CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-350

Name:	Gabapentin Capsules, 100 mg, 300 mg and 400 mg
Sponsor:	Purepac Pharmaceutical Co.
Approval Date:	September 12, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-350

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-350

APPROVAL LETTER

ANDA 75-350

SEP 12 2003

Purepac Pharmaceutical Co.
Attention: Joan Janulis
200 Elmora Avenue
Elizabeth, NJ 07207

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated March 30, 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 made to our approvable letter dated April 25, 2002, and to your amendments dated November 10, 2002, and August 25, September 3, and September 12, 2003. We also refer to our letter dated January 28, 2003, addressing issues associated with 180-day generic drug exclusivity for this drug product.

The listed drug product (RLD) referenced in your application, Neurontin® Capsules 100 mg, 300 mg, and 400 mg, 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", 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 both the '476 and '482 patents under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of Gabapentin Capsules 100 mg, 300 mg, and 400 mg will not infringe upon either patent. 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 Purepac Pharmaceutical Co. (Purepac) for infringement of one or more of the patents that were the subjects of the paragraph IV certifications. This action must be brought against

Purepac prior to the expiration of forty-five (45) days from the date the notice you provided under paragraph (2)(B)(i) was received by the NDA/patent holder(s). You have notified the agency that Purepac complied with the requirements of Section 505(j)(2)(B) of the Act. As a result, Purepac was sued for patent infringement in the United States District Court for the District of New Jersey involving your challenge to the '476 patent (Warner Lambert Company v. Purepac Pharmaceutical Co. and Faulding Inc., Civil Action No. 98 2479(JCL). You have informed the agency that Purepac's motion for Summary Judgement on Noninfringement of the '476 patent was granted by the district court on May 22, 2003. Purepac was also sued in the United States District Court for the District of New Jersey involving your challenge to the '482 patent (Pfizer Inc., Warner-Lambert Company and Godecke Aktiengesellschaft v. Purepac Pharmaceutical Co. and Faulding Inc., Civil Action No. 00-CV3522). With respect to the ongoing 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. The agency also recognizes that a similar 30-month period has expired with respect to the litigation on the '476 patent.

In addition, Pfizer Inc. is entitled to a period of marketing exclusivity with respect to the labeling providing for the use of Neurontin® Capsules in the pediatric population. This exclusivity, identified as I-311 in the "Orange Book", will expire on April 12, 2004. Section 11 of the Best Pharmaceuticals for Children Act (BPCA), signed into law in January 2002, allows certain portions of Pfizer's approved labeling which is subject to pediatric exclusivity protection to be omitted from the labeling of products approved under Section 505(j). The BCPA also permits the addition of language to the labeling of products approved under Section 505(j) that serves to inform health care practitioners that Pfizer's drug product has been approved for pediatric use. The agency has determined that the final printed labeling you have submitted to support the approval of this ANDA is in compliance with the BCPA with respect to pediatric use protected by exclusivity.

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 listed drug (Neurontin Capsules, 100 mg, 300 mg, and 400 mg, respectively, of Pfizer, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

With respect to 180-day generic drug exclusivity, we note that Purepac Pharmaceutical Co. was the first to submit a substantially complete ANDA with paragraph IV certification to the '482 patent. Therefore, with this approval Purepac is eligible for 180-days of market exclusivity. This exclusivity will begin to run from the date Purepac begins commercial marketing of the drug product. Alternatively, in the absence of marketing, the exclusivity will begin with the date of a court decision finding the '482 patent to be invalid or not infringed [505(j)(5)(B)(iii) (I), (II), or (III), which has been interpreted by the agency to mean the date of a final order or judgement of that court from which no appeal can be or has been taken; whichever event occurs earlier [Section 505(j)(5)(B)(iv)].

With respect to the "first commercial marketing" trigger for the commencement of exclusivity, please refer to 21 CFR 314.107(c)(4). The Agency expects that you will begin commercial marketing of this drug product in a prompt manner. Please submit correspondence to your application stating the date you commence commercial marketing of this product, or the date of a decision of the court holding the relevant patent invalid, unenforceable or not infringed.

If you have any questions concerning the effective date of approval of an abbreviated new drug application and the Agency's elimination of the requirement that an ANDA applicant successfully defend a patent infringement suit to be eligible for 180-days of marketing exclusivity, please refer to the interim rule published in the November 5, 1998 Federal Register (Volume 63, No. 214, 59710).

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.

Post-marketing 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.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 9/12/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-350
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205

Endorsements:
HFD-645/K.Bernard 3-25-03 K Bernard 8/27/03
HFD-645/B.Arnwine 3-31-03 B Arnwine 9/5/03
HFD-617/N.Park 3-27-03 N Park 9/2/03
HFD-613/M.Dillahunt/1/9/03;3-31-03 M Dillahunt 9/3/03
HFD-613/L.Golson/1/9/03;3-31-03 9/3/03 for (No Changes in RLD labeling or Patents & Exclusivities)

V:\firmsnz\purepac\ltrs&rev\75350apd.doc

F/T by: EW 3/25/03

APPROVAL

Robert West 9/12/2003

Cont satisfactory. Hoyte Sayre 9/12/03.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-350

APPROVABLE LETTER(S)

ANDA 75-350

APR 25 2002

Purepac Pharmaceutical Co.
Attention: Joan Janulis
200 Elmora Avenue
Elizabeth, NJ 07207

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated March 30, 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 November 10, and December 22, 2000; and February 28 and April 24, 2001, and to your communications dated April 30, and May 7, 1998; May 9, May 25, and October 9, 2000; May 7, and December 14, 2001; and January 10, 2002 pertaining to patent and exclusivity issues related to the drug product. Reference is also made to our communication dated April 8, 2002 regarding your statement submitted pursuant to section 505(j)(2)(A)(viii) of the Act (section viii statement) with respect to U.S. Patent No. 5,084,479.

We have completed the review of this ANDA as submitted, and have concluded that the application is approvable.

However, before the application may receive final approval, patent issues described below must be adequately resolved. Furthermore, 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) will require resolution. The Best Pharmaceuticals for Children Act (BPCA) was signed into law in January 2002. As authorized under Section 11 of BCPA, 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. Alternative labeling will be proposed. 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 of this drug product, there are no additional materials you should submit to FDA at this time.

Furthermore, 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. The patent protection expires 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 the '476 and '482 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 Purepac Pharmaceutical Co. (Purepac) for infringement of one or more of the patents that are the subject of the certifications. You have notified the agency that Purepac has complied with the requirements of Section 505(j)(2)(B) of the Act. As a result, litigation is currently underway in the United States District Court for the District of New Jersey involving your challenge to the '476 patent (Warner Lambert Company v. Purepac Pharmaceutical Co. and Faulding Inc., Civil Action No. 98 2479(JCL). Litigation is also underway in the United States District Court for the District of New Jersey involving your challenge to the '482 patent (Pfizer Inc., Warner-Lambert Company and Godecke Aktiengesellschaft v. Purepac Pharmaceutical Co. and Faulding Inc., Civil Action No. 00-CV3522). In addition, your ANDA contains a statement pursuant to section 505(j)(2)(A)(viii) of the Act (section viii statement) with respect to the '479 patent. This statement claims that your ANDA will not claim the use (U-258 - Treatment of Neurodegenerative Diseases) listed for this patent in the agency's publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations", the "Orange Book". As stated in our letter dated April 8, 2002, the agency disagrees with your

submission of the section viii statement for the '479 patent and recommends that you submit a certification under section 505(j)(2)(A)(vii)(III) or (IV) of the Act for this patent.

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, you have revised your patent certification to the '479 patent, and:

1. the expiration of the 30-month periods for the litigation involving the '476 and '482 patents provided for in Section 505(j)(5)(B)(iii) beginning with the date of receipt of the 45-day notice required 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 on the '476 or '482 patents [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. the patents have expired, and

4. issues resulting from your revised patent certification to the '479 patent have been resolved or satisfactorily adjudicated, and

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

In order to reactivate your application prior to final approval, please submit a MINOR AMENDMENT - FINAL APPROVAL REQUESTED approximately 60 to 90 days prior to the date you believe the application may receive final approval. This amendment is intended 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 supplement should also contain data or information necessary to update the application since the date of this action 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 litigation issues noted above and an acceptable certification to the '479 patent be received, the office will reevaluate the status of this application. Once all issues other then ongoing legislative issues have been satisfactorily resolved, the agency will proceed to 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 Nicole Park, Pharm.D., Project Manager at (301) 827-5849 if you have further questions about the status of this application.

Sincerely yours,

Gary Buehler 4/25/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-350
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/Kbernard/ K Bernard 2/11/02
HFD-645/BArnwine/1/31/02 B Arnwine 2/12/02
HFD-617/KSherrod/1/24/02 K Sherrod 2/12/02
HFD-613/Klee/ 2/12/02

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F/t by rad1/31/02

Robert West 4/25/02

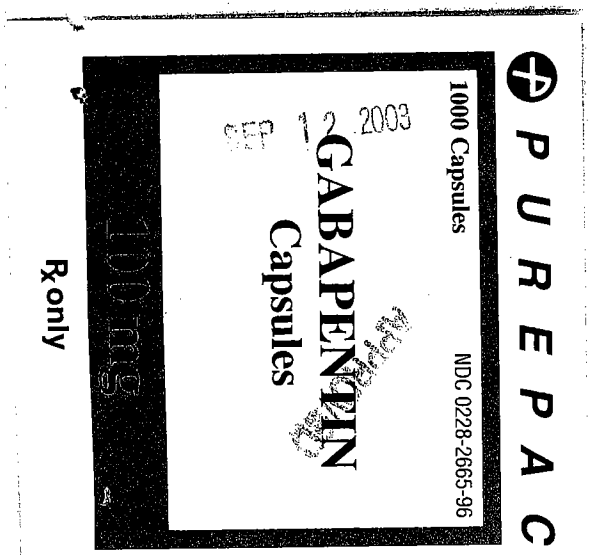
APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-350

APPROVED LABELING

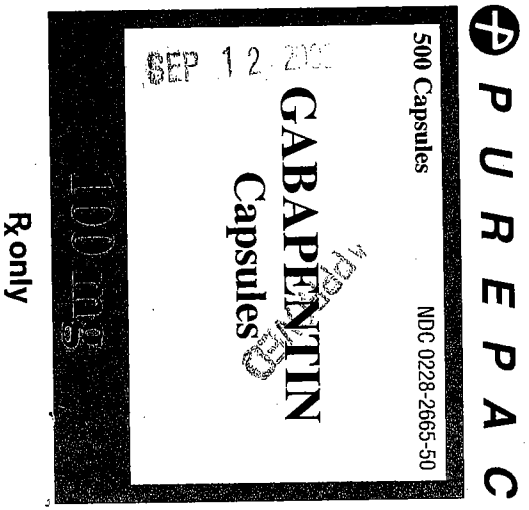


EACH CAPSULE CONTAINS:
Gabapentin ..... 100 mg
Dispense in a tight, light-resistant container as defined in the USP.
Keep this and all drugs out of the reach of children.
USUAL DOSAGE: See package insert for full prescribing information.
Store at controlled room temperature 15°-30°C (59°-86°F).
PHARMACIST: Container closure is not child-resistant.

Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA
Rev. 3/00

Lot No.: SAMPLE

3 0228-2665-96 1



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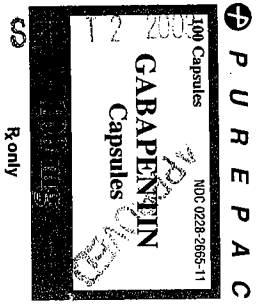
PHARMACIST: Container closure is not child-resistant.

Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA
Rev. 3/00

Lot No.: SAMPLE

3 0228-2665-50 3



EACH CAPSULE CONTAINS:
Gabapentin ..... 100 mg
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Keep this and all drugs out of the reach of children.
USUAL DOSAGE: See package insert for full prescribing information.
Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA
Rev. 3/00

Lot No.:

SAMPLE

3 0228-2665-11 4

PUREPAC

1000 Capsules

NDC 0228-2666-96

GABAPENTIN
Capsules

300 mg

SEP 12 2003

APPROVED

Rx only

EACH CAPSULE CONTAINS:
Gabapentin ..... 300 mg
Dispense in a tight, light-resistant container as defined in the USP.
Keep this and all drugs out of the reach of children.
USUAL DOSAGE: See package insert for full prescribing information.
Store at controlled room temperature 15°-30°C (59°-86°F).
PHARMACIST: Container closure is not child-resistant.

Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA

Rev. 3/00

Lot No.: SAMPLE

3 0228-2666-96 8

PUREPAC

500 Capsules

NDC 0228-2666-50

GABAPENTIN
Capsules

300 mg

SEP 12 2003

APPROVED

Rx only

EACH CAPSULE CONTAINS:
Gabapentin ..... 300 mg
Dispense in a tight, light-resistant container as defined in the USP.
Keep this and all drugs out of the reach of children.
USUAL DOSAGE: See package insert for full prescribing information.
Store at controlled room temperature 15°-30°C (59°-86°F).
PHARMACIST: Container closure is not child-resistant.

Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA

Rev. 3/00

Lot No.: SAMPLE

3 0228-2666-50 0

PUREPAC

100 Capsules

NDC 0228-2666-10

GABAPENTIN
Capsules

SEP 300 mg

APPROVED

Rx only

EACH CAPSULE CONTAINS:
Gabapentin ..... 300 mg
Dispense in a tight, light-resistant container as defined in the USP.
Keep this and all drugs out of the reach of children.
USUAL DOSAGE: See package insert for full prescribing information.
Store at controlled room temperature 15°-30°C (59°-86°F).
PHARMACIST: Container closure is not child-resistant.

Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA

Rev. 3/00

Lot No.: SAMPLE

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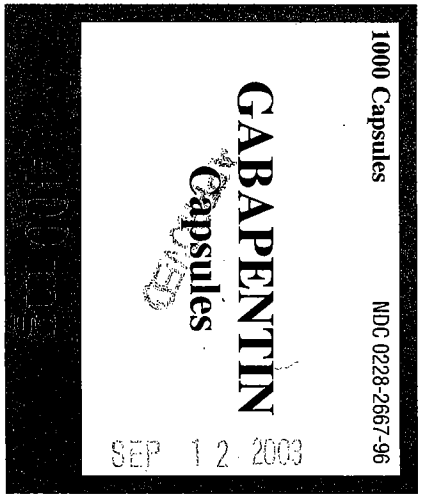


PUREPAC

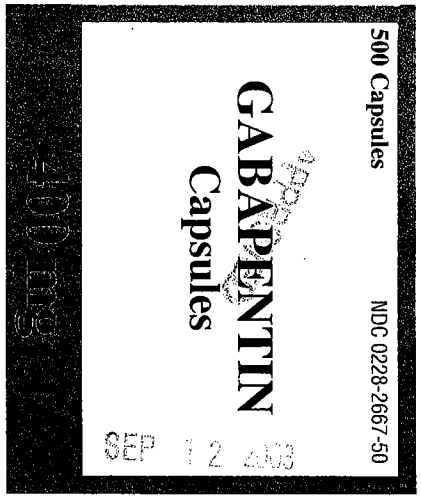
Rx only

EACH CAPSULE CONTAINS:
Gabapentin ..... 400 mg
Dispense in a tight, light-resistant container as defined in the USP.
Keep this and all drugs out of the reach of children.
USUAL DOSAGE: See package insert for full prescribing information.
Store at controlled room temperature 15°-30°C (59°-86°F).
PHARMACIST: Container closure is not child-resistant.

Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA

Rev. 3/00

Lot No.: SAMPLE



PUREPAC

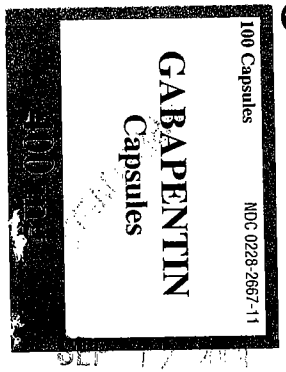
Rx only

EACH CAPSULE CONTAINS:
Gabapentin ..... 400 mg
Dispense in a tight, light-resistant container as defined in the USP.
Keep this and all drugs out of the reach of children.
USUAL DOSAGE: See package insert for full prescribing information.
Store at controlled room temperature 15°-30°C (59°-86°F).
PHARMACIST: Container closure is not child-resistant.

Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA

Rev. 3/00

Lot No.: SAMPLE



PUREPAC

Rx only

EACH CAPSULE CONTAINS:
Gabapentin ..... 400 mg
Dispense in a tight, light-resistant container as defined in the USP.
Keep this and all drugs out of the reach of children.
USUAL DOSAGE: See package insert for full prescribing information.
Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA

Rev. 3/00

Lot No.:

SAMPLE

GABAPENTIN CAPSULES

Revised — December 2002

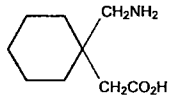
SAMPLE

DESCRIPTION:

Gabapentin Capsules are supplied as imprinted hard shell capsules containing 100 mg, 300 mg, and 400 mg of gabapentin.

The inactive ingredients are: black iron oxide, corn starch, D&C Yellow #10 aluminum lake, FD&C blue #1 aluminum lake, FD&C blue #2 aluminum lake, FD&C red #40 aluminum lake, gelatin, mannitol, pharmaceutical glaze, propylene glycol, red iron oxide T3469, silicon dioxide, sodium lauryl sulfate, synthetic black iron oxide, talc, titanium dioxide, and yellow iron oxide T3506.

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. The structural formula of gabapentin is:



APPROVED

APR 12 2003

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.

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 μM 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 2**).

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: Pediatric pharmacokinetic information is approved for Pfizer Inc.'s gabapentin. However, due to Pfizer Inc.'s marketing exclusivity rights, this product is not labeled for pediatric use.

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 patients with refractory partial seizures. Evidence of effectiveness was obtained in three trials conducted in 705 patients (age 12 years and above). 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. In patients continuing to have

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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 TID 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 TID 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 TID (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).

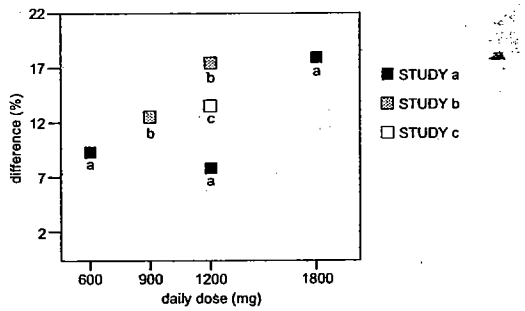

Figure 1. Responder Rate in Patients Receiving Gabapentin Expressed as a Difference From Placebo by Dose and Study: Adjunctive Therapy Studies in Patients ≥ 12 Years of Age With Partial Seizures

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.

Clinical Study information on the use of gabapentin in pediatric patients 1 month to 12 years is approved for Pfizer Inc.'s gabapentin. However, due to Pfizer Inc.'s marketing exclusivity rights, this drug product is not labeled for pediatric use.

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.

Information relating to the use of gabapentin as adjunctive therapy in the treatment of partial seizures in pediatric patients 3 years to 12 years is approved for Pfizer Inc.'s gabapentin. However, due to Pfizer Inc.'s marketing exclusivity rights, this drug product is not labeled for pediatric use.

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.

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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 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 µg/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 µg/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 TID) 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 TID; 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 TID; 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 TID; 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 QID (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 Contraceptives: 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 TID; 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 (Aluminum Hydroxide and Magnesium Hydroxide Suspension): Aluminum Hydroxide and Magnesium Hydroxide Suspension reduced the bioavailability of gabapentin (N=16) by about 20%. This decrease in bioavailability was about 5% when gabapentin was administered 2 hours after aluminum hydroxide and magnesium hydroxide suspension. It is recommended that gabapentin be taken at least 2 hours following aluminum hydroxide and magnesium hydroxide suspension 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 per 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.

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