in those 5 years of age and older. Accordingly, oral clearance normalized per body weight was higher in the younger children. Apparent oral clearance of gabapentin was directly proportional to creatinine clearance. Gabapentin elimination half-life averaged 4.7 hours and was similar across the age groups studied.

A population pharmacokinetic analysis was performed in 253 pediatric subjects between 1 month and 13 years of age. Patients received 10 to 65 mg/kg/day give T.I.D. Apparent oral clearance (CL/F) was directly proportional to creatinine clearance and this relationship was similar following a single dose and at steady state. Higher oral clearance values were observed in children <5 years of age compared to those observed in children 5 years of age and older, when normalized per body weight. The clearance was highly variable in infants <1 year of age. The normalized CL/F values observed in pediatric patients 5 years of age and older were consistent with values observed in adults after a single dose. The oral volume of distribution normalized per body weight was constant across the age range.

These pharmacokinetic data indicate that the effective daily dose in pediatric patients with epilepsy ages 3 and 4 years should be 40 mg/kg/day to achieve average plasma concentrations similar to those achieved in patients 5 years of age and older receiving gabapentin at 30 mg/kg/day. (See **DOSAGE AND ADMINISTRATION.**)

Gender: Although no formal study has been conducted to compare the pharmacokinetics of gabapentin in men and women, it appears that the pharmacokinetic parameters for males and females are similar and there are no significant gender differences.

Race: Pharmacokinetic differences due to race have not been studied. Because gabapentin is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

Clinical Studies

Epilepsy

The effectiveness of gabapentin as adjunctive therapy (added to other antiepileptic drugs) was established in multicenter placebo-controlled, double-blind, parallel-group clinical trials in adult and pediatric patients (3 years and

Gabapentin did not demonstrate mutagenic or genotoxic potential in three *in vitro* and four *in vivo* assays. It was negative in the Ames test and the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay; it was negative in the *in vivo* chromosomal aberration assay and in the *in vivo* micronucleus test in Chinese hamster bone marrow; it was negative in the *in vivo* mouse micronucleus assay; and it did not include unscheduled DNA synthesis in hepatocytes from rats given gabapentin.

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately 5 times the maximum recommended human dose on a mg/m^2 basis).

Pregnancy

Pregnancy Category C: Gabapentin has been shown to be fetotoxic in rodents, causing delayed ossification of several bones in the skull, vertebrae, forelimbs, and hindlimbs. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during the period of organogenesis, or approximately 1 to 4 times the maximum dose of 3600 mg/day given to epileptic patients on a mg/m^2 basis. The no-effect level was 500 mg/kg/day or approximately 1/2 of the human dose on a mg/m^2 basis.

When rats were dosed prior to and during mating, and throughout gestation, pups from all dose groups (500, 1000 and 2000 mg/kg/day) were affected. These doses are equivalent to less than approximately 1 to 5 times the maximum human dose on a mg/m^2 basis. There was an increased incidence of hydroureter and/or hydronephrosis in rats in a study of fertility and general reproductive performance at 2000 mg/kg/day with no effect at 1000 mg/kg/day, in a teratology study at 1500 mg/kg/day with no effect at 300 mg/kg/day, and in a perinatal and postnatal study at all doses studied (500, 1000 and 2000 mg/kg/day). The doses at which the effects occurred are approximately 1 to 5 times the maximum human dose of 3600 mg/day on a mg/m^2 basis; the no-effect doses were approximately 3 times (Fertility and General Reproductive Performance study) and approximately equal to (Teratogenicity study) the maximum human dose on a mg/m^2 basis. Other than hydroureter and hydronephrosis, the etiologies of which are unclear, the incidence of malformations was not increased compared to controls in offspring of mice, rats, or rabbits given doses up to 50 times (mice), 30 times (rats), and 25 times (rabbits) the human daily dose on a mg/kg basis, or 4 times (mice), 5 times (rats), or 8 times (rabbits) the human daily dose on a mg/m^2 basis.

In a teratology study in rabbits, an increased incidence of postimplantation fetal loss occurred in dams exposed to 60, 300 and 1500 mg/kg/day, or less than approximately 1/4 to 8 times the maximum human dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Nursing Mothers

Gabapentin is secreted into human milk following oral administration. A nursed infant could be exposed to a maximum dose of approximately 1 mg/kg/day of gabapentin. Because the effect on the nursing infant is unknown, gabapentin should be used in women who are nursing only if the benefits clearly outweigh the risks.

Pediatric Use

Effectiveness as adjunctive therapy in the treatment of partial seizures in pediatric patients below the age of 3 years has not been established (see **CLINICAL PHARMACOLOGY, Clinical Studies**).

Geriatric Use

Clinical studies of gabapentin in epilepsy did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions 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 dose should be adjusted based on creatinine clearance values in these patients (see **CLINICAL PHARMACOLOGY, ADVERSE REACTIONS,** and **DOSAGE AND ADMINISTRATION** sections).

ADVERSE REACTIONS

Epilepsy

The most commonly observed adverse events associated with the use of gabapentin in combination with other antiepileptic drugs in patients >12 years of age, not seen at an equivalent frequency among placebo-treated patients, were somnolence, dizziness, ataxia, fatigue, and nystagmus. The most commonly observed adverse events reported with the use of gabapentin in combination with other antiepileptic drugs in pediatric patients 3 to 12 years of age, not seen at an equal frequency among placebo-treated patients, were viral infection, fever, nausea and/or vomiting, somnolence, and hostility (see **WARNINGS, Neuropsychiatric Adverse Events**).

Approximately 7% of the 2074 patients >12 years of age and approximately 7% of the 449 pediatric patients 3 to 12 years of age who received gabapentin in premarketing clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal in patients >12 years of age were somnolence (1.2%), ataxia (0.8%), fatigue (0.6%), nausea and/or vomiting (0.6%), and dizziness (0.6%). The adverse events most commonly associated with withdrawal in pediatric patients were emotional lability (1.6%), hostility (1.3%), and hyperkinesia (1.1%).

Incidence in Controlled Clinical Trials

Table 1 lists treatment-emergent signs and symptoms that occurred in at least 1% of gabapentin-treated patients >12 years of age with epilepsy participating in placebo-controlled trials and were numerically more common in the gabapentin group. In these studies, either gabapentin or placebo was added to the patient's current antiepileptic drug therapy. Adverse events were usually mild to moderate in intensity.

The prescriber should be aware that these figures, obtained when gabapentin was added to concurrent antiepileptic drug therapy, cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescribing physician with one basis to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

TABLE 1. Treatment - Emergent Adverse Event Incidence in Controlled Add-On Trials in Patients >12 years of age (Events in at Least 1% of Gabapentin Patients and Numerically More Frequent Than in the Placebo Group)

Body System/ Adverse Event	Gabapentin[a] N = 543 %	Placebo[a] N = 378 %
Body As A Whole		
Fatigue	11.0	5.0
Weight Increase	2.9	1.6
Back Pain	1.8	0.5
Peripheral Edema	1.7	0.5
Cardiovascular		
Vasodilatation	1.1	0.3
Digestive System		
Dyspepsia	2.2	0.5
Mouth or Throat Dry	1.7	0.5
Constipation	1.5	0.8
Dental Abnormalities	1.5	0.3
Increased Appetite	1.1	0.8
Hematologic and Lymphatic Systems		
Leukopenia	1.1	0.5
Musculoskeletal System		
Myalgia	2.0	1.9
Fracture	1.1	0.8
Nervous System		
Somnolence	19.3	8.7
Dizziness	17.1	6.9
Ataxia	12.5	5.6
Nystagmus	8.3	4.0
Tremor	6.8	3.2
Nervousness	2.4	1.9
Dysarthria	2.4	0.5
Amnesia	2.2	0.0
Depression	1.8	1.1
Thinking Abnormal	1.7	1.3
Twitching	1.3	0.5
Coordination Abnormal	1.1	0.3
Respiratory System		
Rhinitis	4.1	3.7
Pharyngitis	2.8	1.6

Gender: Although no formal study has been conducted to compare the pharmacokinetics of gabapentin in men and women, it appears that the pharmacokinetic parameters for males and females are similar and there are no significant gender differences.

Race: Pharmacokinetic differences due to race have not been studied. Because gabapentin is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

Clinical Studies

Epilepsy
The effectiveness of gabapentin as adjunctive therapy (added to other antiepileptic drugs) was established in multicenter placebo-controlled, double-blind, parallel-group clinical trials in adult and pediatric patients (3 years and older) with refractory partial seizures.

Evidence of the effectiveness was obtained in three trials conducted in 705 patients (age 12 years and above) and one trial conducted in 247 pediatric patients (3 to 12 years of age). The patients enrolled had a history of at least 4 partial seizures per month in spite of receiving one or more antiepileptic drugs at therapeutic levels and were observed on their established antiepileptic drug regimen during a 12-week baseline period (6 weeks in the study of pediatric patients). In patients continuing to have at least 2 (or 4 in some studies) seizures per month, gabapentin or placebo was then added on to the existing therapy during a 12-week treatment period. Effectiveness was assessed primarily on the basis of the percent of patients with a 50% or greater reduction in seizure frequency from baseline to treatment (the "responder rate") and a derived measure called response ratio, a measure of change defined as (T - B)/(T + B), where B is the patient's baseline seizure frequency and T is the patient's seizure frequency during treatment. Response ratio is distributed within the range -1 to +1. A zero value indicates no change while complete elimination of seizures would give a value of -1; increased seizure rates would give positive values. A response ratio of -0.33 corresponds to a 50% reduction in seizure frequency. The results given below are for all partial seizures in the intent-to-treat (all patients who received any doses of treatment) population in each study, unless otherwise indicated.

One study compared gabapentin 1200 mg/day divided T.I.D. with placebo. Responder rate was 23% (14/61) in the gabapentin group and 9% (6/66) in the placebo group; the difference between groups was statistically significant. Response ratio was also better in the gabapentin group (-0.199) than in the placebo group (-0.044), a difference that also achieved statistical significance.

A second study compared primarily 1200 mg/day divided T.I.D. gabapentin (N = 101) with placebo (N = 98). Additional smaller gabapentin dosage groups (600 mg/day, N = 53; 1800 mg/day, N = 54) were also studied for information regarding dose response. Responder rate was higher in the gabapentin 1200 mg/day group (16%) than in the placebo group (8%), but the difference was not statistically significant. The responder rate at 600 mg (17%) was also not significantly higher than in the placebo, but the responder rate in the 1800 mg group (26%) was statistically significantly superior to the placebo rate. Response ratio was better in the gabapentin 1200 mg/day group (-0.103) than in the placebo group (-0.022); but this difference was also not statistically significant ($p = 0.224$). A better response was seen in the gabapentin 600 mg/day group (-0.105) and 1800 mg/day group (-0.222) than in the 1200 mg/day group, with the 1800 mg/day group achieving statistical significance compared to the placebo group.

A third study compared gabapentin 900 mg/day divided T.I.D. (N = 111) and placebo (N = 109). An additional gabapentin 1200 mg/day dosage group (N = 52) provided dose-response data. A statistically significant difference in responder rate was seen in the gabapentin 900 mg/day group (22%) compared to that in the placebo group (10%). Response ratio was also statistically significantly superior in the gabapentin 900 mg/day group (-0.119) compared to that in the placebo group (-0.027), as was response ratio in 1200 mg/day gabapentin (-0.184) compared to placebo.

Analyses were also performed in each study to examine the effect of gabapentin on preventing secondarily generalized tonic-clonic seizures. Patients who experienced a secondarily generalized tonic-clonic seizure in either the baseline or in the treatment period in all three placebo-controlled studies were included in these analyses. There were several response ratio comparisons that showed a statistically significant advantage for gabapentin compared to placebo and favorable trends for almost all comparisons.

Analysis of responder rate using combined data from all three studies and all doses (N = 162, gabapentin; N = 89, placebo) also showed a significant advantage for gabapentin over placebo in reducing the frequency of secondarily generalized tonic-clonic seizures.

In two of the three controlled studies, more than one dose of gabapentin was used. Within each study the results did not show a consistently increased response to dose. However, looking across studies, a trend toward increasing efficacy with increasing dose is evident (see Figure 1).

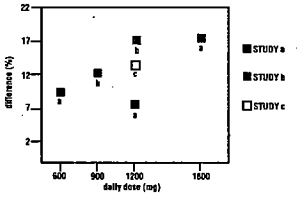


FIGURE 1. Responder Rate in Patients Receiving Gabapentin Expressed as a Difference From Placebo by Dose and Study: Adjunctive Therapy Studies in Patients ≥12 Years of Age With Partial Seizures.

In the figure, treatment effect magnitude, measured on the Y axis in terms of the difference in the proportion of gabapentin and placebo assigned patients attaining a 50% or greater reduction in seizure frequency from baseline, is plotted against the daily dose of gabapentin administered (X axis).

Although no formal analysis by gender has been performed, estimates of response (Response Ratio) derived from clinical trials (398 men, 307 women) indicate no important gender differences exist. There was no consistent pattern indicating that age had any effect on the response to gabapentin. There were insufficient numbers of patients of races other than Caucasian to permit a comparison of efficacy among racial groups.

A fourth study in pediatric patients age 3 to 12 years compared 25-35 mg/kg/day gabapentin (N=118) with placebo (N=127). For all partial seizures in the intent-to-treat population, the response ratio was statistically significantly better for the gabapentin group (-0.146) than for the placebo group (-0.079). For the same population, the responder rate for gabapentin (21%) was not significantly different from placebo (18%).

A study in pediatric patients age 1 month to 3 years compared 40 mg/kg/day gabapentin (N=38) with placebo (N=38) in patients who were receiving at least one marketed antiepileptic drug and had at least one partial seizure during the screening period (within 2 weeks prior to baseline). Patients had up to 48 hours of baseline and up to 72 hours of double-blind video EEG monitoring to record and count the occurrence of seizures. There were no statistically significant differences between treatments in either the response ratio or responder rate.

INDICATIONS AND USAGE

Epilepsy
Gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy. Gabapentin is also indicated as adjunctive therapy in the treatment of partial seizures in pediatric patients age 3-12 years.

CONTRAINDICATIONS

Gabapentin is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS

Neuropsychiatric Adverse Events - Pediatric Patients 3-12 years of age
Gabapentin use in pediatric patients with epilepsy 3-12 years of age is associated with the occurrence of central nervous system related adverse events. The most significant of these can be classified into the following categories: 1) emotional lability (primarily behavioral problems), 2) hostility, including aggressive behaviors, 3) thought disorder, including concentration problems and change in school performance, and 4) hyperkinesia (primarily restlessness and hyperactivity). Among the gabapentin-treated patients, most of the events were mild to moderate in intensity.

In controlled trials in pediatric patients 3-12 years of age, the incidence of these adverse events was: emotional lability 6% (gabapentin-treated patients) vs 1.3% (placebo-treated patients); hostility 5.2% vs 1.3%; hyperkinesia 4.7% vs 2.9%; and thought disorder 1.7% vs 0%. One of these events, a report of hostility, was considered serious. Discontinuation of gabapentin treatment occurred in 1.3% of patients reporting emotional lability and hyperkinesia and 0.9% of gabapentin-treated patients reporting hostility and thought disorder. One placebo-treated patient (0.4%) withdrew due to emotional lability.

Nystagmus	8.3	4.0
Tremor	6.8	3.2
Nervousness	2.4	1.9
Dysarthria	2.4	0.5
Amnesia	2.2	0.0
Depression	1.8	1.1
Thinking Abnormal	1.7	1.3
Twitching	1.3	0.5
Coordination Abnormal	1.1	0.3
Respiratory System		
Rhinitis	4.1	3.7
Pharyngitis	2.8	1.6
Coughing	1.8	1.3
Skin and Appendages		
Abrasion	1.3	0.0
Pruritus	1.3	0.5
Urogenital System		
Impotence	1.5	1.1
Special Senses		
Diplopia	5.9	1.9
Amblyopia[b]	4.2	1.1
Laboratory Deviations		
WBC Decreased	1.1	0.5

[a]Plus background antiepileptic drug therapy
[b]Amblyopia was often described as blurred vision.

Other events in more than 1% of patients >12 years of age but equally or more frequent in the placebo group included: headache, viral infection, fever, nausea and/or vomiting, abdominal pain, diarrhea, convulsions, confusion, insomnia, emotional lability, rash, acne.

Among the treatment-emergent adverse events occurring at an incidence of at least 10% of gabapentin-treated patients, somnolence and ataxia appeared to exhibit a positive dose-response relationship.

The overall incidence of adverse events and the types of adverse events seen were similar among men and women treated with gabapentin. The incidence of adverse events increased slightly with increasing age in patients treated with either gabapentin or placebo. Because only 3% of patients (28/921) in placebo-controlled studies were identified as nonwhite (black or other), there are insufficient data to support a statement regarding the distribution of adverse events by race.

Table 2 lists treatment-emergent signs and symptoms that occurred in at least 2% of gabapentin-treated patients age 3 to 12 years of age with epilepsy participating in placebo-controlled trials and were numerically more common in the gabapentin group. Adverse events were usually mild to moderate in intensity.

TABLE 2. Treatment-Emergent Adverse Event Incidence in Pediatric Patients Age 3 to 12 Years in a Controlled Add-On Trial (Events in at Least 2% of Gabapentin Patients and Numerically More Frequent Than in the Placebo Group)

Body System/ Adverse Event	Gabapentin[a] N=119 %	Placebo[a] N=128 %
Body As A Whole		
Viral Infection	10.9	3.1
Fever	10.1	3.1
Weight Increase	3.4	0.8
Fatigue	3.4	1.6
Digestive System		
Nausea and/or Vomiting	8.4	7.0
Nervous System		
Somnolence	8.4	4.7
Hostility	7.6	2.3
Emotional Lability	4.2	1.6
Dizziness	2.5	1.6
Hyperkinesia	2.5	0.8
Respiratory System		
Bronchitis	3.4	0.8
Respiratory Infection	2.5	0.8

[a]Plus background antiepileptic drug therapy

Other events in more than 2% of pediatric patients 3 to 12 years of age but equally or more frequent in the placebo group included: pharyngitis, upper respiratory infection, headache, rhinitis, convulsions, diarrhea, anorexia, coughing, and otitis media.

Other Adverse Events Observed During All Clinical Trials

Clinical Trials in Adults and Adolescents (Except Clinical Trials in Neuropathic Pain)
Gabapentin has been administered to 2074 patients >12 years of age during all adjunctive therapy clinical trials (except clinical trials in patients with neuropathic pain), only some of which were placebo-controlled. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. These categories are used in the listing below. The frequencies presented represent the proportion of the 2074 patients >12 years of age exposed to gabapentin who experienced an event of the type cited on at least one occasion while receiving gabapentin. All reported events are included except those already listed in Table 1, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body As A Whole: *Frequent :* asthenia, malaise, face edema; *Infrequent :* allergy, generalized edema, weight decrease, chill; *Rare :* strange feelings, lassitude, alcohol intolerance, hangover effect.

Cardiovascular System: *Frequent :* hypertension; *Infrequent :* hypotension, angina pectoris, peripheral vascular disorder, palpitation, tachycardia, migraine, murmur; *Rare :* atrial fibrillation, heart failure, thrombophlebitis, deep thrombophlebitis, myocardial infarction, cerebrovascular accident, pulmonary thrombosis, ventricular extrasystoles, bradycardia, premature atrial contraction, pericardial rub, heart block, pulmonary embolus, hyperlipidemia, hypercholesterolemia, pericardial effusion, pericarditis.

Digestive System: *Frequent :* anorexia, flatulence, gingivitis; *Infrequent :* glossitis, gum hemorrhage, thirst, stomatitis, increased salivation, gastroenteritis, hemorrhoids, bloody stools, fecal incontinence, hepatomegaly; *Rare :* dysphagia, eructation, pancreatitis, peptic ulcer, colitis, blisters in mouth, tooth discolor, perlèche, salivary gland enlarged, lip hemorrhage, esophagitis, hiatal hernia, hematemesis, proctitis, irritable bowel syndrome, rectal hemorrhage, esophageal spasm.

Endocrine System: *Rare :* hyperthyroid, hypothyroid, goiter, hypoestrogen, ovarian failure, epididymitis, swollen testicle, cushingoid appearance.

Hematologic and Lymphatic System: *Frequent :* purpura most often described as bruises resulting from physical trauma; *Infrequent :* anemia, thrombocytopenia, lymphadenopathy; *Rare :* WBC count increased, lymphocytosis, non-Hodgkin's lymphoma, bleeding time increased.

Musculoskeletal System: *Frequent :* arthralgia; *Infrequent :* tendinitis, arthritis, joint stiffness, joint swelling, positive Romberg test; *Rare :* costochondritis, osteoporosis, bursitis, contracture.

Nervous System: *Frequent :* vertigo, hyperkinesia, paresthesia, decreased or absent reflexes, increased reflexes, anxiety, hostility; *Infrequent :* CNS tumors, syncope, dreaming abnormal, aphasia, hypesthesia, intracranial hemorrhage, hypotonia, dysesthesia, paresis, dystonia, hemiplegia, facial paralysis, stupor, cerebellar dysfunction, positive Babinski sign, decreased position sense, subdural hematoma, apathy, hallucination, decrease or loss of libido, agitation, paranoia, depersonalization, euphoria, feeling high, doped-up sensation, suicidal, psychosis; *Rare :* choreoathetosis, orofacial dyskinesia, encephalopathy, nerve palsy, personality disorder, increased libido, subdued temperament, aprazia, fine motor control disorder, meningismus, local myoclonus, hyperesthesia, hypokinesia, mania, neurosis, hysteria, antisocial reaction, suicide gesture.

Respiratory System: *Frequent :* pneumonia; *Infrequent :* epistaxis, dyspnea, apnea; *Rare :* mucositis, aspiration pneumonia, hyperventilation, hiccup, laryngitis, nasal obstruction, snoring, bronchospasm, hypoventilation, lung edema.

Dermatological: *Infrequent :* alopecia, eczema, dry skin, increased sweating, urticaria, hirsutism, seborrhea, cyst, herpes simplex; *Rare :* herpes zoster, skin discolor, skin papules, photosensitive reaction, leg ulcer, scalp seborrhea, psoriasis, desquamation, maceration, skin nodules, subcutaneous nodule, melanosis, skin necrosis, local swelling.

Urogenital System: *Infrequent :* hematuria, dysuria, urination frequency, cystitis,

with the occurrence of central nervous system related adverse events. The most significant of these can be classified into the following categories: 1) emotional lability (primarily behavioral problems), 2) hostility, including aggressive behaviors, 3) thought disorder, including concentration problems and change in school performance, and 4) hyperkinesia (primarily restlessness and hyperactivity). Among the gabapentin-treated patients, most of the events were mild to moderate in intensity.

In controlled trials in pediatric patients 3-12 years of age, the incidence of these adverse events was: emotional lability 6% (gabapentin-treated patients) vs 1.3% (placebo-treated patients); hostility 5.2% vs 1.3%; hyperkinesia 4.7% vs 2.9%; and thought disorder 1.7% vs 0%. One of these events, a report of hostility, was considered serious. Discontinuation of gabapentin treatment occurred in 1.3% of patients reporting emotional lability and hyperkinesia and 0.9% of gabapentin-treated patients reporting hostility and thought disorder. One placebo-treated patient (0.4%) withdrew due to emotional lability.

Withdrawal Precipitated Seizure, Status Epilepticus
Antiepileptic drugs should not be abruptly discontinued because of the possibility of increasing seizure frequency.

In the placebo-controlled studies in patients >12 years of age, the incidence of status epilepticus in patients receiving gabapentin was 0.6% (3 of 543) versus 0.5% in patients receiving placebo (2 of 378). Among the 2074 patients >12 years of age treated with gabapentin across all studies (controlled and uncontrolled) 31 (1.5%) had status epilepticus. Of these, 14 patients had no prior history of status epilepticus either before treatment or while on other medications. Because adequate historical data are not available, it is impossible to say whether or not treatment with gabapentin is associated with a higher or lower rate of status epilepticus than would be expected to occur in a similar population not treated with gabapentin.

Tumorigenic Potential
In standard preclinical *in vivo* lifetime carcinogenicity studies, an unexpectedly high incidence of pancreatic acinar adenocarcinomas was identified in male, but not female, rats (see **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility**). The clinical significance of this finding is unknown. Clinical experience during gabapentin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies in adjunctive therapy in epilepsy comprising 2085 patient-years of exposure in patients >12 years of age, new tumors were reported in 10 patients (2 breast, 3 brain, 2 lung, 1 adrenal, 1 non-Hodgkin's lymphoma, 1 endometrial carcinoma *in situ*), and pre-existing tumors worsened in 11 patients (9 brain, 1 breast, 1 prostate) during or up to 2 years following discontinuation of gabapentin. Without knowledge of the background incidence and recurrence in a similar population not treated with gabapentin, it is impossible to know whether the incidence seen in this cohort is or is not affected by treatment.

Sudden and Unexplained Death in Patients With Epilepsy
During the course of premarketing development of gabapentin 8 sudden and unexplained deaths were recorded among a cohort of 2203 patients treated (2103 patient-years of exposure).

Some of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. This represents an incidence of 0.0038 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving gabapentin (ranging from 0.0005 for the general population of epileptics to 0.003 for a clinical trial population similar to that in the gabapentin program, to 0.005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or raise further concern depends on comparability of the populations reported upon to the gabapentin cohort and the accuracy of the estimates provided.

PRECAUTIONS

Information for Patients
Patients should be instructed to take gabapentin only as prescribed.

Patients should be advised that gabapentin may cause dizziness, somnolence and other symptoms and signs of CNS depression. Accordingly, they should be advised neither to drive a car nor to operate other complex machinery until they have gained sufficient experience on gabapentin to gauge whether or not it affects their mental and/or motor performance adversely.

Patients who require concomitant treatment with morphine may experience increases in gabapentin concentrations. Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately (see **Drug Interactions**).

Laboratory Tests
Clinical trials data do not indicate that routine monitoring of clinical laboratory parameters is necessary for the safe use of gabapentin. The value of monitoring gabapentin blood concentrations has not been established. Gabapentin may be used in combination with other antiepileptic drugs without concern for alteration of the blood concentrations of gabapentin or of other antiepileptic drugs.

Drug Interactions
In vitro studies were conducted to investigate the potential of gabapentin to inhibit the major cytochrome P450 enzymes (CYP1A2, CYP2A5, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) that mediate drug and xenobiotic metabolism using isoform selective marker substrates and human liver microsomal preparations. Only at the highest concentration tested (171 mcg/mL; 1 mM) was a slight degree of inhibition (14%-30%) of isoform CYP2A6 observed. No inhibition of any of the other isoforms tested was observed at gabapentin concentrations up to 171 mcg/mL (approximately 15 times the C_{max} at 3600 mg/day).

Gabapentin is not appreciably metabolized nor does it interfere with the metabolism of commonly coadministered antiepileptic drugs.

The drug interaction data described in this section were obtained from studies involving healthy adults and adult patients with epilepsy.

Phenytoin: In a single (400 mg) and multiple dose (400 mg T.I.D.) study of gabapentin in epileptic patients (N = 8) maintained on phenytoin monotherapy for at least 2 months, gabapentin had no effect on the steady-state trough plasma concentrations of phenytoin and phenytoin had no effect on gabapentin pharmacokinetics.

Carbamazepine: Steady-state trough plasma carbamazepine and carbamazepine 10, 11 epoxide concentrations were not affected by concomitant gabapentin (400 mg T.I.D.; N = 12) administration. Likewise, gabapentin pharmacokinetics were unaltered by carbamazepine administration.

Valproic Acid: The mean steady-state trough serum valproic acid concentrations prior to and during concomitant gabapentin administration (400 mg T.I.D.; N = 17) were not different and neither were gabapentin pharmacokinetic parameters affected by valproic acid.

Phenobarbital: Estimates of steady-state pharmacokinetic parameters for phenobarbital or gabapentin (300 mg T.I.D.; N = 12) are identical whether the drugs are administered alone or together.

Naproxen: Coadministration (N = 18) of naproxen sodium capsules (250 mg) with gabapentin (125 mg) appears to increase the amount of gabapentin absorbed by 12% to 15%. Gabapentin had no effect on naproxen pharmacokinetic parameters. These doses are lower than the therapeutic doses for both drugs. The magnitude of interaction within the recommended dose ranges of either drug is not known.

Hydrocodone: Coadministration of gabapentin (125 to 500 mg; N = 48) decreases hydrocodone (10 mg; N = 50) C_{max} and AUC values in a dose-dependent manner relative to administration of hydrocodone alone; C_{max} and AUC values are 3% to 4% lower, respectively, after administration of 125 mg gabapentin and 21% to 22% lower, respectively, after administration of 500 mg gabapentin. The mechanism for this interaction is unknown. Hydrocodone increases gabapentin AUC values by 14%. The magnitude of interaction at other doses is not known.

Morphine: A literature article reported that when a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule (N = 12), mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine (see **PRECAUTIONS**). Morphine pharmacokinetic parameter values were not affected by administration of gabapentin 2 hours after morphine. The magnitude of interaction at other doses is not known.

Cimetidine: In the presence of cimetidine at 300 mg Q.I.D. (N = 12) the mean apparent oral clearance of gabapentin fell by 14% and creatinine clearance fell by 10%. Thus cimetidine appeared to alter the renal excretion of both gabapentin and creatinine, an endogenous marker of renal function. This small decrease in excretion of gabapentin by cimetidine is not expected to be of clinical importance. The effect of gabapentin on cimetidine was not evaluated.

Oral Contraceptive: Based on AUC and half-life, multiple-dose pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of tablets containing 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol were similar with and without coadministration of gabapentin (400 mg T.I.D.; N = 13). The C_{max} of norethindrone was 13% higher when it was coadministered with gabapentin; this interaction is not expected to be of clinical importance.

Antacid (Maalox®†): Maalox® reduced the bioavailability of gabapentin (N = 16) by about 20%. This decrease in bioavailability was about 5% when gabapentin was administered 2 hours after Maalox®. It is recommended that gabapentin be taken at least 2 hours following Maalox® administration.

Effect of Probenecid: Probenecid is a blocker of renal tubular secretion. Gabapentin pharmacokinetic parameters without and with probenecid were

palsy, personality disorder, increased libido, subdued temperament, apraxia, fine motor control disorder, meningismus, local myoclonus, hyperesthesia, hypokinesia, mania, neurosis, hysteria, antisocial reaction, suicide gesture.

Respiratory System: *Frequent :* pneumonia; *Infrequent :* epistaxis, dyspnea, apnea; *Rare :* mucositis, aspiration pneumonia, hyperventilation, hiccup, laryngitis, nasal obstruction, snoring, bronchospasm, hypoventilation, lung edema.

Dermatological: *Infrequent :* alopecia, eczema, dry skin, increased sweating, urticaria, hirsutism, seborrhea, cyst, herpes simplex; *Rare :* herpes zoster, skin discolor, skin papules, photosensitive reaction, leg ulcer, scalp seborrhea, psoriasis, desquamation, maceration, skin nodules, subcutaneous nodule, melanosis, skin necrosis, local swelling.

Urogenital System: *Infrequent :* hematuria, dysuria, urination frequency, cystitis, urinary retention, urinary incontinence, vaginal hemorrhage, amenorrhea, dysmenorrhea, menorrhagia, breast cancer, unable to climax, ejaculation abnormal; *Rare :* kidney pain, leukorrhea, pruritus genital, renal stone, acute renal failure, anuria, glycosuria, nephrosis, nocturia, pyuria, urination urgency, vaginal pain, breast pain, testicle pain.

Special Senses: *Frequent :* abnormal vision; *Infrequent :* cataract, conjunctivitis, eyes dry, eye pain, visual field defect, photophobia, bilateral or unilateral ptosis, eye hemorrhage, hordeolum, hearing loss, earache, tinnitus, inner ear infection, otitis, taste loss, unusual taste, eye twitching, ear fullness; *Rare :* eye itching, abnormal accommodation, perforated ear drum, sensitivity to noise, eye focusing problem, watery eyes, retinopathy, glaucoma, iritis, corneal disorders, lacrimal dysfunction, degenerative eye changes, blindness, retinal degeneration, miosis, chorioretinitis, strabismus, eustachian tube dysfunction, labyrinthitis, otitis externa, odd smell.

Clinical Trials in Pediatric Patients With Epilepsy
Adverse events occurring during epilepsy clinical trials in 449 pediatric patients 3 to 12 years of age treated with gabapentin that were not reported in adjunctive trials in adults are:

Body as a Whole: dehydration, infectious mononucleosis

Digestive System: hepatitis

Hemic and Lymphatic System: coagulation defect

Nervous System: aura disappeared, occipital neuralgia

Psychobiologic Function: sleepwalking

Respiratory System: pseudocroup, hoarseness

Postmarketing and Other Experience
In addition to the adverse experiences reported during clinical testing of gabapentin, the following adverse experiences have been reported in patients receiving marketed gabapentin. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: angioedema, blood glucose fluctuation, erythema multiforme, elevated liver function tests, fever, hyponatremia, jaundice, movement disorder such as dyskinesia, Stevens-Johnson syndrome.

Adverse events following the abrupt discontinuation of gabapentin have also been reported. The most frequently reported events were anxiety, insomnia, nausea, pain and sweating.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of gabapentin has not been evaluated in human studies.

OVERDOSAGE

A lethal dose of gabapentin was not identified in mice and rats receiving single oral doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, sedation, hypoactivity, or excitation.

Acute oral overdoses of gabapentin up to 49 grams have been reported. In these cases, double vision, slurred speech, drowsiness, lethargy and diarrhea were observed. All patients recovered with supportive care.

Gabapentin can be removed by hemodialysis. Although hemodialysis has not been performed in the few overdose cases reported, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

DOSAGE AND ADMINISTRATION

Gabapentin is given orally with or without food.

If gabapentin dose is reduced, discontinued or substituted with an alternative medication, this should be done gradually over a minimum of 1 week.

Epilepsy
Gabapentin is recommended for add-on therapy in patients 3 years of age and older. Effectiveness in pediatric patients below the age of 3 years has not been established.

Patients >12 years of age: The effective dose of gabapentin is 900 to 1800 mg/day and given in divided doses (three times a day) using 300 or 400 mg capsules. The starting dose is 300 mg three times a day. If necessary, the dose may be increased using 300 mg or 400 mg capsules three times a day up to 1800 mg/day. Dosages up to 2400 mg/day have been well tolerated in long-term clinical studies. Doses of 3600 mg/day have also been administered to a small number of patients for a relatively short duration, and have been well tolerated. The maximum time between doses in the T.I.D. schedule should not exceed 12 hours.

Pediatric Patients Age 3-12 years: The starting dose should range from 10-15 mg/kg/day in 3 divided doses, and the effective dose reached by upward titration over a period of approximately 3 days. The effective dose of gabapentin in patients 5 years of age and older is 25-35 mg/kg/day and given in divided doses (three times a day). The effective dose in pediatric patients ages 3 and 4 years is 40 mg/kg/day and given in divided doses (three times a day) (See **CLINICAL PHARMACOLOGY, Pediatrics**). Dosages up to 50 mg/kg/day have been well tolerated in a long-term clinical study. The maximum time interval between doses should not exceed 12 hours.

It is not necessary to monitor gabapentin plasma concentrations to optimize gabapentin therapy. Further, because there are no significant pharmacokinetic interactions among gabapentin and other commonly used antiepileptic drugs, the addition of gabapentin does not alter the plasma levels of these drugs appreciably.

If gabapentin is discontinued and/or an alternate anticonvulsant medication is added to the therapy, this should be done gradually over a minimum of 1 week.

Dosage in Renal Impairment
Creatinine clearance is difficult to measure in outpatients. In patients with stable renal function, creatinine clearance (C_{Cr}) can be reasonably well estimated using the equation of Cockcroft and Gault:

for females: $C_{Cr} = [(0.85)(140\text{-age})(\text{weight})]/[(72)(S_{Cr})]$

for males: $C_{Cr} = [(140\text{-age})(\text{weight})]/[(72)(S_{Cr})]$

where age is in years, weight is in kilograms and S_{Cr} is serum creatinine in mg/dL.

Dosage adjustment in patients ≥12 years of age with compromised renal function or undergoing hemodialysis is recommended as follows (see dosing recommendations above for effective doses in each indication).

TABLE 3. Gabapentin Dosage Based on Renal Function

Renal Function Creatinine Clearance (mL/min)	Total Daily Dose Range (mg/day)	Dose Regimen (mg)				
≥60	900-3600	300 TID	400 TID	600 TID	800 TID	1200 TID
>30-59	400-1400	200 BID	300 BID	400 BID	500 BID	700 BID
>15-29	200-700	200 QD	300 QD	400 QD	500 QD	700 QD
<15[a]	100-300	100 QD	125 QD	150 QD	200 QD	300 QD
		Post-Hemodialysis Supplemental Dose (mg)[b]				
Hemodialysis		125[b]	150[b]	200[b]	250[b]	350[b]

[a] For patients with creatinine clearance <15 mL/min, reduce daily dose in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 mL/min should receive one-half the daily dose that patients with a creatinine clearance of 15 mL/min receive).

[b] Patients on hemodialysis should receive maintenance doses based on estimates of creatinine clearance as indicated in the upper portion of the table and a supplemental post-hemodialysis dose administered after each 4 hours of hemodialysis as indicated in the lower portion of the table.

The use of gabapentin in patients <12 years of age with compromised renal function has not been studied.

Dosage in Elderly
Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and dose should be adjusted based on creatinine clearance values in these patients.

HOW SUPPLIED

Gabapentin Capsules 100 mg are available for oral administration as hard gelatin capsules with a white opaque body and a white opaque cap. "APO 112" is imprinted on each capsule in black ink; supplied in bottles of 100 (NDC 60505-0112-1).

Gabapentin Capsules 300 mg are available for oral administration as hard gelatin capsules with a white opaque body and a yellow opaque cap. "APO 113" is imprinted on each capsule in black ink; supplied in bottles of 100 (NDC 60505-0113-1).

Gabapentin Capsules 400 mg are available for oral administration as hard gelatin capsules with a white opaque body and an orange opaque cap. "APO 114" is imprinted on each capsule in black ink; supplied in bottles of 100 (NDC 60505-0114-1).

Pharmacy

excretion of gabapentin by cimetidine is not expected to be of clinical importance. The effect of gabapentin on cimetidine was not evaluated.

Oral Contraceptive: Based on AUC and half-life, multiple-dose pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of tablets containing 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol were similar with and without coadministration of gabapentin (400 mg T.I.D.; N = 13). The C_{max} of norethindrone was 13% higher when it was coadministered with gabapentin; this interaction is not expected to be of clinical importance.

Antacid (Maalox®*): Maalox® reduced the bioavailability of gabapentin (N = 16) by about 20%. This decrease in bioavailability was about 5% when gabapentin was administered 2 hours after Maalox®. It is recommended that gabapentin be taken at least 2 hours following Maalox® administration.

Effect of Probenecid: Probenecid is a blocker of renal tubular secretion. Gabapentin pharmacokinetic parameters without and with probenecid were comparable. This indicates that gabapentin does not undergo renal tubular secretion by the pathway that is blocked by probenecid.

Drug/Laboratory Tests Interactions
Because false positive readings were reported with the Ames N-Multistix SG® dipstick test for urinary protein when gabapentin was added to other antiepileptic drugs, the more specific sulfosalicylic acid precipitation procedure is recommended to determine the presence of urine protein.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for 2 years. A statistically significant increase in the incidence of pancreatic acinar cell adenomas and carcinomas was found in male rats receiving the high dose; the no-effect dose for the occurrence of carcinomas was 1000 mg/kg/day. Peak plasma concentrations of gabapentin in rats receiving the high dose of 2000 mg/kg were 10 times higher than plasma

HOW SUPPLIED

Gabapentin Capsules 100 mg are available for oral administration as hard gelatin capsules with a white opaque body and a white opaque cap. "APO 112" is imprinted on each capsule in black ink; supplied in bottles of 100 (NDC 60505-0112-1).

Gabapentin Capsules 300 mg are available for oral administration as hard gelatin capsules with a white opaque body and a yellow opaque cap. "APO 113" is imprinted on each capsule in black ink; supplied in bottles of 100 (NDC 60505-0113-1).

Gabapentin Capsules 400 mg are available for oral administration as hard gelatin capsules with a white opaque body and an orange opaque cap. "APO 114" is imprinted on each capsule in black ink; supplied in bottles of 100 (NDC 60505-0114-1).

Storage

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant container [see USP].

*Maalox® is a registered trademark of Novartis Consumer Health, Inc.

APOTEX INC.
GABAPENTIN CAPSULES 100 mg, 300 mg and 400 mg

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, Florida
33326

(GAB/C-R03-51X138MM-LFLT-090104)

Revised: December 2004

Rev. 1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-360

LABELING REVIEW(S)

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-360** Date of Submission: **April 17, 1998**

Applicant's Name: **Torpharm**

Established Name: **Gabapentin Capsules, 100 mg, 300 mg and 400 mg**

Labeling Deficiencies:

1. CONTAINER (100 mg and 300 mg - 100s and 1000s and 400 mg 100s and 500s)

   a. We encourage you to differentiate your product strengths with the use of boxing, contrasting colors or some other means.

   b. Revise the storage temperature recommendations to read as follows:

      Store at controlled room temperature 15° to 30°C (59° to 86°F).

   c. Include a statement directed to the pharmacist specifying the type of container to be used in dispensing the drug product to maintain its identity, strength, quality and purity to be in accord with 21 CFR 201.100(b)(7).

   d. Section 126 of Title I of the FDA Modernization Act of 1997, amends Section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act to require, at a minimum, that prior to dispensing, the label of prescription products contain the symbol "Rx only." A GUIDANCE FOR INDUSTRY entitled "Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 —Elimination of Certain Labeling Requirements", was revised July 1998 and posted at Internet site http://www.fda.gov/cder/guidance/index.htm. Please note that Section IV, "Frequently Asked Questions" offers guidance on placement of the symbol on all labels and labeling.

e. Increase the prominence of the product strength.

2. INSERT

a. DESCRIPTION

i. Relocate the first paragraph to appear as the last paragraph and revise to read as follows:

Each capsule for oral administration, contains .....In addition, each capsule contains the following inactive ingredients...

ii. Inactive ingredients - We encourage you to include the components/composition of "Black SW-9008/SW-9009" or at a minimum include the dye.

iii. Combine paragraphs two and three and revise to read as follows:

Gabapentin is described as 1-(Aminomethyl...with a molecular formula of...aqueous solutions. It has the following structural formula:

b. CLINICAL PHARMACOLOGY

i. Oral Bioavailability - Delete ——— that appears following "400" and "100" in the second sentence. In addition, revise throughout the remainder of the text.

ii. Elimination, paragraph two - Insert " ——— " prior to "Special Populations".

c. INDICATIONS AND USAGE

Gabapentin ——— indicated...

d. CONTRAINDICATIONS

Gabapentin ——— contraindicated...

e. PRECAUTIONS

i. Antacid - Replace "Maalox®" with " ——— ". [3 places]

ii. Pregnancy - Revise this subsection heading to read "[redacted] Pregnancy Category C".

iii. Pediatric Use - Replace "[redacted]" with "pediatric patients".

f. HOW SUPPLIED

See comments b and d under CONTAINER.

Please revise your container labels and insert labeling, as instructed above, and submit final printed labels and labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

John P. Grace for/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No

Container Labels:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Neurontin® Capsules

NDA Number: 20-235/S-001

NDA Drug Name: Neurontin® Capsules

NDA Firm: Parke-Davis Pharmaceutical Research

Date of Approval of NDA Insert and supplement #:
Has this been verified by the MIS system for the NDA? Yes No

Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Container label submitted in jacket for side-by-side review.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR. First Generic ?	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. Review based on the labeling of the listed drug (Neurontin®; Approved November 14, 1994, Revised June 1994).

2. Patent/ Exclusivities:

   NCE exclusivity expires on December 30, 1998.

   Patent 5084479 - U-125 - Treatment of neurogenerative Diseases. Expires January 2, 2010. The firm filed a paragraph IV certification stating they will not infringe on this patent because the labeling does not contain any information.

   Patent 4087544 - U-86 - Method of treating certain forms of epilepsy. The firm filed a paragraph III certification.

   Contacted Mary Ann Holovac regarding patent "5084479" and its listing in the Orange Book. She said generally they do not list patents for uses that are not approved in the labeling. This use is not listed in the labeling. She explained the abstract on the paten database page is not always the same as what the firm submits to them.

3. Storage/Dispensing Conditions:

   NDA: Store at controlled room temperature 15° to 30°C (59° to 86°F).

   ANDA: Store at 25°C (77° F); excursions permitted to 15° to 30°C (59° to 86°F)[see USP Controlled Room Temperature).

   USP: NOT USP and NOT PF.

4. Product Line:

   The innovator markets their product in three strengths (100 mg, 300 mg and 400 mg). They are packaged in bottles of 100s and unit dose packages of 50s.

   The applicant proposes to market their product in three strengths (100 mg, 300 mg and 400 mg). They plan to market in bottles of 100s and 100s for the 100 mg and 300 mg and 100 s ——— for the 400 mg.

5. The capsule imprintings have been accurately described

in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). See pages 2307, 2380, and 2460, Vol. 1.2.

6. Inactive Ingredients:

   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 1868, Vol. 1.1.

7. All manufacturing will be performed by Torpharm. All outside firms are utilized for testing. See pages 2124 and 2118, Vol. 1.2.

8. Container/Closure:

   This product will be packaged in HDPE bottles with a CRC cap with 100s [redacted]. See page 2541, Vol. 1.3.

Date of Review: **August 18, 1998**

Date of Submission: **April 17, 1998**

Reviewer: Carol A. Holquist **Date:** 8/18/98

Team Leader: John D. Grace **Date:** 8/19/98

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cc:

ANDA 75-360
DUP/DIVISION FILE
HFD-613/CHolquist/JGrace (no cc)
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Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-360** Date of Submission: **December 10, 1998**

Applicant's Name: **Torpharm**

Established Name: **Gabapentin Capsules, 100 mg, 300 mg & 400 mg**

1. GENERAL

   a. The reference listed drug, Neurontin® is entitled to a new marketing exclusivity (D-43). Please update your patent certification and exclusivity statement to indicate that your product will not be marketed until the exclusivity expires on September 29, 2001. We refer you to the 19th edition of the "Orange Book" for guidance.

   b. Increase the prominence of the superscripts in your tables to 4 point font.

2. INSERT

   a. CLINICAL PHARMACOLOGY

      i. Replace " ——— " with "pediatric patients" in the "Pediatric" subsection of "Special Populations".

      ii. We encourage that you more clearly differentiate the boxes that represent "a" and "b" in figure 1.

   b. PRECAUTIONS

      Delete "———". (3 places)

   c. ADVERSE REACTIONS

      Add the following subsection '————————————————

      Postmarketing and Other Experience

      In addition to the adverse experiences reported during clinical testing of gabapentin, the following adverse experiences have been reported in patients receiving marketed gabapentin. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: angioedema, blood glucose fluctuation, erythema multiforme, elevated liver function tests, fever, jaundice, Stevens-Johnson syndrome.

d. DOSAGE AND ADMINISTRATION

i. The second sentence of the first paragraph should read as "..."

ii. [redacted]

paragraph.

iii. Delete the line of text that appears immediately above the "HOW SUPPLIED" heading.

Please revise your labeling, as instructed above, and submit final printed, or if your prefer, draft insert labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Cynthia Capps for

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No

Container Labels:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:
*Was this approval based upon a petition? No
*What is the RLD on the 356(h) form: Neurontin® Capsules
*NDA Number: 20-235/S-011
*NDA Drug Name: Neurontin® Capsules
*NDA Firm: Parke-Davis Pharmaceutical Research
*Date of Approval of NDA Insert and supplement#: September 29, 1998
*Has this been verified by the MIS system for the NDA? **Yes**
*Was this approval based upon an OGD labeling guidance? NO
*Basis of Approval for the Container Labels: Container label submitted in jacket for side-by-side review.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR. First Generic ?	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or			X

cap incorrect?			
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	

Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. Review based on the labeling of the referenced listed drug, Neurontin®; NDA 20-235/S-011, approved on September 29, 1998. This supplement provides for revision of the DOSAGE AND ADMINISTRATION section of the package insert. Specifically, directions for use to permit initiation of treatment with 900 mg/day by deletion of the requirement to titrate to 900 mg/day over a 3-day period. The new dosing direction was granted exclusivity therefore generic firms need to wait until September 29, 2001 and also recertify.

2. Patent/ Exclusivities:

   NCE exclusivity expired on December 30, 1998.

   D-43 exclusivity expires on September 29, 2001. It provides for "INITIATION OF TREATMENT WITH 900 MG/DAY BY DELETION OF THE REQUIREMENT TO TITRATE TO 900 MG/DAY OVER A 3-DAY PERIOD". A consult was submitted to the new drug review division to get clarification whether generic applications for gabapentin can be approved without this provision in the DOSAGE AND ADMINISTRATION section. The new drug review division said that the omission of the titration was not a result of safety concerns. There were discussions at higher levels to determine whether this application could be approved with the original dosing schedule. On July 19, 1999, Bob West said that we should go ahead and request that all generic firms revise their labeling to delete the titration and also require them to recertify.

   Patent 5084479 - U-125 - Treatment of neurogenerative Diseases. Expires January 2, 2010. The firm filed a paragraph IV certification stating they will not infringe on this patent because the labeling does not contain any information.

   Patent 4087544 - U-86 - Method of treating certain forms of epilepsy. The firm filed a paragraph III certification.

   Contacted Mary Ann Holovac regarding patent "5084479" and its listing in the Orange Book. She said generally they do not list patents for uses that are not approved in the labeling. This use is not listed in the labeling. She explained the abstract on the paten database page is not always the same as what the firm submits to them.

3. Storage/Dispensing Conditions:

NDA: Store at controlled room temperature 15° to 30°C (59° to 86°F).

ANDA: Store at controlled room temperature 15° to 30°C (59° to 86°F).

USP: NOT USP and NOT PF.

4. Product Line:

The innovator markets their product in three strengths (100 mg, 300 mg and 400 mg). They are packaged in bottles of 100s and unit dose packages of 50s.

The applicant proposes to market their product in three strengths (100 mg, 300 mg and 400 mg). They plan to market in bottles of 100s and 100s for the 100 mg and 300 mg and 100 s ——— for the 400 mg.

5. The capsule imprintings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). See pages 2307, 2380, and 2460, Vol. 1.2.

6. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statementof components and composition appearing on page 1868, Vol. 1.1.

7. All manufacturing will be performed by Torpharm. All outside firms are utilized for testing. See pages 2124 and 2118, Vol. 1.2.

8. Container/Closure:

This product will be packaged in HDPE bottles with a CRC cap with 100s ———————————. See page 2541, Vol. 1.3.

Date of Review: July 23, 1999
Date of Submission: December 10, 1998

Reviewer: Koung Lee KL **Date:** 1/27/99

Team Leader: Charlie Hoppes **Date:** 7/28/99

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cc: ANDA 75-360
DUP/DIVISION FILE
HFD-613/KLee/CHoppes (no cc)
V:\FIRMSNZ\TORPHARM\LTRS&REV\75360NA2.Labeling Review

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-360

Dates of Submission: December 13, 2002 , October 12, 1999

Applicant's Name: TorPharm

Established Name: Gabapentin Capsules, 100 mg, 300 mg & 400 mg

---

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes

Combined container and insert labeling -100s (Code # 201981, Rev. December 2002).
Satisfactory in FPL as of the December 13, 2002 submission (vol 7.1).

Revisions needed post-approval:.
CLINICAL PHARMACOLOGY- second paragraph, second sentence- change "100 mcM" to "100 mcgM"
ADVERSE REACTIONS- Epilepsy, second paragraph, last sentence-correct the spelling of "withdrawal".

BASIS OF APPROVAL:

Patent Data – 20-235

No	Expiration	Use Code	Use	File
4,894,476	11-02-08		Gabapentin monohydrate and a process for producing the same	IV
5,084,479	6--02-10		Novel methods for treating neurodegenerative diseases	IV
6,054,482	10-25-17		Lactam-free amino acids	IV

Exclusivity Data - 20-235

Code/sup	Expiration	Use Code	Description	Labeling Impact
I-354	5-24-05		Management of post herpetic neuralgia	Carved out
I-311	10-12-2003		Adjunctive therapy in the treatment of partial seizures in pediatric patients Age 3 to 12 years	Used pediatric labeling disclaimer statement
PED	4-12-04		" " "	" "

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Neurontin® Capsules
NDA Number: 20-235
NDA Drug Name: Neurontin® (gabapentin) Capsules
NDA Firm: Pfizer Inc.
Date of Approval of NDA Insert and supplement #: S-023/August 15. 2002
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR. First Generic ?		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been		X	

adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

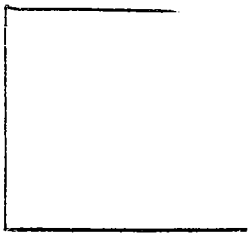
1. Review based on the labeling of the referenced listed drug, Neurontin®; NDA 20-235/S-023, approved on August 15, 2002. This supplement administratively provides for labeling reviewed and approved under NDA 21-397, NDA 21-423, AND NDA 21-424.

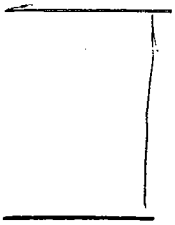
2. Torpharm has carved out all information pertaining to the management of post herpetic neuralgia, which is covered by exclusivity.

   The changes in labeling resulting from the Waxman Hatch exclusivity are as follows:

LABELING REVIEW
SIGNED OFF 12/16/02

1 page(s) of draft labeling has been removed from this portion of the review.





3. Storage/Dispensing Conditions:

NDA: Store at controlled room temperature 15^0 to 30^0C (59^0 to 86^0F).

ANDA: Store at controlled room temperature 15^0 to 30^0C (59^0 to 86^0F) (see USP)

USP: NOT USP

4. Product Line:

The innovator markets their product in the following strengths (100 mg, 300 mg, and 400 mg). They are packaged in bottles of 100s and unit dose packages of 50s.

The applicant proposes to market their product in three strengths (100 mg, 300 mg and 400 mg). They plan to market in bottles of 100s for the 100 mg, 300 mg and 400 mg.

The applicant originally proposed to market their product in bottles of —— for the 100 mg and 300 mg strengths and —— for the 400 mg. The applicant withdrew these package sizes because they do not intend to market these sizes. However, these sizes will remain in their stability program. (see Vol 4.1)

5. The capsule imprintings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). See pages 2307, 2380, and 2460, Vol. 1.6, 1.7.

6. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 1868, Vol. 1.5.

7. All manufacturing will be performed by Torpharm. All outside firms are utilized for testing. See pages 2124 and 2118, Vol. 1.6.

8. Container/Closure:

This product will be packaged in HDPE bottles with a CRC cap. See page 2541, Vol. 1.7.

Date of Review: December 16, 2002
Date of Submission: December 13, 2002, October 12, 1999 NC

Reviewer: Michelle Dillahunt Date: 12/16/02

Acting Team Leader: Lillie Golson Date: 12/16/02

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cc: ANDA 75-360
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
V:\FIRMSNZ\TORPHARM\LTRS&REV\75360AP.Labeling Review

THIS APPROVAL SUMMARY SUPERSEDES THE APPROVAL SUMMARY DATED 12/13/02

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-360

Dates of Submission: January 7, 2005

Applicant's Name: Apotex Inc.

Established Name: Gabapentin Capsules, 100 mg, 300 mg & 400 mg

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APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? No, electronic

Combined container and insert labeling -100s
Satisfactory in FPL as of the January 7, 2005 submission.
(electronic- \CDSESUBOGD1\N75360\N_000\2005-01-07)

Revisions needed pre-approval.
Apotex provided a commitment on 3/2/05 to make the changes indicated below in 1(b) and 2 prior to commercial distribution.
Apotex provided a commitment on 3/2/05 to make the change indicated below in 1(a) at the next revision of the labeling.

INSERT

1. ADVERSE REACTIONS
   a. Other Adverse Events Observed During All Clinical Trials, Clinical Trials in Adults and Adolescents, delete '[redacted]'

   b. Postmarketing and Other Experience, last sentence, delete " [redacted] ".

2. DOSAGE AND ADMINISTRATION
   Second paragraph, add the following as the last sentence, "...1 week (a longer period may be needed at the discretion of the prescriber).

BASIS OF APPROVAL:

Patent Data – 20-235

No	Expiration	Use Code	Use	File
4,894,476	11-02-08		Gabapentin monohydrate and a process for producing the same	IV
6,054,482	10-25-17		Lactam-free amino acids	IV

Exclusivity Data - 20-235

Code/sup	Expiration	Use Code	Description	Labeling Impact
I-354	5-24-05		Management of post herpetic neuralgia	Carved out

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Neurontin® Capsules
NDA Number: 20-235
NDA Drug Name: Neurontin® (gabapentin) Capsules
NDA Firm: Pfizer Inc.
Date of Approval of NDA Insert and supplement #: S-029/February 18, 2005
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 28		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR. First Generic ?		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling (continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X

Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. Review based on the labeling of the referenced listed drug, Neurontin®; NDA 20-235/S-029, approved on February 18, 2005.

2. Apotex has carved out all information pertaining to the management of post herpetic neuralgia, which is covered by exclusivity.

3. Storage/Dispensing Conditions:

   NDA: Store at 25° C (777°); excursions permitted to 15° to 30°C (59° to 86°F)[See USP Controlled Room Temperature]
   ANDA: Store at 20 to 25° C (68 to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature)
   USP: NOT USP

4. Product Line:

The innovator markets their product in the following strengths (100 mg, 300 mg, and 400 mg). They are packaged in bottles of 100s and unit dose packages of 50s.

The applicant proposes to market their product in three strengths (100 mg, 300 mg and 400 mg). They plan to market in bottles of 100s for the 100 mg, 300 mg and 400 mg.

The applicant originally proposed to market their product in bottles of —— for the 100 mg and 300 mg strengths and —— for the 400 mg. The applicant withdrew these package sizes because they do not intend to market these sizes. However, these sizes will remain in their stability program. (see Vol 4.1)

5. The capsule imprintings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). See pages 2307, 2380, and 2460, Vol. 1.6, 1.7.

6. Inactive Ingredients:

   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 1868, Vol. 1.5.

7. All manufacturing will be performed by Torpharm. All outside firms are utilized for testing. See pages 2124 and 2118, Vol. 1.6.

8. Container/Closure:

   This product will be packaged in HDPE bottles with a CRC cap. See page 2541, Vol. 1.7.

9. Torpharm, Inc has assumed the name of Apotex Inc. to reflect the name of its parent company effective April 1, 2004.

Date of Review: February 28, 2005
Date of Submission: January 7, 2005

Reviewer: Michelle Dillahunt Date: 3/3/05

Team Leader: Lillie Golson Date: 3/3/05

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cc: ANDA 75-360
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
V:\FIRMSNZ\TORPHARM\LTRS&REV\75360ap2.Labeling Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-360

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1

2. ~~ANDA # 75-360~~

APPEARS THIS WAY
ON ORIGINAL

3. NAME AND ADDRESS OF APPLICANT
Apotex Corp.
U.S. Agent for: Torpharm, a Division of Apotex, Inc.
Attention: Marcy MacDonald
50 Lakeview Parkway, Suite 127
Vernon Hills, Illinois 60061

4. LEGAL BASIS FOR SUBMISSION
Basis for submission is approved application for Neurontin capsules 100 mg, 200 mg and 400 mg held by Parke Davis. Patents 4,894,476 and 5,084,479, held by Warner-Lambert, expire on May 2, 2008 and Jan 2, 2010, respectively.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Gabapentin Capsules

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Orig Sub	04/17/98
NC	05/04/98
Ack Ltr	05/12/98
Amendment	06/03/98

10. PHARMACOLOGICAL CATEGORY
Treatment of Epilepsy

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Capsule

14. POTENCY
100 mg, 300 mg and 400 mg

15. CHEMICAL NAME AND STRUCTURE

Non-USP drug substance and drug product.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
See item #38.

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable.

19. REVIEWER:
Andrew J. Langowski

DATE COMPLETED:
07/01/98

Redacted 16 page(s)

of trade secret and/or

confidential commercial

information from

CHEM REVIEW #1

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-360

3. NAME AND ADDRESS OF APPLICANT
Apotex Corp.
U.S. Agent for: Torpharm, a Division of Apotex, Inc.
Attention: Marcy MacDonald
50 Lakeview Parkway, Suite 127
Vernon Hills, Illinois 60061

4. LEGAL BASIS FOR SUBMISSION
Basis for submission is approved application for Neurontin capsules 100 mg, 200 mg and 400 mg held by Parke Davis. Patents 4,894,476 and 5,084,479, held by Warner-Lambert, expire on May 2, 2008 and Jan 2, 2010, respectively.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Gabapentin Capsules

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Orig Sub	04/17/98
NC	05/04/98
Ack Ltr	05/12/98
Amendment	06/03/98
NA Ltr	09/29/98
Amendment	12/10/98

10. PHARMACOLOGICAL CATEGORY
Treatment of Epilepsy

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Capsule

14. POTENCY
100 mg, 300 mg and 400 mg

15. CHEMICAL NAME AND STRUCTURE
Non-USP drug substance and drug product.

17. COMMENTS
See item #38.

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable; Facsimile

19. REVIEWER:
Andrew J. Langowski

DATE COMPLETED:
06/14/99; 7/26/99

Redacted 16 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-360

3. NAME AND ADDRESS OF APPLICANT
Apotex Corp.
U.S. Agent for: Torpharm, a Division of Apotex, Inc.
Attention: Marcy MacDonald
50 Lakeview Parkway, Suite 127
Vernon Hills, Illinois 60061

4. LEGAL BASIS FOR SUBMISSION
Basis for submission is approved application for Neurontin capsules 100 mg, 200 mg and 400 mg held by Parke Davis. Patents 4,894,476 and 5,084,479, held by Warner-Lambert, expire on May 2, 2008 and Jan 2, 2010, respectively.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Gabapentin Capsules

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Orig Sub	04/17/98
NC	05/04/98
Ack Ltr	05/12/98
Amendment	06/03/98
NA Ltr	09/29/98
Amendment	12/10/98
NA Letter	07/29/99
Amendment	10/12/99

10. PHARMACOLOGICAL CATEGORY
Treatment of Epilepsy

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Capsule

14. POTENCY
100 mg, 300 mg and 400 mg

15. CHEMICAL NAME AND STRUCTURE
Non-USP drug substance and drug product.

17. COMMENTS
See item #38.

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable. Minor.

19. REVIEWER:
Andrew J. Langowski

DATE COMPLETED:
10/30/00

Redacted 11 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #3

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 75-360

3. NAME AND ADDRESS OF APPLICANT
Apotex Corp.
U.S. Agent for: Torpharm, a Division of Apotex, Inc.
Attention: Marcy MacDonald
50 Lakeview Parkway, Suite 127
Vernon Hills, Illinois 60061

4. LEGAL BASIS FOR SUBMISSION
Basis for submission is approved application for Neurontin capsules 100 mg, 200 mg and 400 mg held by Parke Davis. Patents 4,894,476 and 5,084,479, held by Warner-Lambert, expire on May 2, 2008 and Jan 2, 2010, respectively.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Gabapentin Capsules

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Orig Sub	04/17/98
NC	05/04/98
Ack Ltr	05/12/98
Amendment	06/03/98
NA Ltr	09/29/98
Amendment	12/10/98
NA Letter	07/29/99
Amendment	10/12/99

10. PHARMACOLOGICAL CATEGORY
Treatment of Epilepsy

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Capsule

14. POTENCY
100 mg, 300 mg and 400 mg

15. CHEMICAL NAME AND STRUCTURE
Non-USP drug substance and drug product.

17. COMMENTS
See item #38.

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable. Minor.

19. REVIEWER:
Andrew J. Langowski

DATE COMPLETED:
10/30/00

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CHEMISTRY REVIEW #4

1. CHEMISTRY REVIEW NO. 5

2. ANDA # 75-360

3. NAME AND ADDRESS OF APPLICANT
Apotex Corp.
U.S. Agent for: Torpharm, a Division of Apotex, Inc.
Attention: Marcy MacDonald
50 Lakeview Parkway, Suite 127
Vernon Hills, Illinois 60061

4. LEGAL BASIS FOR SUBMISSION
Basis for submission is approved application for Neurontin capsules 100 mg, 200 mg and 400 mg held by Parke Davis. Patents 4,894,476 and 5,084,479, held by Warner-Lambert, expire on May 2, 2008 and Jan 2, 2010, respectively.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Gabapentin Capsules

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Orig Sub	04/17/98
NC	05/04/98
Ack Ltr	05/12/98
Amendment	06/03/98
NA Ltr	09/29/98
Amendment	12/10/98
NA Letter	07/29/99
Amendment	10/12/99
Amendment	01/04/01

10. PHARMACOLOGICAL CATEGORY
Treatment of Epilepsy

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Capsule

14. POTENCY
100 mg, 300 mg and 400 mg

15. CHEMICAL NAME AND STRUCTURE
Non-USP drug substance and drug product.

17. COMMENTS
See item #38.

18. CONCLUSIONS AND RECOMMENDATIONS
Approve. Pending labeling.

19. REVIEWER: Andrew J. Langowski

DATE COMPLETED: 01/30/01

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CHEMISTRY REVIEW #5

1. CHEMISTRY REVIEW NO. 6

2. ANDA # 75-360

3. NAME AND ADDRESS OF APPLICANT

Torpharm
50 Steinway Boulevard
Etobicoke, Ontario
M9W 6Y3
Canada

U.S. Agent
Apotex Corpp.
Attention: Marcy MacDonald
50 Lakeview Parkway, Suite 127
Vernon Hills, Illinois 60061

4. LEGAL BASIS FOR SUBMISSION

Basis for submission is the approved application for Neurontin capsules 100 mg, 200 mg, and 400 mg held by Parke Davis. Patents 4,894,476, 5,084,479, and 6054482 held by Warner-Lambert, expire on May 2, 2008, Jan 2, 2010, and April 25, 2017, respectively.

Updated exclusivity statement is provided in the 6/7/02 Amendment. Torpharm labeling does not include the I-311 exclusivity, which expires on 10/12/03.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Gabapentin Capsules

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Orig Sub	04/17/98
NC	05/04/98
Ack Ltr	05/12/98
Amendment	06/03/98
NA Ltr	09/29/98
Amendment	12/10/98
NA Letter	07/29/99
Amendment	10/12/99
Amendment	01/04/01
Amendment	02/14/02
Amendment	06/07/02
T-con	06/13/02
Amendment	06/27/02

10. PHARMACOLOGICAL CATEGORY
Treatment of Epilepsy

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Capsule

14. POTENCY
100 mg, 300 mg, and 400 mg

15. CHEMICAL NAME AND STRUCTURE
Non-USP drug substance and drug product.

17. COMMENTS
Method validation request was submitted in 7/99. Results of MV are acceptable on 11/5/099.

Labeling is pending.

Bio-study for the 400 mg capsule and waiver request for the 100 mg and 300 mg capsules were found acceptable per review dated 9/15/98. Comparative in-vitro dissolution profiles have been submitted for the exhibit batches manufactured using the originally proposed drug substance source and the alternate drug substance source.

DMF ——— is adequate, 6/10/02. DMF ——— is inadequate, 6/10/02.

An acceptable EIR was issued from the Office of Compliance on 5/8/02. However, Apotex and ——————— are also used for testing the actives and will be added to the EER.

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable - Minor Amendment

19. REVIEWER:
Tao-Chin L. Wang

DATE COMPLETED:
6/11/02, 6/18/02, 7/1/02

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CHEMISTRY REVIEW #6

1. CHEMISTRY REVIEW NO. 7

2. ANDA # 75-360

3. NAME AND ADDRESS OF APPLICANT

Torpharm
50 Steinway Boulevard
Etobicoke, Ontario
M9W 6Y3
Canada

U.S. Agent
Apotex Corp.
Attention: Marcy MacDonald
50 Lakeview Parkway, Suite 127
Vernon Hills, Illinois 60061
Tel: 847-573-9999
Fax: 847-573-0857

4. LEGAL BASIS FOR SUBMISSION

Basis for submission is the approved application for Neurontin capsules 100 mg, 200 mg, and 400 mg held by Parke Davis. Patents 4,894,476, 5,084,479, and 6054482 held by Warner-Lambert, expire on May 2, 2008, Jan 2, 2010, and April 25, 2017, respectively.

Updated exclusivity statement is provided in the 6/7/02 Amendment. Torpharm labeling does not include the I-311 exclusivity, which expires on 10/12/03.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Gabapentin Capsules

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Orig Submission	04/17/98
NC	05/04/98
Ack Letter	05/12/98
Amendment	06/03/98
NA Letter	09/29/98
Amendment	12/10/98
NA Letter	07/29/99
Amendment	10/12/99
Amendment	01/04/01
Amendment	02/14/02
Amendment	06/07/02
T-con	06/13/02
Amendment	06/27/02
NA Letter	07/05/02
Amendment	07/22/02
Amendment	10/18/02

10. PHARMACOLOGICAL CATEGORY
Treatment of Epilepsy

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Capsule

14. POTENCY
100 mg, 300 mg, and 400 mg

15. CHEMICAL NAME AND STRUCTURE
Non-USP drug substance and drug product.

17. COMMENTS
Method validation request was submitted in 7/99. Results of MV are acceptable on 11/5/99.

Labeling is Pending. Labeling issues remain to be resolved.

Bio-study for the 400 mg capsule and waiver request for the 100 mg and 300 mg capsules were found acceptable per review dated 9/15/98. Comparative in-vitro dissolution profiles have been submitted for the exhibit batches manufactured using the originally proposed drug substance source and the alternate drug substance source.

DMF ——— is adequate, 6/26/02. DMF ——— is adequate, 10/29/02.

An acceptable EIR was issued from the Office of Compliance on 7/10/02.

The CMC section has been found satisfactory, 10/31/02.

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable

19. REVIEWER:
Tao-Chin L. Wang

DATE COMPLETED:
10/31/02

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CHEMISTRY REVIEW #7

1. CHEMISTRY REVIEW NO. 8

2. ANDA # 75-360 (Amendment of 8/19/2004)

Note: This amendment is nearly identical to the amendment of 7/29/2003, which was withdrawn. The review of the 7/29/2003 amendment was completed prior to withdrawal notification, and that review is the basis for this review.

3. NAME AND ADDRESS OF APPLICANT

Apotex (Torpharm)
50 Steinway Boulevard
Etobicoke, Ontario
M9W 6Y3
Canada

U.S. Agent
Apotex Corp.
Attention: Marcy MacDonald
50 Lakeview Parkway, Suite 127
Vernon Hills, Illinois 60061
Tel: 847-573-9999
Fax: 847-573-0857

4. LEGAL BASIS FOR SUBMISSION

Basis for submission is the approved application for Neurontin capsules 100 mg, 200 mg, and 400 mg held by Parke Davis. Patents 4,894,476, 5,084,479, and 6054482 held by Warner-Lambert, expire on May 2, 2008, Jan 2, 2010, and April 25, 2017, respectively.

Updated exclusivity statement is provided in the 6/7/02 Amendment. Torpharm labeling does not include the I-311 exclusivity, which expires on 10/12/03.

X 1742

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Gabapentin Capsules

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Orig Submission	04/17/98
NC	05/04/98
Ack Letter	05/12/98
Amendment	06/03/98
NA Letter	09/29/98
Amendment	12/10/98
NA Letter	07/29/99
Amendment	10/12/99
Amendment	01/04/01
Amendment	02/14/02
Amendment	06/07/02

T-con		06/13/02
Amendment		06/27/02
NA Letter		07/05/02
Amendment		10/18/02
Amendment	*(major)*	*7/29/03 (withdrawn)*
Amendment		*2/17/04 (response to Agency letter)*
Amendment	*(major)*	*8/19/04 (re-submitted)*

10. PHARMACOLOGICAL CATEGORY
Treatment of Epilepsy

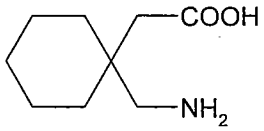
11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Capsule

14. POTENCY
100 mg, 300 mg, and 400 mg

15. CHEMICAL NAME AND STRUCTURE
Non-USP drug substance and drug product.



17. COMMENTS
The subject of this review is the MAJOR Amendment submitted on August 19, 2004 requesting an alternate source of the drug substance and adding Apotex, Inc. Signet campus as an alternate packaging and analytical site. The proposed supplier is ——— (DMF ———). The DMF was reviewed and found adequate on December 11, 2004 by DSkanchy. One batch of the dose proportional 400 mg strength (biobatch) was manufactured with ——— API and was shown to meet *current* release specifications and is comaparable to previously manufactured drug product. The amendment contains supporting stability data one lot for the 400 mg strength. Batch (FD2109) manufactured with the supplied API meets *currently approved* stability specifications and comparable dissolution profiles are provided. Additionally the applicant provides adequate specifications and validated test methods to ensure the strength, quality and purity of the ——— API. The specifications for the ——— material compare favorably to specifications approved for current suppliers.

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable (Minor)

19. REVIEWER: David Skanchy

DATE COMPLETED: 12/16/04

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CHEMISTRY REVIEW #8

1. CHEMISTRY REVIEW NO. 9

2. ANDA # 75-360 (Amendment of 2/1/2005)

Note: This amendment is the response to deficiencies for the 8/19/2004 amendment that was nearly identical to the amendment of 7/29/2003, which was withdrawn. The review of the 7/29/2003 amendment was completed prior to withdrawal notification, and that review is the basis for the review of the 8/19/2004 amendment.

3. NAME AND ADDRESS OF APPLICANT

Apotex (Torpharm)
50 Steinway Boulevard
Etobicoke, Ontario
M9W 6Y3
Canada

U.S. Agent
Apotex Corp.
Attention: Marcy MacDonald
50 Lakeview Parkway, Suite 127
Vernon Hills, Illinois 60061
Tel: 847-573-9999
Fax: 847-573-0857

4. LEGAL BASIS FOR SUBMISSION

Basis for submission is the approved application for Neurontin capsules 100 mg, 200 mg, and 400 mg held by Parke Davis. Patents 4,894,476, 5,084,479, and 6054482 held by Warner-Lambert, expire on May 2, 2008, Jan 2, 2010, and April 25, 2017, respectively.

Updated exclusivity statement is provided in the 6/7/02 Amendment. Torpharm labeling does not include the I-311 exclusivity, which expires on 10/12/03.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Gabapentin Capsules

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Orig Submission	04/17/98
NC	05/04/98
Ack Letter	05/12/98
Amendment	06/03/98
NA Letter	09/29/98
Amendment	12/10/98
NA Letter	07/29/99
Amendment	10/12/99
Amendment	01/04/01

Amendment	02/14/02	
Amendment	06/07/02	
T-con	06/13/02	
Amendment	06/27/02	
NA Letter	07/05/02	
Amendment	07/22/02	
Amendment	10/18/02	
Amendment (major)	*7/29/03*	*(withdrawn)*
Amendment	*2/17/04*	*(response to Agency letter)*
Amendment (major)	*8/19/04*	*(re-submitted)*
Amendment	*2/1/05*	*(response to Agency letter)*

10. PHARMACOLOGICAL CATEGORY
Treatment of Epilepsy

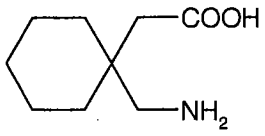
11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Capsule

14. POTENCY
100 mg, 300 mg, and 400 mg

15. CHEMICAL NAME AND STRUCTURE
Non-USP drug substance and drug product.



17. COMMENTS
The subject of this review is the response to deficiencies (amendment of 2/1/2005) issued for the MAJOR Amendment submitted on August 19, 2004 requesting an alternate source of the drug substance and adding Apotex, Inc. Signet campus as an alternate packaging and analytical site. The proposed supplier is ——— (DMF ———). The DMF was reviewed and found adequate on December 11, 2004 by DSkanchy. One batch of the dose proportional 400 mg strength (biobatch) was manufactured with——— API and was shown to meet *current* release specifications and is comaparable to previously manufactured drug product. The amendment contains supporting stability data one lot for the 400 mg strength. Batch (FD2109) manufactured with the ——— supplied API meets *currently approved* stability specifications and comparable dissolution profiles are provided. Additionally the applicant provides adequate specifications and validated test methods to ensure the strength, quality and purity of the——— API. The specifications for the ———material compare favorably to specifications approved for current suppliers. ***All chemistry deficiencies have been resolved and the***

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CHEMISTRY REVIEW #9

application is approvable pending review of the current labeling.

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable (pending labeling)

19. REVIEWER: David Skanchy

DATE COMPLETED: 3/01/05

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-360

BIOEQUIVALENCE REVIEW(S)

Gabapentin Capsules, 100 mg, 300 mg & 400 mg
ANDA #75-360
Reviewer: Hoainhon Nguyen
WP #75360sdw.498

Torpharm (Apotex Corp.)
Vernon Hills, IL
Submission Date:
April 17, 1998
July 15, 1998

Review of Three Bioequivalence Studies, Dissolution Data and a Waiver Request

I. Background:

Gabapentin is an anticonvulsant which is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but does not interact with GABA receptors, not converted metabolically into GABA or a GABA agonist, and not an inhibitor of GABA uptake or degradation. Gabapentin is indicated as an adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy.

All pharmacological actions following gabapentin administration are due to the activity of the parent compound; gabapentin is not appreciably metabolized in humans. Gabapentin bioavailability is not dose proportional; i.e., as dose is increased, bioavailability decreases. A 400-mg dose, for example, is about 25% less bioavailable than a 100-mg dose. Over the recommended dose range of 300 to 600 mg T.I.D., however, the differences in bioavailability are not large, and bioavailability is about 60%. Food has no effect on the rate and extent of absorption of gabapentin.

Gabapentin circulates largely unbound (<3%) to plasma protein. The apparent volume of distribution of gabapentin after 150 mg intravenous administration is approximately 58 L. In patients with epilepsy, steady-state predose (CMIN) concentrations of gabapentin in cerebralspinal fluid were approximately 20% of the corresponding plasma concentrations.

Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug. Gabapentin is not appreciably metabolized in humans.

Gabapentin elimination half-life is 5 to 7 hours and is unaltered by dose or following multiple dosing. Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance. In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced.

The most commonly observed adverse events associated with the use of gabapentin in combination with other antiepileptic drugs were somnolence, dizziness, ataxia, fatigue, and nystagmus.

Gabapentin is recommended for add-on therapy in patients over 12 years of age, with the effective dose being 900 to 1800 mg/day and given in divided doses (3 times a day) using 300- or 400-mg capsules.

The RLD product of gabapentin oral capsules is Neurontin® gabapentin capsules, 100 mg, 300 mg and 400 mg, manufactured by Parke-Davis.

On April 17, 1998, the firm submitted the results of a fasting, single-dose bioequivalence study and a post-prandial bioequivalence study comparing its Gabapentin Capsules, 400 mg, with Neurontin® Capsules, 400 mg. Comparative dissolution data for the test and RLD products of the 100 mg, 300 mg and 400 mg strengths are also submitted in support of the *in vivo* bioequivalence study waiver requests for the 100 mg and 300 mg strengths.

On July 15, 1998, the firm submitted, in addition, the results of a fasting, single-dose bioequivalence study comparing its Gabapentin Capsules, 100 mg, with Neurontin® Capsules, 100 mg.

II. Bioequivalence Studies:

A. Single-Dose Fasting Study of the **400 mg** Strength: (Protocol No. GACP/FA/0400-970715-(1)) Comparative Bioavailability Study of Gabapentin Capsules (Torpharm Inc.) and Neurontin Capsules

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Torpharm's Gabapentin 400 mg Capsules compared to Parke-Davis' Neurontin® 400 mg gabapentin capsules following a single 400 mg dose under fasting conditions.

Study Investigators and Facilities:

The study was conducted at Apotex Research Inc., Biomedical Division, Weston, Ontario, Canada, between November 14 and November 23, 1997. The principal investigator was A. Rein, M.D.. Plasma samples were assayed in the Bioanalytical Laboratory of Apotex Research Inc., Biomedical Division, Weston, Ontario, Canada, under the supervision of D. Watson, between January 23 and February 27, 1998.

Demographics:

Twenty-six normal, healthy non-smoking male volunteers between 18-50 years of age, and within 15% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a two-treatment, two-period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 65 - 93 kgs and 161 - 188 cms., respectively. Twenty subjects were caucasians, 3 blacks, 1 asian and 2 others.

Inclusion/exclusion criteria: See review attachment.

Restrictions:

They were free of all medications for at least 14 days prior to the study and allowed no concomitant medications during the study sessions. No alcoholic beverages and no xanthine-containing beverages or food were allowed for 48 hours prior to until 32 hours after dosing for each study period. The subjects fasted for overnight prior to and 4 hours after each drug administration. The washout duration between the phases was 7 days. Duration of confinement was at least 10 hours pre-dose to

approximately 32 hours post-dose.

Treatments and Sampling:

The two treatments consisted of a single 400 mg dose of either the test product or reference product taken orally with 240 ml of water, under fasting conditions.

Treatment A(Test Product): Torpharm's Gabapentin 400 mg capsules, lot # FD7077A(Batch size of ————————, potency of 100.8%).

Treatment B(Reference Product): Parke-Davis' Neurontin® 400 mg gabapentin capsules, lot # 09337V (Potency of 100.9%).

Blood samples were collected at predose, 0.33, 0.66, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24 and 32 hours following drug administration. Blood samples were centrifuged; the plasma was separated and stored at -20^{0}C pending assay.

Assay Methodology: The analytical method was developed and validated by Bioanalytical Laboratory of Apotex Research Inc., Biomedical Division. The assay of gabapentin included solid phase extraction of the drug and internal standard followed by derivatization and liquid-liquid clean up of the samples, and GC with EC detection.

Assay Specificity:

The assay was specific for gabapentin with no significant interferences seen at the retention time of the drug and internal standard in the chromatograms of the predose subject samples and blank plasma standards.

Linearity:

(Based on actual study standard curves)

The assay was linear in the range of 40.0 to 4000.0 ng/mL.

Reproducibility:

(Based on the interday CV of the actual study quality controls)

CV = 6.6% at 97.1 ng/mL, 6.3% at 1184.7 ng/mL and 10.5% at 2890.6 ng/ml.

Sensitivity:

(Based on actual study back-calculated standard data)

Sensitivity limit was 40.0 ng/mL (CV% = 3.2). Any level below these limits was reported as BLQ.

Prestudy assay validation CV% for LOQ (40.0 ng/mL) as a quality control was 12.2% (n=5), with mean S/N ratio of 13.6.

Accuracy:

(Based on the percent recovery of the actual study quality controls)

102.6% at 97.1 ng/mL, 102.7% at 1184.7 ng/mL and 100.7% at 2890.6 ng/mL.

NOTE: As an additional quality assurance procedure, the laboratory also selected 15% of the total samples analyzed and repeated them as blinded samples. 21% of the blind repeats exceeded the 20% difference from the initial results (There was no acceptance/rejection criteria for blind repeats).

Stability:

Long-term stability of frozen samples was demonstrated **in a pre-study validation study** using frozen control samples which were prepared, stored at -20°C, analyzed on Day 189 and compared to freshly prepared QC samples. The ratios of means Low (125.0 ng/mL) and High (2500.0 ng/mL) were

within 1.07 and 1.04. The actual freezer storage duration for the study samples was not more than 105 days (from November 14, 1997 to February 27, 1998).

Short-term stability (19 hours at room temperature), acidified plasma stability (90 minutes), freeze-thaw stability (3 cycles) and extracted sample stability (30 hours at room temperature and 168 hours at +4°C) were evaluated and acceptable.

Pharmacokinetic Results:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : AUC(0-Infinity) = AUC(0-T) + [last measured concentration/ KEL]. CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Analyses:

Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for log-transformed AUCs and CMAX. The 90% confidence intervals for lnAUCs and lnCMAX were calculated, based on least squares means, using the two, one-sided t-test.

Results:

Twenty-five of 26 enrolled volunteers completed the clinical portion of the study. Subject #7 was withdrawn from the study due to positive drug screen (nicotine). Subject #16 also had positive drug screen (caffeine) but was allowed to complete the study. In the data analysis, these two subjects were replaced with alternates #25 and 26. Data of 24 subjects therefore were analyzed.

There was no significant difference (alpha=0.05) between treatments for LAUC(0-T), LAUC(0-Inf) or LCMAX. The results are summarized in the tables below:

Table I
Gabapentin Comparative Pharmacokinetic Parameters
Dose=400 mg; n=24
Fasting Study

Parameters	Test Mean(CV%)	Reference Mean(CV%)	90% C.I.	Ratio T/R
AUC (0-T) ng.hr/mL	27250*	27751*	[0.93;1.04]	0.98
AUC(0-Inf) ng.hr/mL	28017*	28531*	[0.93;1.04]	0.98
CMAX ng/mL	3013*	3152*	[0.89;1.02]	0.96
TMAX (hrs)	2.54(37)	3.03(31)		
KEL (1/hrs)	0.1262(16)	0.1255(16)		
T1/2 (hrs)	5.65(18)	5.71(22)		

*Geometric LSMeans

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Table II
Comparative Mean Plasma Levels of Gabapentin
Dose=400 mg; n=24
ng/ml(CV%)
Fasting Study

Hour	Test	Reference
0	0	0
0.33	240.4(92)	268.1(80)
0.66	1369(38)	1462(35)
1	1940(35)	1983(24)
1.50	2373(26)	2263(20)
2	2801(24)	2794(19)
2.50	2801(25)	2888(22)
3	2718(24)	2797(26)
3.50	2708(25)	2685(19)
4	2606(23)	2599(19)
5	2261(18)	2272(23)
6	1958(22)	1972(21)
8	1476(22)	1477(21)
10	1150(24)	1155(17)
12	861.5(22)	895.0(29)
16	502.8(24)	508.9(28)
24	188.6(30)	194.2(36)
32	71.5(60)	80.5(69)
$AUC(0\text{-}T)_{ng.hr/ml}$	27797(20)	28208(18)
$AUC(0\text{-}Inf)_{ng.hr/ml}$	28533(19)	29017(18)
CMAX	3086(22)	3202(18)

Adverse Effects:

There was no serious adverse event reported. Four and five mild adverse reactions were reported during the reference and test treatment, respectively. The possibly drug-related reactions included drowsiness, lightheadedness and headache.

B. Non-Fasting, Single-Dose Study of the **400 mg** Strength: (Protocol No. GACP/FF/0400-980416-(1)) Comparative Bioavailability Study of Gabapentin Capsules (Torpharm) and Neurontin Capsules (Parke-Davis) Under Fed and Fasted Conditions

Study Objective:

The purpose of this study is to determine the relative bioavailability of two preparations of gabapentin under both fasted and fed conditions.

Study Investigators and Facilities:

The study was conducted at the Apotex Research Inc., Biomedical Division, Clinical Studies Dept., Weston, Ontario, Canada, between April 21 and May 7, 1998. The principal investigator was A. Rein, M.D.. Plasma samples were assayed by Bioanalytical Laboratory of Apotex, Weston, Canada, under the supervision of Doug Watson, between May 9 and June 12, 1998.

Demographics:

Eighteen normal, healthy male volunteers between 19-37 years of age, and within 15% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a three-treatment, three-period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 62 - 92 kgs and 168 - 188 cms., respectively. Subjects included caucasian(12), black(4) and asian(2).

Inclusion/exclusion criteria and Restriction: Same as in Fasting Study Protocol above, except that:

For the fasting leg of the study, the subjects fasted for overnight prior to and 4 hours after each drug administration. For the non-fasting legs of the study, the subjects fasted for overnight until 30 minutes prior to their scheduled dosing times, when they were given a standard breakfast. The standard breakfast consisted of 1

buttered English muffin, 1 fried egg, 1 slice of processed cheese, 1 slice bacon, one serving of hash brown potatoes, 180 ml of orange juice and 250 ml whole milk.

Treatments and Sampling:

The three treatments consisted of a single 400 mg dose of either the test product or reference product taken orally with 240 ml of water.

Treatment A(Test Product/Fasting): Torpharm's Gabapentin 400 mg capsules, lot # FD7077A (Batch size of ————————, potency of 101.3%), taken after an overnight fast.

Treatment B(Test Product/Non-Fasting): same as above except the test product was taken immediately after the standard breakfast.

Treatment C(Reference product/Non-Fasting): Parke-Davis's Neurontin® 400 mg capsules, lot # 09337V (Potency of 102.4%).

Blood samples were collected at predose, 0.33, 0.66, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24 and 32 hours following drug administration. For blood collection procedure, see Fasting Study Protocol above.

Assay Methodology: Same as in Fasting Study Protocol except that:

Reproducibility:

(Based on the interday CV of the actual study quality controls)

6.3% at 102.9 ng/mL, 6.4% at 1182 ng/mL and 8.6% at 3008 ng/mL.

Accuracy:

(Based on the percent recovery of the actual study quality controls)

94.9% at 102.9 ng/mL, 101.4% at 1182 ng/mL and 101.1% at 3008

ng/mL.

Stability:

The maximum actual freezer storage duration for the study samples was not more than 52 days (from April 21 to June 12, 1998). The stability studies as reported in the Fasting Study above are acceptable for the Non-Fasting Study also.

Pharmacokinetic Results:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : AUC(0-Infinity) = AUC(0-T) + [last measured concentration/ KEL]. CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Analyses:

Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for log-transformed AUCs and CMAX.

Results:

All 18 enrolled volunteers completed the clinical portion of the study. Data from 18 subjects were included in the final statistical analyses.

There was no significant difference (alpha=0.05) between treatments for lnAUC(0-T), lnAUC(0-Inf), or lnCMAX. The results are summarized in the tables below:

Table III
Gabapentin Comparative Pharmacokinetic Parameters
Dose=400 mg; n=18
Non-Fasting Study

Parameters	Test's (Fasted)A Mean(CV%)	Test's (Fed)B Mean(CV%)	Reference's (Fed)C Mean(CV%)	Ratio T(fed)/R(fed) (B/C)
AUC (0-T) ng.hr/mL	28063*	30021*	28778*	1.04
AUC(0-Inf) ng.hr/mL	28730*	30850*	29531*	1.04
CMAX ng/mL	3183.4*	3431.3*	3228.6*	1.06
TMAX (hrs)	3.139(31)	3.806(13)	3.361(17)	
KEL (1/hrs)	0.124(13)	0.129(12)	0.128(12)	
T1/2 (hrs)	5.672(11)	5.452(11)	5.501(11)	

*Geometric LSMeans

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Table IV
Comparative Mean Plasma Levels of Gabapentin
Dose=400 mg; n=18
ng/ml(CV%)
Non-Fasting Study

Hour	Test(fasted)(A)	Test(fed)(B)	Reference(fed)(C)
0	0	0	0
0.33	324.7(81)	20.2(244)	3.8(424)
0.66	1592(39)	177.1(175)	148.4(100)
1	2215(35)	527.9(104)	542.4(67)
1.50	2670(33)	1353(56)	1366(48)
2	2781(35)	2054(38)	2134(34)
2.50	2889(36)	2665(30)	2506(23)
3	2778(27)	2971(18)	2969(26)
3.50	2893(31)	3347(19)	3018(18)
4	2879(30)	3315(21)	3086(20)
5	2332(22)	2927(12)	2717(18)
6	1979(23)	2328(11)	2257(18)
8	1462(20)	1808(17)	1772(28)
10	1119(20)	1378(16)	1322(25)
12	849.5(23)	1038(15)	988.0(30)
16	514.9(27)	573.9(18)	571.6(32)
24	194.2(28)	226.4(28)	227.1(30)
32	76.2(38)	82.3(47)	80.0(46)
$AUC(0\text{-}T)_{ng.hr/ml}$	28674(22)	30327(14)	29359(21)
$AUC(0\text{-}Inf)_{ng.hr/ml}$	29347(21)	31164(14)	30103(21)
CMAX	3334(31)	3491(19)	3297(21)

Adverse Effects:

There was no serious adverse event reported. Eleven, seven and six mild adverse reactions were reported during the test(fasted), test(fed) and reference(fed) treatment, respectively. The possibly drug-related reactions included mental slowdown, sleepiness and lightheadedness.

C. Single-Dose Fasting Study: (Protocol No. GACP/FA/0100-970612-(1)) Comparative Bioavailability Study of Gabapentin **(100 mg)** Capsules (Torpharm Inc.) and Neurontin **(100 mg)** Capsules

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Torpharm's Gabapentin 100 mg Capsules compared to Parke-Davis' Neurontin® 100 mg gabapentin capsules following a single 100 mg dose under fasting conditions.

Study Investigators and Facilities:

The study was conducted at Apotex Research Inc., Biomedical Division, Weston, Ontario, Canada, between October 31 and November 9, 1997. The principal investigator was A. Rein, M.D.. Plasma samples were assayed in the Bioanalytical Laboratory of Apotex Research Inc., Biomedical Division, Weston, Ontario, Canada, under the supervision of D. Watson, between January 15 and April 2, 1998.

Demographics:

Twenty-six normal, healthy non-smoking male volunteers between 24-44 years of age, and within 15% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a two-treatment, two-period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 62 - 93 kgs and 164 - 189 cms., respectively. The subjects included caucasians(21), black(3) and asian(2).

Inclusion/exclusion criteria/restrictions: See Fasting Study for the 400 mg strength above.

Treatments and Sampling:

The two treatments consisted of a single 100 mg dose of either the test product or reference product taken orally with 240 ml of water, under fasting conditions.

Treatment A(Test Product): Torpharm's Gabapentin 100 mg capsules, lot # FD7074A(Batch size of _____, potency of 103.0%).

Treatment B(Reference Product): Parke-Davis' Neurontin® 100 mg gabapentin capsules, lot # 01747VA (Potency of 102.6%).

Blood samples were collected as in the Fasting Study for the 400 mg strength above.

Assay Methodology: Same as in Fasting Study Protocol except that:

Linearity:

(Based on actual study standard curves)

The assay was linear in the range of 20.0 to 2000.0 ng/mL.

Reproducibility:

(Based on the interday CV of the actual study quality controls)

7.3% at 50.1 ng/mL, 5.3% at 589.9 ng/mL and 9.3% at 1485 ng/mL.

Accuracy:

(Based on the percent recovery of the actual study quality controls)

97.1% at 50.1 ng/mL, 96.0% at 589.9 ng/mL and 97.2% at 1485 ng/mL.

NOTE: As an additional quality assurance procedure, the laboratory also selected 15% of the total samples analyzed and repeated them as blinded samples. 36% of the blind repeats exceeded the 20% difference from the initial results (There was no acceptance/rejection criteria for blind repeats).

Sensitivity:

(Based on actual study back-calculated standard data)

Sensitivity limit was 20.0 ng/mL (CV% = 14.8). Any level below these limits was reported as BLQ.

Prestudy assay validation CV% for LOQ (20.0 ng/mL) as a quality control was 9.8% (n=5), with mean S/N ratio of 36.4.

Stability:

The maximum actual freezer storage duration for the study samples was not more than 181 days (from October 3, 1997 to April 2, 1998). The stability studies as reported in the Fasting Study of the 400 mg strength above are acceptable for the Fasting Study of the 100 mg strength also.

Pharmacokinetic Results:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : AUC(0-Infinity) = AUC(0-T) + [last measured concentration/ KEL]. CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Analyses:

Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for log-transformed AUCs and CMAX. The 90% confidence intervals for lnAUCs and lnCMAX were calculated, based on least squares means, using the two, one-sided t-test.

Results:

Twenty-five of 26 (including 2 alternates) enrolled volunteers completed the clinical portion of the study. Subject #8 was withdrawn from the study due to positive drug screen (caffeine), and was replaced by Subject #25. Data from alternate Subject #26 was not analyzed per protocol. Data of 24 subjects therefore were analyzed.

There was no significant difference (alpha=0.05) between treatments for LAUC(0-

WP# 75360 sdw. 498 Attachment (1 of 4)

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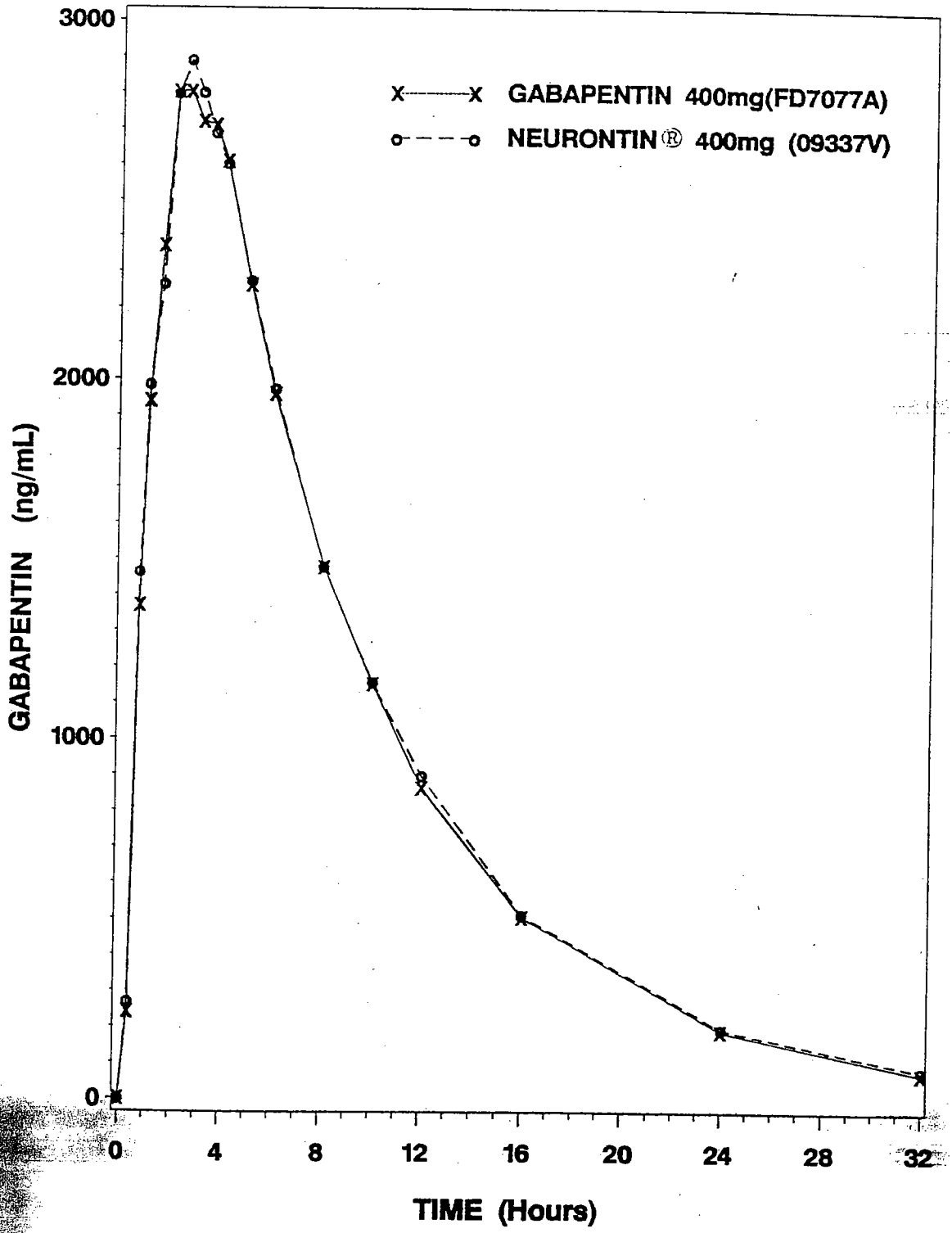
A SINGLE DOSE COMPARATIVE BIOAVAILABILITY STUDY IN FASTING HEALTHY VOLUNTEERS:
GABAPENTIN 400mg(FD7077A) CAPSULES vs NEURONTIN ® 400mg (09337V) CAPSULES

Fig. 1.1 Average Concentration – Time Profile for All Subjects



T), LAUC(0-Inf), LCMAX, TMAX, T1/2 or KEL. The results are summarized in the tables below:

Table V
Gabapentin Comparative Pharmacokinetic Parameters
Dose=100 mg; n=24
Fasting Study

Parameters	Test Mean(CV%)	Reference Mean(CV%)	90% C.I.	Ratio T/R
AUC (0-T) ng.hr/mL	9312*	9335*	[0.96;1.04]	1.00
AUC(0-Inf) ng.hr/mL	9622*	9638*	[0.98;1.10]	1.04
CMAX ng/mL	1103*	1064*	[0.98;1.10]	1.04
TMAX (hrs)	2.81(47)	2.63(50)		
KEL (1/hrs)	0.1358(10)	0.1330(12)		
T1/2 (hrs)	5.15(9)	5.27(10)		

*Geometric LSMeans

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Table VI
Comparative Mean Plasma Levels of Gabapentin
Dose=100 mg; n=24
ng/ml(CV%)
Fasting Study

Hour	Test	Reference
0	0	0
0.33	124.6(76)	136.3(99)
0.66	605.0(40)	614.2(45)
1	794.8(31)	815.0(28)
1.50	884.7(26)	930.4(22)
2	1047(22)	1026(21)
2.50	1017(19)	980.6(22)
3	953.1(19)	904.5(19)
3.50	909.9(21)	877.0(22)
4	868.4(19)	877.0(22)
5	767.7(20)	742.1(18)
6	652.6(18)	633.3(19)
8	499.0(19)	500.6(18)
10	390.2(20)	388.2(20)
12	292.1(20)	289.1(21)
16	167.8(23)	170.4(26)
24	60.5(29)	63.6(32)
32	9.2(138)	11.7(123)
$AUC(0\text{-}T)_{ng.hr/ml}$	9436(16)	9411(16)
$AUC(0\text{-}Inf)_{ng.hr/ml}$	9740(16)	9718(16)
CMAX	1120(17)	1084(19)

Adverse Effects:

There was no serious adverse event reported. Three and one mild adverse reactions were reported during the reference and test treatment, respectively. One possibly drug-related reaction was lightheadedness.

III. Dissolution Testing: **FDA-recommended method**

Drug (Generic Name): Gabapentin Capsules Firm: Torpharm/Apotex Inc.
Dose Strength: 100 mg, 300 mg & 400 mg ANDA# 75-360
Submission Date: April 17 and July 15, 1998

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:
USP XXIII Basket__ Paddle X RPM 50 rpm Units Tested: 12
Medium: 0.1N HCl Volume: 900 ml
Reference Drug: (Manuf.) Neurontin Capsules (Parke-Davis)
Assay Methodology: Not given
Specifications: NLT—% in 20 minutes

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Lot # FD7077 Strength (mg) 400		Reference Product Lot # (L)09337V Strength (mg) 400	
	Mean % Dissolved(CV%)	Range	Mean % Dissolved(CV%)	Range
10	92(4)	———	92(7)	———
15	97(3)	———	98(2)	———
20	99(2)	———	99(2)	———
30	101(2)	———	100(2)	———

Sampling Times (Min.)	Test Product Lot # FD7074 Strength (mg) 100		Reference Product Lot # (L) 01747VA Strength (mg) 100	
	Mean % Dissolved(CV%)	Range	Mean % Dissolved(CV%)	Range
10	98(6)	———	95(4)	———
15	102(2)	———	100(2)	———
20	103(2)	———	101(2)	———
30	103(3)	———	102(1)	———

Sampling Times (Min.)	Test Product Lot # FD7075 Strength (mg) 300		Reference Product Lot # (L) 06017V Strength (mg) 300	
	Mean % Dissolved(CV%)	Range	Mean % Dissolved(CV%)	Range
10	92(5)	———	89(7)	———
15	98(3)	———	96(3)	———
20	101(2)	———	99(2)	———
30	101(2)	———	102(2)	———

IV. Comments:

1. The single-dose, fasting bioequivalence study and the single-dose postprandial bioequivalence study for the 400 mg strength demonstrate that the test product is equivalent to the reference product in their rate and extent of absorption as measured by lnCMAX, lnAUC(0-T) and lnAUC(0-Infinity) under fasting and non-fasting conditions.

2. The single-dose, fasting bioequivalence study for the 100 mg strength demonstrates that the test product is equivalent to the reference product in their rate and extent of absorption as measured by lnCMAX, lnAUC(0-T) and lnAUC(0-Infinity) under fasting.

3. The in vitro dissolution data for the test and reference products of all strengths are acceptable.

4. The formulations of the 300 mg strength of the test product is proportionally similar to that of both the 100 mg and 400 mg which underwent the bio studies (See comparative formulations attached).

5. A single-dose, non-fasting bioequivalence study is not required for the 100 mg strength.

V. Recommendations:

1. The single-dose, fasting bioequivalence study and the single-dose post-prandial bioequivalence study conducted by Torpharm (Apotex) on the test product,

Gabapentin 400 mg, lot # FD7077, comparing it with the reference product, Parke-Davis' Neurontin® Capsules, 400 mg, lot # (L)09337V, have been found acceptable by the Division of Bioequivalence. The studies demonstrate that the test product, Torpharm's Gabapentin Capsules, 400 mg, is bioequivalent to the reference product, Parke-Davis' Neurontin® 400 mg Capsules, under fasting and non-fasting conditions.

2. The single-dose, fasting bioequivalence study conducted by Torpharm (Apotex) on the test product, Gabapentin 100 mg, lot # FD7074, comparing it with the reference product, Parke-Davis' Neurontin® Capsules, 100 mg, lot # (L)01747VA, has been found acceptable by the Division of Bioequivalence. The studies demonstrate that the test product, Torpharm's Gabapentin Capsules, 100 mg, is bioequivalent to the reference product, Parke-Davis' Neurontin® 100 mg Capsules.

A single-dose, non-fasting bioequivalence study is not required for the 100 mg strength.

3. The in-vitro dissolution testing conducted by Torpharm on its Gabapentin Capsules, 100 mg, 300 mg and 400 mg, has been found acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP XXIII apparatus II(paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than —% of the labeled amount of the drug in the dosage form is dissolved in 20 minutes.

4. ~~3~~. The firm has demonstrated that the formulation of its Gabapentin Capsules, 300 mg, is proportionally similar to that of both the 100 mg and 400 mg strengths that underwent acceptable in vivo bioequivalence testing. The waiver of in vivo bioequivalence study requirements for the 300 mg capsules is granted. The firm's Gabapentin Capsules, 300 mg, are therefore deemed bioequivalent to Parke-Davis' Neurontin®Capsules, 300 mg.

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 9/28/98

Concur: Dale P. Conner Date: 10/2/98
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

cc: ANDA # 75-360 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
HNguyen/09-15-98/WP #75360sdw.498
Also as X:\new\firmsnz\torpharm\ltrs&rev\75360sdw.498
Attachment: 4 pages

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WP #75360sdw.498 Attachment I

Criteria for Inclusion:

a) Meeting the sex, age and weight requirements.
b) Passing the medical examination.
c) Signing the Informed Consent Form.
d) Acceptable alcohol and/or drug screen at check-in.
e) Subjects must be non-smokers.

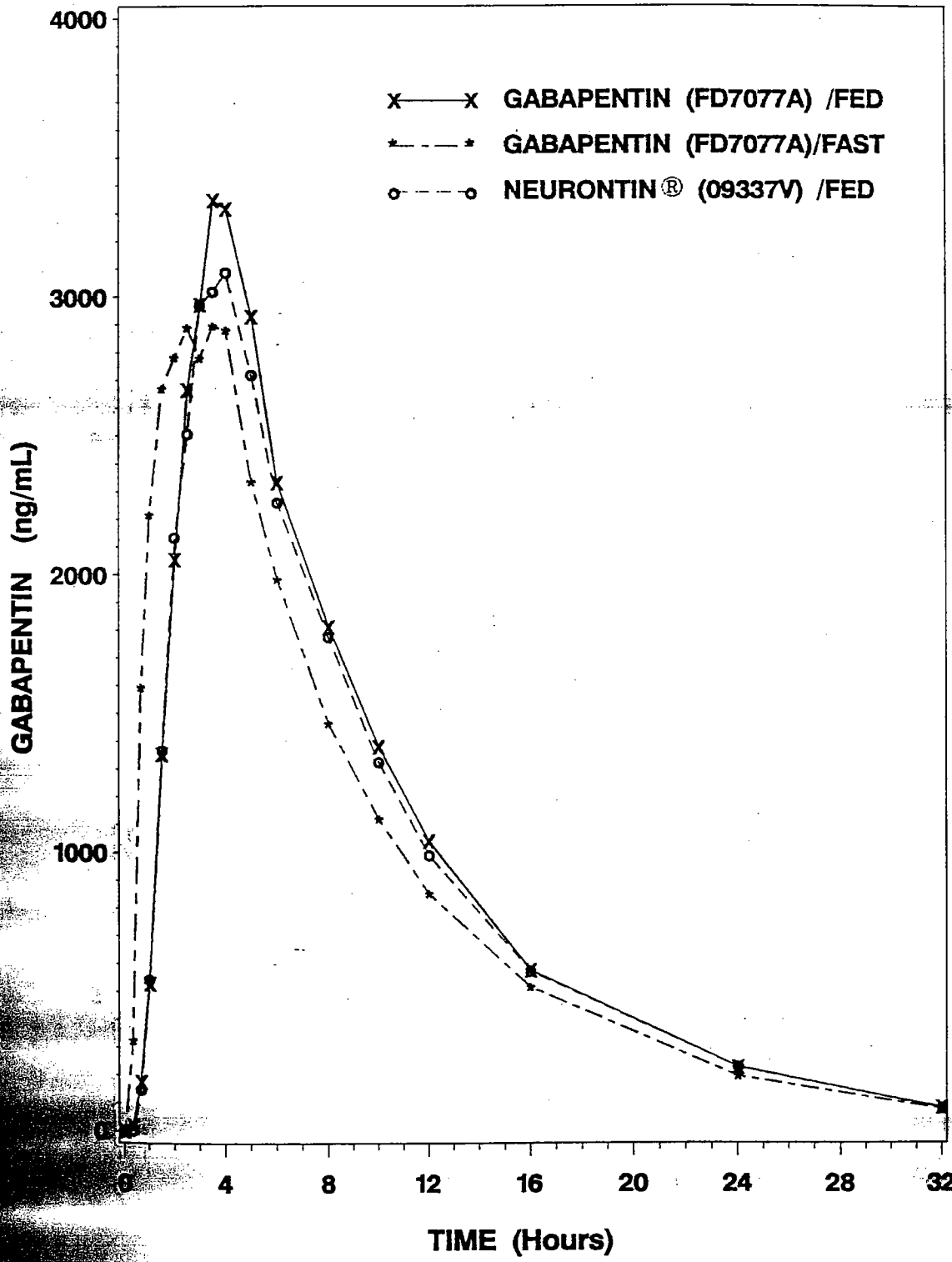
Criteria for Exclusion:

a) A history or presence of significant asthma, chronic bronchitis, migraine, hypertension, cardiovascular, pulmonary, neurological, hepatic, renal, hematopoietic or gastrointestinal or ongoing infectious diseases, as evidenced by a medical history and physical examination.
b) Blood chemistry (glucose, urea, creatinine, urate, total bilirubin, aspartate transaminase, alkaline phosphatase, laccate dehydrogenase, calcium, total protein, albumin), hematology (red blood cell count, white blood cell count, hemoglobin, hematocrit, platelet count, absolute differential, RBC morphology, WBC morphology, platelets, sedimentation rate), and urinalysis (pH, specific gravity, appearance, color, protein, glucose, ketone, blood) values outside clinically acceptable limits upon evaluation by the investigator.
c) Significant abnormality found in the medical history, physical examination, laboratory tests or ECG.
d) Known sensitivity to gabapentin.
e) Requiring other medication at the time of the study.
f) History of drug or alcohol abuse.
g) Poor veins, fear of venipuncture or sight of blood.
h) Participation in an investigational drug study within a minimum of 30 days prior to the study.
i) Blood donation of 100 mL or more within a minimum of 30 days prior to the study.
J) Positive urine screen for diazepam
k) History of renal problems

WPA 75360 sdw. 498 Attachment (2 of 4)

A SINGLE DOSE COMPARATIVE BIOAVAILABILITY STUDY IN FED HEALTHY VOLUNTEERS:
GABAPENTIN CAPSULES 400 mg (TorPharm) vs. NEURONTIN ® CAPSULES 400 mg (Parke-Davis)

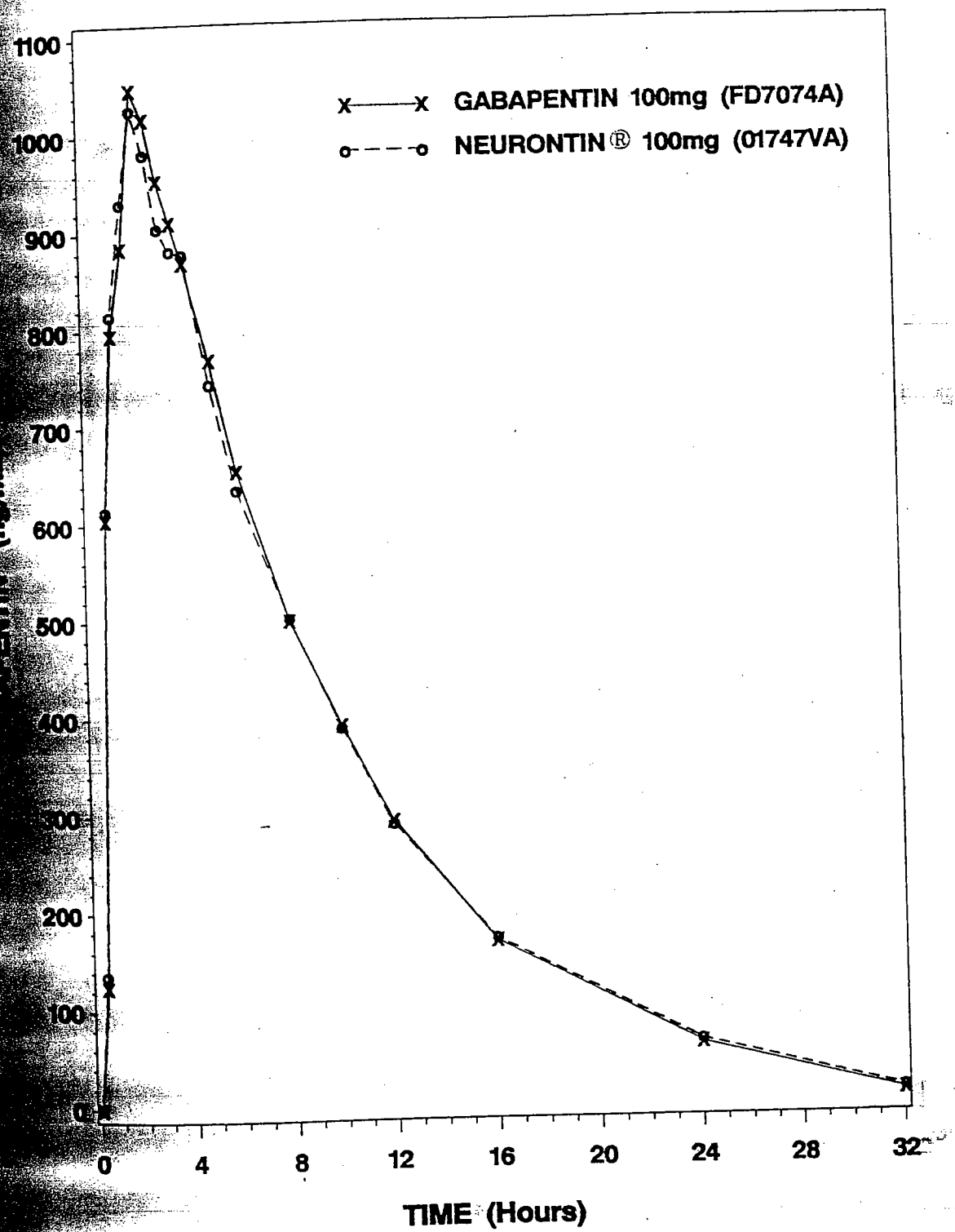
Fig. 1.1 Average Concentration-Time Profile for All Subjects



WP# 75360sdw.498 Attachment (3 of 4)
010005

SINGLE DOSE COMPARATIVE BIOAVAILABILITY STUDY IN FASTING HEALTHY VOLUNTEERS:
GABAPENTIN 100mg (FD7074A) CAPSULES vs NEURONTIN ® 100mg (01747VA) CAPSULES

Fig. 1.1 Average Concentration – Time Profile for All Subjects



WP# 75360 sdw. 498 Attachment (4 of 4)

4. Formulation Data

The following table summarizes, by strength, the components and composition of Gabapentin Capsules 100 mg, 300 mg and 400 mg.

THEORETICAL AMOUNT PER Capsule (mg)			
Ingredient	Gabapentin Capsules		
	100 mg	300 mg	400 mg
Gabapentin	100.0	300.0	400.0
Croscarmellose Sodium NF			
Magnesium Stearate NF			
Total			
Total to encapsulation			
ENCAPSULATION			
Capsule Hard Gelatin Size 4 coded APO 112		N/A	N/A
Capsule Hard Gelatin Size 1 coded APO 113	N/A		N/A
Capsule Hard Gelatin Size 0 coded APO 114	N/A	N/A	

was not required.

CC:ANDA 75-360
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ YHuang 9/28/98
HFD-617/ L. Sanchez or N.Chamberlin
HFD-650/ D. Conner 10/2/98

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BIOEQUIVALENCY - ACCEPTABLE Submission date: 04-17-98
07-15-98

1. FASTING STUDY (STF) 4/17/98 Strengths: 400 MG
   Clinical: Apotex Research **Outcome: AC**
   Analytical: Apotex Research

2. NON-FASTING STUDY (STP) 7/15/98 Strengths: 400 MG
   Clinical: Apotex Research **Outcome: AC**
   Analytical: Apotex Research

3. FASTING STUDY (STF) 7/15/98 Strengths: 100 MG
   Clinical: Apotex Research **Outcome: AC**
   Analytical: Apotex Research

4. DISSOLUTION WAIVER (DIW) 4/17/98 Strengths: 300 MG, 100 mg & ~~400 mg~~
   Outcome: AC

Outcome: AC

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable

WINBIO COMMENTS:

BIOEQUIVALENCY COMMENTS

ANDA: 75-360 APPLICANT: Torpharm (Apotex)

DRUG PRODUCT: Gabapentin Capsules, 100 mg, 300 mg & 400 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following, FDA-recommended dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of 0.1N HCl, at 37°C using USP23 Apparatus II(paddle) at 50 rpm. The test product should meet the following specifications:
>
> Not less than ___% (Q) of the labeled amount of the drug in the dosage form is dissolved in 20 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Gabapentin Capsules	Torpharm (Apotex Corp.)
100 mg, 300 mg & 400 mg	Vernon Hills, IL
ANDA # 75-360	Submission Date:
Reviewer: Hoainhon Nguyen	April 17, 1998*
W #75360a.498	July 15, 1998*

*Addendum to a Previous Review

This addendum is to clarify the current FDA-recommended dissolution method and specification for the above drug product.

1. In the previous review of the referenced submissions, the Division of Bioequivalence has found acceptable the firm's dissolution data, along with *in vivo* bioequivalence study results. In the agency's correspondence following this review, the firm was informed that *"The following, FDA-recommended dissolution testing will need to be incorporated into your stability and quality control programs: The dissolution testing should be conducted in 900 mL of 0.1N HCl, at 37°C using USP23 Apparatus II(paddle) at 50 rpm. The test product should meet the following specifications: Not less than —%(Q) of the labeled amount of the drug in the dosage form is dissolved in 20 minutes."*

At this time, the dissolution medium of 0.1N HCl was also recommended for another ANDA (See the review of ANDA#75-350 (Gabapentin Capsules by Purepac Pharm.) submission dated March 30, 1998 by Dr. S.P. Shrivastava). For another gabapentin product, however, the dissolution medium of 0.06N HCl was recommended (Gabapentin Capsules by Geneva, Protocol No. 97-022). Since the reviewer of ANDA #75-360 considered the difference between 0.1 N HCl and 0.06N HCl not significant, the dissolution data obtained using 0.1N HCl were judged acceptable. The firm was therefore recommended to keep its original dissolution method using 0.1 N HCl, as shown above.

Presently, in the effort to maintain the consistency in dissolution testing of the drug product, the dissolution medium of 0.06N HCl instead of 0.1N HCl is confirmed and required for the product's stability and quality control program. The firm is not required to repeat the dissolution testing for its test product, but only to follow the requirement

in the future testing. The firm is asked to commit to submit to the Division of Bioequivalence the earliest dissolution results obtained using the dissolution medium of 0.06 N HCl.

2. In addition, the firm is reminded that the specification for the dissolution testing remains *"Not less than —%(Q) of the labeled amount of the drug in the dosage form is dissolved in 20 minutes"*. The specification should be reflected in the firm's stability and quality control document such as the CMC files.

In summary, the following, FDA-recommended dissolution testing will need to be incorporated into the firm's stability and quality control programs: **The dissolution testing should be conducted in 900 mL of 0.06N HCl, at 37°C using USP23 Apparatus II(paddle) at 50 rpm. The test product should meet the following specifications: Not less than —%(Q) of the labeled amount of the drug in the dosage form is dissolved in 20 minutes.**

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 7/20/99

Concur: Dale P. Conner Date: 7/20/99
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 75-360 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
HNguyen/07-08-99/W #75360a.498
Also as V:\firmsnz\torpharm\ltrs&rev\75360a.498
Attachment: 0 page

CC:ANDA 75-360
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ YHuang 7/20/99
HFD-617/ E. Hu 7/21/99
HFD-650/ D. Conner 7/20/99

V:\FIRMSNZ\torpharm\ltrs&rev\75360a.498
Printed in final on / /

REVIEW ADDENDUM Submission date: 4-17-98
7-15-98

Please enter as US DOCUMENT. AC

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable

WINBIO COMMENTS:

BIOEQUIVALENCY COMMENTS

ANDA: 75-360 APPLICANT: Torpharm (Apotex)

DRUG PRODUCT: Gabapentin Capsules, 100 mg, 300 mg & 400 mg

The Division of Bioequivalence has amended its previous recommendations for the submissions dated April 17, 1998 and July 15, 1998 concerning the dissolution testing method and specification. The amendment is as follows.

1. In the effort to maintain the consistency in dissolution testing of the drug product, the dissolution medium of **0.06N HCl**, instead of 0.1N HCl, is now confirmed and required for the above drug product's stability and quality control program. You do not need to repeat the dissolution testing for your test product using 0.06N HCl, but are recommended to use 0.06N HCl as the dissolution medium in the future testing. You are also asked to commit to submit to the Division of Bioequivalence the earliest dissolution results obtained using this now-comfirmed dissolution medium.

The dissolution testing should be conducted in 900 mL of 0.06N HCl, at 37°C using USP23 Apparatus II(paddle) at 50 rpm.

2. In addition, you are reminded that the specification for the dissolution testing remains ***"Not less than —%(Q) of the labeled amount of the drug in the dosage form is dissolved in 20 minutes"***. The specification should be reflected in your stability and quality control documents such as the CMC files.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of
Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and
Research

9.1

BIOEQUIVALENCY COMMENTS

ANDA: 75-360 APPLICANT: Torpharm (Apotex)

DRUG PRODUCT: Gabapentin Capsules, 100 mg, 300 mg & 400 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The Division of Bioequivalence acknowledges that the following, FDA-recommended dissolution testing is being incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of 0.06N HCl, at 37°C using USP23 Apparatus II(paddle) at 50 rpm. The test product should meet the following specifications:
>
> Not less than —%(Q) of the labeled amount of the drug in the dosage form is dissolved in 20 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Barbara M Davit

for Dale P. Conner, Pharm. D.
Director, Division of
Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and
Research

CC:ANDA 75-360
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen 10/21/99
HFD-652/ YHuang 10/21/99
HFD-617/ E. Hu 11/15/99
for HFD-650/ D. Conner 11/15/99

V:\FIRMSNZ\torpharm\ltrs&rev\75360a.o99
Printed in final on / /

AMENDMENT Submission date: 10-12-99

1. STUDY AMENDMENT (OTH) Strength: 100 mg, 300 mg & 400 mg
Outcome: **AC**

OUTCOME DECISIONS: **AC** - Acceptable

WINBIO COMMENTS:

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-360 Amendment SPONSOR : Torpharm(Apotex)
DRUG AND DOSAGE FORM : Gabapentin Capsules
STRENGTH(S) : 100 mg, 300 mg & 400 mg
TYPES OF STUDIES : Food Study & Fasting Study for 400 mg; Fasting Study for 100 mg
CINICAL STUDY SITE(S) : Apotex Research Inc., Weston, Canada
ANALYTICAL SITE(S) : Apotex' Bioanalytical Laboratory, Weston, Canada

STUDY SUMMARY : Acceptable
DISSOLUTION : Acceptable / 900mL 0.06N HCl, paddle 50 rpm

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic _____	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH : I
INITIAL : HN DATE : 10-21-99

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : YCH DATE : 10/21/99

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC DATE : 11/15/99

Gabapentin Capsules
100 mg, 300 mg & 400 mg
ANDA # 75-360
Reviewer: Hoainhon Nguyen
W #75360a.099

Torpharm (Apotex Corp.)
Vernon Hills, IL
Submission Date:
October 12, 1999

Review of an Amendment

The firm has submitted dissolution data in response to the agency's deficiency letter dated July 29, 1999. The agency's deficiency comments were as follows:

"1. In the effort to maintain the consistency in dissolution testing of the drug product, the dissolution medium of 0.06N HCl, instead of 0.1N HCl, is now confirmed and required for the above drug product's stability and quality control program. You do not need to repeat the dissolution testing for your test product using 0.06N HCl, but are recommended to use 0.06N HCl as the dissolution medium in the future testing. You are also asked to commit to submit to the Division of Bioequivalence the earliest dissolution results obtained using this now-comfirmed dissolution medium.

The dissolution testing should be conducted in 900 mL of 0.06N HCl, at 37°C using USP23 Apparatus II(paddle) at 50 rpm.

2. In addition, you are reminded that the specification for the dissolution testing remains "Not less than — %(Q) of the labeled amount of the drug in the dosage form is dissolved in 20 minutes". The specification should be reflected in your stability and quality control documents such as the CMC files."

The firm has revised its CMC files to include the correct dissolution testing method and specification for the test product. The firm has also conducted dissolution testing for the test product using the correct procedure.

III. Dissolution Testing: FDA's method

Drug (Generic Name): Gabapentin Capsules Firm: Apotex Corp.
Dose Strength: 100 mg, 300 mg & 400 mg ANDA# 75-360
Submission Date: October 12, 1999

Conditions for Dissolution Testing:

USP XXIII Basket__ Paddle X__ RPM 50 rpm Units Tested: 6
Medium: 0.06 N HCl or 0.1N HCl Volume: 900 ml
Reference Drug: (Manuf.) None*
Assay Methodology: HPLC/UV@210nm
Specifications: NLT —% in 20 minutes
*NOTE: Testing of the RLD product is not required for the purpose of method comparison.

Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	With 0.1 N HCl Test Lot # FD7074A Strength (mg) 100 Mean % Dissolved(CV%)	Range	With 0.06N HCl Test Lot # FD7074A Strength (mg) 100 Mean % Dissolved(CV%)	Range
5	61(22)	———	50(48)	———
10	96(6)	———	86(15)	———
15	103(2)	———	95(7)	———
20	103(3)	———	99(4)	———

Sampling Times (Min.)	With 0.1N HCl Test Lot # FD7075C Strength (mg) 300 Mean % Dissolved(CV%)	Range	With 0.06N HCl Test Lot # FD7075C Strength (mg) 300 Mean % Dissolved(CV%)	Range
5	54(14)	———	59(7)	———
10	79(13)	———	77(8)	———
15	92(4)	———	93(3)	———
20	97(2)	———	98(2)	———

Sampling Times (Min.)	With 0.1N HCl Test Lot # FD7077A Strength (mg) 400		With 0.06N HCl Test Lot # FD7077A Strength (mg) 400	
	Mean % Dissolved(CV%)	Range	Mean % Dissolved(CV%)	Range
5	60(15)	———	62(9)	———
10	85(7)	———	86(5)	———
15	94(2)	———	93(4)	———
20	98(1)	———	96(3)	———

Comments:

The dissolution data above show that there is no significant difference between the test results generated using 0.1N HCl and those using 0.06N HCl as dissolution medium.

Recommendations:

The Division of Bioequivalence acknowledges Torpharm (Apotex)'s revision of its CMC files to comply with the agency's *in vitro* dissolution testing requirements. The dissolution data comparing the agency's method (using 0.06N HCl medium) with the previous method (using 0.1N HCl medium) are acceptable.

Hoaihon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 10/21/99

Concur: Barbara M Davit Date: 11/15/99
for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 75-360 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
HNguyen/10-20-99/W #75360a.o99
Also as V:\firmsnz\torpharm\ltrs&rev\75360a.o99
Attachment: 0 page

APPEARS THIS WAY
ON ORIGINAL

6-1

Gabapentin Capsules, 100 mg, 300 mg & 400 mg
ANDA #75-360
Reviewer: Hoainhon Nguyen
W #75360dw0202.doc

TorPharm
Ontario, Canada
Submission Date:
February 14, 2002
June 7, 2002

Review of Dissolution Data and a Waiver Request
(An Alternate Bulk Supplier)

The firm has submitted the current amendment for using gabapentin raw material from an alternate manufacturer, ———————. On April 17, 1998 and July 15, 1998, the firm submitted the results of bioequivalence studies on the 400 mg and 100 mg and the studies were found acceptable. The biowaiver request for the 300 mg was also granted based on comparable dissolution profiles and formulation proportionality between all strengths. The biobatches used in the studies were manufactured using gabapentin raw material from ———————. The firm is establishing the bioequivalence for the test product manufactured using gabapentin raw material from ———————, in accordance with 21CFR 320.24(b)(5). Comparative dissolution data for the test product manufactured by ——— and ——— were submitted. *"The components and composition of the capsules have not changed from the components and composition of the product that underwent the acceptable bioavailability study."*

NOTE: The firm originally submitted, in the February 14 amendment, the comparative dissolution data of the approved and proposed test products for demonstrating the bioequivalence between the approved and proposed test products in accordance with 21 CFR 320.24 (b)(5). In the June 7, 2002, the firm provided additional dissolution data of the RLD product side by side with the dissolution data of the approved and proposed test products.

The dissolution data are summarized below.

Dissolution Testing: **FDA-recommended method**

Drug (Generic Name): Gabapentin Capsules Firm: Torpharm/Apotex Inc.
Dose Strength: 100 mg, 300 mg & 400 mg ANDA# 75-360
Submission Date: February 14 & June 7, 2002

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:
USP Basket__ Paddle X RPM 50 rpm Units Tested: 12
Medium: 0.06N HCl Volume: 900 ml
Reference Drug: (Manuf.) Neurontin Capsules (Parke-Davis)
Assay Methodology: Not given
Specifications: NLT —% in 20 minutes

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product (using ———) Lot # FD0069 Strength (mg) 400		Reference Product (using ———) Lot # FD7077 Strength (mg) 400	
	Mean % Dissolved(CV%)	Range	Mean % Dissolved(CV%)	Range
5	57(20)	———	61(11)	———
10	89(9)	———	87(11)	———
15	96(4)	———	95(5)	———
20	98(2)	———	98(3)	———

Sampling Times (Min.)	Reference Product (Neurontin) Lot # 087N1V Strength (mg) 400	
	Mean % Dissolved(CV%)	Range
5	56(15)	———
10	81(11)	———
15	88(6)	———
20	92(4)	———

Sampling Times (Min.)	Test Product (using ———) Lot # FD0067 Strength (mg) 100		Reference Product (using ———) Lot # FD7074 Strength (mg) 100	
	Mean % Dissolved(CV%)	Range	Mean % Dissolved(CV%)	Range
5	90(8)	———	76(30)	———
10	98(2)	———	94(12)	———
15	99(2)	———	99(5)	———
20	99(2)	———	100(3)	———

Sampling Times (Min.)	Reference Product (Neurontin) Lot # 080N1V Strength (mg) 100	
	Mean % Dissolved(CV%)	Range
5	86(19)	———
10	94(6)	———
15	97(4)	———
20	99(4)	———

Sampling Times (Min.)	Test Product (using ———) Lot # FD0068 Strength (mg) 300		Reference Product (using ——) Lot # FD7075 Strength (mg) 300	
	Mean % Dissolved(CV%)	Range	Mean % Dissolved(CV%)	Range
5	68(13)	———	56(18)	———
10	91(10)	———	91(9)	———
15	98(3)	———	97(4)	———
20	100(3)	———	99(2)	———

Sampling Times (Min.)	Reference Product (Neurontin) Lot # 080N1V Strength (mg) 300	
	Mean % Dissolved(CV%)	Range
5	65(11)	———
10	88(6)	———
15	93(4)	———
20	95(3)	———

Comments:

The dissolution data for the test product manufactured using ——— and ——— are acceptable. The dissolution profiles of the test product from the approved gabapentin raw material and proposed gabapentin raw material, as well as the dissolution profiles of the RLD product, are comparable and meet the FDA-recommended specification.

Recommendation:

1. The in-vitro dissolution testing conducted by Torpharm on its Gabapentin Capsules, 100 mg, 300 mg and 400 mg, manufactured using ——— gabapentin raw material, has been found acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.06N HCl at 37°C using USP apparatus II(paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than —% of the labeled amount of the drug in the dosage form is dissolved in 20 minutes.

2. The Division of Bioequivalence agrees that the information submitted by TorPharm demonstrates the bioequivalence of its Gabapentin Capsules, 100 mg, 300 mg and 400 mg, manufactured using the alternate raw material from ——— , in accordance with 21 CFR 320.24(b)(5) of the Bioavailability/Bioequivalence Regulations. The firm's Gabapentin Capsules, 100 mg, 300 mg and 400 mg, manufactured using the alternate raw material from ——— , are therefore deemed bioequivalent to the firm's Gabapentin Capsules, 100 mg, 300 mg and 400 mg, manufactured using the original raw material from ———.

Hoanhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 7/2/2002

Concur: _____ Date: 7/11/2002

for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 75-360 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File

Hnguyen/06-17-02/W #75360dw0202.doc
Attachments: None

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS

ANDA: 75-360 APPLICANT: TorPharm

DRUG PRODUCT: Gabapentin Capsules, 100 mg, 300 mg & 400 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

In future applications, please include the address of the laboratories conducting the dissolution testing in the bioequivalence section of the ANDA.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs.

> The dissolution testing should be conducted in 900 mL of 0.06N HCl, at 37°C using USP Apparatus II(paddle) at 50 rpm. The test product should meet the following specifications:
>
> Not less than —% (Q) of the labeled amount of the drug in the dosage form is dissolved in 20 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-360
ANDA DUPLICATE
DIVISION FILE
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen

V:\firmsnz\torpharm\ltrs&rev\75360dw0202.doc
Printed in final on / /00

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ YHuang
HFD-617/ K. Scardina
HFD-650/ D. Conner

BIOEQUIVALENCY - ACCEPTABLE Submission Date: 02-14-02
06-07-02

1. **DISSOLUTION WAIVER** (DIW) Strengths: 100 mg, 300 mg & 400 mg
Outcome: AC

2. **OTHERS** (Additional dissolution data) Strengths: 100 mg, 300 mg & 400 mg
Outcome: AC

Outcome Decisions:
AC - Acceptable

WINBIO COMMENTS:

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-360 SPONSOR : TorPharm
DRUG AND DOSAGE FORM : Gapabentin Capsules
STRENGTH(S) : 100 mg, 300 mg & 400 mg
TYPES OF STUDIES : N/A
CINICAL STUDY SITE(S) : N/A
ANALYTICAL SITE(S) : N/A

STUDY SUMMARY : N/A
DISSOLUTION : Acceptable

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic _____ New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH : I
INITIAL : HN DATE : 7/2/02

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : YCH DATE : 7/2/2002

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.
for INITIAL : Ne Gabhain DATE : 7/11/2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-360

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

DATE: October 28, 1998

PRODUCT NAME: Gabapentin

ANDA/AADA NUMBER: 75-360

FIRM NAME: Torpharm

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION HELD: Ester Barber

TELEPHONE: (416) 675-8394

MINUTES OF CONVERSATION: I called Ms Barber in response to a request for clarification of 5 questions (#'s 3,4,6,7,10) that were issued in our deficiency letter dated September 29,1998. For questions 3, 6, and 10, the firm agreed to the requests as indicated in the deficiency letter. For question # 4 regarding [redacted], the firm is requesting to use [redacted], but indicated they would not use it to exceed the [redacted] for any particular dosage strength. The executed batch records submitted were for [redacted] per strength. They agreed that they would only make a maximum of [redacted] for any particular strength from the [redacted]. For question # 7, I informed them that the question was asked in error.

NAME OF OGD REPRESENTATIVE: Brenda T. Arnwine

SIGNATURE OF OGD REPRESENTATIVE: Brenda T. Arnwine

DIVISION/BRANCH: Div Chem II/Br 5

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 10, 1999

FROM: Sriram Subramnaim, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. CTV 8/10/99
Associate Director
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering ANDA 75-360
Gabapentin Capsules, 100/300/400 mg
Sponsored by TorPharm, Ontario, Canada.

TO: Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence (HFD-650)

At the request of HFD-650, the Division of Scientific Investigations conducted an audit of the following bioequivalence study:

Study: GACP/FA/0400-970715-(1): Comparative Bioavailability Study of GABAPENTIN and NEURONTIN® 400 mg Capsules

The clinical and analytical portions of this study was conducted at Apotex Research Inc., Ontario, Canada. At the conclusion of the inspection, a Form 483 was issued at Apotex Research.

The significant findings and our evaluation of them follows:

Clincal and Analytical Site: Apotex Research, Ontario, Canada.

1. Quality Assurance was Not Effective.
For example, the clinical report submitted to the Agency was dated 4/3/98. In contrast, the same report on site was dated 4/7/98. Also, there was a discrepancy between the body weight in the clinical report and the body weight in the source document for Subject GA 13. Our investigations revealed that the reported body weight for Subject GA 13 was recorded at screening. As the value did not meet the

inclusion criteria, Subject GA 13's body weight was rechecked at check-in and was found to be acceptable. The repeated value, however, was not reported.

These findings should not affect the results of the study. The firm, however, should ensure that their quality assurance is effective.

2. Pharmacokinetic (PK) Anomalies.

The 12 hour plasma concentration for Subject GA 12 (Period 1) was not used to calculate the elimination rate constant (Kel) as it did not meet the expected PK profile. Also, AUC calculations were based on scheduled times instead of observed times, although deviations in blood draws were noted for six time points.

These observations, however, are not likely to significantly alter the reported AUC levels.

Conclusion:

The data from Study GACP/FA/0400-970715-(1) are acceptable for Agency review.

Following your review of this transmittal memo, please append it to the original ANDA submission.

Sriram Subramaniam, Ph.D.

cc:
HFD-45/Lepay
HFD-48/Viswanathan/Fujiwara/Subramaniam(2)/cf
HFD-652/Nguyen
HFD-615/Hu/Beers-Block
HFR-MW350/Matson
Class:VAI
Draft:SS 8/5/99
Edited:MKY MKY 8/10/99
Final:CTV
File:5211;O:\BE\75360tor.gab

File in archive

[redacted]

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 12, 2002

FROM: Russell Katz, M.D. 1/16/03
Director
Division of Neuropharmacological Drug Products
HFD-120

THRU: Rosemary Roberts, M.D. 1/13/2003
Deputy Director
Office of Counter Terrorism & Pediatric Development

SUBJECT: Pediatric Sections: Proposed Labeling for Generic Gabapentin Drug Products

TO: Gary Buehler
Director, Office of Generic Drugs
HFD-600

The Office of Generic Drugs (OGD) consulted this division regarding acceptable package insert labeling for generic Neurontin (gabapentin) capsules, tablets, and oral solution. OGD has asked if the generic firms could carve out information from pediatric studies, without compromising safety or effectiveness for the remainder of the non-exclusivity protected uses. This labeling, which was approved on August 15, 2002, has been granted 3 years of Hatch/Waxman exclusivity. A meeting was held to address this issue on October 21, 2002.

The meeting included representatives from The Office of Chief Counsel, Office of Generic Drugs, and the Office of Pediatric Drug Development and Program Initiatives. The approved pediatric protected additions to the Neurontin labeling, and the proposed generic carve-outs were discussed. The meeting participants reviewed the pertinent sections of the current Neurontin package insert and commented on the impact of each proposed deletion on the safety and effectiveness of the drug product. The conclusion reached was that generic firms **could** carve-out the pediatric labeling sections without rendering generic products less safe or effective for all remaining non-protected conditions of use.

Under the approach proposed by OGD and acceptable to this division, these **bolded** sections of the package insert for generic Neurontin (gabapentin) Capsules, Tablets, and Oral Solution will have the following changes:

FROM MEMO DATED 12/12/02

7 page(s) of draft labeling has been removed from this portion of the review.

Green, Wayne*

ɔm:	Hinchliffe, Thomas
ıt:	Thursday, January 22, 2004 9:35 PM
ɔ:	Green, Wayne*; CDER-DDR600
Cc:	Rosencrance, Susan M; Sayeed, Vilayat A; Fang, Florence S; Skanchy, David
Subject:	ANDA 75-360 July 29, 2003 AC and Jan. 15 & 16, 2004 AC

Wayne, et al,

At the request of the firm's (Torpharm) NC dated January 14, 2004 for Gabapentin Capsules 100 mg, 300 mg, and 400 mg (ANDA 75-360), Chemistry requests that the ***July 29, 2003*** AC please be closed out based on their communication and this e-mail communication.

The July 29, 2003 AC pertained to the addition of another drug substance supplier. The DMF was found to be deficient and the firm then chose to withdraw this Amendment returning back to their Tentative Approval status granted January 29, 2003 and corrected February 26, 2003.

***** ALSO, due to this withdraw please convert the TWO (2) remaining in-house amendments dated January 15, 2004 and January 19, 2004 to ***Minor Amendment Status (AM)*** from Major Amendment status (AC). ***These two pieces were originally submitted as AM by the ANDA firm but because of the in-house open Major they were not given Minor status.***

Thank you,

ɔm

LT Thomas O. Hinchliffe, PharmD
Chemistry Project Manager
Office of Generic Drugs, HFD-617
Division of Labeling and Program Support
MPNII, RM. E230
(301) 827-5771

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 6, 2004

FROM: Susan Rosencrance,
Team Leader,
Division of Chemistry II

SUBJECT: ANDA 75-360
Torpharm
Gabapentin Capsules

TO: The Record

Torpharm's new correspondence dated February 17, 2004 is in response to the Agency's letter dated February 5, 2004 in which it was requested all applicants for gabapentin dosage forms tighten unknown impurities to 0.1% (see Attachment 2 for copy of letter). The applicant (Torpharm) has agreed to the request and has submitted updated release and shelf life specifications revised accordingly. The revised specifications are now as follows:

Finish Product Release Specifications:

TEST	SPECIFICATION	METHOD
Appearance	See individual capsule description*	Visual
Identification	[redacted]	#FP0114-01 #FP0114-05
Dissolution	NLT [redacted] % (Q = [redacted]%) of the labeled amount of Gabapentin is dissolved in 20 min	#FP0114-03
Related Compounds	[redacted]	#FP0114-02
Assay	[redacted] % of labeled amount of Gabapentin	#FP0114-01
Content Uniformity	[redacted]	#FP0114-01

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

7/6/2004 MEMO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-360

CORRESPONDENCE

ACK for filing
5-4-98
S. MacLeod

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

April 17, 1998

Document Control Room
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Gabapentin Capsules, 100 mg, 300 mg, and 400 mg
Original Abbreviated New Drug Application

To Whom It May Concern:

Pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act as amended September 24, 1994, Apotex Corp., as the U.S. agent for TorPharm, a Division of Apotex Inc. of Ontario, Canada, hereby submits an original abbreviated new drug application for Gabapentin Capsules, 100 mg, 300 mg, and 400 mg.

We are submitting an archival copy under a blue cover (9 volumes), a chemistry review copy, an additional copy of the analytical methods section under a red cover, and the bioavailability/bioequivalence review section under an orange cover.

Apotex Corp. hereby certifies that in accordance with 21 CFR 214.94 (d) (5) a true field copy of the technical sections of this submission under a burgundy cover is also included as this ANDA is being submitted by a foreign applicant.

We appreciate an expeditious review of this application. Please direct any inquiries regarding this application to me at the address listed above.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs

RECEIVED
APR 20 1998
GENERIC DRUGS

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

May 4, 1998

NEW CORRESP

NC

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-360
Gabapentin Capsules 100, 300 and 400 mg
Corrected Field Certification Copy

To Whom It May Concern:

Apotex Corp. as the US agent for TorPharm, a Division of Apotex Inc. of Ontario Canada, is submitting a corrected Field Certification Copy as requested in the telephone conversation of May 4, 1998 with Sandra Middleton.

If you have further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director,
Regulatory Affairs

ANDA 75-360

MAY 12 1998

Apotex Corp.
U.S. Agent for: TorPharm, a Division of Apotex, Inc.
Attention: Marcy Macdonald
50 Lakeview Parkway, Suite 127
Vernon Hills, Illinois 60061

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated May 4, 1998 and your correspondence dated May 4, 1998.

NAME OF DRUG: Gabapentin Capsules, 100 mg, 300 mg and 400 mg

DATE OF APPLICATION: April 17, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: April 20, 1998

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(I)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the District Court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Peter Rickman, Chief, Regulatory Support Branch, at (301)827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Project Manager
(301) 827-5849

Sincerely yours,

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-360
DUP/Jacket
Division File
Field Copy
HFD-610/J.Phillips
HFD-92
HFD-615/M.Bennett

Endorsement: HFD-615/PRickman, Chief, RSB _____ date 5/12/98
HFD-615, SMiddleton, CSO _____ date
HFD-645, BArnwine, Sup. Chem._____ date
WP File x:\new\firmsnz\torphar\ltrs&rev\75360.ack
FT by/mjl/5/5/98
ANDA Acknowledgment Letter!

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

June 3, 1998

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

cc
NAI 6/16/98

PATENT AMENDMENT

RE: ANDA 75-360
Gabapentin Capsules
100 mg, 300 mg, and 400 mg

To Whom It May Concern:

Apotex Corp, as the U.S. agent for TorPharm, A Division of Apotex Inc, is hereby submitting acknowledgment that Parke-Davis Co. Inc., the holder of the approved application for Neurotin® Capsules 100 mg, 300 mg, and 400 mg, and Warner-Lambert Co., the record owner of U.S. Patents Nos. 4,894,476 and 5,084,479, have received the notice of non-infringement from TorPharm. A photocopy of the acknowledgments are attached.

If you have any questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs

RECEIVED
JUN 0 9 1998
GENERIC DRUGS

Marcy 6-9-98

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

July 15, 1998

ORIG AMENDMENT

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/AB

BIOEQUIVALENCE AMENDMENT

Re: ANDA 75-360
Gabapentin Capsules
100 mg, 300 mg, and 400 mg

To Whom It May Concern:

Apotex Corp., as the U.S. agent for TorPharm, a Division of Apotex, Inc., is submitting this amendment to provide additional biostudies per telephone conversation with Lizzie Sanchez on April 15, 1998.

If you have any questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs

RECEIVED
JUL 20 1998
GENERIC DRUGS

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

FPL

December 10, 1998

NDA ORIG AMENDMENT

Ac

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MAJOR AMENDMENT

RE: ANDA 75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

To Whom It May Concern:

Apotex Corp., as the U.S. agent for TorPharm, a Division of Apotex Inc., of Ontario, Canada, hereby submits a major amendment for the above-referenced ANDA in response to the deficiency letter dated September 29, 1998.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

RECEIVED

DEC 14 1998

GENERIC DRUGS

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

February 26, 1999

NAF
Amendment
Notice of Litigation
3/15/99
D Smalley

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

PATENT AMENDMENT

RE: ANDA 75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

To Whom It May Concern:

Apotex Corp., as the U.S. agent for TorPharm, a Division of Apotex Inc., of Ontario, Canada, hereby submits Notice of Litigation pursuant to the accepted for filing letter dated May 12, 1998.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

RECEIVED
MAR 0 3 1999
GENERIC DRUGS

3-4-99

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

NDA ORIG AMENDMENT
N/AM

October 12, 1999

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

MINOR AMENDMENT

RE: ANDA 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg.

To Whom It May Concern:

Apotex Corp., as the U.S. agent for TorPharm, a Division of Apotex Inc., of Ontario, Canada, is hereby submitting in duplicate a minor amendment in response to the deficiency letter dated July 29, 1999.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
OCT 14 1999
OGD

10-18-99

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

June 13, 2000

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

NEW CORRESP

NC

PATENT AMENDMENT

RE: ANDA 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg.

To Whom It May Concern:

Apotex Corp., as the U.S. agent for TorPharm, of Ontario, Canada, is hereby submitting in duplicate a patent amendment to provide certification for U.S. Patent Number 6,054,482.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

August 17, 2000

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

NEW CORRESP
NC

PATENT AMENDMENT

RE: ANDA 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg.

To Whom It May Concern:

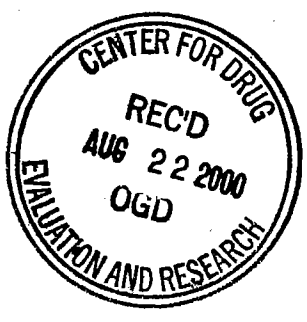
Apotex Corp., as the U.S. agent for TorPharm, of Ontario, Canada, is hereby providing a copy of the return receipt cards from notifications sent on June 13, 2000, showing that each person identified under 314.95(a) has received notice. We also certify that the notices meet the content requirements under 314.95(c).

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223



noted
ES 1/10/01

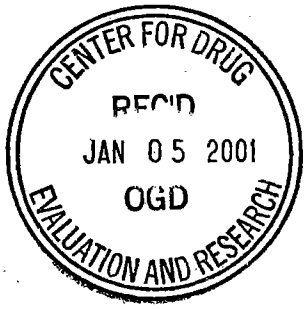
Tor Pharm

ORIG AMENDMENT
N/AM

COVER LETTER

MINOR AMENDMENT

TorPharm, 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3, is hereby amending ANDA number 75-360 for Gabapentin Capsules 100 mg, 300 mg and 400 mg. The amendment is being submitted in response to the FDA Deficiency Letter dated November 16, 2000.



Esther Barber
Esther Barber
Manager, Regulatory Compliance

4 Jan 01
Date

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

NAI mailed 3-5-02

January 31, 2002

NC

Office of Generic Drugs
FDA, CDER
MPN II, HFD-600
7500 Standish Place
Rochville, MD 20855

NEW CORRESP

Re: ANDA # 75-369
Gabapentin Capsules, 100, 300 and 400 mg
Notice Of Final Court Decision Triggering The 180-Day First-Filer Exclusivity

Dear Madame or Sir:

In accordance with 21 C.F.R. § 314.107(e) (2001), Apotex Corp., as the U.S. agent for TorPharm, Inc. ("TorPharm"), hereby notifies the agency of a final decision of a court holding that a listed patent for gabapentin capsules, which was the subject of a paragraph IV certification, is not infringed. We also submit herewith copies of the relevant orders and judgment for the agency's convenience.

As we explain below, as of October 14, 2001, this court decision constituted a final judgment from which no appeal can be or has been taken under 21 C.F.R. § 314.107(c) and (e) (1999)—the regulation applicable to all relevant ANDAs for gabapentin capsules with paragraph IV certifications submitted before March 2000. Accordingly, by virtue of this final court decision, the 180-day first-filer exclusivity for gabapentin capsules was triggered and began to run on October 15, 2001.

Background

Based on publicly available information, it is our understanding that, on or about March 30, 1998, Purepac Pharmaceutical Co. ("Purepac") submitted ANDA No. 75-350 for 100 mg, 300 mg, and 400 mg gabapentin capsules. Purepac's ANDA No. 75-350 references the listed drug, Neurontin® (gabapentin) capsules, which is the subject of NDA No. 20-235 formerly held by the Parke-Davis Division of Warner-Lambert Company ("Warner-Lambert"), which is now a division of Pfizer, Inc. In 1998, two

relevant patents[1] were listed in the Orange Book in connection with NDA No. 20-235 and Neurontin® (gabapentin) capsules: U.S. Patent No.4,894,476 ("the '476 patent") and U.S. Patent No. 5,084, 479 ("the '479 patent").[2] Only the '476 patent is relevant here.

With its ANDA No. 75-350, Purepac submitted a paragraph IV certification, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), for the '476 patent, stating that the '476 patent will not be infringed by the manufacture, sale, or use of Purepac's gabapentin capsules, and that the '476 patent is invalid. Purepac did *not* submit a paragraph IV certification for the '479 patent, but instead submitted a statement of inapplicable use pursuant to 21 U.S.C. § 355(j)(2)(A)(viii). After providing the requisite notice of its ANDA and paragraph IV certification to the current NDA-holder and patentee, Warner-Lambert, Purepac was sued by Warner-Lambert in the United States District Court for the District of New Jersey (Lifland, J.) for infringement of both the '476 patent and the '479 patent under 35 U.S.C. § 271(e)(2)(A). That litigation is still pending and no court decision has been rendered on either patent.

On April 17, 1998, TorPharm, through its U.S. agent, Apotex Corp., submitted ANDA No. 75-360 for 100 mg, 300 mg, and 400 mg gabapentin capsules. TorPharm's ANDA No. 75-360 also references Neurontin® (gabapentin) capsules and NDA No. 20-235. With its ANDA No. 75-360, TorPharm submitted paragraph IV certifications, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii), for both the '476 patent *and* the '479 patent, stating that such patents will not be infringed by the manufacture, sale, or use of TorPharm's gabapentin capsules. TorPharm also provided the requisite notice of its ANDA and paragraph IV certifications for the '476 and '479 patents to Warner-Lambert.

On July 14, 1998, Warner-Lambert sued TorPharm for infringement of the '476 and '479 patents under 35 U.S.C. § 271(e)(2)(A) in the United States District Court for the Northern District of Illinois, Eastern Division (Plunkett, J.).[3] On March 2, 2001, the

---

[1] The third listed patent, U.S. Patent No. 4,087,544 ("'544 patent"), is not relevant to this discussion, since it was scheduled to, and did, expire on July 16, 2000, and, to TorPharm's knowledge, was never the subject of a paragraph IV certification. Rather, all gabapentin capsule ANDA applicants in 1998, including Purepac and TorPharm, submitted paragraph III certifications for the '544 patent.

[2] In 2000, Warner-Lambert listed another patent, U.S. Patent No. 6,054,482 ("the '482 patent"), in the Orange Book for which both Purepac and TorPharm submitted paragraph IV certifications. The '482 patent is not pertinent to the present discussion.

[3] After TorPharm certified to the later-listed '482 patent, Warner-Lambert sued TorPharm (and four other generic companies, including Purepac) for infringement of the '482 patent in the United States District Court for the District of New Jersey. That litigation is still ongoing. But again, the '482 patent is not relevant here; nor is the pending litigation on that patent.

district court granted summary judgment of noninfringement for TorPharm on the '476 patent, stating:

> Because plaintiff has not responded to defendants' motion for summary judgment with facts sufficient to prevent the entry of summary judgment, and because plaintiff agrees that summary judgment in favor of defendants is appropriate, we grant defendant's [sic] motion for summary judgment. Moreover, because there is no just reason for delay or appeal of such order, it is hereby ordered that defendants are entitled to summary judgment as to plaintiff's patent infringement claim (Patent No. 4,894,476) pursuant to Fed. R. Civ. P. 54(b). This is a final and appealable order.

(Tab A). The district court initially made its order final and appealable under Rule 54(b), Fed. R. Civ. P., even though the '479 patent remained at issue in the lawsuit. On Warner-Lambert's timely Rule 59(e) motion, the district court amended the order to remove the Rule 54(b) certification, making the summary judgment of noninfringement on the '476 patent nonfinal (*i.e.* unappealable until the remaining issues regarding the '479 patent were resolved). (Tab B).

On September 13, 2001, the district court granted summary judgment of noninfringement for TorPharm on the '479 patent as well, effectively resolving all remaining issues in the case, and entered a final and appealable judgment in favor of TorPharm, which was docketed on September 14, 2001. (Tab C).

On October 12, 2001, Warner-Lambert filed a notice of appeal to the United States Court of Appeals for the Federal Circuit ("the Federal Circuit"), from the final judgment entered on September 13, 2001, "and from all interlocutory and other Orders entered prior to entry of final judgment in this matter." (Tab D).

TorPharm subsequently moved for summary affirmance of the district court's March 2, 2001 grant of summary judgment of noninfringement for TorPharm on the '476 patent.[4] In response, Warner-Lambert indicated that it was "not pursuing an appeal of the United States District Court for the Northern District of Illinois' decision to grant summary judgment for [TorPharm] on the '476 patent." (Tab E).

As a consequence, on January 15, 2002, the Federal Circuit held that TorPharm's "motion for summary affirmance regarding the '476 patent is moot" because Warner-Lambert is "not seeking review of the grant of summary judgment of noninfringement of the '476 patent." (Tab F).[5] Warner-Lambert's time for appealing the district court's

---

[4] TorPharm also moved for summary affirmance of the district court's grant of summary judgment for TorPharm on the '479 patent.

[5] The Federal Circuit denied TorPharm's motion for summary affirmance on the '479 patent and ordered full briefing of the appeal, which is currently underway.

summary judgment of noninfringement for TorPharm on the '476 patent expired 30 days after September 14, 2001, or on October 15, 2001. As such, the decision on the '476 patent is final and can no longer be appealed by Warner-Lambert.

The 180-Day First-Filer Exclusivity Began to Run On October 15, 2001, The Day Warner-Lambert's Right To Appeal Expired.

Under the agency's current regulatory scheme for ANDAs with paragraph IV certifications submitted before March 2000, the running of the 180-day first-filer exclusivity period is governed by the relevant provisions of 21 C.F.R. § 314.107(c) and (e) (1999). *See* Guidance for Industry, *Court Decisions, ANDA Approvals, and 180-day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act*, March 2000. That regulation provides in pertinent part:

> (c) Subsequent abbreviated new drug application submission.
>
> > (1) If an abbreviated new drug application contains a certification that a relevant patent is invalid, unenforceable, or will not be infringed and the application is for a generic copy of the same listed drug for which one or more substantially complete abbreviated new drug applications were previously submitted containing a certification that the same patent was invalid, unenforceable, or would not be infringed, approval of the subsequent abbreviated new drug application will be made effective no sooner than 180 days from whichever of the following dates is earlier:
> >
> > > (i) The date the applicant submitting the first application commences commercial marketing of its drug product; or
> > >
> > > (ii) The date of a decision of a court holding the relevant patent invalid, unenforceable, or not infringed.
> >
> > * * *
>
> (e) Court actions.
>
> > (1) References to actions of "the court" in paragraphs (b) and (c) of this section are to the court that enters final judgment from which no appeal can be or has been taken.
> >
> > (2) For the purposes of establishing the effective date of approval based on a court judgment, the following dates

shall be deemed to be the date of the final decision of the court on the patent issues:

> (i) If the district court enters a decision that the patent is invalid, unenforceable, or not infringed, and the decision is not appealed, the date on which the right to appeal lapses.

* * *

21 C.F.R. § 314.107(c) and (e) (1999).

In the past, and in particular with regard to the first-filer exclusivity for ranitidine hydrochloride, the agency has interpreted this regulation, consistent with its plain language, to mean that, in a case in which there is no appeal of the court decision, the 180-day first-filer exclusivity begins to run on the date that the right to appeal expires. *See Granutec, Inc. v. Shalala*, 139 F.3d 889. 1998 WL 153410, at * 5 (4th Cir. April 3, 1998) ("FDA measured Genpharm's exclusivity period from March 3, 1997, the date that Glaxo's right to appeal expired in *Glaxo, Inc. v. Boehringer Ingelheim Corp.*,... a wholly unrelated suit in which a district court determined that Boehringer Ingelheim's generic version of Form 1 ranitidine did not infringe upon Glaxo's 431 patent.").

As applied to gabapentin capsules, the same result is appropriate and consistent with both the agency's regulation and previous application of that regulation. Specifically, the relevant gabapentin capsule ANDAs with paragraph IV certifications for the '476 patent were filed before March 2000. According to the agency's March 2000 Guidance for Industry, the relevant provisions of 21 C.F.R. § 314.107(c) and (e) (1999) therefore apply here. Under that regulation, TorPharm's summary judgment of noninfringement on the '476 patent constitutes a final judgment from which no appeal can be or has been taken, since Warner-Lambert did not appeal that judgment, and because the time for doing so expired on October 15, 2001. As a consequence, pursuant to the regulation and the agency's previous application of it, the 180-day first-filer exclusivity for gabapentin capsules was triggered and began to run on October 15, 2001.

If you have any questions, or require any further information, please do not hesitate to call.

Very Truly Yours,

Mary Macdonald

Marcy Macdonald
Associate Director, Regulatory Affairs
Apotex Corp.

Attachments

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

February 01, 2002

Office of Generic Drugs
FDA, CDER
MPN II, HFD-600
7500 Standish Place
Rochville, MD 20855

NEW CORRESP

Re: ANDA # 75-360 cover letter to replace Incorrect ANDA # 75-369 referenced on same communication sent 01/31/02
Gabapentin Capsules, 100, 300 and 400 mg
Notice Of Final Court Decision Triggering The 180-Day First-Filer Exclusivity

Dear Madame or Sir:

In accordance with 21 C.F.R. § 314.107(e) (2001), Apotex Corp., as the U.S. agent for TorPharm, Inc. ("TorPharm"), hereby notifies the agency of a final decision of a court holding that a listed patent for gabapentin capsules, which was the subject of a paragraph IV certification, is not infringed. We also submit herewith copies of the relevant orders and judgment for the agency's convenience.

As we explain below, as of October 14, 2001, this court decision constituted a final judgment from which no appeal can be or has been taken under 21 C.F.R. § 314.107(c) and (e) (1999)—the regulation applicable to all relevant ANDAs for gabapentin capsules with paragraph IV certifications submitted before March 2000. Accordingly, by virtue of this final court decision, the 180-day first-filer exclusivity for gabapentin capsules was triggered and began to run on October 15, 2001.

Background

Based on publicly available information, it is our understanding that, on or about March 30, 1998, Purepac Pharmaceutical Co. ("Purepac") submitted ANDA No. 75-350 for 100 mg, 300 mg, and 400 mg gabapentin capsules. Purepac's ANDA No. 75-350 references the listed drug, Neurontin® (gabapentin) capsules, which is the subject of NDA No. 20-235 formerly held by the Parke-Davis Division of Warner-Lambert Company ("Warner-Lambert"), which is now a division of Pfizer, Inc. In 1998, two

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

NAI MAPS 3-5-02

NC

NEW CORRESP

February 08, 2002

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

RE: ANDA No. 75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg.

To Whom It May Concern:

Apotex Corp., as the U.S. agent for TorPharm, of Ontario, Canada, hereby submits Notice of Litigation in relation to the patent 6,054,482 pursuant to the accepted for filing letter dated May 12, 1998.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

Tor Pharm Inc.

EER requested
5/8/02
mA

ORIG AMENDMENT
AM AC

COVER LETTER

MAJOR AMENDMENT

TorPharm, 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3 is hereby filing an amendment to ANDA number 75-360 for Gabapentin Capsules 100 mg, 300 mg and 400 mg. This major amendment is being submitted to request approval to use an alternate manufacturer for the raw material Gabapentin. TorPharm proposes using ——— as the alternate manufacturer of Gabapentin.

Samantha Law
Supervisor, Regulatory Affairs

February 14, 2002
Date

CENTER FOR DRUG EVALUATION AND RESEARCH
FEB 15 2002

2/15/02

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

Tor Pharm

ORIG AMENDMENT
N/AC

COVER LETTER

MINOR AMENDMENT

TorPharm, 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3 is submitting an amendment to ANDA number 75-360 for Gabapentin Capsules 100 mg, 300 mg and 400 mg. The amendment is being submitted to provide an exclusivity statement for indication I-311 and revised labeling. The amendment is being submitted as per FDA Guidance for Industry, "Revising ANDA Labeling Following Revision of the RLD Labeling", July 2001. Also included in this amendment is additional Bioavailability/Bioequivalence information and updated finished product stability specifications, pertaining to the amendment dated February 14, 2002. That amendment was submitted requesting approval for TorPharm to use [redacted]. as the alternate manufacturer of Gabapentin.

Samantha Law

Samantha Law
Supervisor, Regulatory Affairs

RECEIVED June 7, 2002.
Date
JUN 10 2002
OGD / CDER

TORPHARM

Amendment to ANDA 75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

Tor Pharm

ORIG AMENDMENT
N/AC

COVER LETTER

TELEPHONE AMENDMENT

TorPharm, 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3, is hereby amending ANDA number 75-360 for Gabapentin Capsules 100 mg, 300 mg and 400 mg. The amendment is being submitted in response to the FDA telephone call dated June 13, 2002 from Andrew Langowski. TorPharm has been requested to revise the ——— limit for the ——— test in the Stability Specifications from — % to — %.

This amendment also includes revised raw material and finished product Testing Specifications for Gabapentin Capsules 100 mg, 300 mg and 400 mg.

Samantha Law
Supervisor, Regulatory Affairs

June 27, 2002
Date

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JUN 2 8 2002
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TORPHARM

Amendment to ANDA #75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

Tor Pharm Inc.

BIOAVAILABILITY

NEW CORRESP

NC/Rao

COVER LETTER

BIOEQUIVALENCY COMMENT ACKNOWLEDGEMENT

TorPharm, 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3, is providing feedback for ANDA 75-360 for Gabapentin Capsules 100 mg, 300 mg and 400 mg, in regards to the bioequivalence comments made in the FDA letter dated July 29, 2002.

Samantha Law

Samantha Law
Supervisor, Regulatory Affairs

August 01, 2002.

Date

RECEIVED

AUG 0 2 2002

OGD / CDER

TORPHARM

Bioequivalency Comment to ANDA #75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

LORD BISSELL BROOK
ATTORNEYS AT LAW

115 S. LASALLE STREET | CHICAGO, ILLINOIS 60603-3901
312.443.0700 | 312.443.0336 FAX | WWW.LORDBISSELL.COM

September 24, 2002

William A. Rakoczy

312.443.0329
Fax: 312.896.6329
wrakoczy@lordbissell.com

NEW CORRESP
NC

BY FEDERAL EXPRESS

Daniel E. Troy, Esq.
Chief Counsel
U.S. Food And Drug Administration
5600 Fishers Lane GCF-1
Room 657
Rockville, Maryland 20857

Re: ANDA No. 75-360 (Gabapentin Capsules 100, 300 and 400 mg)---

(1) Expiration Of 30-Month Stay And The 180-Day First-Filer Exclusivity For Gabapentin Capsules; and,

(2) *Purepac v. Thompson*, Case No. 02-02657 (D.D.C.) (Huvelle, J.)

Dear Mr. Troy:

We represent TorPharm, a Canadian manufacturer of generic drugs, and its U.S. agent, Apotex Corp. TorPharm has submitted, through Apotex Corp., ANDA No. 75-360 for 100 mg, 300 mg, and 400 mg gabapentin capsules, which references the listed drug Neurontin® (gabapentin) capsules and NDA No. 20-235.

From your recent discussions with TorPharm's Canadian counsel, Tim Gilbert, we understand that you are willing to meet with us to discuss TorPharm's June 27, 2002 request for an agency determination that, subject to any technical or scientific issues or concerns, TorPharm's ANDA No. 75-360 for gabapentin capsules will be eligible for and receive final agency approval upon the expiration of the purported second 30-month stay on December 15, 2002, and that such final approval will not be subject to or precluded by Purepac's purported first-filer exclusivity. To guide such a discussion, we provide you with the following statement summarizing TorPharm's position that: (1) the first-filer exclusivity for gabapentin has been triggered and expired; and, (2) the recently filed *Purepac v. Thompson* case (regarding Purepac's failure to certify to the listed '479 patent) has no effect or bearing on TorPharm's ANDA, and further that Purepac must certify to the listed '479 patent.

Because these issues are of significant concern to TorPharm and its future business plans regarding gabapentin, we respectfully request a meeting to discuss these issues with you at your earliest convenience.

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SEP 25 2002
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(1) 180-day first-filer exclusivity. The pertinent facts, and TorPharm's position, are fully set forth in my previous letter to you, dated June 27, 2002, and so will not be repeated here. For your convenience, we enclose another copy of that letter, with attachments, at Tab A. Put simply, as of October 15, 2001, TorPharm obtained a final judgment of noninfringement on the listed '476 patent from which no appeal has been or can be taken. As set forth in my June 27 letter, it remains TorPharm's position that, under any interpretation of the statute, or any of the agency's regulations, guidances, or past practices, this judgment triggered the 180-day first-filer exclusivity period for gabapentin capsules as of October 15, 2001.

(2) *Purepac v. Thompson*, Case No. 02-02657 (D.D.C.) (Huvelle, J.). The pertinent facts are also set forth in my June 27 letter, as well as Purepac's Complaint, a copy of which is attached hereto at Tab B. In short, the listed '479 patent claims a method of using gabapentin to treat neurodegenerative diseases. The '479 patent is listed in the Orange Book with use code U-285-"treatment of neurodegenerative diseases." Gabapentin is approved for treating partial seizure in persons with epilepsy, as well as the treatment of postherpetic neuralgia in adults. Purepac has submitted ANDAs for gabapentin capsules and tablets. To date, however, Purepac has not submitted any type of patent certification (IV or III) for the listed '479 patent, but rather only a "little (viii) statement of inapplicable use" pursuant to 21 U.S.C. § 355(j)(2)(A)(viii). TorPharm was the first ANDA applicant to submit a paragraph IV certification for the '479 patent.

According to Purepac's Complaint, the agency has issued a "letter ruling" (which we have not seen) stating that it will not finally approve Purepac's capsule or tablet ANDAs unless and until Purepac submits a patent certification for the '479 patent. (*See, e.g.*, Tab B, Compl. ¶¶ 49-50.) Purepac alleges that this "letter ruling" is arbitrary and capricious (*id.* ¶¶ 56-63) and seeks, *inter alia*, a declaratory judgment to this effect, together with injunctive relief: (a) requiring FDA to approve Purepac's ANDAs without a paragraph IV certification for the listed '479 patent; and, (b) enjoining FDA from approving any gabapentin ANDA that contains a paragraph IV certification for the listed '479 patent. In effect, Purepac's position is that the agency is required by statute to accept Purepac's section (viii) statement for the listed '479 patent.

First, regardless of whether Purepac is correct that it does not need to file a paragraph IV certification, this cannot have any bearing on whether ANDAs that contain a paragraph IV certification for the '479 patent are approvable. We are aware of no authority, and Purepac has cited none, that even remotely supports such a proposition, *i.e.* that one company's failure to file a paragraph IV certification (*e.g.* Purepac) can somehow be grounds for not approving a second company's ANDA that actually contains a paragraph IV certification for the patent in question (*e.g.* TorPharm). Indeed, such a rule, as suggested by Purepac, would contradict Hatch-Waxman's incentive of encouraging ANDA applicants to challenge listed patents, as TorPharm

did here, by being the first applicant to submit a paragraph IV certification for the listed '479 patent.

Second, TorPharm believes that, in view of the agency's past practices, Purepac must submit a paragraph IV certification for the listed '479 patent.

As you know, an NDA holder may submit information on a use patent, along with a use code designation, for listing in the Orange Book. It is our understanding that the agency will not look behind Orange Book listings or designations of approved uses to determine whether, in fact, a patent actually covers an approved use. Instead, the agency will rely on the declaration and use code designation submitted by the NDA holder. In other words, it is our understanding that the agency, consistent with its purported policy of not reviewing patents, will not interpret the claims of a patent to determine whether a patent is properly listed or claims an approved use of the drug.

Thus, if the NDA holder asserts that the patent covers an approved use, as indicated by the use designation for that patent, and it is a use for which the ANDA applicant is seeking approval, the ANDA applicant will be required to submit a patent certification, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii), together with a "little (viii) statement of inapplicable use" under subsection (viii). However, if the patent submitted to FDA for listing in the Orange Book does not claim a use for which the ANDA applicant seeks approval, as indicated by the use code associated with that patent, no patent certification under subparagraph (vii) is required, but rather only a section statement of inapplicable use under subsection (viii).

For example, in the case of 50 mg tramadol hydrochloride tablets, the agency did not require TorPharm to submit a patent certification, but rather only a little (viii) statement of inapplicable use, because the patent at issue, as indicated by the use code associated with it, did not claim a use for which TorPharm was seeking approval. Specifically, in that situation, the NDA holder submitted a patent for listing in the Orange Book which purportedly claimed a 16 day/25 mg titration dosing schedule. The accompanying use code U-435 provided for "a titration dosing regiment for the treatment of pain using an initial does of about 25mg." Notably, however, there was an approved use of the drug apart from the titration dosing regiment that was the subject of the listed patent and use code. TorPharm's product and labeling therefore made no reference to the dosing regiment that was the subject of the newly listed patent and use code, but rather referred only to other approved use. As such, the agency appropriately did *not* require TorPharm to file a paragraph IV certification, but rather only a "little (viii)" statement of inapplicable use for the recently listed patent.

In the case of paroxetine hydrochloride, however, the agency did require TorPharm to submit a patent certification for the new use patent. Specifically, the NDA holder submitted the '291 patent for listing in the Orange Book, which claimed a method of using paroxetine for the treatment of post traumatic stress disorder and depression associated with withdrawal from

heroin abuse. Notably, the use code employed by the agency and published in the Orange Book was U-286 – "depression." Paroxetine is approved for, *inter alia*, treating depression.

Unlike the case of tramadol, above, the agency would not permit TorPharm to submit solely a section (viii) statement for what TorPharm believed to be a patent on a method of use that had not been approved by FDA, in part because it would have required the agency---purportedly in violation of its long-standing policy not to substantively review patents---to actually review the patent to determine exactly what it claims, *i.e.* whether the patent claims a method of using paroxetine to treat depression. Instead, for paroxetine, the agency accepted the NDA holders statement, as indicated by the use code, that the use patent claimed an approved use of the drug and, as a consequence, required TorPharm to submit a paragraph IV certification, in addition to a previously filed section (viii) statement.

TorPharm believes that the same result is warranted for gabapentin here. Warner-Lambert submitted the '479 patent (which claims a method of using gabapentin for treating neurodegenerative diseases) for listing in the Orange Book with use code U-258-"treatment of neurodegenerative diseases." Purepac, of course, has taken the position that the listed '479 patent does not claim a use for which Purepac is seeking approval. That could be the case. However, from the face of the use code description alone, which is all that agency will look to in such cases, it is our understanding that it is not immediately apparent to the agency that the patent claims an unapproved use. To answer this question definitively, the agency would have to substantively review the listed '479 patent to determine exactly what it claims, *i.e.* whether the claim for neurodegenerative diseases does or does not include the treatment of partial seizures in person with epilepsy. But this is a question of patent claim interpretation, which is precisely what the agency has refused to do in accordance with its policy of not reviewing patents. Rather, it is our understanding that the agency will rely upon and look to the NDA holder as the final arbiter in such matters.

That appears to be exactly what happened here. In response to Purepac's inquiries, the agency conferred with Warner-Lambert, which purportedly stated that the '479 patent is properly listed (*i.e.* claims an approved use of the drug). In turn, the agency appears to have refused to look behind that statement to determine exactly what the '479 patent claims and whether Purepac's section (viii) statement is correct, but rather has required Purepac to submit a paragraph IV certification for the '479 patent.

This is consistent with the agency's past practices, and in particular its treatment of TorPharm in the case of paroxetine. In view of those past practices, Purepac must therefore submit a patent certification for the listed '479 patent.

And finally, it would be inequitable for Purepac to gain an unfair advantage over TorPharm by failing to submit a patent certification for the listed '479 patent where, as here, TorPharm has in fact certified to the '479 patent---and was the first to do so. In essence, Purepac

is attempting to nullify the fact that TorPharm was the first to file a paragraph IV certification for the '479 patent. Purepac should not be permitted to use a section (viii) statement in this fashion to manipulate and avoid the patent certification requirements.

For at least these reasons, it is TorPharm's position that Purepac must certify to the '479 patent, or else Purepac should not receive final approval for its gabapentin ANDAs.

Conclusion

We respectfully request a meeting with you to discuss these issues at your earliest convenience, and in particular TorPharm's June 27, 2002 request for an agency determination that, subject to any technical or scientific issues or concerns, TorPharm's ANDA No. 75-360 for gabapentin capsules will be eligible for and receive final agency approval upon the expiration of the purported second 30-month stay on December 15, 2002, and that such final approval will not be subject to or precluded by Purepac's purported first-filer exclusivity.

Very truly yours,

LORD, BISSELL & BROOK

William A. Rakoczy

WAR/nas

Attachments

cc: Office of Generic Drugs
FDA, CDER
MPN II, HFD-600
7500 Standish Place
Rockville, Maryland 20855

Kevin M. Fain

Dr. Bernard C. Sherman
Dr. David Coffin-Beach

Tor Pharm Inc.

ORIG AMENDMENT
N/Am

COVER LETTER

ADDENDUM TO AMENDMENT

TorPharm, 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3, is hereby submitting an addendum to the amendment dated July 22, 2002 for ANDA number 75-360 for Gabapentin Capsules 100 mg, 300 mg and 400 mg. The amendment is being submitted to request FDA approval for the addition of an alternate manufacturing equipment. TorPharm proposes to add an alternate encapsulator of the same design and operating principles as the one submitted in the original scale-up manufacturing documents, with the exception that this proposed encapsulator is _____.

Samantha Law
Samantha Law
Supervisor, Regulatory Affairs

October 18, 2002
Date

TORPHARM

Amendment to ANDA #75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

RECEIVED

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

OCT 21 2002

OGD / CDER

Tor Pharm Inc.

ORIG AMENDMENT

M/AM

COVER LETTER

MINOR AMENDMENT – FINAL APPROVAL REQUESTED

FBL

TorPharm, 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3, is hereby amending ANDA number 75-360 for Gabapentin Capsules 100 mg, 300 mg and 400 mg. The amendment is being submitted in response to the Approvable Letter dated December 6, 2002.

TorPharm requests final approval for ANDA #75-360, Gabapentin Capsules 100 mg, 300 mg and 400 mg based on the following:

- As of December 15, 2002, the expiration of the 30-month period provided for in Section 505 (j) (5) (B) (iii) beginning with the date of receipt of the 45-day notice required for the '482 patent under Section 505 (j) (2) (B) (i).
- Labeling revised as per the OGD Gabapentin Labeling (provided in the electronic mail dated December 10, 2002, from Michelle Dillahunt). Final printed labeling is included in this amendment.
- No changes have been made to the chemistry, manufacturing, and controls information.

Samantha Law

Samantha Law
Supervisor, Regulatory Affairs

December 13, 2002.
Date

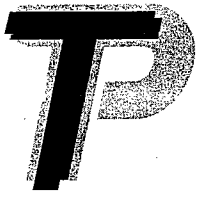
RECEIVED

DEC 1 6 2002

OGD / CDER
TORPHARM

Amendment to ANDA #75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340



Tor Pharm Inc.

December 17, 2002

Via Facsimile and E-mail

NEW CORRESP

NC

Mr. Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
HFD-600, Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773
U.S.A.

Re: ANDA No. 75-360—Gabapentin Capsules 100, 300 and 400 mg

Dear Mr. Buehler:

On December 16, 2002, the Court in *Purepac Pharmaceutical Co. v,. Thompson et al.*, Civil Action No. 02-1657 (ESH) (D.D.C.), issued its final ruling and explicitly refused to enjoin or prohibit FDA from approving TorPharm's Abbreviated New Drug Application ("ANDA") No. 75-360 for Gabapentin Capsules, 100 mg, 300 mg, and 400 mg. Because the Court has not enjoined FDA from granting final approval of TorPharm's ANDA, and because TorPharm's ANDA meets all other requirements for final approval, TorPharm hereby requests that the agency grant final approval of that ANDA immediately.

Specifically, as you know, the agency issued an approvable letter, dated December 6, 2002, indicating that TorPharm's ANDA would receive final approval after: (1) resolution of certain labeling issues identified in the December 6 letter for which the agency would provide a template for the package insert labeling; and, (2) expiration of the 30-month stay for the '482 patent, or the date of a court decision from which no appeal has been or can be taken. Those conditions for final approval have now been satisfied. TorPharm submitted its final printed labeling on December 16, 2002, in accordance with the agency's express instructions and labeling template, thus resolving the labeling issues referenced in the agency's December 6 letter. Moreover, the 30-month stay for the '482 patent expired on December 15, 2002.

RECEIVED

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50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

Accordingly, having satisfied all requirements, TorPharm hereby requests final approval of its ANDA No. 75-360 for Gabapentin Capsules, 100 mg, 300 mg, and 400 mg immediately, and in no event later than the end of business today, December 17, 2002.

Please do not hesitate to contact me if you have any questions.

Yours very truly,

Dr. David Coffin-Beach Dec 17, 2002
President, TorPharm

cc: Thomas Hinchcliffe, *Project Manager*
Daniel Troy, *Office of Chief Counsel*
Elizabeth Dickinson, *Office of Chief Counsel*
William Rakoczy, *Lord Bissell Brook*
Tim Gilbert, *Gilbert's*
Arthur Tsien, *Olsen Frank and Weeda*
David Bederman, *Emory University School of Law*

7.1
west

ANDA 75-360 (Capsules, 100 mg, 300 mg and 400 mg)

Apotex Corp.
Attention: Marcy Macdonald
U.S. Agent for: TorPharm
50 Lakeview Parkway, Suite #127
Vernon Hills, IL 60061

Dear Madam,

You have pending before the Food and Drug Administration an abbreviated new drug application (ANDA) for gabapentin capsules referencing Neurontin. As you may be aware, on Monday, December 16, 2002, Judge Huvelle of the U.S. District Court for the District of Columbia issued a decision regarding patent certification requirements with respect to U.S. Patent No. 4,084,479 (the '479 patent), which is listed in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) for Neurontin. *Purepac Pharmaceuticals Co. v. Thompson, et al.*, No. 02-1657 (D.D.C. Dec. 16, 2002). Judge Huvelle concluded that Purepac Pharmaceuticals Co. could maintain a "section viii" statement to the '479 patent pursuant to section 505(j)((2)(A)(viii) of the Federal Food, Drug, and Cosmetic Act, but left it to the agency to "sort out the considerable complexities" relating to whether other gabapentin ANDAs could maintain a paragraph IV certification, and the impact of FDA's decision on 180-day exclusivity.

With this letter, we are providing you with an opportunity to comment on how FDA should implement Judge Huevelle's decision regarding the propriety of a section viii statement to the '479 patent, the related issue of ANDA applicants maintaining a paragraph IV certification to that patent, and implications for 180-day exclusivity.

FDA is well aware of both the complexity of these issues and the need for a prompt decision regarding the pending applications. Therefore, we request that you send your comments on this matter to the Office of Generic Drugs for receipt by 5 PM Monday, December 30, 2002. FDA intends to make a decision regarding approval of pending applications during the week of January 6, 2003.

If you have any questions, please contact W. Peter Rickman, Director, Division of Labeling and Program Support, Office of Generic Drugs, at (301) 827-5846.

Sincerely,

Robert Lee West / for
12/18/2002

Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: 75-360
Daniel E. Troy, OCC
Andrew D. Clark, USDOJ
Charles J. Raubicheck, Counsel for Purepac
Tim Gilbert, Counsel for Torpharm
Jeremy M. Jay, Counsel for Mutual

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F\T by cll/12/18/02

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JAN 28 2003

Dear ANDA Applicant for Gabapentin:

This is in reference to your abbreviated new drug application (ANDA) submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Gabapentin Capsules, Tablets, or Oral Solution.

As described in the attached letter addressed to TorPharm and Purepac Pharmaceutical Company, the FDA has removed U.S. Patent No. 5,084,479 (the '479 patent) from the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book).

Applicants with pending ANDAs for gabapentin drug products must amend their applications, as required by 21 C.F.R. 314.94(a)(12)(viii)(B), to withdraw any prior certification or section viii statement as to this patent.

Please indicate at the top of your cover letter accompanying your submission that it is intended as a "Patent Amendment".

Sincerely yours,

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:
Capsule ANDAs:

75-350/Purepac
75-360/TorPharm
75-539/Eon
75-435/TEVA

75-477/IVAX
75-428/Geneva
75-485/Watson
75-537/Mutual

Tablet ANDAs:

75-694/Purepac
76-017/IVAX

75-827/TEVA
76-120/Geneva

Oral Solution ANDA:

HFD-600/G.Buehler G Buehler 1/28/03
/C.Parise
/R.West
/G.Davis
/P.Rickman
/D.Hare
/R.Hassall
/T.Ames
GCF-1/E.Dickinson
GCF-1/K.Schifter
Endorsed:1/28/03/E.Dickinson,C.Parise,R.West

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LETTER OUT

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 75-360 Torpharm (Gabapentin Capsules, 100 mg, 300 mg and 400 mg)
ANDA 75-350 Purepac (Gabapentin Capsules, 100 mg, 300 mg and 400 mg)

Apotex Corp.
Attention: Marcy Macdonald
U.S. Agent for: TorPharm, a Division of Apotex, Inc.
50 Lakeview Parkway, Suite 127
Vernon Hills, Illinois 60061

JAN 28 2003

Purepac Pharmaceutical Co.
Attention: Joan Janulis
200 Elmora Ave.
Elizabeth, NJ 07207

Dear Ms. McDonald and Ms. Janulis:

This letter addresses approval and 180-day exclusivity issues related to your pending abbreviated new drug applications (ANDAs) for gabapentin capsules. Two patents for the reference listed drug, Neurontin (gabapentin) capsules, raise questions of eligibility for 180-day exclusivity under section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act (the Act) which were left unresolved after recent litigation. This letter describes FDA's resolution of these novel and complex issues. In resolving these matters, the agency has considered the relevant provisions of the Act; FDA's regulations in 21 C.F.R. § 314; the preambles to those regulations where relevant; *Purepac Pharmaceutical Co. v. Thompson*, No. 02-1657 (D.D.C. Dec. 16, 2002); *Warner-Lambert v. Apotex, Inc.*, No. 02-1073 (Fed. Cir. Jan. 16, 2003); and the submissions made by Torpharm, Purepac, and others on this issue.

U.S. Patent Number 5,084,479

Pfizer Inc., by assignment from Warner-Lambert, Co., is the holder of the approved NDA for Neurontin (gabapentin) capsules, which was originally approved for adjunctive therapy in the treatment of partial seizures associated with epilepsy. At the time of the original NDA submission for the capsules, Warner-Lambert submitted information on patents claiming, *inter alia*, a method of treating certain forms of epilepsy. Shortly after the NDAs were approved, Warner-Lambert submitted information to FDA on U.S. Patent Number 5,084,479 (the '479 patent), claiming a method for using gabapentin to treat neurodegenerative diseases. Warner-Lambert submitted declarations to FDA that the '479 patent covered the method of use of Neurontin, and FDA listed the patent in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book).

On August 20, 2002, Purepac filed suit against FDA in the United States District Court for the District of Columbia challenging FDA's determination that applicants seeking approval of generic gabapentin were required to submit patent certifications to the '479 patent, on the ground that the '479 patent did not claim a method of use for which a drug product has been approved. *Purepac Pharmaceutical Co. v. Thompson*, No. 02-1657 (D.D.C.)

Right after the conclusion of oral argument on Purepac's motion for summary judgment on December 13, 2002, FDA received a letter from Pfizer addressing Warner-Lambert's submission to FDA of the '479 patent for publication in the Orange Book as protection for the approved Neurontin NDAs. Pfizer's letter states that Warner-Lambert never represented to FDA that the '479 patent claims the approved use of gabapentin to treat epilepsy, nor was the listing intended to convey that it covers the approved use.

On December 16, 2002, the court issued its decision in *Purepac.* Judge Huvelle concluded that the '479 patent does not claim the approved use of gabapentin. *Purepac* slip op. at 24-26.

Because the '479 patent does not claim an approved use of gabapentin, it may not be listed in the Orange Book under FDA's regulations. Based upon the information provided in Pfizer's letter, and upon Judge Huvelle's finding, FDA requested by letter of January 6, 2003, that Pfizer withdraw the '479 patent from the list of patents covering Neurontin. FDA explained that if Pfizer did not withdraw the '479 patent, FDA reserved the right to take any action appropriate to conform the patents listed as protection for Neurontin with the requirements of FDA's regulations and the Act.

By letter of January 8, 2003, Pfizer notified FDA that it "agrees that the '479 patent does not claim methods of use for which Neurontin has been approved" and "reconfirms that neither Pfizer nor Warner-Lambert ever represented to FDA that the '479 patent claimed an approved use." Pfizer's letter also states a number of arguments in support of its listing of the patent.

On January 16, 2003, the Federal Circuit issued a decision regarding the scope of infringement of patents on unapproved uses under 35 U.S.C. § 271(e)(2)(A). *Warner-Lambert Co. v. Apotex Corp.*, Civil No. 02-1073 (Fed. Cir.). The '479 patent was one of the patents at issue in that litigation. On January 17, 2003, Pfizer notified FDA that, based upon the *Warner-Lambert* decision, it was going to withdraw the '479 patent from the Orange Book.

Before FDA withdraws the '479 patent from the Orange Book pursuant to Pfizer's letter, it must make a determination, as required by 21 C.F.R.. § 314.94(a)(12)(viii)(B), that the removal of the patent will not affect an applicant's 180-day exclusivity. Torpharm has argued that it is eligible for exclusivity as to the '479 patent because it was the first to file a substantially complete ANDA containing a paragraph IV certification to that patent. Therefore, Torpharm asserts, FDA may not remove the '479 patent from the Orange Book until Torpharm's exclusivity has expired. FDA disagrees with Torpharm. The agency has concluded that 1) Torpharm is not eligible for exclusivity as to the '479 patent, and 2) FDA may therefore remove the '479 patent from the Orange Book.

180-Day Exclusivity as to the '479 Patent

FDA has determined that, under the provisions of section 505(j) of the Act and related FDA regulations, Torpharm is not eligible for 180-day exclusivity as to the '479 patent.

i. Exclusivity

The statutory provision governing 180-day exclusivity reads:

> If the application contains a certification described in subclause IV of paragraph (2)(A)(vii) and is for a drug for which a previous application has been submitted under this subsection [containing] such a certification, the application shall be made effective not earlier than one hundred and eighty days after-
>
> (I) the date the Secretary receives notice from the applicant under the previous application of first commercial marketing of the drug under the previous application, or
>
> (II) the date of a decision of a court in action described in clause (ii) holding the patent which is the subject of the certification to be invalid or not infringed,
>
> whichever is earlier.

Section 505(j)(5)(B)(iv).

Although this "exclusivity" provision is commonly characterized as granting 180-day exclusivity to the first applicant to submit an ANDA containing a paragraph IV certification, the statute does not provide for that directly. Instead, this end is accomplished by delaying the approval of subsequent ANDAs containing a paragraph IV certification for 180 days after the exclusivity period for the first ("previous") applicant has begun. Thus, if, by the time the first applicant's ANDA is ready for approval, it no longer contains a valid paragraph IV certification, the first applicant is not eligible for exclusivity. Similarly, where subsequent applications do not contain paragraph IV certifications, their approval is not delayed under this statutory provision. Therefore, the Torpharm ANDA and at least one subsequent ANDA would have to contain paragraph IV certifications to the '479 patent for there to be any exclusivity as to this patent.

ii. Paragraph IV Certifications and Section viii Statements

The relevant provisions at section 505(j)(2)(A)(vii) and (viii) state that an ANDA must include:

> (vii) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the listed drug referred to in clause (i) or which

claims a use for such listed drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under subsection (b) or (c) of this section –

(I) that such patent information has not been filed,
(II) that such patent has expired,
(III)of the date on which such patent will expire, or
(IV)that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(viii) if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

(emphases added).

Thus, if an ANDA applicant is seeking approval for a use claimed by a listed patent, the applicant must submit a certification pursuant to section 505(j)(2)(A)(vii). If an ANDA applicant is not seeking approval for a use claimed by a listed patent, it must submit a statement pursuant to section 505(j)(2)(A)(viii). As FDA's preamble to the final rule implementing these provisions noted, the statute distinguishes between ANDAs seeking approval for a use claimed in a patent and ANDAs not seeking approval for a use claimed in a patent. 59 Fed. Reg. 50338, 50347 (October 3, 1994). The two provisions of the statute – and the corresponding implementing regulations at 21 C.F.R. § 314.94(a)(12)(i) – do not overlap. An applicant does not have the option of making a paragraph IV certification in lieu of, or in addition to, a section viii statement; either the ANDA applicant is seeking approval for the use claimed in the patent, or it is not. The character of the patent and of the specific ANDA determine what the applicant must - and may - submit in response to a listed patent.

iii. This Case

FDA has reviewed the statute and its regulations in light of the statements in Pfizer's recent letters, Judge Huvelle's decision in *Purepac,* and the Federal Circuit's decision in *Warner-Lambert,* and determined that neither Torpharm nor subsequent applicants with ANDAs that contain a paragraph IV certification to the '479 patent may retain a paragraph IV certification. In determining whether a paragraph IV certification or section viii statement is appropriate, the relevant factual inquiry is whether the ANDA applicant is seeking approval for a use claimed in the patent. In this case, it is now clear that no ANDA applicant is seeking approval for the use of gabapentin claimed in the '479 patent. As clarified in Pfizer's recent submissions to FDA, and as found by Judge Huvelle and the Federal Circuit, the '479 patent claims the use of gabapentin to treat neurodegenerative diseases. *See Purepac*, slip op. at 24-25; *Warner-Lambert*, slip op. at 2-3. The ANDA applicants are seeking approval for gabapentin products labeled for use in treating epilepsy; not for the treatment of neurodegenerative disease. *See Purepac*, slip op. at 12,14; *Warner-Lambert*, slip op. at 4. Further, as Judge Huvelle noted, "[t]here is no dispute that epilepsy is *not* a neurodegenerative disease." *Purepac*, slip op. at 24, n. 21 (emphasis in the

original). Because the '479 patent claims neurodegenerative disease, and none of the applicants is seeking approval of a gabapentin product for the treatment of neurodegenerative diseases, all of the ANDA applicants for gabapentin would be required to submit a statement pursuant to section 505(j)(2)(A) (viii) -- not a patent certification pursuant to section 505(j)(2)(A)(vii) -- with respect to the '479 patent.

Thus, if the '479 patent were to remain listed in the Orange Book, all ANDA applicants for gabapentin would be required to submit a "section viii statement" to the '479 patent. Once Torpharm submitted a section viii statement to the '479 patent, it would no longer be eligible for exclusivity; once subsequent applicants amended their ANDAs to contain section viii statements, they would no longer be blocked by Torpharm's paragraph IV certification. Because no ANDA applicant for gabapentin, including Torpharm, could maintain a paragraph IV certification to the '479 patent, Torpharm would not be eligible for exclusivity under section 505(j)(5)(B)(iv).[1]

Removal of the '479 patent from the Orange Book

As discussed above, FDA has concluded that Torpharm is not eligible for exclusivity as to the '479 patent. Because FDA has made the determination that no applicant is eligible for exclusivity as to the '479 patent, 21 C.F.R. § 314.94 does not prevent its removal from the Orange Book. Accordingly, FDA has removed the patent. Applicants with pending ANDAs for gabapentin must amend their applications, as required by 21 C.F.R. § 314.94(a)(12)(viii)(B), to withdraw any certification or section viii statement as to the '479 patent. As stated in the regulation, once the amendment has been submitted, the ANDA will "no longer be considered to be one containing a certification under [paragraph IV]." *Id. See also Mylan Pharmaceuticals, Inc. v. Henney*, 94 Supp. 2d 36, 56-58 (D.D.C. 2000)(removal of paragraph IV certification terminates eligibility for exclusivity).[2]

U.S. Patent Number 6,054,482

During the *Purepac* litigation, FDA's position was that, based upon its review of the ANDA records, Purepac was the first to submit an ANDA amendment containing a paragraph IV certification to the '482 patent. Beginning on January 7, 2003, Torpharm submitted to FDA a series of letters analyzing the administrative record related to the Purepac gabapentin capsule ANDA. Based upon its analysis, Torpharm asserted that Torpharm, not Purepac, was first to submit an amendment containing a paragraph IV certification to the '482 patent. The crux of

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[1] FDA notes that, even if Torpharm were to refuse to withdraw its paragraph IV certification to the '479 patent, because of Judge Huvelle's decision that the '479 patent doesn't claim a use for which the applicants are seeking approval, FDA would have no basis to prevent subsequent ANDA applicants from amending their paragraph IV certifications for the '479 patent to section viii statements. Once such a change was made, Torpharm's paragraph IV certification would not delay approval of the subsequent ANDA. Although FDA's regulations state, that under certain circumstances, a subsequent applicant may not change its certification to circumvent a first applicant's exclusivity, that approach is premised upon the paragraph IV certification having been an appropriate certification to the listed patent. That is not the case here.

[2] Note that the withdrawal of the '479 patent from the Orange Book will affect pending ANDAs for all gabapentin drug products (capsule, tablet, and solution). Applicants must amend pending ANDAs accordingly.

Torpharm's argument is that Purepac's ANDA was not complete at the time of submission. Torpharm asserts that, when Purepac's ANDA amendment with the paragraph IV certification to the '482 patent was both sent to (May 25, 2000) and received by (May 26, 2000) FDA, Purepac did not comply with the statute or regulations because it did not indicate that it was sending (or had sent) concurrent notice of the certification to the NDA holder/patent owner. Torpharm argues that it was the first applicant to submit an amended ANDA that meets the statutory notice requirements, and, therefore, it is eligible for 180-day exclusivity.

The agency agrees with Torpharm that ,under the Act, an ANDA applicant submitting an amendment containing a paragraph IV certification to a listed patent must provide notice of the submission at the time the amendment is submitted. However, after reviewing the ANDA records, FDA has concluded that Purepac remains eligible for 180-day exclusivity as to the '482 patent. Even after taking into account the delay in notice, Purepac was still the first ANDA applicant to both submit an amended ANDA containing a paragraph IV certification and provide notice of the submission to the NDA holder and patent owner.

The Act has separate provisions addressing notice of a paragraph IV certification when the certification is submitted in an ANDA or in an amendment to an ANDA. Section 505(j)(2)(B)(i) states that "an applicant who makes a [paragraph IV certification] shall include in the application a statement that the applicant will give the notice required by clause (ii)...." In contrast, section 505(j)(2)(B)(iii) states that "if an application is amended to include a [paragraph IV certification], the notice required by clause (ii) shall be given when the amended application is submitted." FDA regulations at 21 C.F.R. §§ 314.94(a)(12)(i) and 314.95(b), and at §§ 314.94(a)(12)(viii) and 314.95(d), respectively, parallel these requirements. An applicant submitting an original ANDA with a paragraph IV certification must provide notice only after receiving acknowledgement from FDA that the ANDA has been received and is sufficiently complete to permit a substantive review. An applicant submitting an ANDA amendment containing a paragraph IV certification must send the notice at the same time it submits the amendment.

FDA's record shows, and correspondence with Purepac confirms, that Purepac did not send the required notice of the paragraph IV certification to the '482 patent until after it had submitted the amendment to FDA. FDA records show that Purepac sent its paragraph IV certification to the '482 patent to FDA on May 25, 2000. It was stamped received by FDA on May 26, 2000. Purepac sent notice of the certification to the NDA holder, Warner-Lambert, on June 13, 2000, the same day it sent notice to the patent owner.

FDA believes that, to resolve the question of who is eligible for 180-day exclusivity in this case, it must look to the fundamental requirements for submission of an ANDA amendment. This entails looking at the requirements of the statute and the regulations, and the date those requirements were met. As discussed above, the statute makes the first applicant to submit a paragraph IV certification to a patent eligible for exclusivity, and it also requires that the ANDA applicant give notice when the ANDA is submitted. Because Purepac did not give notice when it submitted the amendment to FDA, FDA will not treat the original receipt date as the relevant date for exclusivity purposes. Instead, the agency will look to the date that Purepac actually sent the required notice, since this is the date upon which Purepac effectively met the statutory

requirements by having both submitted a paragraph IV certification and sent notice of the submission. This date is June 13, 2000.

Torpharm, in turn, sent its amendment with the paragraph IV certification to the '482 patent to FDA on June 13, 2000. It was stamped received on June 16, 2000. Torpharm sent notice of the paragraph IV certification to Warner-Lambert by letter dated June 12, 2000, which was sent on June 13, 2000. Therefore, the date upon which Torpharm had both submitted its amendment to FDA and sent the required notice was June 16, 2000. Because this date is later than the June 13, 2000, date applicable to Purepac, Purepac remains eligible for 180-day exclusivity as to the '482 patent exclusivity.

In making this decision, FDA has rejected Purepac's argument that the 2½ week time lag between submission of the ANDA amendment and sending of the notice should be disregarded because it was a reasonable period for preparing and sending the detailed statement of factual and legal basis required by the statute. The statute clearly contemplates that an ANDA applicant will have determined whether its product infringes a listed patent – or whether that patent is infringed - before it submits a patent certification, not after, since it is precisely this analysis that is the basis for the paragraph IV certification itself.[3]

FDA also rejects Torpharm's argument that this conclusion gives Purepac some reward for having submitted its amendment without sending the notice. The agency's calculations are based upon when – in the case of both Torpharm and Purepac – the agency had received the ANDA amendment and notice of the paragraph IV certification had been sent.

Sufficiency of Notice Re the '482 patent

The regulations require that notice of a paragraph IV certification be sent to both the NDA holder and the patent owner. 21 C.F.R. § 314.95(a). There is no dispute that both applicants gave notice to the NDA holder, Parke Davis/Warner Lambert. Purepac's notice was received by Parke Davis on June 14, 2000; Torpharm's notice was received on June 15, 2000 by both Parke Davis and Warner-Lambert. However, both Purepac and Torpharm have raised questions about the adequacy and timing of notice to the patent owner, Godecke Aktiengesellshaft (Godecke), a Germany company. Purepac has documented that it sent notice to Godecke on June 13, 2000, which was received on June 26, 2000. Torpharm did not send notice directly to Godecke. Torpharm argues that, under 21 C.F.R. § 314.95(a)(1), notice to Warner-Lambert is sufficient because Warner-Lambert is identified in the patent declarations for the '482 patent as the U.S. agent for Godecke. FDA agrees. Because Warner-Lambert is the agent for Godecke, notice to Warner-Lambert is sufficient. Moreover, notice to Warner-Lambert is sufficient notice for both Purepac and Torpharm. The 30 month stays are calculated from the date notice was received by Warner-Lambert. Therefore, the 30 month stays on approval of the Purepac and Torpharm

[3] As noted above, an ANDA applicant may wait to send the notice of a paragraph IV certification in an original ANDA because FDA must determine whether the application is sufficiently complete to permit a substantive review. Once that determination has been made, however, an applicant must send the notice. 21 C.F.R. § 314.95(b).

ANDAs with respect to the '482 patent expired on December 14, 2002, and December 15, 2002, respectively.

Shared Exclusivity

Judge Huvelle's December 16, 2002, decision finding that Purepac properly submitted a section viii statement to the '479 patent remanded to the agency the question whether Torpharm still had a claim to immediate approval and/or 180-day exclusivity for its gabapentin capsule ANDA. The court noted that "FDA has not decided whether it could, or would, approve Torpharm's application with a paragraph IV certification to the '479 patent even if the Court were to direct the agency to accept Purepac's application with a section viii statement." *Purepac*, slip op. at 34-35. The court determined it was appropriate to let FDA sort out the "considerable complexities" of this matter. *Id.* Even though Judge Huvelle did not directly decide the question of shared exclusivity, the fundamental basis of her decision effectively decided the matter.

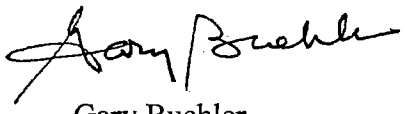
Judge Huvelle's finding that Purepac's section viii statement was appropriate **because the '479 patent does not claim a use for which Purepac – or Torpharm – was seeking approval** was fatal to any claim Torpharm had to exclusivity. It is possible the court could have found a different basis for permitting Purepac's section viii statement that would have given the agency more discretion in making an exclusivity decision. However, given the court's specific conclusions and subsequent events, FDA believes it has little choice but to find that no applicant is eligible for 180-day exclusivity as to the patent and delist the '479 patent. With no possibility of blocking exclusivities, as described in the November 2001 letter regarding omeprazole ANDAs, there is no possibility that Torpharm and Purepac will have shared exclusivity for gabapentin capsules. Only the '482 patent remains relevant for exclusivity purposes. Purepac is eligible for 180-day exclusivity as to that patent. Therefore, Torpharm, and other ANDA applicants for gabapentin capsules, must wait for final approval until the end of Purepac's exclusivity period, which will be triggered by either commercial marketing of gabapentin capsules, or by a court decision finding the '482 patent invalid or not infringed, whichever comes first.

FDA is aware that the outcome in this case may seem inequitable. Torpharm submitted a paragraph IV certification to a listed patent as required by FDA. Moreover, it successfully defended a hard-fought patent infringement case, which established important new parameters for litigation under 35 U.S.C. § 271(e)(2). However, there is no guarantee in the statute that, even in such compelling circumstances, an ANDA applicant will benefit from exclusivity. The value of exclusivity appears to be a function of timing, strategy, and luck. In Torpharm's case, exclusivity was lost to Purepac's successful defense of its section viii statement to the '479 patent.

This is not a tentative approval or approval letter for any ANDA. Tentative approval and approval status will be communicated separately to each applicant. A copy of this letter will be sent to all applicants with pending ANDAs for gabapentin capsules.

If you have questions regarding these issues, please contact Ms. Cecelia Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs, (301) 827-5845.

Sincerely yours,



Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: Timothy H. Gilbert, counsel for Torpharm/Apotex
Arthur Y. Tsien, counsel for Torpharm/Apotex
William A. Rakoczy, counsel for Torpharm/Apotex
Charles J. Raubicheck, counsel for Purepac
Andrew M Berdon (by Edgar H. Haug), counsel for Purepac
ANDA Applicants for Gabapentin
Daniel E. Troy, OCC

cc:
Capsule ANDAs:

ANDA 75-350/Purepac
ANDA 75-360/TorPharm
ANDA 75-539/Eon
ANDA 75-435/TEVA
ANDA [redacted]
ANDA 75-477/IVAX
ANDA 75-428/Geneva
ANDA 75-485/Watson
ANDA 76-537/Mutual

Tablet ANDAs:

ANDA 75-694/Purepac
ANDA 76-017/IVAX
ANDA [redacted]
ANDA 75-827/TEVA
ANDA 76-120/Geneva

Oral Solution ANDA:

ANDA [redacted]

HFD-600/C.Parise
/G.Buehler
/R.West
/G.Davis
/P.Rickman
/D.Hare
/R.Hassall
/T.Ames
GCF-1/E.Dickinson
GCF-1/K.Schifter
Endorsed:1/27/03/E.Dickinson, C.Parise, G.Davis, R.West; 1/28/03 E.Dickinson

G Buehler 1/28/03

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LETTER OUT

N/L in OB
a Thomas
5/30/03

APOTEX CORP.

616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

May 20, 2003

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

NEW CORRESP
NC.

PATENT AMENDMENT

RE: ANDA 75-360
Gabapentin Capsules 100 mg, 300 mg, and 400 mg

To Whom It May Concern:

Apotex Corp., as the U.S. Agent for TorPharm, of Ontario, Canada, is hereby submitting in duplicate a patent amendment to provide certification for U.S. Patent Number 6,566,400 B1.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs

E Thomas
NAI
PYL w 08
7/23/03

APOTEX CORP.

616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

May 22, 2003

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

NEW CORRESP
No

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RE: ANDA 75-360
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If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs

RECEIVED
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OGD / CDER

APOTEX CORP.

616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

May 23, 2003

NEW CORRESP

NC

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

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Marcy Macdonald
Director, Regulatory Affairs

RECEIVED
MAY 2 3 2003
OGD / CDER

APOTEX CORP.

818 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

May 27, 2003

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

NEW CORRESP
NC

PATENT AMENDMENT

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Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs

Ethan
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APOTEX CORP.

616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

May 28, 2003

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

NEW CORRESP
NC

PATENT AMENDMENT

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Sincerely,

Marcy Macdonald (signature) EYT

Marcy Macdonald
Director, Regulatory Affairs

RECEIVED
MAY 28 2003
OGD / CDER

APOTEX CORP.

616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

May 29, 2003

NEW CORRESP

NC

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

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Director, Regulatory Affairs

RECEIVED
MAY 29 2003
OGD / CDER

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APOTEX CORP.

616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

May 30, 2003

NEW CORRESP

NC

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

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Marcy Macdonald
Director, Regulatory Affairs

E Thomas
NAS
#4 - 603
7/23/03

APOTEX CORP.

816 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

June 2, 2003

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

NEW CORRESP
NC

PATENT AMENDMENT

RE: ANDA 75-360
Gabapentin Capsules 100 mg, 300 mg, and 400 mg

To Whom It May Concern:

Apotex Corp., as the U.S. Agent for TorPharm, of Ontario, Canada, is hereby submitting in duplicate a patent amendment to provide certification for U.S. Patent Number 6,566,400 B1.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs

E Thomas
NPS
HFD-600
7/23/03

APOTEX CORP.

816 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

June 3, 2003

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

NEW CORRESP
NC

PATENT AMENDMENT

RE: ANDA 75-360
Gabapentin Capsules 100 mg, 300 mg, and 400 mg

To Whom It May Concern:

Apotex Corp., as the U.S. Agent for TorPharm, of Ontario, Canada, is hereby submitting in duplicate a patent amendment to provide certification for U.S. Patent Number 6,566,400 B1.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs

APOTEX CORP.

616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-6005 • FAX: (847) 821-1001

June 4, 2003

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

NEW CORRESP
NC

PATENT AMENDMENT

RE: ANDA 75-360
Gabapentin Capsules 100 mg, 300 mg, and 400 mg

To Whom It May Concern:

Apotex Corp., as the U.S. Agent for TorPharm, of Ontario, Canada, is hereby submitting in duplicate a patent amendment to provide certification for U.S. Patent Number 6,566,400 B1.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs

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JUN 04 2003
OGD / CDER

Thomas
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7/8/03

APOTEX CORP.

816 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

June 6, 2003

NEW CORRESP
NC

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

RE: ANDA 75-360
Gabapentin Capsules 100 mg, 300 mg, and 400 mg

To Whom It May Concern:

Apotex Corp., as the U.S. Agent for TorPharm, of Ontario, Canada, is hereby submitting in duplicate a patent amendment to provide certification for U.S. Patent Number 6,566,400 B1.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald AYT

Marcy Macdonald
Director, Regulatory Affairs

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OGD / CDER

S. Thomas
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7/23/03

APOTEX CORP.

816 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

June 9, 2003

NEW CORRESP
NC

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

RE: ANDA 75-360
Gabapentin Capsules 100 mg, 300 mg, and 400 mg

To Whom It May Concern:

Apotex Corp., as the U.S. Agent for TorPharm, of Ontario, Canada, is hereby submitting in duplicate a patent amendment to provide certification for U.S. Patent Number 6,566,400 B1.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs

RECEIVED
JUN 09 2003
OGD / CDER

Thomas
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NYL-OB
7/23/03

APOTEX CORP.

616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-5005 • FAX: (847) 821-1001

June 10, 2003

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

NEW CORRESP
NC

PATENT AMENDMENT

RE: ANDA 75-360
Gabapentin Capsules 100 mg, 300 mg, and 400 mg

To Whom It May Concern:

Apotex Corp., as the U.S. Agent for TorPharm, of Ontario, Canada, is hereby submitting in duplicate a patent amendment to provide certification for U.S. Patent Number 6,566,400 B1.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs

RECEIVED
JUN 10 2003
OGD / CDER

8/19/03 Beverly Fitzsimmons NAI Not yet listed in orange Book

APOTEX CORP.

618 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

NEW LETTER

NC

June 11, 2003

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

RE: ANDA 75-360
Gabapentin Capsules 100 mg, 300 mg, and 400 mg

To Whom It May Concern:

Apotex Corp., as the U.S. Agent for TorPharm, of Ontario, Canada, is hereby submitting in duplicate a patent amendment to provide certification for U.S. Patent Number 6,566,400 B1.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs

RECEIVED
JUN 11 2003
OGD / CDER

APOTEX CORP.

616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-6005 • FAX: (847) 821-1001

June 12, 2003

NEW CORRESP

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

RE: ANDA 75-360
Gabapentin Capsules 100 mg, 300 mg, and 400 mg

To Whom It May Concern:

Apotex Corp., as the U.S. Agent for TorPharm, of Ontario, Canada, is hereby submitting in duplicate a patent amendment to provide certification for U.S. Patent Number 6,566,400 B1.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs

8/19/03
Beth T. Juten
NA1
Not yet listed in Orange Book

APOTEX CORP.

816 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

June 13, 2003

(NC)

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

NEW COMPANY

PATENT AMENDMENT

RE: ANDA 75-360
Gabapentin Capsules 100 mg, 300 mg, and 400 mg

To Whom It May Concern:

Apotex Corp., as the U.S. Agent for TorPharm, of Ontario, Canada, is hereby submitting in duplicate a patent amendment to provide certification for U.S. Patent Number 6,566,400 B1.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs

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JUN 13 2003
OGD / CDER

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APOTEX CORP.

616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-6005 • FAX: (847) 821-1001

June 16, 2003

NEW CORRESP
NC

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

RE: ANDA 75-360
Gabapentin Capsules 100 mg, 300 mg, and 400 mg

To Whom It May Concern:

Apotex Corp., as the U.S. Agent for TorPharm, of Ontario, Canada, is hereby submitting in duplicate a patent amendment to provide certification for U.S. Patent Number 6,566,400 B1.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs

E Thomas
NAI
NYL – 08
7/23/03

APOTEX CORP.

616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

June 17, 2003

NEW CORRESP
NC

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

RE: ANDA 75-360
Gabapentin Capsules 100 mg, 300 mg, and 400 mg

To Whom It May Concern:

Apotex Corp., as the U.S. Agent for TorPharm, of Ontario, Canada, is hereby submitting in duplicate a patent amendment to provide certification for U.S. Patent Number 6,566,400 B1.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs

APOTEX CORP.

616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-6005 • FAX: (847) 821-1001

NEW CORRESP

June 18, 2003

NC

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

RE: ANDA 75-360
Gabapentin Capsules 100 mg, 300 mg, and 400 mg

To Whom It May Concern:

Apotex Corp., as the U.S. Agent for TorPharm, of Ontario, Canada, is hereby submitting in duplicate a patent amendment to provide certification for U.S. Patent Number 6,566,400 B1.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs

APOTEX CORP.

616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

June 19, 2003

NEW CORRESP
NC

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

RE: ANDA 75-360
Gabapentin Capsules 100 mg, 300 mg, and 400 mg

To Whom It May Concern:

Apotex Corp., as the U.S. Agent for TorPharm, of Ontario, Canada, is hereby submitting in duplicate a patent amendment to provide certification for U.S. Patent Number 6,566,400 B1.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs

Stamp
NAT
NYL-03
7/23/03

APOTEX CORP.

816 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

June 20, 2003

NEW CORRESP

NC

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

RE: ANDA 75-360
Gabapentin Capsules 100 mg, 300 mg, and 400 mg

To Whom It May Concern:

Apotex Corp., as the U.S. Agent for TorPharm, of Ontario, Canada, is hereby submitting in duplicate a patent amendment to provide certification for U.S. Patent Number 6,566,400 B1.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs

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JUN 20 2003
OGD / CDER

APOTEX CORP.

818 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

23 gen

June 20, 2003

NEW CORRESP

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

RE: ANDA 75-360
Gabapentin Capsules 100 mg, 300 mg, and 400 mg

To Whom It May Concern:

Apotex Corp., as the U.S. Agent for TorPharm, of Ontario, Canada, is hereby submitting in duplicate a patent amendment to provide certification for U.S. Patent Number 6,566,400 B1.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs

Tor Pharm Inc.

GPG AMENDMENT

N/W.D.

EEA submitted

COVER LETTER

MAJOR AMENDMENT

TorPharm, 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3 is hereby filing an amendment to ANDA number 75-360 for Gabapentin Capsules 100 mg, 300 mg and 400 mg. This major amendment is being filed to request FDA approval to use an alternate manufacturer for the raw material, Gabapentin. TorPharm proposes using ———— as an alternate manufacturer of Gabapentin.

Jennifer Docherty
Manager, Regulatory Affairs

July 29/03
Date

RECEIVED
JUL 31 2003
OGD/CDER

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

APOTEX CORP.

616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

January 14, 2004

NC to NIAC

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

REQUEST FOR WITHDRAWAL
AMENDMENT DATED JULY 29, 2003

RE: Gabapentin Capsules,
100 mg, 300 mg and 400 mg
ANDA No.75-360

To Whom It May Concern:

Apotex Corp., as the U.S. agent for TorPharm wishes to withdraw the above referenced amendment for an additional active manufacturer ——.

Upon the withdrawal of this amendment, we request a return to our tentative approval status originally granted on January 29, 2003 and corrected on February 26, 2003.

We request this withdrawal without prejudice to further reinstatement or refiling.

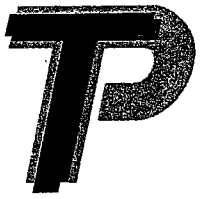
If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs
Ext. 847-279-7740

RECEIVED
JAN 15 2004
OGD/CDER



Tor Pharm Inc.

NEW CORRESP

January 15, 2004

BY FACSIMILE AND E-MAIL

XP

Mr. Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
HFD-600, Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: MINOR AMENDMENT — FINAL APPROVAL REQUESTED
TorPharm, Inc.'s ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg, and 400 mg

Dear Mr. Buehler:

TorPharm, Inc. ("TorPharm") respectfully submits this Minor Amendment requesting that the Agency immediately grant final approval of TorPharm's Abbreviated New Drug Application ("ANDA") No. 75-360 for Gabapentin Capsules 100 mg, 300 mg, and 400 mg. There have been no significant changes in the conditions under which the product was tentatively approved pursuant to your letter dated February 26, 2003 (attached hereto at Tab A).[1]

In your February 26 tentative approval letter, you stated that TorPharm's drug product is safe and effective for use as recommended in the submitted labeling, but that the Agency is unable to grant final approval at this time due to 180-day generic drug exclusivity issues arising out of U.S. Patent Nos. 4,894,476 ("the '476 patent") and 6,054,482 ("the '482 patent"). Because there are no longer any exclusivity issues barring or delaying TorPharm's approval, we respectfully request that the Agency issue final approval for TorPharm's gabapentin capsule ANDA immediately.

As you know, on January 8, 2004, in *TorPharm, Inc. v. Food and Drug Administration*, Civil No. 03-2401 (RWR) (D.D.C.), Judge Richard W. Roberts of the United States District Court for the District of Columbia entered final judgment for TorPharm holding that the Agency acted contrary to the plain language of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j)(5)(B)(iv), by awarding so-called "shared exclusivity" to different applicants that had certified first to different listed patents. Rather, the court held that the statute must be interpreted

[1] Please note that TorPharm submitted an amendment dated July 29, 2003, to qualify an additional supplier of raw material. That amendment was withdrawn on January 14, 2004, and will be resubmitted after final approval.

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0388 Fax: (416) 675-0340

to provide exclusivity only to the first applicant to submit an ANDA with a paragraph IV certification to any listed patent—what the Agency calls the "one first applicant approach." A copy of this final order, together with the final transcript, are attached at Tab B for your reference. This decision and interpretation of the statute—which should be applied fairly and consistently to all products—unequivocally resolves any remaining exclusivity hurdles for gabapentin.

Pursuant to your letter and the Administrative Record from previous gabapentin litigations, Purepac was the first applicant to submit an ANDA for gabapentin capsules with a paragraph IV certification to a listed patent, here the '476 patent. Under Judge Roberts' ruling and the Agency's "one first applicant approach," Purepac would have been entitled to exclusivity, if at all, only in connection with its first certification to the '476 patent, but *not* certifications to subsequently listed patents such as the '482 patent. As you know, however, any exclusivity arising out of the '476 patent was triggered and has long since expired by virtue of TorPharm's March 2001 judgment of noninfringement on the '476 patent, which was never appealed. Indeed, as your letter states, "[e]xclusivity as to the '476 patent was triggered with the unappealed district court decision and has expired." And under Judge Roberts' ruling in paroxetine, which is equally applicable here, there are no other potential exclusivity periods for gabapentin capsules. The Agency is estopped from taking a contrary position here on the very issue and interpretation it lost in paroxetine. *See, e.g., United States v. Montana*, 440 U.S. 147, 153 (1979) ("once an issue has been actually and necessarily determined by a court of competent jurisdiction, that determination is conclusive in subsequent suits involving a party to the prior litigation")

Accordingly, there are no remaining 180-day exclusivity periods preventing or delaying final approval of TorPharm's gabapentin capsule ANDA. Having otherwise satisfied all other requirements for final approval, TorPharm hereby requests immediate final approval of its ANDA No. 75-360 for Gabapentin Capsules, 100 mg, 300 mg, and 400 mg. Should the Agency refuse to grant such approval, please articulate the basis for such refusal immediately.

Please do not hesitate to contact me if you have any questions.

Very truly yours,

TorPharm, Inc.

David Coffin-Beach

Dr. David Coffin-Beach
President

Enclosure

cc: Thomas Hinchcliffe, *Project Manager*
Daniel Troy, *Office of Chief Counsel*
Elizabeth Dickinson, *Office of Chief Counsel*
William A. Rakoczy, *Lord, Bissell & Brook LLP*
Marcy MacDonald, *Apotex Corp.*
Jennifer Docherty, *TorPharm, Inc.*

Tor Pharm Inc.

NEW CORRESP

NC

Requested please be made a New Correspondence on 1/6/04. 1/6/04

Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: MINOR AMENDMENT – FINAL APPROVAL REQUESTED
TorPharm's Inc.'s ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

TorPharm Inc., 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3, is hereby amending ANDA number 75-360 for Gabapentin Capsules 100 mg, 300 mg and 400 mg. This minor amendment is being submitted requesting that the Agency immediately grant final approval of TorPharm's ANDA No. 75-360 for Gabapentin Capsules 100 mg, 300 mg and 400 mg.

Should you have any questions or concerns regarding the enclosed, please do not hesitate to contact me at (416) 675-0338 extension #4489 or by fax at (416) 675-0340.

Best Regards,

Eveline Eilert
Supervisor, Regulatory Affairs

JAN 19, 2004
Date

RECEIVED
JAN 20 2004
OGD / CDER

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

V 10.1

ANDA 75-360

Apotex Corp.
US Agent for Torpharm, Inc.
Attention: Marcy Macdonald
616 Heathrow
Lincolnshire, IL 60069

FEB 05 2004

To: All ANDA Applicants for Gabapentin Dosage Forms

Dear Madam:

The purpose of this letter is to bring to your attention the Office of Generic Drug's (OGD's) current position with regard to unknown impurities in gabapentin dosage forms.

The OGD is aware of the proposed monograph for Gabapentin Capsules published in *Pharmacopeial Forum* 28(2) [Mar.-Apr. 2002] in which unknown impurities are limited to not more than 0.2% of the drug substance. Initially OGD supported this limit for unknowns, but after acquiring more information on gabapentin, OGD became aware that this drug substance has the potential to form reaction products with the formulation excipients.

Not knowing the biological safety of these reaction (or degradation) products, OGD questioned the appropriateness of the 0.2% limit for unknown impurities in the proposed monograph, and decided it was prudent from a scientific standpoint to recommend to the USP that this limit be tightened from 0.2% to 0.1%. The 0.1% limit would correspond with that published in *Pharmacopeial Forum* 27(5) [Sept.-Oct. 2001] for gabapentin drug substance, which is supported by OGD.

Consequently, we are also requesting all applicants hold unknowns in the drug product to a limit of not more than 0.1% of the drug substance. When an unknown degradation product in the drug product is present at a level greater than 0.1%, it must be identified and qualified in accordance with ICH Q3B(R). Furthermore, OGD will apply this approach to ANDAs for all dosage forms of gabapentin (e.g., capsules, tablets, oral suspension).

This approach represents OGD's best scientific judgment at the present time. We appreciate your consideration of the issue raised in this letter, and your attention to this matter will assist the approval process for the gabapentin applications.

Sincerely yours,

2/5/04

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 75-360
Field Copy
Division File

V:\FIRMSAM\Apotex\LTRS&REV\gabimpletter.doc

APPEARS THIS WAY
ON ORIGINAL

FEB 6 2004

TorPharm Inc.
Attention: David Coffin-Beach, Ph.D.
50 Steinway Blvd.
Etobicoke, Ontario
Canada, M9W 6Y3

Apotex Corp.
Attention: Marcy Macdonald
U.S. Agent for TorPharm
616 Heathrow Drive
Lincolnshire, IL 60069

Sent Via Facsimile and U.S. Mail

Dear Dr. Coffin-Beach and Ms. Macdonald:

On January 15, 2004, you submitted a letter to the FDA requesting that the agency immediately grant final approval for TorPharm's ANDA 75-360 for gabapentin capsules, 100 mg, 300 mg, and 400 mg. This was also submitted in a minor amendment dated January 19, 2004. You assert that exclusivity for gabapentin capsules has expired under the "one first applicant approach" adopted by United States District Judge Roberts in litigation over the approval of paroxetine ANDAs. TorPharm, Inc. v. FDA, Civ. No. 03-2401 (Jan. 8, 2004). You assert that consistency and estoppel require the agency to apply that ruling to the gabapentin ANDAs. The agency disagrees.

As you are well aware, the approval of TorPharm's ANDA for gabapentin has been the subject of litigation since August 2002. United States District Court Judge Huvelle has issued two published opinions on the matter: Purepac Pharm. Co. v. Thompson, 238 F. Supp. 2d 191 (D.D.C. 2002); TorPharm, Inc. v. Thompson, 260 F. Supp. 2d 69 (D.D.C. 2003). TorPharm appealed both decisions to the D.C. Circuit. On January 20, 2003, the D.C. Circuit issued an opinion affirming both district court decisions. Purepac Pharm. Co. v. Thompson, Nos. 02-5410 & 03-5121, 2004 WL 76594 (D.C. Cir. Jan. 20, 2004).

At no time before TorPharm's January 15, 2004, letter did TorPharm argue to the agency or the courts that the agency should apply the one first applicant approach to conclude that 180-day marketing exclusivity could attach only to the '476 patent. TorPharm could have raised this argument in 2002 when the litigation began – the arguments that TorPharm made in the recent paroxetine litigation that began in November 2003 were available to them in the gabapentin litigation. However, TorPharm failed to argue, in either district court proceedings or on appeal, that FDA's patent-by-patent approach was invalid and that, under the one first applicant

approach, exclusivity attached only to the '476 patent. In fact, it argued *the opposite* – that TorPharm was entitled to "shared exclusivity:"

> . . . even if this Court concludes that Purepac is entitled to exclusivity on the '482 patent, TorPharm is still entitled to exclusivity as to the '479 patent, together with final approval of its ANDA and an award of shared exclusivity with Purepac. In the Purepac opinion, this Court determined just that, noting that, even with Purepac's section (viii) statement as to the '479 patent, TorPharm would still "be the first generic manufacturer to have filed a successful ANDA with such a certification as to the '479 patent. As such, it would be entitled to share a 180-day exclusivity period under 21 U.S.C. § 355(j)(5)(B)(iv), which would force Purepac to share the exclusivity which it is entitled by virtue of being the first applicant to file a paragraph IV certification as to the '482 patent." Purepac Pharm., 2002 WL 31840631 at *17 n.27.
>
> * * *
>
> [T]here is nothing in the omeprazole letter that precludes FDA from awarding shared exclusivity to TorPharm and Purepac, even though Purepac has not certified to the '479 patent, and thus FDA is clearly entitled to extend the shared exclusivity concept to situations not strictly involving a so-called "exclusivity stand-off." Indeed, one of the purposes of shared exclusivity is to permit those that are first to amend their ANDA's by filing paragraph IV certifications on newly listed patents to share in an award of exclusivity to improve the chances for an earlier launch of a generic product. (Rakoczy Decl. Tab K, Omeprazole Ltr. at 5.) The Purepac opinion itself acknowledges as much, noting that TorPharm would be entitled to shared exclusivity . . . . Purepac Pharm., 2002 WL 31840631, at *17 n.27. That is the approach that should – and indeed must – be followed here. Any other approach would lead to the absurd result . . . .

TorPharm's Memorandum of Points and Authorities in Support of its Motion for Preliminary Injunction (Feb. 14, 2003) at 35-37 (emphasis added).

Thus, TorPharm not only failed to argue in the gabapentin litigation that the court should apply the one first applicant approach, it also argued in favor of shared exclusivity. Now, after full litigation of the gabapentin ANDAs, including two district court preliminary injunction proceedings, and a full appeal, TorPharm is precluded under the doctrines of waiver and estoppel from raising a new argument.

First, a party who fails to raise an argument in the district court waives it on appeal. See United States v. Olano, 507 U.S. 725, 731 (1993) ("No procedural principle is more familiar to this Court than that a constitutional right, or a right of any other sort, may be forfeited in criminal as well as civil cases by the failure to make timely assertion of the right before a tribunal having jurisdiction to determine it.") (internal quotation marks omitted). Surely, if an argument could not be raised on appeal, it cannot be raised after appellate briefing and argument has been concluded, and the appellate court has issued its decision.

Second, judicial estoppel prevents a party from making inconsistent arguments at different stages of the same case. As the Supreme Court has recently explained,

> "[W]here a party assumes a certain position in a legal proceeding, and succeeds in maintaining that position, he may not thereafter, simply because his interests have changed, assume a contrary position, especially if it be to the prejudice of the party who has acquiesced in the position formerly taken by him." Davis v. Wakelee, 156 U.S. 680, 689, 15 S.Ct. 555, 39 L.Ed. 578 (1895). . . . 18 C. Wright, A. Miller, & E. Cooper, Federal Practice and Procedure § 4477, p. 782 (1981) (hereinafter Wright) ("absent any good explanation, a party should not be allowed to gain an advantage by litigation on one theory, and then seek an inconsistent advantage by pursuing an incompatible theory").
>
> [The] purpose [of judicial estoppel] is "to protect the integrity of the judicial process," Edwards v. Aetna Life Ins. Co., 690 F.2d 595, 598 (C.A.6 1982), by "prohibiting parties from deliberately changing positions according to the exigencies of the moment," United States v. McCaskey, 9 F.3d 368, 378 (C.A.5 1993).

New Hampshire v. Maine, 532 U.S. 742, 749-50 (2001).

Initially, in the gabapentin litigation, TorPharm hoped to prevail on a theory that it was entitled to sole or shared exclusivity. Now that that tact has failed, TorPharm has reversed course and is arguing that exclusivity for all applicants has expired. Thus, it appears TorPharm is "pursuing an incompatible theory" "according to the exigencies of the moment." See New Hampshire, 532 U.S. at 749-50. As the Supreme Court explained, such tactics are not permitted because it damages the integrity of the judicial process. Id. If the agency were to accept your new theory now, the preceding gabapentin litigation would be rendered meaningless.

Your letter asserts that the government must apply Judge Roberts' decision in the paroxetine litigation to your gabapentin ANDA under the doctrine of issue preclusion. Issue preclusion attaches only when an issue is actually litigated and determined by a valid and final judgment, and would not work an unfairness. Arizona v. California, 530 U.S. 392, 414, 120 S. Ct. 2304, 2319 (2000); Milton S. Kronheim & Co. v. District of Columbia, 91 F.3d 193, 197 (D.C. Cir. 1996). Given the circumstances here, where Judge Roberts issued a brief oral opinion from the bench, where the government is seeking to stay and appeal that opinion, and where that opinion will be subject to de novo review, we believe that issue preclusion would not apply. In any event, because TorPharm is precluded from even raising the one first applicant argument at this late stage in the litigation, the doctrine of issue preclusion need not be reached.

FDA will continue to apply a patent-by-patent exclusivity approach to the ANDAs for gabapentin capsules. For the reasons described in detail in FDA's letter of January 28, 2003 (enclosed), and affirmed by the D.C. Circuit in Purepac, 2004 WL 76594 , the agency has concluded that application of the patent-by patent approach to the gabapentin ANDAs results in Purepac having 180-day exclusivity as to U.S. Patent Number 6,054,482. This is the sole

remaining exclusivity for this drug product. The Purepac ANDA is approved, but the sponsor has not begun to commercially market the drug. The exclusivity period has not been triggered.

If you have questions regarding these issues, please contact Ms. Cecelia Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs, at (301) 827-5845.

Sincerely,

Gary Buehler 2/6/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure: FDA's Letter to Apotex Corp. and Purepac Pharmaceutical Co.
Dated January 28, 2003

cc: William A. Rakoczy, Counsel for Torpharm/Apotex
Daniel E. Troy, OCC

cc: ANDA 75-360
Dup
Division File
GCF-1/D. Troy/K. Dettelbach/L. Dickinson/K. Schifter
HFD-600/G. Buehler/R. West/D. Hare/R. Hassall/C. Parise/D. Read
HFD-610/P. Rickman/G. Davis/R. Shimer/T. Ames/T. Hinchliffe

Q:\firms-nz\torpharm\04-01-29gabapentinltr.doc

Tor Pharm Inc.

February 17, 2004

NEW CORRESP
NC
Requested per be made a 1/New Correspondence on 7/16/04.
7/16/04

Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: MINOR AMENDMENT
Gabapentin Capsules, 100 mg, 300 mg and 400 mg, ANDA #75-360

To Whom It May Concern:

TorPharm Inc. is hereby filing a minor amendment to our pending ANDA for Gabapentin Capsules, 100 mg, 300 mg and 400 mg (ANDA No. 75-360). This amendment is being submitted in triplicate (Archival, Review and Field copies), and the required Field Copy Certification can be found in the last section of the amendment.

We are revising our Largest Unknown Impurity limit for Gabapentin Capsules from 0.2% to 0.1%. This change is submitted in response to the FDA Letter to All ANDA Applicants for Gabapentin Dosage Forms dated February 5, 2004. Details of the proposed change and supporting documentation are enclosed in the relevant sections of this amendment.

Should you have any questions or concerns regarding the enclosed, please do not hesitate to contact me by telephone at (416) 675-8406, by FAX at (416) 675-0340 or by e-mail at jdochert@apotex.com.

Sincerely,

for Jennifer Docherty
Manager, Regulatory Affairs

RECEIVED
FEB 18 2004
OGD/CDER

Cc: Marcy Macdonald

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

75.360

APR 15 2004

William A. Rakoczy, Esq.
Rakoczy, Molino, Mazzochi, L.L.P.
6 West Hubbard Street, Suite 500
Chicago, IL 60610

Sent Via Facsimile and U. S. Mail

Dear Mr. Rakoczy:

This responds to your letter of April 12, 2004, on behalf of Apotex Inc., in which you request an administrative stay of approval of Purepac Pharmaceutical Company's ANDA 75-350 for gabapentin capsules, 100, 300, and 400 mg, and ANDA 75-694 for gabapentin tablets, 600 and 800 mg. Purepac's ANDA 75-350 was given final approval on September 12, 2003. Purepac's ANDA 75-694 has not been approved. You assert that a stay of approval for these ANDAs is warranted to prevent Purepac from immediately marketing its gabapentin products and enjoying a period of marketing exclusivity "to which it may not be statutorily entitled." For the reasons discussed below, your request is denied.

On January 15, 2004, Apotex submitted a letter to FDA asking that FDA grant immediate final approval for Apotex's ANDA 75-360 for gabapentin capsules 100, 300, and 400 mg. Apotex asserted that exclusivity for gabapentin capsules has expired under the "one first applicant approach" adopted by United States District Judge Roberts in litigation over the approval of paroxetine ANDAs. *TorPharm, Inc. v. FDA*, Civ. No. 03-2401 (Jan. 8, 2004). You argued that consistency and estoppel require the agency to apply that ruling to the gabapentin ANDAs.

FDA responded to the January 15 letter on February 6, 2004, denying Apotex's request for immediate approval of its ANDA 75-360. As FDA explained in detail in its response (attached), FDA will continue to apply a patent-by-patent exclusivity approach to the ANDAs for gabapentin capsules. This patent-by-patent approach for the gabapentin ANDAs results in Purepac having 180-day exclusivity as to U.S. Patent Number 6,054,482. Because Purepac has 180-day exclusivity for gabapentin capsules, 100, 200, and 300 mg, FDA will not give final approval to Apotex's ANDA for gabapentin capsules, 100, 200, and 300 mg, until Purepac's exclusivity has expired.

Apotex, having failed to obtain approval of its own ANDA because of Purepac's eligibility for exclusivity, now seeks to have FDA stay the approval it has already granted to Purepac's ANDA for gabapentin capsules, 100, 200, and 300 mg. Your letter asserts that Apotex is entitled to this relief because, absent such a stay, Purepac may "attempt to partially moot Apotex's upcoming legal challenge and obtain a *de facto* exclusivity to which Purepac is not statutorily entitled by immediately marketing its product."

FDA does not agree that a stay is appropriate. First, there is no statutory basis for FDA to stay the effectiveness of Purepac's approval to protect Apotex's "ability to compete in the gabapentin market." Purepac has met the requirements of section 505(j) of the Federal Food, Drug, and Cosmetic Act for approval of its ANDA, and thus that approval will stand. Second, Apotex seeks this relief more than two months after the February 6, 2004, agency denial of Apotex's request for approval of its ANDA. Apotex has had ample time to seek recourse to the courts on its claim that Purepac is not entitled to exclusivity, but has not done so. This unexplained delay undercuts both Apotex's unreasonable request that FDA respond in one day to its letter asking for a stay in Purepac's ANDA approvals, and the urgency and necessity of the remedy Apotex seeks. For these reasons, Apotex's request for a stay of the approval of Purepac's ANDA 75-350 is denied.

Apotex's request for a stay in approval of Purepac's ANDA 75-694 for gabapentin tablets, 600 and 800 mg, is also denied. Apotex does not have an ANDA pending for gabapentin tablets. Therefore, Apotex has no legitimate interest in any FDA decisions regarding 180-day exclusivity determinations for gabapentin tablets. The drug products that have been the subject of administrative proceedings and litigation with Apotex regarding 180-day exclusivity have been gabapentin capsules, not gabapentin tablets. *See TorPharm, Inc. v. Thompson*, 260 F. Supp. 2d 69 (D.D.C. 2003), *aff'd*, *Purepac Pharm. Co. v. Thompson*, 354 F.3d 877 (D.C. Cir. 2004).

If you have questions regarding these issues, please contact Ms. Cecelia Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs, at (301) 827-5845.

Sincerely,

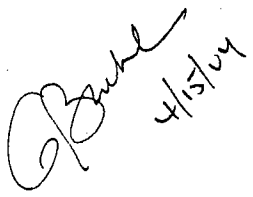
Gary Buehler 4/15/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: February 6, 2004 Letter to TorPharm, Inc. and Apotex Corp.

cc: Daniel E. Troy, OCC

q:\firmsnz\torpharm\04-04-15Apotexgabexcl.doc

cc: ANDA 75-360
Dup
Division File
GCF-1/D. Troy/K. Dettelbach/L. Dickinson/K. Schifter
HFD-600/G. Buehler/R. West/D. Hare/R. Hassall/C. Parise/D. Read
HFD-610/P. Rickman/R. Shimer/T. Ames/T. Hinchliffe



TorPharm Inc.

NAI
Name change
11
XA
8/12/04

July 22, 2004

Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

To Whom It May Concern:

Re: Company Name Change from TorPharm Inc. to Apotex Inc.
Gabapentin Capsules 100 mg, 300 mg and 400 mg
ANDA No. 75-360

Please be advised that TorPharm Inc. has assumed the name Apotex Inc. to reflect the name of its parent company, effective April 1, 2004. The FDA Form 356h has been provided.

Please also note that, where necessary, in order to distinguish between the Apotex sites, the company formerly known as TorPharm Inc. will now be referred to as Apotex Inc. – Etobicoke Site and the parent site will be referred to as Apotex Inc. – Signet Campus.

Establishment Registration and Drug Listing forms have been revised and submitted accordingly.

Should you have any questions or concerns regarding the above changes, please do not hesitate to contact me by telephone at 416-675-0338 ext. 4207, by fax at (416) 675-0340 or by email at bsandhu@apotex.com .

Sincerely,

Barinder Sandhu
Project Leader, Regulatory Affairs
Apotex Inc. – Etobicoke Site
(formerly TorPharm Inc.)

RECEIVED
JUL 23 2004
OGD / CDER

cc: John Hems, Director, US and Canadian Regulatory Affairs, Apotex Inc.
Marcy Macdonald, Director, Regulatory Affairs, Apotex Corp.

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

APOTEX INC.

ORIG AMENDMENT

N/A'm

EEI Submitted 9/13/04

August 19, 2004

Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

To Whom It May Concern:

Re: AMENDMENT – ALTERNATE RAW MATERIAL MANUFACTURER
Gabapentin Capsules, 100mg, 300 mg and 400 mg, ANDA No. 75-360

Apotex Inc. – Etobicoke Site, 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3 is hereby filing an amendment to ANDA number 75-360 for Gabapentin Capsules 100 mg, 300 mg and 400 mg. This is a resubmission of the amendment filed on July 30, 2003 to request FDA approval to use an alternate manufacturer – [redacted] for the raw material Gabapentin. The amendment was subsequently withdrawn on January 14, 2004 without prejudice placed on future resubmission. The amendment has been updated since its previous submission. Apotex Inc. is also requesting approval to use Apotex Inc. – Signet Campus as an alternate packaging and analytical site.

As required by 21 CFR 314.71(b), Apotex Inc. is forwarding a true copy of the technical sections of the amendment (including a copy of the FDA Form 356h). Apotex Inc. certifies that the technical sections contained in this "field copy" are true copies of the same sections of the amendment that were submitted to FDA headquarters. The enclosed field copy is contained in a burgundy folder.

Please note that TorPharm Inc. has assumed the name Apotex Inc. to reflect the name of its parent company, effective April 1, 2004. A letter outlining the details of this change was submitted July 22, 2004.

Should you have any questions or concerns regarding the enclosed, please do not hesitate to contact me by telephone at (416) 675-0338 ext. 4489, by fax at (416) 675-0340 or by e-mail at eeilert@apotex.com.

Sincerely,

Eveline Eilert
Project Leader, Regulatory Affairs

cc: John Hems, Director, U.S. and Canadian Regulatory Affairs, Apotex Inc.
Marcy Macdonald, Director, Regulatory Affairs, Apotex Corp.

RECEIVED
AUG 20 2004
OGD/CDER

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3
Tel. 416.675.0338 Fax. 416.675.0340 www.apotex.com

NAI patent `782 not listed in OB or dockets C. Bina
10/18/04

APOTEX CORP.
616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

October 6, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

ORIG AMENDM
N/XP

ANDA AMENDMENT

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald 2YT

Marcy McDonald
Director, Regulatory Affairs,

APOTEX INC.

150 Signet Drive, Weston, Ontario, Canada M9L 1T9

COVER LETTER

ANDA AMENDMENT

Apotex Inc., of 150 Signet Drive, Weston, Ontario, Canada M9L 1T9, is submitting an amendment to its ANDA No. 75-360 for gabapentin capsules 100 mg, 300 mg and 400 mg. This amendment is being submitted to provide certification for U.S. Patent No. 6,800,782 B2.

Regards,

Bernice Tao

Bernice Tao
Associate Director, Regulatory Affairs,
Solid Dosage Forms

Apotex Inc.

Amendment to ANDA No. 75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

NAI patent `782 not listed in OB or dockets C. Bina
10/18/04

APOTEX CORP.
616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

October 7, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

N/xp

ANDA AMENDMENT

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs

APOTEX INC.
150 Signet Drive, Weston, Ontario, Canada M9L 1T9

COVER LETTER

ANDA AMENDMENT

Apotex Inc., of 150 Signet Drive, Weston, Ontario, Canada M9L 1T9, is submitting an amendment to its ANDA No. 75-360 for gabapentin capsules 100 mg, 300 mg and 400 mg. This amendment is being submitted to provide certification for U.S. Patent No. 6,800,782 B2.

Regards,

Bernice Tao 24T

Bernice Tao
Associate Director, Regulatory Affairs,
Solid Dosage Forms

Apotex Inc.

Amendment to ANDA No. 75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

NAI patent '782 not listed in OB or dockets C. Bina
10/18/04

APOTEX CORP.
616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

October 8, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

NEW CORRESP
XP

ANDA AMENDMENT

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs,

NAI patent '782 not listed in OB or dockets C. Bina
10/18/04

APOTEX CORP.
616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

October 12, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

N/A

ANDA AMENDMENT

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald 2+T

Marcy Macdonald
Director, Regulatory Affairs,

RECEIVED
OCT 12 2004

NAI patent `782 not listed in OB or dockets C. Bina
10/18/04

APOTEX CORP.
616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

October 13, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

N/xP

ANDA AMENDMENT

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs,

NAI patent '782 not listed in OB or dockets C. Bina
10/18/04

APOTEX CORP.
616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

October 14, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

N/xP

ANDA AMENDMENT

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald
Director, Regulatory Affairs,

APOTEX INC.
150 Signet Drive, Weston, Ontario, Canada M9L 1T9

COVER LETTER

ANDA AMENDMENT

Apotex Inc., of 150 Signet Drive, Weston, Ontario, Canada M9L 1T9, is submitting an amendment to its ANDA No. 75-360 for gabapentin capsules 100 mg, 300 mg and 400 mg. This amendment is being submitted to provide certification for U.S. Patent No. 6,800,782 B2.

Regards,

Bernice Tao

Bernice Tao
Associate Director, Regulatory Affairs,
Solid Dosage Forms

Apotex Inc.

Amendment to ANDA No. 75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

NAI patent '782 not listed in OB or dockets C. Bina
10/20/04

APOTEX CORP.
616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

October 15, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

ANDA AMENDMENT

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Mary Macdonald

Marcy Macdonald
Director, Regulatory Affairs,

RECEIVED
OCT 15 2004
OGD/CDER

NAS patent 6782 not listed in OB or dockets C. Bina 10/20/04

APOTEX CORP.

616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

October 18, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

N/CP

ANDA AMENDMENT

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald AYT

Marcy Macdonald
Director, Regulatory Affairs,

RECEIVED
OCT 18 2004

NAI patent '782 not listed in OB or dockets C. Bina 10/20/04

APOTEX CORP.

616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

October 19, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

XP

ANDA AMENDMENT

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald
24T

Marcy Macdonald
Director, Regulatory Affairs,

RECEIVED
OCT 19 2004
OGD / CDER

NAI patent _____ not listed in OB or dockets C. Bina
10/20/04

APOTEX CORP.
616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

October 20, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT

ANDA AMENDMENT N/xp

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald AYT

Marcy Macdonald
Director, Regulatory Affairs,

RECEIVED
OCT 20 2004
OGD/CDER

RECEIVED
20
OCT 19 2004
OGD/CDER

APOTEX CORP.

616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

October 21, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

NAI patent 782 not listed in OB or dockets C. Bina 11/1/04

ANDA AMENDMENT

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs,

APOTEX INC.
150 Signet Drive, Weston, Ontario, Canada M9L 1T9

COVER LETTER

ANDA AMENDMENT

Apotex Inc., of 150 Signet Drive, Weston, Ontario, Canada M9L 1T9, is submitting an amendment to its ANDA No. 75-360 for gabapentin capsules 100 mg, 300 mg and 400 mg. This amendment is being submitted to provide certification for U.S. Patent No. 6,800,782 B2.

Regards,

Bernice Tao

Bernice Tao
Associate Director, Regulatory Affairs,
Solid Dosage Forms

Apotex Inc.

Amendment to ANDA No. 75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

NAI patent 782 not listed in OB or dockets C. Bina 11/1/04

APOTEX CORP.

616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

October 22, 2004

RECEIVED
OCT 2 2 2004
OGD / CDER

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

ANDA AMENDMENT

AMENDMENT
N/XP

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs,

RECEIVED
OCT 2 2 2004
OGD / CDER

APOTEX INC.
150 Signet Drive, Weston, Ontario, Canada M9L 1T9

COVER LETTER

ANDA AMENDMENT

Apotex Inc., of 150 Signet Drive, Weston, Ontario, Canada M9L 1T9, is submitting an amendment to its ANDA No. 75-360 for gabapentin capsules 100 mg, 300 mg and 400 mg. This amendment is being submitted to provide certification for U.S. Patent No. 6,800,782 B2.

Regards,

Bernice Tao

Bernice Tao
Associate Director, Regulatory Affairs,
Solid Dosage Forms

Apotex Inc.

Amendment to ANDA No. 75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

APOTEX CORP.
616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-6005

October 25, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
N/xp

ANDA AMENDMENT

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs,

APOTEX INC.
150 Signet Drive, Weston, Ontario, Canada M9L 1T9

COVER LETTER

ANDA AMENDMENT

Apotex Inc., of 150 Signet Drive, Weston, Ontario, Canada M9L 1T9, is submitting an amendment to its ANDA No. 75-360 for gabapentin capsules 100 mg, 300 mg and 400 mg. This amendment is being submitted to provide certification for U.S. Patent No. 6,800,782 B2.

Regards,

Bernice Tao

Bernice Tao
Associate Director, Regulatory Affairs,
Solid Dosage Forms

Apotex Inc.

Amendment to ANDA No. 75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

NA patent '782 not listed in OB or dockets C. Bina

APOTEX CORP.
616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

October 26, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
N | XP

ANDA AMENDMENT

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs,

APOTEX INC.
150 Signet Drive, Weston, Ontario, Canada M9L 1T9

COVER LETTER

ANDA AMENDMENT

Apotex Inc., of 150 Signet Drive, Weston, Ontario, Canada M9L 1T9, is submitting an amendment to its ANDA No. 75-360 for gabapentin capsules 100 mg, 300 mg and 400 mg. This amendment is being submitted to provide certification for U.S. Patent No. 6,800,782 B2.

Regards,

Bernice Tao 24T

Bernice Tao
Associate Director, Regulatory Affairs,
Solid Dosage Forms

Apotex Inc.

Amendment to ANDA No. 75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

NAI patent 782 not listed in OB or dockets C. Bina 11/1/04

APOTEX CORP.
616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

October 27, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
N/xp

ANDA AMENDMENT

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs,

APOTEX INC.
150 Signet Drive, Weston, Ontario, Canada M9L 1T9

COVER LETTER

ANDA AMENDMENT

Apotex Inc., of 150 Signet Drive, Weston, Ontario, Canada M9L 1T9, is submitting an amendment to its ANDA No. 75-360 for gabapentin capsules 100 mg, 300 mg and 400 mg. This amendment is being submitted to provide certification for U.S. Patent No. 6,800,782 B2.

Regards,

Bernice Tao

Bernice Tao
Associate Director, Regulatory Affairs,
Solid Dosage Forms

Apotex Inc.

Amendment to ANDA No. 75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

APOTEX CORP.
616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

October 28, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

N/xp

ANDA AMENDMENT

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs,

APOTEX INC.
150 Signet Drive, Weston, Ontario, Canada M9L 1T9

COVER LETTER

ANDA AMENDMENT

Apotex Inc., of 150 Signet Drive, Weston, Ontario, Canada M9L 1T9, is submitting an amendment to its ANDA No. 75-360 for gabapentin capsules 100 mg, 300 mg and 400 mg. This amendment is being submitted to provide certification for U.S. Patent No. 6,800,782 B2.

Regards,

Bernice Tao 24T

Bernice Tao
Associate Director, Regulatory Affairs,
Solid Dosage Forms

Apotex Inc.

Amendment to ANDA No. 75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

NAI patent '782 not listed in OB or dockets C. Bina
11/1/04

APOTEX CORP.
616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

October 29, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

N/XP

ANDA AMENDMENT

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs,

APOTEX INC.
150 Signet Drive, Weston, Ontario, Canada M9L 1T9

COVER LETTER

ANDA AMENDMENT

Apotex Inc., of 150 Signet Drive, Weston, Ontario, Canada M9L 1T9, is submitting an amendment to its ANDA No. 75-360 for gabapentin capsules 100 mg, 300 mg and 400 mg. This amendment is being submitted to provide certification for U.S. Patent No. 6,800,782 B2.

Regards,

Bernice Tao

Bernice Tao
Associate Director, Regulatory Affairs,
Solid Dosage Forms

Apotex Inc.

Amendment to ANDA No. 75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

APOTEX CORP.

616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

November 2, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

NAI patent 6782 not listed in OB or dockets C. Bina
NOV 23 2004

ANDA AMENDMENT

AMENDMENT
N\xP

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs,

RECEIVED
NOV 02 2004
OGD / CDER

APOTEX INC.
150 Signet Drive, Weston, Ontario, Canada M9L 1T9

COVER LETTER

ANDA AMENDMENT

Apotex Inc., of 150 Signet Drive, Weston, Ontario, Canada M9L 1T9, is submitting an amendment to its ANDA No. 75-360 for gabapentin capsules 100 mg, 300 mg and 400 mg. This amendment is being submitted to provide certification for U.S. Patent No. 6,800,782 B2.

Regards,

Bernice Tao 24T

Bernice Tao
Associate Director, Regulatory Affairs,
Solid Dosage Forms

Apotex Inc.

Amendment to ANDA No. 75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

APOTEX CORP.
616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

November 1, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

NAI patent '782 not listed in OB or dockets C. Bina
NOV 23 2004

N/xP

ANDA AMENDMENT

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald 24T

Marcy Macdonald
Director, Regulatory Affairs,

RECEIVED
NOV 0 1 2004
OGD / CDER

APOTEX INC.
150 Signet Drive, Weston, Ontario, Canada M9L 1T9

COVER LETTER

ANDA AMENDMENT

Apotex Inc., of 150 Signet Drive, Weston, Ontario, Canada M9L 1T9, is submitting an amendment to its ANDA No. 75-360 for gabapentin capsules 100 mg, 300 mg and 400 mg. This amendment is being submitted to provide certification for U.S. Patent No. 6,800,782 B2.

Regards,

Bernice Tao

Bernice Tao
Associate Director, Regulatory Affairs,
Solid Dosage Forms

Apotex Inc.

Amendment to ANDA No. 75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

APOTEX CORP.
616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

November 3, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

NEW CORRESP
XP

ANDA AMENDMENT

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald ART

Marcy Macdonald
Director, Regulatory Affairs,

APOTEX INC.
150 Signet Drive, Weston, Ontario, Canada M9L 1T9

COVER LETTER

ANDA AMENDMENT

Apotex Inc., of 150 Signet Drive, Weston, Ontario, Canada M9L 1T9, is submitting an amendment to its ANDA No. 75-360 for gabapentin capsules 100 mg, 300 mg and 400 mg. This amendment is being submitted to provide certification for U.S. Patent No. 6,800,782 B2.

Regards,

Bernice Tao 2nd

Bernice Tao
Associate Director, Regulatory Affairs,
Solid Dosage Forms

Apotex Inc.

Amendment to ANDA No. 75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

APOTEX INC.
150 Signet Drive, Weston, Ontario, Canada M9L 1T9

SECTION III

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 6,800,782 B2

In accordance with the Federal Food, Drug and Cosmetic Act, as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 6,800,782 B2 ("the '782 patent") is hereby provided for our Abbreviated New Drug Application No. 75-360 for gabapentin capsules 100 mg, 300 mg and 400 mg.

Apotex Inc. hereby certifies that, in its opinion and to the best of its knowledge, the '782 patent, expiring on or about September 25, 2022, will not be infringed upon by the manufacture, use or sale by Apotex Inc. of gabapentin capsules 100 mg, 300 mg and 400 mg for which Apotex Inc.'s abbreviated application has been submitted, and/or that the '782 patent is invalid.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B)(i) of the Federal Food, Drug and Cosmetic Act and 21 C.F.R. § 314.94(a)(12)(i)(A)(4) and 21 C.F.R. § 314.95, Apotex hereby states that the notice required by Section 505(j)(2)(B)(iv) of the Federal Food, Drug and Cosmetic Act and 21 C.F.R. § 314.95 is being sent to Warner-Lambert Co., the record owner of U.S. Patent No. 6,800,782 B2 and Pfizer Inc., the holder of the approved application for Neurontin® capsules 100 mg, 300 mg, and 400 mg.

As required by 21 C.F.R § 314.95(b) and (d), concurrently with sending notice of this certification to Warner-Lambert Co. and Pfizer Inc., Apotex is amending its ANDA No. 75-360 for gabapentin capsules 100 mg, 300 mg and 400 mg to include a certification that the notices have been provided to each person identified under 21 C.F.R. § 314.95(a) and that the notices met the content requirements of 21 C.F.R. § 314.95(c).

Bernice Tao

Bernice Tao
Associate Director, Regulatory Affairs,
Solid Dosage Forms

Nov. 3, 2004
Date

APOTEX CORP.
616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

November 4, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

ANDA AMENDMENT

N/XP

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs,

APOTEX INC.

150 Signet Drive, Weston, Ontario, Canada M9L 1T9

COVER LETTER

ANDA AMENDMENT

Apotex Inc., of 150 Signet Drive, Weston, Ontario, Canada M9L 1T9, is submitting an amendment to its ANDA No. 75-360 for gabapentin capsules 100 mg, 300 mg and 400 mg. This amendment is being submitted to provide certification for U.S. Patent No. 6,800,782 B2.

Regards,

Bernice Tao

Bernice Tao
Associate Director, Regulatory Affairs,
Solid Dosage Forms

Apotex Inc.

Amendment to ANDA No. 75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

APOTEX CORP.
616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

November 5, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

N/XP

ANDA AMENDMENT

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs,

APOTEX INC.
150 Signet Drive, Weston, Ontario, Canada M9L 1T9

COVER LETTER

ANDA AMENDMENT

Apotex Inc., of 150 Signet Drive, Weston, Ontario, Canada M9L 1T9, is submitting an amendment to its ANDA No. 75-360 for gabapentin capsules 100 mg, 300 mg and 400 mg. This amendment is being submitted to provide certification for U.S. Patent No. 6,800,782 B2.

Regards,

Bernice Tao

Bernice Tao
Associate Director, Regulatory Affairs,
Solid Dosage Forms

Apotex Inc.

Amendment to ANDA No. 75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

APOTEX CORP.

616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

November 8, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

N/xp

ANDA AMENDMENT

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs,

APOTEX INC.
150 Signet Drive, Weston, Ontario, Canada M9L 1T9

COVER LETTER

ANDA AMENDMENT

Apotex Inc., of 150 Signet Drive, Weston, Ontario, Canada M9L 1T9, is submitting an amendment to its ANDA No. 75-360 for gabapentin capsules 100 mg, 300 mg and 400 mg. This amendment is being submitted to provide certification for U.S. Patent No. 6,800,782 B2.

Regards,

Bernice Tao 24T

Bernice Tao
Associate Director, Regulatory Affairs,
Solid Dosage Forms

Apotex Inc.

Amendment to ANDA No. 75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

APOTEX CORP.
616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

November 9, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

AMENDMENT
N/xP

ANDA AMENDMENT

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs,

APOTEX INC.
150 Signet Drive, Weston, Ontario, Canada M9L 1T9

COVER LETTER

ANDA AMENDMENT

Apotex Inc., of 150 Signet Drive, Weston, Ontario, Canada M9L 1T9, is submitting an amendment to its ANDA No. 75-360 for gabapentin capsules 100 mg, 300 mg and 400 mg. This amendment is being submitted to provide certification for U.S. Patent No. 6,800,782 B2.

Regards,

Bernice Tao

Bernice Tao
Associate Director, Regulatory Affairs,
Solid Dosage Forms

Apotex Inc.

Amendment to ANDA No. 75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

APOTEX CORP.
616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

November 10, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

N\ xP

ANDA AMENDMENT

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs,

APOTEX INC.
150 Signet Drive, Weston, Ontario, Canada M9L 1T9

COVER LETTER

ANDA AMENDMENT

Apotex Inc., of 150 Signet Drive, Weston, Ontario, Canada M9L 1T9, is submitting an amendment to its ANDA No. 75-360 for gabapentin capsules 100 mg, 300 mg and 400 mg. This amendment is being submitted to provide certification for U.S. Patent No. 6,800,782 B2.

Regards,

Bernice Tao

Bernice Tao
Associate Director, Regulatory Affairs,
Solid Dosage Forms

Apotex Inc.

Amendment to ANDA No. 75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

APOTEX CORP.
616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

November 12, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

NEW CORRESP
XP

ANDA AMENDMENT

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs,

APOTEX INC.
150 Signet Drive, Weston, Ontario, Canada M9L 1T9

COVER LETTER

ANDA AMENDMENT

Apotex Inc., of 150 Signet Drive, Weston, Ontario, Canada M9L 1T9, is submitting an amendment to its ANDA No. 75-360 for gabapentin capsules 100 mg, 300 mg and 400 mg. This amendment is being submitted to provide certification for U.S. Patent No. 6,800,782 B2.

Regards,

Bernice Tao

Bernice Tao
Associate Director, Regulatory Affairs,
Solid Dosage Forms

Apotex Inc.

Amendment to ANDA No. 75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

APOTEX CORP.
616 Heathrow Drive, Lincolnshire, Illinois 60069 – Tel (847) 821-8005

November 15, 2004

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

N/XP

ANDA AMENDMENT

RE: ANDA No. 75-360
Gabapentin Capsules 100 mg, 300 mg and 400 mg

To whom it may concern:

Apotex Corp., as the U.S. Agent for Apotex Inc., of Canada, is hereby submitting in duplicate an amendment to its ANDA No. 75-360 to provide certification for U.S. Patent No. 6,800,782 B2.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs,

APOTEX INC.
150 Signet Drive, Weston, Ontario, Canada M9L 1T9

COVER LETTER

ANDA AMENDMENT

Apotex Inc., of 150 Signet Drive, Weston, Ontario, Canada M9L 1T9, is submitting an amendment to its ANDA No. 75-360 for gabapentin capsules 100 mg, 300 mg and 400 mg. This amendment is being submitted to provide certification for U.S. Patent No. 6,800,782 B2.

Regards,

Bernice Tao

Bernice Tao
Associate Director, Regulatory Affairs,
Solid Dosage Forms

Apotex Inc.

Amendment to ANDA No. 75-360
Gabapentin Capsules
100 mg, 300 mg and 400 mg

APOTEX INC.

ORIG AMENDMENT
N/AF

January 7, 2005

Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Labeling Amendment to Gabapentin Capsules 100 mg, 300 mg and 400 mg, ANDA #75-360

Apotex Inc., 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3, is hereby amending ANDA number 75-360 for Gabapentin Capsules 100 mg, 300 mg and 400 mg. The amendment is being submitted to update Apotex Inc.'s labeling to match the approved reference listed drug labeling. This Labeling Amendment is being submitted in duplicate (Review and Archival copies). An updated exclusivity statement, as per the Electronic Orange Book for PED, I-311 and I-354 has been submitted today under a separate cover.

Please note that TorPharm Inc. has assumed the name of Apotex Inc. to reflect the name of its parent company, effective April 1, 2004. A letter outlining the details of this change was submitted on July 22, 2004. In addition, the Establishment Registration and Drug Listing forms have also been revised and submitted to the FDA.

Should you have any questions or concerns regarding the enclosed, please do not hesitate to contact me at 416-401-7889, by fax at 416-675-0340 or by e-mail at btao@apotex.com.

Sincerely,

Bernice Tao
Associate Director, Regulatory Affairs Solid Dose (US)

cc: Marcy Macdonald, Director, Regulatory Affairs, Apotex Corp.

RECEIVED
JAN 10 2005
OGD / CDER

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3
Tel. 416.675.0338 Fax. 416.675.0340 www.apotex.com

APOTEX INC.

XR

January 7, 2005

Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Gabapentin Capsules 100 mg, 300 mg and 400 mg
ANDA #75-360

To Whom It May Concern:

Apotex Inc., 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3, is hereby amending ANDA number 75-360 for Gabapentin Capsules 100 mg, 300 mg and 400 mg. The amendment is being submitted to provide an updated exclusivity statement for PED, I-311 and I-354 as per the Electronic Orange Book. In addition, the updated labeling is being submitted today under a separate cover.

Please note that TorPharm Inc. has assumed the name of Apotex Inc. to reflect the name of its parent company, effective April 1, 2004. A letter outlining the details of this change was submitted on July 22, 2004. In addition, the Establishment Registration and Drug Listing forms have also been revised and submitted to the FDA.

Should you have any questions or concerns regarding the enclosed, please do not hesitate to contact me at 416-401-7889, by fax at 416-675-0340 or by e-mail at btao@apotex.com.

Sincerely,

Bernice Tao
Associate Director, Regulatory Affairs Solid Dose (US)

cc: Marcy Macdonald, Director, Regulatory Affairs, Apotex Corp.

RECEIVED
JAN 10 2005
OGD / CDER

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3
Tel. 416.675.0338 Fax. 416.675.0340 www.apotex.com

APOTEX INC.

February 1, 2005

ORIG AMENDMENT

Nlam

Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

To Whom It May Concern:

RE: MINOR AMENDMENT
(Includes Chemistry, Manufacturing and Controls Information)
Gabapentin Capsules 100 mg, 300 mg and 400 mg
ANDA #75-360

Apotex Inc. (formerly TorPharm Inc.) is hereby amending its ANDA #75-360 for Gabapentin Capsules 100 mg, 300 mg and 400 mg in response to the FDA Deficiency Letter dated December 27, 2004. This amendment is being submitted in triplicate (Archival, Review and Field copies), and consists of one volume. The required Field Copy Certification can be found in the last section of the amendment.

Should you have any questions or concerns regarding the enclosed, please do not hesitate to contact me by telephone at (416) 675-0338 ext. 4489, by FAX at (416) 675-0340 or by e-mail at eeilert@apotex.com.

Sincerely,

Eveline Eilert
Project Leader, Regulatory Affairs

cc: Bernice Tao, Apotex Inc.
Marcy Macdonald, Apotex Corp.

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FEB 02 2005
OGD / CDER

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3
Tel. 416.675.0338 Fax. 416.675.0340 www.apotex.com

APOTEX INC.

NEW CORRESP

NC
Faxed
MDillahunt
3/10/05

March 3, 2005

Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

To Whom It May Concern:

RE: TELEPHONE AMENDMENT
Gabapentin Capsules 100 mg, 300 mg and 400 mg
ANDA #75-360

Apotex Inc. is hereby amending its ANDA #75-360 for Gabapentin Capsules 100 mg, 300 mg and 400 mg as per the telephone discussion with Michelle Dillahunt (Labeling Review Branch, FDA) on March 2, 2005 to provide a labeling commitment. A fax copy of this commitment has been sent to the FDA on March 2, 2005. This amendment is being submitted in triplicate (Archival, Review and Field Copies), and consists of one volume. The required FDA Form 365h and the Field Copy Certification are included.

Should you have any questions or concerns regarding the enclosed, please do not hesitate to contact me by telephone at (416) 675-0338 ext. 4489, by FAX at (416) 675-0340 or by e-mail at eeilert@apotex.com.

Sincerely,

Eveline Eilert
Project Leader, Regulatory Affairs

cc: Bernice Tao, Apotex Inc.
Marcy Macdonald, Apotex Corp.

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