

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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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 (BCPA), 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).

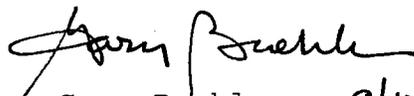
Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

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 8/2/03*
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 *L Golson 9/3/03 for (No Change: in 210 labeling or Patents & Exclusivities)*

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F/T by: EW 3/25/03

APPROVAL

coml safe factory
Wayne 9/12/03

Robert West
9/12/2003

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.

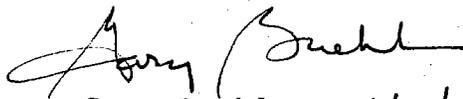
This is not an approval letter. This drug product may not be marketed without final agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 301(d) of the Act. Also, 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 than 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,

A handwritten signature in black ink, appearing to read "Gary Buehler". The signature is fluid and cursive, with a long horizontal stroke at the end.

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/
HFD-645/BArnwine/1/31/02
HFD-617/KSherrrod/1/24/02
HFD-613/Klee/

K Bernard 2/11/02
K Sherrrod 2/12/02 *(B) 2/12/02*

CLW 2/12/02

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F/t by rad1/31/02

Rob Dettelbach
4/25/02

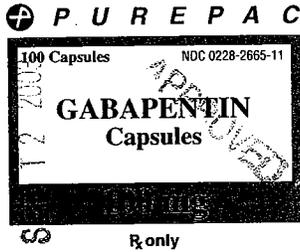
APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

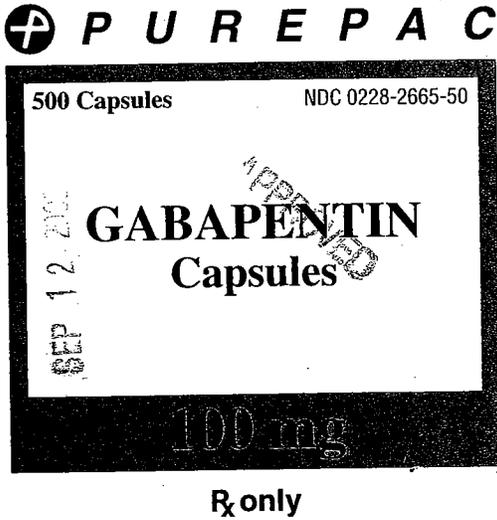
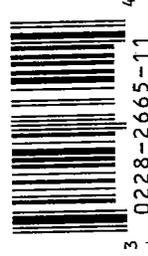
APPLICATION NUMBER:

ANDA 75-350

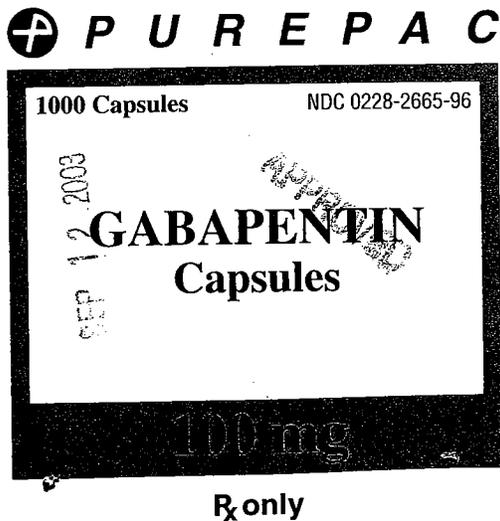
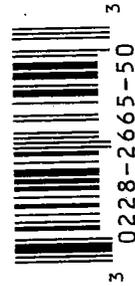
APPROVED LABELING



EACH CAPSULE CONTAINS:
 Gabapentol 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).
 Manufactured by:
 PUREPAC PHARMACEUTICAL CO.
 Elizabeth, NJ 07207 USA
 Rev. 3/00
 Lot No.:

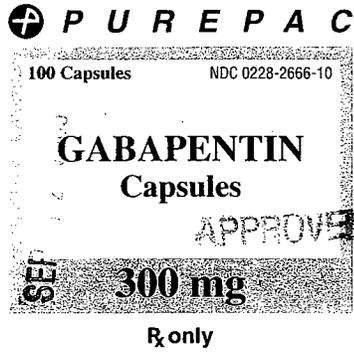


EACH CAPSULE CONTAINS:
 Gabapentin 100 mg
 Dispense in a tight, light-resistant container as defined in the USP.
Keep this and all drugs out of the reach of children.
 USUAL DOSAGE: See package insert for full prescribing information.
 Store at controlled room temperature 15°-30°C (59°-86°F).
 PHARMACIST: Container closure is not child-resistant.
 Manufactured by:
 PUREPAC PHARMACEUTICAL CO.
 Elizabeth, NJ 07207 USA
 Rev. 3/00
 Lot No.:

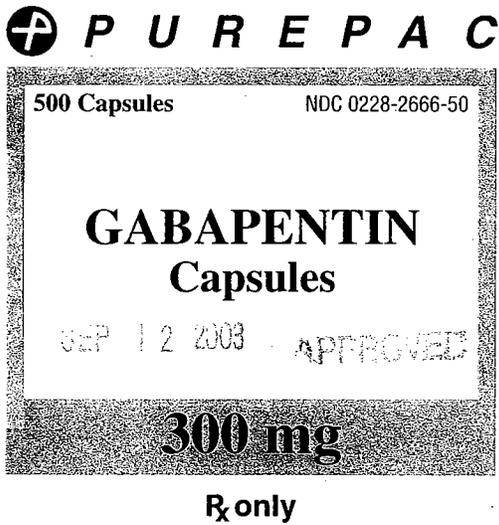


EACH CAPSULE CONTAINS:
 Gabapentin 100 mg
 Dispense in a tight, light-resistant container as defined in the USP.
Keep this and all drugs out of the reach of children.
 USUAL DOSAGE: See package insert for full prescribing information.
 Store at controlled room temperature 15°-30°C (59°-86°F).
 PHARMACIST: Container closure is not child-resistant.
 Manufactured by:
 PUREPAC PHARMACEUTICAL CO.
 Elizabeth, NJ 07207 USA
 Rev. 3/00
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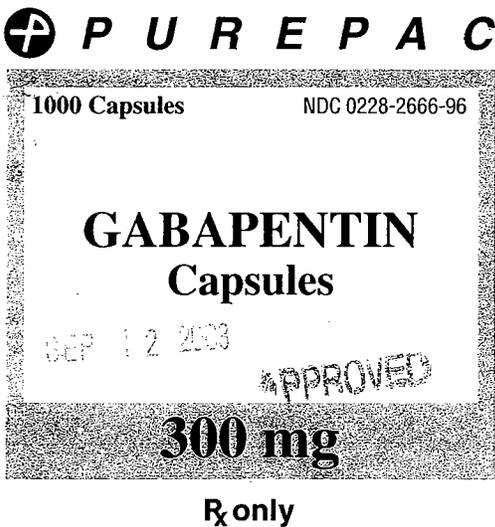




EACH CAPSULE CONTAINS:
 Gabapentin 300 mg
 Dispense in a tight, light-resistant container as defined in the USP.
Keep this and all drugs out of the reach of children.
 USUAL DOSAGE: See package insert for full prescribing information.
 Store at controlled room temperature 15°-30°C (59°-86°F).
 PHARMACIST: Container closure is not child-resistant.
 Manufactured by:
 PUREPAC PHARMACEUTICAL CO.
 Elizabeth, NJ 07207 USA
 Rev. 3/00
 Lot No.: **SAMPLE**



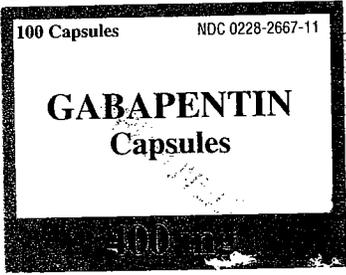
EACH CAPSULE CONTAINS:
 Gabapentin 300 mg
 Dispense in a tight, light-resistant container as defined in the USP.
Keep this and all drugs out of the reach of children.
 USUAL DOSAGE: See package insert for full prescribing information.
 Store at controlled room temperature 15°-30°C (59°-86°F).
 PHARMACIST: Container closure is not child-resistant.
 Manufactured by:
 PUREPAC PHARMACEUTICAL CO.
 Elizabeth, NJ 07207 USA
 Rev. 3/00
 Lot No.: **SAMPLE**



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**



PUREPAC



Rx only

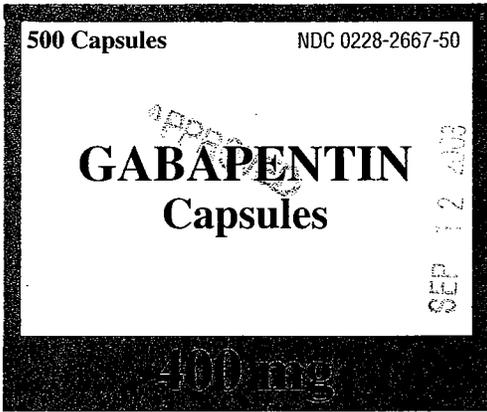
EACH CAPSULE CONTAINS:
 Gabapentin 400 mg
 Dispense in a tight, light-resistant container as defined in the USP.
Keep this and all drugs out of the reach of children.
 USUAL DOSAGE: See package insert for full prescribing information.
 Store at controlled room temperature 15°-30°C (59°-86°F).
 Manufactured by:
 PUREPAC PHARMACEUTICAL CO.
 Elizabeth, NJ 07207 USA
 Rev. 3/00
 Lot No.:



3 0228-2667-11 8

SAMPLE

PUREPAC



Rx only

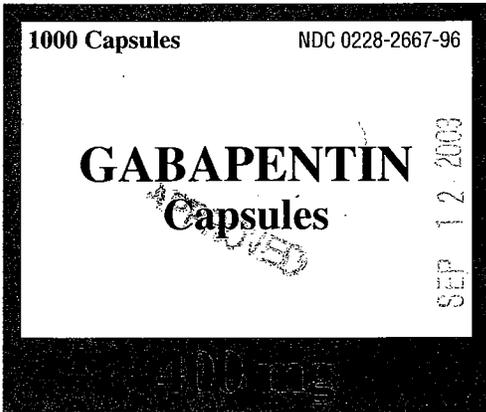
EACH CAPSULE CONTAINS:
 Gabapentin 400 mg
 Dispense in a tight, light-resistant container as defined in the USP.
Keep this and all drugs out of the reach of children.
 USUAL DOSAGE: See package insert for full prescribing information.
 Store at controlled room temperature 15°-30°C (59°-86°F).
 PHARMACIST: Container closure is not child-resistant.
 Manufactured by:
 PUREPAC PHARMACEUTICAL CO.
 Elizabeth, NJ 07207 USA
 Rev. 3/00
 Lot No.:



3 0228-2667-50 7

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.:



3 0228-2667-96 5

SAMPLE

GABAPENTIN CAPSULES

Revised — December 2002

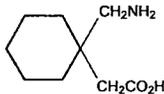
SAMPLE

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) cyclohexanecarboxylic 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

07/12/2003

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 μ M 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 nifedipine 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 \pm 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 (CL_r) and CL_r 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).

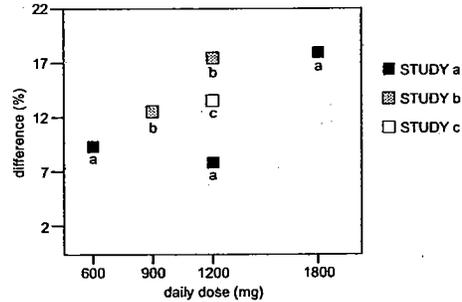


Figure 1. Responder Rate in Patients Receiving Gabapentin Expressed as a Difference From Placebo by Dose and Study: Adjunctive Therapy Studies in Patients ≥ 12 Years of Age With Partial Seizures

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.

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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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/m² 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/m² basis. The no-effect level was 500 mg/kg/day or approximately 1/2 of the human dose on a mg/m² 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/m² basis. There was an increased incidence of hydronephrosis and/or hydroureter 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/m² 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/m² basis. Other than hydronephrosis and hydroureter and hydroureter, 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/m² basis.

In a teratology study in rabbits, an increased incidence of post implantation 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/m² 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.

Geriatric Use: Clinical studies of gabapentin in epilepsies 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**).

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.

Approximately 7% of the 2074 patients >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%).

Adverse event information in pediatric patients 3 years to 12 years related to the use of gabapentin with other antiepileptic drugs 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.

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	Placebo ^a
	N = 543 %	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

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Neurological 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 ^a	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.

Adverse event information in pediatric patients 3 years to 12 years related to the use of gabapentin with other antiepileptic drugs 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.

Other Adverse Events Observed During All Clinical Trials: Clinical Trials in Adults and Adolescents With Epilepsy: Gabapentin has been administered to 2074 patients >12 years of age during all adjunctive therapy clinical trials in epilepsy, 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, perleche, 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.

PANEL 5 of 6

Clinical Trials in Pediatric Patients With Epilepsy: Information relating to adverse events that occurred during clinical trials in pediatric patients 3 years to 12 years treated with gabapentin that were not reported in adjunctive trials in adults 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.

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, Stevens-Johnson syndrome.

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.

Epilepsy: Gabapentin is recommended for add-on therapy. 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 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 TID schedule should not exceed 12 hours.

Pediatric Patients Age 3-12 years: Dosing information for pediatric patients age 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.

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:

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

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

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 2. Gabapentin Dosage Based on Renal Function

Renal Function Creatinine Clearance (mL/min)	Total Daily Dose Range (mg/day)	Dose Regimen (mg)				
		300 TID	400 TID	600 TID	800 TID	1200 TID
≥ 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 are supplied as follows:

100 mg — Each light brown/white capsule imprinted R 665 with black ink contains 100 mg of gabapentin. Capsules are supplied in bottles of 100 with a child-resistant closure (NDC 0228-2665-11) and bottles of 100 (NDC 0228-2665-10), 500 (NDC 0228-2665-50), and 1000 (NDC 0228-2665-96) without a child-resistant closure.

300 mg — Each light brown/yellow capsule imprinted R 666 with black ink contains 300 mg of gabapentin. Capsules are supplied in bottles of 100 with a child-resistant closure (NDC 0228-2666-11) and bottles of 100 (NDC 0228-2666-10), 500 (NDC 0228-2666-50), and 1000 (NDC 0228-2666-96) without a child-resistant closure.

400 mg — Each light brown/orange capsule imprinted R 667 with black ink contains 400 mg of gabapentin. Capsules are supplied in bottles of 100 with a child-resistant closure (NDC 0228-2667-11) and bottles of 100 (NDC 0228-2667-10), 500 (NDC 0228-2667-50), and 1000 (NDC 0228-2667-96) without a child-resistant closure.

Dispense in a tight, light-resistant container as defined in the USP.

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

R only

PANEL 6 of 6

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-350

LABELING REVIEW(S)

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

ANDA Number: **75-350** Date of Submission: **March 30, 1998**

Applicant's Name: **Purepac Pharmaceutical Co.**

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

Labeling Deficiencies:

1. CONTAINER (100s, 500s and 1000s)

Satisfactory in draft.

2. INSERT

- a. DESCRIPTION

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



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

Gabapentin is described as 1-
(Aminomethyl... _____ the
_____ 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. CONTRAINDICATIONS

Gabapentin _____ contraindicated...

d. PRECAUTIONS

- i. Antacid - Replace " _____ " with "Aluminum Hydroxide, Magnesium Hydroxide _____ Suspension". [3 places]
- ii. Pregnancy - Revise this subsection heading to read "Pregnancy: _____ Pregnancy Category C".

f. HOW SUPPLIED

Relocate "Rx only" to appear in the title.

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

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.

**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 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 bioequivalency values: insert to study. List C _{max} , T _{max} , 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.

~~Patent 4894476 - Expires May 2, 2008 - 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 patent 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, 500s and 1000s.

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 2076, 2077, and 2078, Vol. 1.1 - red jacket.

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 pages 2076, 2077 and 2078, Vol. 1.1. - Red jacket.

7. All manufacturing will be performed by purepac. No outside firms are utilized. See pages 2258 and 2277, Vol. 1.1 - red jacket.

8. Container/Closure:

This product will be packaged in HDPE bottles with a CRC cap with 100s and non-CRC 100s. 500s and 1000s will have a screw cap. See page 2852, Vol. 1.3 - red jacket.

Date of Review: August 20, 1998

Date of Submission: March 30, 1998

Reviewer: Carol A. Holquist

Date: 8/25/98

Team Leader:

Date:

John L. Grace

8/2/98

CC:

ANDA 75-350
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: 75-350 Date of Submission: January 11, 1999

Applicant's Name: Purepac Pharmaceutical Co.

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

Labeling Deficiencies:

1. GENERAL

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.

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".

b. ADVERSE REACTIONS

Add the following subsection (——— after "Special Senses" subsection)

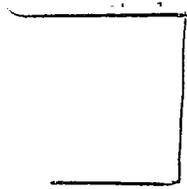
Postmarketing and Other Experience

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.

c. DOSAGE AND ADMINISTRATION

i. The second sentence of the first paragraph should read as "...pediatric patients below the age of — years —"

ii. Replace "



with "The starting dose is 300 mg three times a day." in the third paragraph.

Please revise your labeling, as instructed above, and submit final printed, or if you 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.

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

Do you have 12 Final Printed Labels and Labeling? Yes

1. CONTAINER - 100s, 500s & 1000s
2. INSERT

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	NA
Is the name different 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	NA
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 bioequivalency values: insert to study. List C _{max} , T _{max} , 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:

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 will need to wait until September 29, 2001 and also recertify.

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. Purepac was asked to recertify on July 19, 1999.

Patent 5084479 - Treatment of neurodegenerative diseases. Expires January 2, 2010. The firm cited 505(j)(2)(A)(viii). The firm states that this patent does not claim any of the proposed indications covered by their application.

Patent 4087544 - Method of treating certain forms of epilepsy. Expires January 16, 2000. The firm filed a paragraph III certification.

Patent 4894476 - Expires May 2, 2008 - The firm filed a paragraph IV certification.

Carol Holquist 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 patent 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°C to 30°C (59°F to 86°F).

ANDA: Store at controlled room temperature 15°C to 30°C (59°F 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, 500s & 1000s for all three strengths.

5. The capsule imprinting 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 2076, 2077, and 2078, Vol. 1.1 - red jacket.

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 appearing on pages 2076, 2077, and 2078, Vol. 1.1 - Red jacket.

7. All manufacturing will be performed by purepac. No outside firms are utilized. See pages 2258 and 2277, Vol. 1.1 - red jacket.

8. Container/Closure:

Container: HDPE

Closure: 100s - CRC & Non-CRC

500s - Non-CRC

1000s - Non-CRC

See page 2852, Vol. 1.3 - red jacket

Date of Review: July 21, 1999

Date of Submission: January 11, 1999

Reviewer: Koung Lee *pl*

Date: 7/28/99

Team Leader: Charlie Hoppes

Date:

cc: ANDA 75-350

DUP/DIVISION FILE

613/KLee/CHoppes/ (no cc)

FIRMSNZ\PUREPAC\LTRS&REV\75350na2.labeling

Review

S. I
Kosman
Shaw

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

ANDA Number: 75-350

Date of Submission: August 2, 1999

Applicant's Name: Purepac Pharmaceutical Co.

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

The firm should be informed of the following in an approvable letter.*

Reference is made to your amendment dated August 2, 1999.

In that amendment, you respectfully declined to recertify not to market Gabapentin Capsules until the expiration of exclusivity D-43.

We have completed the review of your application and it is approvable. Tentative approval is dependent upon the resolution of the D-43 exclusivity and its impact on generic applications for Gabapentin Capsule applications. Meetings are scheduled within the Agency to determine whether exclusivity D-43 will block the approval of generic applications for Gabapentin Capsules until its expiration or whether generic Gabapentin Capsules may be marketed before its expiration provided that labeling does not include labeling protected under the D-43 exclusivity.

APPROVAL SUMMARY

Do you have 12 Final Printed Labels and Labeling? Yes

1. CONTAINER - 100s, 500s & 1000s
Satisfactory in FPL as of January 11, 1999 submission
2. INSERT
Possibly satisfactory in FPL as of August 2, 1999.

Revisions needed post-approval:

Dependent on the outcome of the meetings scheduled to discuss the D-43 exclusivity matter. If it's determined that the D-43 exclusivity may not block the approval of generic applications before its expiration, the insert labeling submitted in FPL on August 2, 1999, is satisfactory for approval. If it's decided the other way around, the firm will need to recertify and also revised the DOSAGE AND ADMINISTRATION section.

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	NA
Is this name different 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	

*The issue of whether to correct "oe" letters for Gabapentin ANDA holders is under discussion in the

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	
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	NA
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	
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 bioequivalency values: insert to study. List Cmax, Tmax, T_{1/2} and date study acceptable)			
Does the firm's 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 will 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. Purepac was asked to recertify on July 19, 1999.

Patent 5084479 - Treatment of neurodegenerative diseases. Expires January 2, 2010. The firm cited 505(j)(2)(A)(viii). The firm states that this patent does not claim any of the proposed indications covered by their application.

Patent 4087544 - Method of treating certain forms of epilepsy. Expires January 16, 2000. The firm filed a paragraph III certification.

Patent 4894476 - Expires May 2, 2008 - The firm filed a paragraph IV certification.

Carol Holquist 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 patent 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, 500s & 1000s for all three strengths.

5. The capsule imprinting 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 2076, 2077, and 2078, Vol. 1.1 - red jacket.

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 appearing on pages 2076, 2077, and 2078, Vol. 1.1 - Red jacket.

7. All manufacturing will be performed by purepac. No outside firms are utilized. See pages 2258 and 2277, Vol. 1.1 – red jacket.

Container/Closure:

Container: HDPE

Closure: 100s - CRC & Non-CRC
500s - Non-CRC
1000s - Non-CRC
See page 2852, Vol. 1.3 – red jacket

9. A decision has not been reached whether generic firms can use the previously approved labeling however, meetings are scheduled within upper management and general counsel to resolve the D-43 exclusivity issue. For now, the labeling reviewer is instructed from the office level that the labeling previously approved for the RLD no longer exists therefore labeling deviating from the currently approved labeling shall be deemed deficient and therefore not approvable at this time.

Date of Review: September 27, 1999

Date of Submission: August 2, 1999

Reviewer: Koung Lee *KL*

Date: 9/29/99

Team Leader: Charlie Hoppes

Date:

cc: ANDA 75-350
DUP/DIVISION FILE
HFD-613/KLee/CHoppes/ (no cc)

RMSNZ/PUREPAC/LTRS&REV75350.NA3.labeling

JW

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

ANDA Number: 75-350

Date of Submission: February 28, 2001

Applicant's Name: Purepac Pharmaceutical Co.

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

1. General Comments

- 6-1
- a. The reference listed drug, Neurontin® is entitled to a new exclusivity (I-311). Please update your patent certification and exclusivity statement. We refer you to the 20th edition of Approved Drug Products with Therapeutic Equivalence Evaluations [Orange Book], for guidance.
 - b. We acknowledge that you revised your insert labeling to be in accord with the October 12, 2000, approved insert labeling of the reference listed drug Neurontin® (Gabapentin) manufactured by Parke-Davis Pharmaceutical Ltd., found on our website.

We defer further comment pending resolution of issues regarding the new indication exclusivity (I-311) for the reference listed drug, Neurontin®.

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.

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.

Shaw

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY

Do you have 12 Final Printed Labels and Labeling? Yes

1. CONTAINER - 100s, 500s & 1000s
2. INSERT

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 [Portions from previous review/reviewer].

Established Name	Yes	N o	NA
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 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	NA
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 bioequivalency values: insert to study. List Cmax, Tmax, T and date study acceptable)			
ert labeling references a food effect or a no-effect? If so, was a food study done?		X	
as 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: [Portions from previous review/reviewer].

1. Review based on the labeling of the referenced listed drug, Neurontin® (Gabapentin) ; NDA 20-235/S-015, approved on October 12, 2000.

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. Purepac was asked to recertify on July 19, 1999.

Patent 5084479 - Treatment of neurodegenerative diseases. Expired July 2, 2010. The firm cited 505(j)(2)(A)(viii). The firm states that this patent does not claim any of the proposed indications covered by their application.

Patent 4087544 - Method of treating certain forms of epilepsy. Expires July 16, 2000. The firm filed a paragraph III certification.

Patent 4894476 - Expires November 2, 2008 - The firm filed a paragraph IV certification.

I-311 exclusivity expires October 12, 2003 for ADJUNCTIVE THERAPY IN THE TREATMENT OF PARTIAL SEIZURES IN PEDIATRIC PATIENTS AGE 3 TO 12 YEARS. We will ask the firm to update the exclusivity statement to include this new exclusivity.

Patent 6054482 expires October 25, 2017

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, 500s & 1000s for all three strengths.

5. The capsule imprinting 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 2076, 2077, and 2078, Vol. 1.1 – red jacket.

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 appearing on pages 2076, 2077, and 2078, Vol. 1.1 – Red jacket.

7. All manufacturing will be performed by purepac. No outside firms are utilized. See pages 2258 and 2277, Vol. 1.1 – red jacket.

8. Container/Closure:

Container: HDPE

Closure: 100s - CRC & Non-CRC

500s – Non-CRC

1000s - Non-CRC

See page 2852, Vol. 1.3 – red jacket

Date of Review: June 1, 2001

Date of Submission: February 28, 2001

Reviewer: *Jacqueline Council, Pharm.D.* 6-11-01

Jacqueline Council, Pharm.D. Date:

Team Leader: *Mike Deppa* Date: 6/12/01

ANDA 75-350

DUP/DIVISION FILE

HFD-613/JCouncil/CHoppes/ (no cc)

V:\FIRMSNZ\PUREPAC\LTRS&REV\75350na3.l

Review

			process for producing the same	
5,084,479	6--02-10		Novel methods for treating neurodegenerative diseases	METHOD OF USE
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 – from previous reviewer

Established Name	Yes	No	NA
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 24		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	NA
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	
Are Manufactured by/Distributor statement incorrect or falsely inconsistent between labels 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	
Do 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 bioequivalency values: insert to study. List Cmax, Tmax, T 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 [portions from previous reviewer]

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. Purepac 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:

a. CLINICAL PHARMACOLOGY

i. (Special Populations) Pediatric- revised the subsection to read:

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.

ii. Clinical studies (first two paragraphs)

Deleted " _____ " from first paragraph.

Deleted " _____ " from first sentence of second paragraph.

Deleted " _____ " from second sentence of the second paragraph.

iii. Clinical studies (last two paragraphs)- revised to read:

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.

b. INDICATIONS AND USAGE

Revised to read:

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.

c. WARNINGS

Neuropsychiatric Adverse Events-Pediatric Patients 3-12 years of age- No change, Safety information retained.

d. PRECAUTIONS

Deleted " _____ " since that subsection has been carved out.

e. ADVERSE REACTIONS

i. Revised first paragraph to read:

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.

Deleted " _____ " from the second paragraph.

Added disclaimer: Adverse event information in pediatric patients 3 years to 12 years related to the use of gabapentin with other antiepileptic drugs 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.

ii. Incidence in Controlled Clinical Trials Subsection

Deleted table 4 and last paragraph

Added disclaimer: Adverse event information in pediatric patients 3 years to 12 years related to the use of gabapentin with other antiepileptic drugs is approved for Pfizer Inc.'s gabapentin. However, due to Pfizer Inc.'s marketing exclusivity rights, this drug product is pediatric use.

iii. Other Adverse Event Observed During All Clinical Trials

Clinical Trials in Pediatric Patients With Epilepsy-revised to read:

Information relating to adverse events that occurred during clinical trials in pediatric patients 3 years to 12 years treated with gabapentin that were not reported in adjunctive trials in adults 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.

f. DOSAGE AND ADMINISTRATION

i. Deleted " _____ " from the first sentence of the first paragraph.

ii. Pediatrics Patients Age 3- 12 years: added disclaimer

Dosing information for pediatric patients age 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.

3. Storage/Dispensing Conditions:

NDA: Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). [see USP Controlled Room Temperature] This storage temperature statement was specifically requested by the Agency.

ANDA: Store at room temperature 15°-30° C (59° -86°F)

USP: NOT USP and NOT PF.

4. Product Line:

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

The applicant proposes to market their 100 mg, 300 mg and 400 mg capsules in bottles of 100s, 500s and 1000s.

5. The capsule imprinting has 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).

6. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package does appear to be consistent with the listing of inactive ingredients found in the statement of components appearing on pages 2076-2078 (Vol 1.4)

The amount of elemental iron for the capsules do not exceed the maximum recommended amount of 5 mg/day when the maximum amount of capsules are taken. (See Vol 1.5 pages 2179-2180)

7. Container/Closure:

Container: White HDPE
Closure: 100s – CRC & Non-CRC
500s & 1000s - Non-CRC

Date of Review: 12/27/02

Date of Submission: 12/11/02

Reviewer:

Michelle Dillahunt *MDillahunt*

Date: *1/8/03*

Team Leader:

Lillie Golson *L Golson*

Date: *1/8/03*

cc:

ANDA 75-350
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson/ (no cc)
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Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-350

CHEMISTRY REVIEW(S)

75350

1. **CHEMISTRY REVIEW #1** 2. **ANDA# 75-350**

3. **NAME AND ADDRESS OF APPLICANT**

Purepac Pharmaceutical Co.
200 Elmora Avenue
Elizabeth, NJ 7207

4. **LEGAL BASIS FOR SUBMISSION**

Innovator Product: Neurontin Capsules

Innovator Company: Parke-Davis Pharmaceutical Research (A Division of Warner Lambert Co.)

Patent Expiration Date: 01/16/00

Patent and Exclusivity Information for the following patents are listed on pages 10-11.

U.S. Patent Number

Expiration Date

5084479

January 2, 2010

4087544

January 16, 2000

4894476

May 2, 2008

5. **SUPPLEMENT(s)**

NA

6. **PROPRIETARY NAME**

Gabapentin Capsules, 100 mg

7. **NONPROPRIETARY NAME**

GABAPENTIN

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**

NA

9. AMENDMENTS AND OTHER DATES:

Submission date	Submission type
03/30/98	original
04/23/98	Acknowledgement Letter

10. PHARMACOLOGICAL CATEGORY

Anticonvulsant

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF number	DMF type
	III:
	II:
	IV:

13. DOSAGE FORM

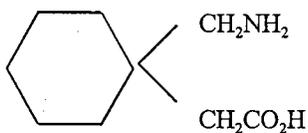
Capsule

14. POTENCY

100 mg, 300 mg and 400 mg

15. CHEMICAL NAME AND STRUCTURE

The chemical name is 1-(aminomethyl)cyclohexaneacetic acid. The active drug substance Gabapentin has the molecular formula $C_9H_{17}NO_2$, and the chemical structure graphic is



16. RECORDS AND REPORTS

NA

17. COMMENTS

This application contains some deficiencies.

18. CONCLUSIONS AND RECOMMENDATIONS

This application is unapprovable at this time.

19. REVIEWER:

Karen A. Bernard, Ph.D.

DATE COMPLETED:

6/21/98

**APPEARS THIS WAY
ON ORIGINAL**

Redacted 29 page(s)

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CHEMISTRY REVIEW #1

cc: ANDA 75-350
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-640/KBernard/7/9/98
HFD-645/BTArnwine/7/30/98
HFD-617/Ksherrod/7/31/98
HFD-640/FHolcombe

K Bernard 9/13/98
BS Arnwine 9/16/98
K Sherrod 9/17/98

F/T by pah/9/3/98
MS Word Doc - shortcut to new/cmccards/75350.1

CHEMISTRY REVIEW - Not APPROVABLE - Major / ~~Minor~~

**APPEARS THIS WAY
ON ORIGINAL**

75350.004

1. **CHEMISTRY REVIEW** 2. **ANDA# 75-350**

3. **NAME AND ADDRESS OF APPLICANT**

Purepac Pharmaceutical Co.
200 Elmora Avenue
Elizabeth, NJ 7207

4. **LEGAL BASIS FOR SUBMISSION**

Innovator Product: Neurontin Capsules

Innovator Company: Parke-Davis Pharmaceutical Research (A Division of Warner Lambert Co.)

Patent Expiration Date: 01/16/00

Patent and Exclusivity Information for the following patents are listed on pages 10-11.

U.S. Patent Number

Expiration Date

5084479

January 2, 2010

4087544

January 16, 2000

4894476

May 2, 2008

5. **SUPPLEMENT(s)**

NA

6. **PROPRIETARY NAME**

Gabapentin Capsules, 100 mg, 300 mg, 400 mg

7. **NONPROPRIETARY NAME**

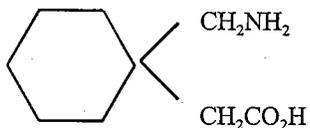
GABAPENTIN

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**

NA

15. CHEMICAL NAME AND STRUCTURE

The chemical name is 1-(aminomethyl)cyclohexaneacetic acid. The active drug substance Gabapentin has the molecular formula $C_9H_{17}NO_2$, and the chemical structure graphic is



16. RECORDS AND REPORTS

NA

17. COMMENTS

This application contains some minor chemistry deficiencies.

Methods Validation sent to Philadelphia DO. Pending.

Bioequivalence acceptable as of 8/26/98 by S.P. Shrivastava.

Labeling is pending.

EER is pending.

18. CONCLUSIONS AND RECOMMENDATIONS

This application is unapprovable at this time. Fax amendment.

19. REVIEWER:

Karen A. Bernard, Ph.D.

DATE COMPLETED:

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CHEMISTRY REVIEW #2

cc: ANDA 75-350
Division File
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Endorsements:

HFD-640/K Bernard/6/20/99
HFD- 645/B.Arnwine/7/1/99
HFD-617/Ksherrod/6/20/99
HFD- 640/FFang

K Bernard 7/6/99
B. Arnwine 7/7/99
K Sherrod 7/8/99

CHEMISTRY REVIEW - Not APPROVABLE - Fax

F/T by:ps/7/5/99

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**APPEARS THIS WAY
ON ORIGINAL**

1. **CHEMISTRY REVIEW #3** **ANDA# 75-350**

3. **NAME AND ADDRESS OF APPLICANT**

Purepac Pharmaceutical Co.
200 Elmora Avenue
Elizabeth, NJ 7207

4. **LEGAL BASIS FOR SUBMISSION**

Innovator Product: Neurontin Capsules

Innovator Company: Parke-Davis Pharmaceutical Research (A Division of Warner Lambert Co.)

Patent Expiration Date: 01/16/00

Patent and Exclusivity Information for the following patents are listed on pages 10-11.

<u>U.S. Patent Number</u>	<u>Expiration Date</u>
5084479	January 2, 2010
4087544	January 16, 2000
4894476	May 2, 2008

5. **SUPPLEMENT(s)**

NA

6. **PROPRIETARY NAME**

NA

7. **NONPROPRIETARY NAME**

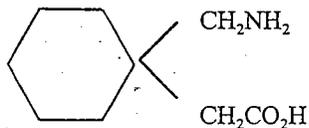
GABAPENTIN

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**

NA

15. CHEMICAL NAME AND STRUCTURE

The chemical name is 1-(aminomethyl)cyclohexaneacetic acid. The active drug substance Gabapentin has the molecular formula $C_9H_{17}NO_2$, and the chemical structure graphic is



16. RECORDS AND REPORTS

NA

17. COMMENTS

The firm is required to address the polymorph issue related to the drug substance. The DMF is also unsatisfactory. All other chemistry issues have been resolved satisfactorily.

Methods Validation sent to Philadelphia DO. Acceptable 9/30/99 by C Becoat. All issues were discussed with the firm and methods are suitable.

Bioequivalence acceptable as of 8/26/98 by S.P. Shrivastava. Firm re-performed dissolution on aged samples as requested. Bio acceptable 11/20/00.

Labeling is pending.

EER is pending. Acceptable 9/21/00.

18. CONCLUSIONS AND RECOMMENDATIONS

This application is not approvable. Minor amendment.

19. REVIEWER:

Karen A. Bernard, Ph.D.

DATE COMPLETED:

10/1/00

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CHEMISTRY REVIEW # 3

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ANDA DUP
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Endorsements:

HFD-645/KBernard/10/1/00
HFD-645/BTArnwine/11/21/00
HFD-617/KSherrod/11/22/00
HFD-640/FFang

KBernard 11/27/00
BTArnwine 11/27/00
KSherrod 11/30/00

F/T by pah/11/27/00
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NOT APPROVABLE MINOR

**APPEARS THIS WAY
ON ORIGINAL**

1. **CHEMISTRY REVIEW #4** **ANDA# 75-350**

3. **NAME AND ADDRESS OF APPLICANT**

Purepac Pharmaceutical Co.
200 Elmora Avenue
Elizabeth, NJ 7207

4. **LEGAL BASIS FOR SUBMISSION**

Innovator Product: Neurontin Capsules

Innovator Company: Parke-Davis Pharmaceutical Research (A Division of Warner Lambert Co.)

Patent Expiration Date: 01/16/00

Patent and Exclusivity Information for the following patents are listed on pages 10-11.

U.S. Patent Number

5084479

4087544

4894476

Expiration Date

January 2, 2010

January 16, 2000

May 2, 2008

5. **SUPPLEMENT(s)**

NA

6. **PROPRIETARY NAME**

NA

7. **NONPROPRIETARY NAME**

GABAPENTIN

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**

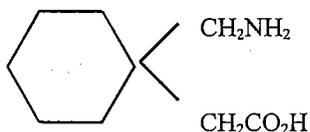
NA

14. POTENCY

100 mg, 300 mg and 400 mg

15. CHEMICAL NAME AND STRUCTURE

The chemical name is 1-(aminomethyl)cyclohexaneacetic acid. The active drug substance Gabapentin has the molecular formula $C_9H_{17}NO_2$, and the chemical structure graphic is



16. RECORDS AND REPORTS

NA

17. COMMENTS

All chemistry issues have been resolved satisfactorily by the applicant.

The DMF (#) is now satisfactory.

Methods Validation sent to Philadelphia DO. Acceptable 9/30/99 by C Becoat. All issues were discussed with the firm and methods are suitable.

Bioequivalence acceptable as of 8/26/98 by S.P. Shrivastava. Firm re-performed dissolution on aged samples as requested. Final Bio acceptable 2/13/01.

Labeling is pending.

EER is acceptable 9/21/00. CHECK ~~_____~~

18. CONCLUSIONS AND RECOMMENDATIONS

This application is approvable.

19. REVIEWER:

Karen A. Bernard, Ph.D.

DATE COMPLETED:

5/10/01

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information from

CHEMISTRY REVIEW #4

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Endorsements:

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HFD-645/BTArnwine/1/31/02

K Bernard 2/19/02
(B) Arnwine 2/19/02

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APPROVABLE

**APPEARS THIS WAY
ON ORIGINAL**

1. **CHEMISTRY REVIEW #5** **ANDA# 75-350**

3. **NAME AND ADDRESS OF APPLICANT**

Purepac Pharmaceutical Co.
200 Elmora Avenue
Elizabeth, NJ 7207

4. **LEGAL BASIS FOR SUBMISSION**

Innovator Product: Neurontin Capsules

Innovator Company: Parke-Davis Pharmaceutical Research (A Division of Warner Lambert Co.)

Patent Expiration Date: 01/16/00

Patent and Exclusivity Information for the following patents are listed on pages 10-11.

<u>U.S. Patent Number</u>	<u>Expiration Date</u>
5084479	January 2, 2010
4087544	January 16, 2000
4894476	May 2, 2008

**Latest Patent Info listed in November 15, 2002 amendment.

5. **SUPPLEMENT(s)**

NA

6. **PROPRIETARY NAME**

NA

7. **NONPROPRIETARY NAME**

GABAPENTIN

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**

NA

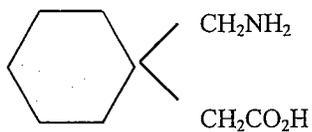
9. **AMENDMENTS AND OTHER DATES:**

14. POTENCY

100 mg, 300 mg and 400 mg

15. CHEMICAL NAME AND STRUCTURE

The chemical name is 1-(aminomethyl)cyclohexaneacetic acid. The active drug substance Gabapentin has the molecular formula $C_9H_{17}NO_2$, and the chemical structure graphic is



16. RECORDS AND REPORTS

NA

17. COMMENTS

The application was found approvable on 4/25/02. The comments pertain to the final approval request amendment.

All chemistry issues were previously resolved satisfactorily by the applicant. The firm submitted a minor CMC change in the 11/15/02 amendment. The firm submitted an alternate method for measuring ~~————~~ in the active drug substance. The new method and specification were submitted and are acceptable. Chemistry is acceptable. Labeling acceptable dated 1/8/03.

18. CONCLUSIONS AND RECOMMENDATIONS

This application is approved.

19. REVIEWER:

Karen A. Bernard, Ph.D.

DATE COMPLETED:

1/6/03

cc: ANDA 75-350
Division File
FIELD COPY

Endorsements:

HFD-645/KBernard/1/6/03

HFD-645/BTArnwine/3/24/03

K. Bernard 3/25/03

(BT Arnwine) 3/31/03

F/T by: EW 3/25/03

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APPROVED

APPEARS THIS WAY
ON ORIGINAL

1. **CHEMISTRY REVIEW #6** **ANDA# 75-350** ✓

3. **NAME AND ADDRESS OF APPLICANT**

Purepac Pharmaceutical Co.
200 Elmora Avenue
Elizabeth, NJ 07207

4. **LEGAL BASIS FOR SUBMISSION**

Innovator Product: Neurontin Capsules

Innovator Company: Parke-Davis Pharmaceutical Research (A Division of Warner Lambert Co.)

Patent Expiration Date: 01/16/00

Patent and Exclusivity Information for the following patents are listed on pages 10-11.

<u>U.S. Patent Number</u>	<u>Expiration Date</u>
5084479	January 2, 2010
4087544	January 16, 2000
4894476	May 2, 2008

**Latest Patent Info listed in November 15, 2002 amendment.

5. **SUPPLEMENT(s)**

NA

6. **PROPRIETARY NAME**

NA

7. **NONPROPRIETARY NAME**

GABAPENTIN

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**

NA

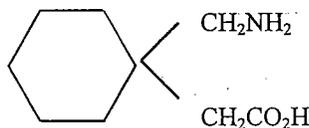
9. **AMENDMENTS AND OTHER DATES:**

14. POTENCY

100 mg, 300 mg and 400 mg

15. CHEMICAL NAME AND STRUCTURE

The chemical name is 1-(aminomethyl)cyclohexaneacetic acid. The active drug substance Gabapentin has the molecular formula $C_9H_{17}NO_2$, and the chemical structure graphic is



16. RECORDS AND REPORTS

NA

17. COMMENTS

All CMC issues are now satisfactory.

The application was found not approvable on 6/30/03 due to gmp issues. The applicant has requested final approval on 8/25/03. The 8/25/03 amendment included a CMC update.

All chemistry issues were previously resolved satisfactorily by the applicant. The CMC update in the 8/25/03 amendment was reviewed. The firm revised their commercial master formula to provide for a _____

incorporated. The change is minor in nature and acceptable.

Chemistry is acceptable. Labeling acceptable dated 1/8/03.

DMF# _____ is adequate as per T.Wang on 6/26/02.

Bio is acceptable dated 11/29/00

18. CONCLUSIONS AND RECOMMENDATIONS

This application is approved.

19. REVIEWER:

Karen A. Bernard, Ph.D.

DATE COMPLETED:

1/6/03

cc: ANDA 75-350
Division File
FIELD COPY

Endorsements:

Read for 9/5/03
HFD-645/KBernard/8/27/03
HFD-645/BTArnwine/8/27/03 *(Signature) 9/5/03*
F/T by: EW 8/27/03
V:firmnsz\purepac\ltrs&rev\75-350c6

APPROVED

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-350

BIOEQUIVALENCE REVIEW(S)

Shewell, K A. 1. 1

Gabapentin Capsules 100, 300, 400 mg
ANDA #75-350
Reviewer: S.P. Shrivastava
WP #75350SDW.398

Purepac Pharm. Co.
Elizabeth, NJ
Submitted:
March 30, 1998

**REVIEW OF TWO BIOEQUIVALENCE STUDIES,
AND DISSOLUTION TESTING DATA**

I. OBJECTIVE

Review of Geneva's protocol for *in vivo* bioequivalence study under fasting conditions comparing its Gabapentin Capsules, 400 mg strength, to Parke-Davis' Neurontin^R Capsules (Gabapentin), 400 mg strength.

II. BACKGROUND

Gabapentin is described as 1-(aminomethyl)cyclohexaneacetic acid with an empirical formula of C₉H₁₇NO₂ and a molecular weight of 171.24. Gabapentin is a white to off-white crystalline solid. It is freely soluble in water and both basic and acidic aqueous solutions.

Gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy. Neurontin(R) (gabapentin capsules) is supplied as imprinted hard shell capsules containing 100 mg, 300 mg, and 400 mg of gabapentin.

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 interact with GABA receptors, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation.

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. 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 percent. Food has no effect on the rate and extent of absorption of gabapentin.

DISTRIBUTION: Gabapentin circulates largely unbound (<3%) 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: 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.

III. SUMMARY OF BIOEQUIVALENCE STUDY PROTOCOLS

A. Single-Dose Fasting Study

1. Protocol # 08117 (Biostudy #1)

This open label, randomized, single-dose, two-way crossover study was conducted with 25 healthy male volunteers in accordance with the protocol. In each period, subjects received a single 400 mg dose of either Purepac gabapentin capsules or Park-Davis's Neurontin^R capsules following an overnight fast. There was a two-week wash-out period between treatments. Blood samples were collected pre-dose and for 72 hours after each dose. Plasma concentration of gabapentin was measured by a fully validated HPLC procedure. Pharmacokinetic and statistical analyses were performed to compare the test and reference products.

2. Objective of the study

The objective of this study was to determine the bioequivalence of two gabapentin formulations after administration of single doses to healthy volunteers under fasting conditions.

3. Study design: Randomized, single-dose, two-way crossover study.

4. Clinical and Analytical Facilities, and Investigators:

A. Analytical Facility:

--	--

B. Clinical Facility:

--	--

C. Pharmacokinetic and Statistical Services:

--	--

5. Study dates: Clinical : 1/3/98 - 1/20/98

Assay Dates: 2/5/98 - 2/20/98

Storage Time: Days: 48 Days

6. Investigators: See above

A. Test: 1 x 400 mg Gabapentin capsule (Purepac); Lot # PI-1015;
Potency - 101.55%; Exp. Date - 12/99; Lot size - _____
Other Lots: 300 mg - PI-1014(Exp. Date-12/99); 100 mg - PI-1013
(Exp. Date-12/99)

B. Reference: 1 x 400 mg Neurontin^R Capsule (Park-Davis), Lot # 09457V;
Potency - 100.25; Exp. Date: 5/00
Other Lots: 300 mg - 04277V (Exp. Date-6/00); 100 mg - 04057V
(Exp. Date-4/00)

Randomization Scheme: See Table-1.

7. Dosing: All doses were administered with 240 mL of water. Subjects fasted overnight and 4 hours post-dosing.

8. Subjects: Thirty subjects recruited were normal healthy male volunteers between the ages 19-41 years, and within 10% of their ideal weight as specified in the protocol. All subjects were selected based on the medical history, physical examination and clinical laboratory

evaluations. Inclusion and exclusion criteria in the protocol were followed in the selection of the subjects. Twenty-five subjects completed the study. Four subjects, #15, 18, 19 and 21 did not show up for the Period I check-in, and Subject #16 withdrew from the study.

9. Food and fluid intake: Standard meals were served at 4 hours post-dose, and at appropriate times as scheduled on each day. The drug products were administered with 240 mL of water. Water was allowed *ad lib.* except during one-hour pre- and one-hour, post-dosing periods.
10. Washout period: Two weeks between dose administration.
11. Blood samples: In each period, 10 mL of blood samples were collected in tubes containing EDTA at 0.0 (pre-dose), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 16, 24, 30, 36, 48, 60 and 72 hours post-dose. Plasma was separated and all plasma samples were stored frozen at -20°C until ready for analysis.
12. Subjects' BP and heart rate were monitored pre-dose and at 3, 36 and 72 hours post-dose.
13. Adverse reactions: In each dosing period subjects were asked to report any signs or symptoms judged to be drug related.
14. Pharmacokinetic and statistical analysis: Statistical analyses were performed on the pharmacokinetic parameters for gabapentin. 90% confidence intervals were calculated for $LAUC_{0-t}$, $LAUC_{0-inf}$ and LC_{max} for gabapentin.

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Table 1. Randomization Code

Subjects will be assigned a subject number at random. Subjects will be dosed in order of subject number.

A = Test Product

B = Reference Product

<u>Subject Number</u>	<u>Period I</u>	<u>Period II</u>
1	A	B
2	B	A
3	B	A
4	A	B
5	B	A
6	A	B
7	B	A
8	A	B
9	B	A
10	B	A
11	A	B
12	B	A
13	B	A
14	B	A
15	B	A
16	A	B
17	A	B
18	B	A
19	A	B
20	A	B
21	A	B
22	A	B
23	A	B
24	B	A
25	A	B
26	B	A
27	A	B
28	A	B
29	B	A
30	B	A

B. Limited-Food Study

1. Protocol # 09237 (Biostudy #2)
2. Study design: Randomized, single-dose, three-way crossover, six sequence study under fasting/non-fasting conditions.
3. Study Sites and Investigators: Same as in the fasting study
4. Study dates: Clinical study: 12/27/97 - 1/27/98
 Analytical study: 2/5/98 - 2/23/98
 Total Storage Period: 58 Days
5. Treatments:
 - A. Test: 1 x 400 mg Purepac Gabapentin capsules (Lot # PI-1015), under fasting conditions).
 - B. Test: 1 X 400 mg Purepac gabapentin capsules (Lot # PI-1015), under non-fasting conditions.
 - C. Reference: 1 X 400 mg Park-Davis Neurontin^R capsule (Lot #09457V) under non-fasting conditions.
6. Dosing: All doses were administered with 240 mL of water at room temperature following an overnight fast or within 30 minutes of starting the breakfast depending on the dosing schedule.
7. Subjects: Eighteen subjects entered and 18 completed the study.
8. Food and fluid intake: Standard lunch and dinner were served on each day of drug administration. The drug products were administered with 240 mL of water. Water was allowed *ad lib.* except during one-hour pre-dose and one-hour post-dose periods.
9. Wash-out period: Two weeks between dosage administration.
10. Blood samples: Ten mL blood samples were collected at 0.0 (pre-dose), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 30, 36, 48, 60 and 72 hours post-dose. Plasma was separated and all plasma samples were stored frozen at -22°C until ready for analysis. Number of samples analyzed for gabapentin were same as in the fasting study.
11. Pharmacokinetics/Statistical Analysis:

AUCT, AUCI, C_{max} , T_{max} , Ke and $T_{1/2}$ were calculated from the individual concentration versus time data for gabapentin.

IV. PRE-STUDY VALIDATION OF ASSAY METHOD FOR PLASMA SAMPLES

PRE-STUDY ASSAY VALIDATION INFORMATION

ANALYTE:	GABAPENTIN
ASSAY METHOD:	HPLC
MATRIX:	plasma
INTERNAL STANDARD:	BACLOFEN
SENSITIVITY:	.02 MCG/ML
STANDARD CURVE HIGHEST CONC.:	6 MCG/ML
STANDARD CURVE LOWEST CONC.:	.02 MCG/ML
R**2 IS GREATER THAN:	0.999684
SPECIFICITY:	Y
ANALYTE RETENTION TIME:	7.6 - 11.4 MINUTES
INTERNAL STANDARD RETENTION TIME:	6.0 - 9.0 MINUTES

Inter-Day Precision:

Standard Curve (n=9)

Conc. mcg/mL)	0.02	0.04	0.1	0.2	0.5	1	3	6	Intercept	Slop
MEAN	0.0194	0.0394	0.1	0.204	0.503	1.02	2.98	5.99	0.001	0.46
S.D.	0.001	0.0017	0.002	0.0059	0.0116	0.0172	0.0309	0.0291	0.0013	0.00
CV%	5.21	4.42	2.01	2.89	2.31	1.69	1.04	0.486	159	1.3

Intra-Day Precision (n=3 x 3 Days)

Conc. mcg/mL)	0.04	0.4	4
MEAN	0.04	0.399	3.99
CV%	2.5	2.1	1.9

Recovery

Conc. mcg/mL	0.04			0.40			4.00		
	INPUT	FOUND	%RECOVERY	INPUT	FOUND	%RECOVERY	INPUT	FOUND	%RECOVER
MEAN	1910	1460	76.2	20700	14100	68	208000	139000	66.9
S.D.	264	31	#DIV/0!	285	469	#DIV/0!	3010	6580	#DIV/0!
CV%	13.8	2.12	#DIV/0!	1.38	3.33	#DIV/0!	1.45	4.73	#DIV/0!

Stability of Analyte: Stability of gabapentin was checked under various conditions, including biological matrix at bench-top, during freeze-thaw cycles, and during long-term storage. The plasma samples were stored for a maximum period of 58 days, and the stability was checked for 61-day period. Therefore, plasma samples were stable under the study conditions (Table 3).

Table 3. Stability of Gabapentin Under Various Conditions

Storage	Test	Conc. mcg/mL	Storage Period	Temperature	% Diff.
Freeze-Thaw Cycles (n=3)		0.04	3Cycles	Room/-20 °C	7.4
		0.40			6.3
		4.00			2.8
Bench-Top (n=6)		0.04	24 Hours	Room Temp.	15.0
		0.40			6.8
		4.00			6.8
In-Process Stability (n=6)		0.04	72 Hours	Room Temp.	10.0
		0.40			5.0
		4.00			3.5
Long-Term Stab. (n=6)		0.04	61 Days	-20 °C	-12.0
		0.40			-2.8
		4.00			-0.5

V. RESULTS

A. Single-Dose Fasting Study

1. Within-Study Validation

Average of Gabapentine Standard Curves and QC Samples

	Conc., mcg/mL	CV, %	%Diff.
Std. Curve; n=24	0.020	10.0	0.0
n=24	0.040	5.1	-2.5
n=23	0.100	5.1	-2.0
n=24	0.200	3.5	-0.5
n=24	0.500	3.6	1.0
n=24	1.000	3.3	2.0
n=24	3.000	2.4	0.0
n=24	6.000	1.1	-0.5
QC Samples; n=50	0.04	7.5	0.0
n=50	0.40	4.2	2.0
n=54	4.00	5.5	4.0

2. **Blood/Plasma Drug Concentration:** The firm analyzed gabapentine data for 25 subjects. Results are given in Tables 4 and 5.

3. **Pharmacokinetic Parameters:** Individual and mean PK parameters are given in Tables 6 and 7.

- The LS means ratios for test and reference for $LAUC_{0-t}$, $LAUC_{0-inf}$ and LC_{max} are within 0.80-1.25 as required (Table 6).
- ANOVA analysis showed significant, period effects on $LAUC_{0-t}$, $LAUC_{0-i}$ and LC_{max} .
- Individual Test/Reference ratios for AUC_{0-t} , AUC_{0-inf} , C_{max} , T_{max} , and T_{half} averaged between 0.94 and 1.03.
- The ratios for test and reference of AUC_{0-t}/AUC_{0-inf} averaged over 80%.
- None of the subjects had C_{max} at first non-zero time point.
- Plasma concentration-time profiles were checked for subjects. $AUC_{0-\infty}$ was obtained correctly for all subjects.

4. **Adverse Reaction**

No significant differences between test and reference products were observed (See the table below).

Summary of Adverse Reactions

<u>Sign/Symptom</u>	<u>Test</u>	<u>No. Of Subjects</u> <u>Reference</u>	<u>Drug Related</u>
Lightheadedness	1	1	Possible
Headache	1	1	Possible
Phlegm Production	1	1	Possible
Nasal Congestion	1	0	Possible

Conclusion: The *in vivo* fasting study is acceptable.

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TABLE 4. GABAPENTIN 400 MG CAPSULE FASTING STUDY
 PUREPAC B-08117
 ARITHMETIC MEANS BY PRODUCT

----- PRODUCT=A:TEST -----

Variable	Label	N	Mean	Std Dev	CV
AUCTLQC		25	35.147	8.174	23.257
AUCINF		25	35.477	8.128	22.912
C _{MAX}		25	3.374	0.789	23.398
T _{MAX}		25	3.240	1.378	42.525
K _{ELM}		25	0.105	0.015	14.611
T _{HALF}		25	6.724	0.976	14.522
LAUCTLQC		25	3.536	0.219	6.194
LAUCINF		25	3.546	0.215	6.074
LC _{MAX}		25	1.191	0.228	19.150
C1	0.00 HR	25	0.000	0.000	.
C2	0.25 HR	25	0.099	0.125	127.001
C3	0.50 HR	25	1.022	0.591	57.823
C4	1.00 HR	25	2.156	0.640	29.682
C5	1.50 HR	25	2.667	0.735	27.561
C6	2.00 HR	25	2.870	0.756	26.352
C7	2.50 HR	25	2.970	0.850	28.622
C8	3.00 HR	25	2.959	0.831	28.099
C9	3.50 HR	25	2.952	0.774	26.220
C10	4.00 HR	25	2.964	0.757	25.524
C11	5.00 HR	25	2.658	0.649	24.400
C12	6.00 HR	25	2.344	0.513	21.899
C13	7.00 HR	25	2.088	0.557	26.672
C14	8.00 HR	25	1.837	0.488	26.555
C15	10.0 HR	25	1.426	0.397	27.820
C16	12.0 HR	25	1.125	0.298	26.504
C17	16.0 HR	25	0.686	0.209	30.483
C18	24.0 HR	25	0.302	0.105	34.678
C19	30.0 HR	25	0.161	0.059	36.581
C20	36.0 HR	25	0.085	0.037	43.131
C21	48.0 HR	25	0.027	0.019	71.906
C22	60.0 HR	25	0.005	0.011	207.604
C23	72.0 HR	25	0.001	0.004	500.000

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TABLE 5. GABAPENTIN 400 MG CAPSULE FASTING STUDY
 PUREPAC B-08117
 ARITHMETIC MEANS BY PRODUCT

----- PRODUCT=B:REFERENCE -----

Variable	Label	N	Mean	Std Dev	CV
AUCLQC		25	36.150	9.962	27.556
AUCINF		25	36.604	9.963	27.219
C _{MAX}		25	3.565	1.081	30.312
T _{MAX}		25	3.100	1.061	34.215
KELM		25	0.109	0.017	15.360
THALF		25	6.497	1.108	17.058
LAUCLQC		25	3.553	0.269	7.560
LAUCINF		25	3.566	0.266	7.458
LC _{MAX}		25	1.228	0.300	24.426
C1	0.00 HR	25	0.000	0.000	.
C2	0.25 HR	25	0.064	0.054	83.347
C3	0.50 HR	25	0.862	0.422	48.933
C4	1.00 HR	25	2.018	0.649	32.168
C5	1.50 HR	25	2.677	0.753	28.122
C6	2.00 HR	25	3.008	1.080	35.895
C7	2.50 HR	25	3.232	1.102	34.107
C8	3.00 HR	25	3.168	1.014	32.005
C9	3.50 HR	25	3.212	0.971	30.239
C10	4.00 HR	25	3.156	0.889	28.171
C11	5.00 HR	25	2.910	0.831	28.554
C12	6.00 HR	25	2.503	0.847	33.825
C13	7.00 HR	25	2.203	0.754	34.240
C14	8.00 HR	25	1.926	0.618	32.084
C15	10.0 HR	25	1.467	0.461	31.411
C16	12.0 HR	25	1.139	0.351	30.792
C17	16.0 HR	25	0.692	0.209	30.159
C18	24.0 HR	25	0.301	0.099	32.943
C19	30.0 HR	25	0.159	0.056	35.462
C20	36.0 HR	25	0.082	0.031	37.851
C21	48.0 HR	25	0.018	0.024	134.193
C22	60.0 HR	25	0.005	0.009	206.172
C23	72.0 HR	25	0.001	0.004	500.000

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Table 6. Pharmacokinetic Parameters (n=25)

Parameter	Test	Reference	Ratio, T/R	90% CI
AUC _{0-T} , μg.Hr/mL	35.15 (23.2)	36.16 (27.6)	0.97	90.2-105.2
ln AUC _{0-T} , μg.Hr/mL	34.40	34.83	0.99	92.0-106.1
AUC _{0-inf} , μg.Hr/mL	35.47 (22.9)	36.60 (27.2)	0.97	90.0-104.8
ln AUC _{0-inf} , μg.Hr/mL	34.74	35.29	0.98	91.7-105.7
C _{max} , μg/mL	3.37 (23.4)	3.57 (30.3)	0.94	87.4-103.0
ln C _{max} , μg/mL	3.30	3.41	0.97	90.2-104.2
T _{max} , Hr	3.24 (42.5)	3.10 (34.2)	1.05	----
T _{1/2} , Hr	6.72 (14.5)	6.50 (17.1)	1.03	----
K _{el} , Hr ⁻¹	0.105 (14.6)	0.109 (15.4)	0.96	----

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B. Single-Dose Non-Fasting Study

1. Within-Study Validation

Average of Gabapentine Standard Curves and QC Samples

	Conc., mcg/mL	CV, %	%Diff.
Std. Curve; n=19	0.020	9.5	5.0
n=18	0.040	7.5	0.0
n=19	0.100	3.0	-1.0
n=19	0.200	3.6	-2.0
n=19	0.500	3.0	-1.4
n=19	1.000	2.4	-1.0
n=19	3.000	1.8	0.0
n=19	6.000	1.1	0.0
QC Samples; n=33	0.04	7.3	3.0
n=38	0.40	5.0	4.0
n=38	4.00	5.4	5.0

2. **Blood/Plasma Drug Concentration:** The firm analyzed gabapentine data for 18 subjects. Results for gabapentine are given in Tables 8-10.

3. **Pharmacokinetic Parameters:** Mean PK parameters and statistical analyses are given in Tables 11-12. Individual data are shown in Table 12.

- The LS means ratios for test and reference for $LAUC_{0-t}$, $LAUC_{0-inf}$ and LC_{max} are within 0.80-1.25 as required (Table 11).
- ANOVA analysis showed significant, period effects on C_{max} and LC_{max} .
- Individual Test/Reference ratios for AUC_{0-t} , AUC_{0-inf} , C_{max} , T_{max} , and T_{half} averaged between 1.00 and 1.09.
- The ratios for test and reference of AUC_{0-t}/AUC_{0-inf} were over 80%.
- None of the subjects had C_{max} at first non-zero time point.
- Plasma concentration-time profiles were checked for subjects. $AUC_{0-\infty}$ was obtained correctly for all subjects.

4. Adverse Reaction

No significant differences between test and reference products were observed (See the table below).

Summary of Adverse Reactions

<u>Sign/Symptom</u>	<u>Test (Fast)</u>	<u>No. Of Subjects</u>		<u>Drug Related</u>
		<u>Test (Fed)</u>	<u>Reference (Fed)</u>	
Elevated SGOT	0	1	0	Possible
Elevated SGPT	0	1	0	Possible
Light Headedness	0	1	0	Probable
Nausea	0	0	1	Possible
Vomiting	0	0	0	Possible

Conclusion: The *in vivo* non-fasting study is acceptable.

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TABLE 8. GABAPENTIN 400 MG CAPSULE FOOD STUDY
 PUREPAC B-09237
 ARITHMETIC MEANS BY PRODUCT

----- PRODUCT=A:TEST FAST -----

Variable	Label	N	Mean	Std Dev	CV
AUCLQC		18	33.237	9.290	27.950
AUCINF		18	33.630	9.246	27.492
C _{MAX}		18	3.237	0.935	28.880
T _{MAX}		18	3.167	1.237	39.053
KELM		18	0.097	0.035	35.595
THALF		18	8.821	5.656	64.120
LAUCLQC		18	3.465	0.293	8.468
LAUCINF		18	3.478	0.287	8.242
LC _{MAX}		18	1.135	0.294	25.883
C1	0.00 HR	18	0.000	0.000	.
C2	0.25 HR	18	0.065	0.076	116.865
C3	0.50 HR	18	0.862	0.328	38.020
C4	1.00 HR	18	2.030	0.566	27.881
C5	1.50 HR	18	2.468	0.686	27.779
C6	2.00 HR	18	2.734	0.809	29.587
C7	2.50 HR	18	2.893	0.941	32.545
C8	3.00 HR	18	2.926	1.045	35.708
C9	3.50 HR	18	2.899	1.050	36.208
C10	4.00 HR	18	2.873	0.886	30.850
C11	5.00 HR	18	2.623	0.812	30.947
C12	6.00 HR	18	2.264	0.640	28.291
C13	8.00 HR	18	1.684	0.524	31.130
C14	12.0 HR	18	1.073	0.352	32.841
C15	16.0 HR	18	0.617	0.207	33.571
C16	24.0 HR	18	0.269	0.109	40.503
C17	30.0 HR	18	0.144	0.062	42.651
C18	36.0 HR	18	0.077	0.038	48.554
C19	48.0 HR	18	0.023	0.023	97.192
C20	60.0 HR	18	0.009	0.015	171.730
C21	72.0 HR	18	0.007	0.011	168.831

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TABLE 9. GABAPENTIN 400 MG CAPSULE FOOD STUDY
 PUREPAC B-09237
 ARITHMETIC MEANS BY PRODUCT

----- PRODUCT=B:TEST FED -----

Variable	Label	N	Mean	Std Dev	CV
AUCLTQC		18	36.163	5.861	16.206
AUCINF		18	36.574	5.794	15.841
C _{MAX}		18	3.671	0.678	18.482
T _{MAX}		18	3.556	0.889	25.011
KELM		18	0.107	0.028	26.686
THALF		18	7.699	5.448	70.769
LAUCLTQC		18	3.577	0.152	4.246
LAUCINF		18	3.589	0.148	4.136
LC _{MAX}		18	1.281	0.212	16.544
C1	0.00 HR	18	0.000	0.000	.
C2	0.25 HR	18	0.007	0.029	424.264
C3	0.50 HR	18	0.110	0.133	121.070
C4	1.00 HR	18	0.867	0.617	71.105
C5	1.50 HR	18	1.818	0.914	50.282
C6	2.00 HR	18	2.532	0.981	38.736
C7	2.50 HR	18	3.103	0.954	30.730
C8	3.00 HR	18	3.337	0.841	25.199
C9	3.50 HR	18	3.381	0.809	23.920
C10	4.00 HR	18	3.403	0.691	20.294
C11	5.00 HR	18	2.961	0.579	19.547
C12	6.00 HR	18	2.664	0.441	16.537
C13	8.00 HR	18	2.048	0.382	18.678
C14	12.0 HR	18	1.213	0.274	22.550
C15	16.0 HR	18	0.700	0.201	28.668
C16	24.0 HR	18	0.304	0.095	31.369
C17	30.0 HR	18	0.149	0.058	38.732
C18	36.0 HR	18	0.078	0.032	40.867
C19	48.0 HR	17	0.021	0.024	115.072
C20	60.0 HR	18	0.007	0.014	204.552
C21	72.0 HR	18	0.005	0.010	231.600

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TABLE 10. GABAPENTIN 400 MG CAPSULE FOOD STUDY
 PUREPAC B-09237
 ARITHMETIC MEANS BY PRODUCT

----- PRODUCT=C:REFERENCE FED -----

Variable	Label	N	Mean	Std Dev	CV
AUCLQC		18	35.278	8.418	23.861
AUCINF		18	35.648	8.397	23.554
C _{MAX}		18	3.628	0.656	18.081
T _{MAX}		18	3.333	1.098	32.944
KELM		18	0.105	0.023	22.104
THALF		18	7.076	2.412	34.086
LAUCLQC		18	3.539	0.224	6.328
LAUCINF		18	3.550	0.221	6.236
LC _{MAX}		18	1.273	0.179	14.067
C1	0.00 HR	18	0.000	0.000	
C2	0.25 HR	18	0.001	0.005	424.264
C3	0.50 HR	18	0.088	0.100	112.944
C4	1.00 HR	18	0.895	0.565	63.145
C5	1.50 HR	18	1.825	0.983	53.899
C6	2.00 HR	18	2.525	1.000	39.591
C7	2.50 HR	18	2.881	0.756	26.241
C8	3.00 HR	18	3.197	0.778	24.337
C9	3.50 HR	18	3.309	0.776	23.460
C10	4.00 HR	18	3.320	0.602	18.133
C11	5.00 HR	18	2.959	0.695	23.500
C12	6.00 HR	18	2.519	0.623	24.720
C13	8.00 HR	18	1.947	0.624	32.050
C14	12.0 HR	18	1.200	0.402	33.496
C15	16.0 HR	18	0.702	0.248	35.265
C16	24.0 HR	18	0.299	0.114	37.981
C17	30.0 HR	18	0.150	0.071	47.262
C18	36.0 HR	18	0.077	0.039	51.015
C19	48.0 HR	17	0.024	0.022	90.898
C20	60.0 HR	18	0.008	0.013	169.348
C21	72.0 HR	18	0.001	0.005	424.264

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Table 11. Pharmacokinetic Parameters (n=18)

Parameter	Test Fast (A)	Test Fed (B)	Ref Fed (C)	Ratio B/C
AUC_{0-T}, μg.Hr/mL	33.23	36.18	35.27	1.03
ln AUC_{0-T}, μg.Hr/mL	31.95	35.77	34.41	1.04
AUC_{0-Inf}, μg.Hr/mL	33.63	36.57	36.64	1.00
ln AUC_{0-Inf}, μg.Hr/mL	32.39	36.18	34.80	1.04
C_{max}, μg/mL	3.24	3.67	3.63	1.01
ln C_{max}, μg/mL	3.11	3.60	3.57	1.01
T_{max}, Hr	3.17	3.56	3.33	1.07
T_{1/2}, Hr	8.82	7.70	7.08	1.09
K_{el}, Hr⁻¹	0.10	0.11	0.11	1.02

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VI. FORMULATION

Table 13. Comparison of Reference and Test Product Formulations (mg/Capsule)

Ingredients/Strength	100 mg	300 mg	400 mg
Gabapentin	100	300	400
Corn Starch NF	—	—	—
Mannitol USP	—	—	—
Talc USP	—	—	—
Total Fill Wt.	133	399	532
Shell (Hard Gelatin)	#3	#1	#0
Shell Cap	Brown Opaque	Brown Opaque	Brown Opaque
Body	White Opaque	Yellow Opaque	Orange Opaque
Imprinting Ink	—	—	—

The two strengths 300 and 100 mg capsules are proportionally similar to 400 mg capsules, which underwent biostudy.

VII. *IN VITRO* RESULTS (DISSOLUTION): (FDA Method)

DISSOLUTION INFORMATION

ANALYTE:	GABAPENTIN
STRENGTH AND UNIT:	100, 300, 400 MG
DISSOLUTION METHOD:	LC/2667/DI
DISSOLUTION MEDIUM:	0.1 N HCL
VOLUME:	900 mL
DISSOLUTION APPARATUS:	2
RPM:	50
ASSAY METHOD:	HPLC
DISSOLUTION SPECIFICATION:	NLT → % (Q) in 20 minutes

DISSOLUTION STUDY 1 TABLE 14

Time(MIN)	Test			Ref		
	MEAN	RANGE	CV%	MEAN	RANGE	CV%
10	89.12	—————	6.42	82.98	—————	8.23
20	95.87	—————	1.46	92.33	—————	2.79
30	97.23	—————	1.44	94.48	—————	2.1
45	98.28	—————	1.27	95.73	—————	1.34

DISSOLUTION STUDY 2 TABLE 15

Time(min)	Test			Ref		
	MEAN	RANGE	CV%	MEAN	RANGE	CV%
10	94.01	—————	6.42	93.38	—————	3.82
20	97.98	—————	3.71	98.33	—————	3.08
30	99.28	—————	2.34	100.92	—————	2.66
45	99.78	—————	2.27	102.09	—————	1.69

DISSOLUTION STUDY 3 TABLE 16

Time(min)	Test			Ref		
	MEAN	RANGE	CV%	MEAN	RANGE	CV%
10	90.44	—————	8.97	93.29	—————	5.26
20	99.05	—————	2.77	98.98	—————	2.1
30	100.33	—————	2.39	100.33	—————	1.79
45	101.11	—————	2.28	100.18	—————	1.09

Conclusion: The dissolution tests for 100, 300 and 400 mg capsules are acceptable (Tables 14-16).

VIII. DEFICIENCIES

None

IX. RECOMMENDATIONS

1. The *in vivo* bioequivalence study conducted under fasting conditions by Purepac on its Gabapentin capsules, 400 mg strength, Lot #PI-1015, comparing it to Park-Davis's 400 mg strength Neurontin^R Capsules, 400 mg strength, Lot #09457V, has been found acceptable by the Division of Bioequivalence.

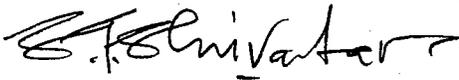
2. The *in vivo* bioequivalence study conducted under non-fasting conditions by Purepac on its Gabapentin capsules, 400 mg strength, Lot #PI-1015, comparing it to Park-Davis's Neurontin^R Capsules, 400 mg strength, Lot #09457V, has been found acceptable by the Division of Bioequivalence.
3. The dissolution testing conducted by Purepac, on its gabapentin 100, 300 and 400 mg capsules, Lot #PI-1015, PI-1014 and PI-1013, respectively, are acceptable.

The dissolution testing should be incorporated into the firm's manufacturing controls and stability program, and it should be conducted in 900 mL of 0.1 N HCl at 37°C using USP 23 Apparatus 2 (Paddle) at 50 rpm. The test products should meet the following specifications:

Not less than $\frac{1}{2}$ of the labeled amount of gabapentin in the dosage form is dissolved in 20 minutes.

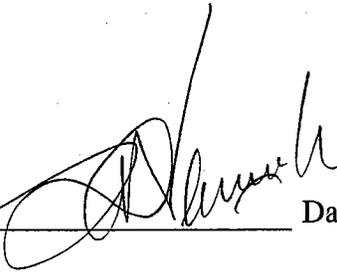
4. From the bioequivalence point of view, the firm has met the *in vivo* bioavailability and *in vitro* dissolution testing requirements for its gabapentin 400 mg capsules, and the application is acceptable.
5. The formulation for 100 and 300 mg strengths are proportionally similar to the 400 mg strength, which underwent bioequivalence testing. The request for waivers of its gabapentin 100 and 300 mg capsules are granted.

The firm should be informed of the recommendations.



S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED S Nerurkar
FT INITIALED S Nerurkar



Date

8/25/1998

Concur:



Date:

8/26/98

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

SPS/sps/8-20-98/75350SDW.398

cc: ANDA #75350 (Original, Duplicate), HFD-655 (SNerurkar, SShrivastava), Drug File,
Division File.

**APPEARS THIS WAY
ON ORIGINAL**

BIOEQUIVALENCY COMMENTS

ANDA: 75-350

APPLICANT: Purepac Pharmaceuticals, Inc.

DRUG PRODUCT: Gabapentin capsules, 100, 300 and 400 mg strengths

The Division of Bioequivalence has completed its review and has no further questions at this time.

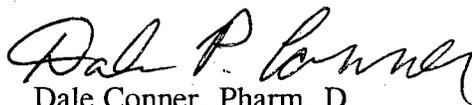
Please acknowledge that the following dissolution testing specifications have been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of 0.1 N HCl, at 37°C using USP Apparatus 2 (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 Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-350
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Secretary - Bio Drug File
HFD-655/ SShrivastava

X:NEW\FIRMSNZ\Purepac\ltrs&rev\75350sdw.398
Printed in final on 8/20/98

Endorsements: (Final with Dates)

HFD-650/ SShrivastava

HFD-655/ SNERURKAR

HFD-617/ L. Sanchez or N. Chamberlin

HFD-650/ D. Conner

[Handwritten signature] 8/25/98

[Handwritten signature] 8/25/98

[Handwritten signature] 8/26/98

BIOEQUIVALENCY - ACCEPTABLE

1. **FASTING STUDY (STF)**

Clinical: _____

Analytical: _____

Strengths: 400 mg

Outcome: **AC**

2. **FOOD STUDY (STP)**

Clinical: _____

Analytical: _____

Strengths: 400 mg

Outcome: **AC**

3. **DISSOLUTION DATA (DIS)**

All Strengths

Outcome: **AC**

4. **DISSOLUTION WAIVER (DIW)**

Strengths: 100 and 300 mg

Outcome: **AC**

Outcome Decisions:

AC - Acceptable

WINBIO COMMENTS:

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 75-350 SPONSOR: Purepac Pharmaceuticals, Inc.

DRUG & DOSAGE FORM: Gabapentin Capsules

STRENGTHS/(s): 100, 300, 400 mg

TYPE OF STUDY: Single dose fasting and non-fasting studies

STUDY SITE: _____

STUDY SUMMARY: Bioequivalence between the test and reference products was determined on the basis of pharmacokinetic and dissolution data of gabapentin capsules. The firm has conducted single-dose fasting and nonfasting studies, and dissolution testing on test and reference products. The results of the studies indicate that Purepac's 400 mg tablets are bioequivalent to the reference product, Park-Davis's Neuropentin® 400 mg tablets. The 90% confidence intervals for LAUC_{0-t}, LAUC_{inf}, and LC_{max} are in the acceptable range of 80-125 for single-dose study. As required, under fed conditions, the test/reference ratios for PK parameters were within 0.8-1.2. THE WAIVER OF BIOSTUDY REQUIREMENT WAS GRANTED FOR 100 MG AND 300 MG CAPSULES.

DISSOLUTION:

The test products 100, 300 and 400 mg tablets meet the agency's dissolution specifications (non-USP Method). The amount of drug dissolved from the test product was NLT 10% in 20 minutes.

PRIMARY REVIEWER: S.P. Shrivastava, Ph.D. **BRANCH:** II

INITIAL: SP **DATE** 8/25/98

BRANCH CHIEF: S. G. Nerurkar, Ph.D. **BRANCH:** II

INITIAL: SN **DATE** 8/25/1998

DIRECTOR

DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.

INITIAL: DP **DATE** 8/26/98

DIRECTOR

OFFICE OF GENERIC DRUGS: Douglas L. Sporn

INITIAL: _____ **DATE** _____

Gabapentin Capsules 100, 300, 400 mg
 ANDA #75-350
 Reviewer: S.P. Shrivastava
 WP #75350o.N00

Purepac Pharm. Co.
 Elizabeth, NJ
 Submitted:
 November 10, 2000

REVIEW OF AN AMENDMENT:
ADDITIONAL DISSOLUTION TESTING DATA

The firm had submitted single dose fasting and nonfasting studies, and dissolution data in 0.1 N HCl (March 30, 1998). The application was approved by the Division (see review, SShrivastava, 8/26/98). However, the dissolution medium was revised to 0.06 N HCl (Re: NTran letter, dated 12/10/98, Attachment-1). The firm has provided additional dissolution data in 0.06 N HCl for all strengths as requested by the Division for review.

I. IN VITRO RESULTS (DISSOLUTION): (FDA Method)

DISSOLUTION INFORMATION

ANALYTE: GABAPENTIN
 STRENGTH AND UNIT: 100, 300, 400 MG
 DISSOLUTION METHOD: LC/2667/DI
 DISSOLUTION MEDIUM: 0.06 N HCL
 VOLUME: 900 mL
 DISSOLUTION APPARATUS: 2
 RPM: 50
 ASSAY METHOD: HPLC
 DISSOLUTION SPECIFICATION: NLT —% (Q) in 20 minutes

100 mg Capsules

TABLE 1

Time(MIN)	Test Lot #PI-1013, Exp. 12/99			Ref Lot # 04057V Exp. 4/00		
	MEAN	RANGE	CV%	MEAN	RANGE	CV%
10	97.1	————	3.4	95.7	————	4.0
20	99.8	————	1.5	99.3	————	1.3
30	100.5	————	1.1	100.5	————	0.9
45	100.9	————	1.2	100.7	————	0.9

300 mg Capsules

TABLE 2

Time(min)	Test Lot #PI-1014, Exp 12/99			Ref Lot # 04277V, Exp. 06/00		
	MEAN	RANGE	CV%	MEAN	RANGE	CV%
10	90.5	—	5.5	89.4	—	4.5
20	96.8	—	2.5	96.0	—	2.3
30	98.4	—	1.8	98.0	—	1.9
45	99.2	—	1.4	99.1	—	1.5

400 mg Capsules

TABLE 3

Time(min)	Test Lot #PI-1015, Exp. 12/99			Ref Lot #09457V Exp. 05/00		
	MEAN	RANGE	CV%	MEAN	RANGE	CV%
10	91.2	—	6.7	86.0	—	6.3
20	97.2	—	2.8	94.9	—	2.1
30	98.4	—	2.1	96.2	—	1.7
45	99.2	—	1.6	97.6	—	1.6

II. COMMENT

1. Although the firm has used all expired lots in the dissolution study, drug substance appear to be stable for longer periods, and no loss in the labeled amount of the active moiety was observed. Lots show — % dissolution at 45 minutes by a specific HPLC method.
2. The lots meet the dissolution specification (Q) of — in 20 minutes.
3. In future, the firm is advised to avoid the use of expired lots in the study.

Conclusion: The dissolution tests for 100, 300 and 400 mg capsules are acceptable (Tables 1-3).

III. RECOMMENDATIONS

1. The dissolution testing conducted by Purepac, on its gabapentin 100, 300 and 400 mg capsules, PI-1013, PI-1014 and Lot #PI-1015, respectively, are acceptable.

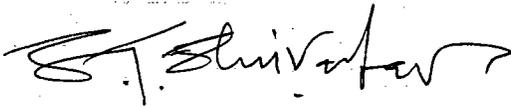
The dissolution testing should be incorporated into the firm's manufacturing controls

and stability program, and it should be conducted in 900 mL of 0.06 N HCl at 37 °C using USP 24 Apparatus 2 (Paddle) at 50 rpm. The test products should meet the following specifications:

Not less than \geq % of the labeled amount of gabapentin in the dosage form is dissolved in 20 minutes.

2. From the bioequivalence point of view, the firm has met the *in vivo* bioavailability and *in vitro* dissolution testing requirements for its gabapentin 400 mg capsules, and the application is acceptable.
3. The formulation for 100 and 300 mg strengths are proportionally similar to the 400 mg strength, which underwent bioequivalence testing. The requests for waivers of its gabapentin 100 and 300 mg capsules are granted.

The firm should be informed of comments #1 and 3, and the recommendations.



S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED S Nerurkar
FT INITIALED S Nerurkar

Date

11/20/2002

Concur:



Date:

11/29/00

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Encl. Attachment-1

SPS/sps/11-13-00/75350o.N00

cc: ANDA #75350 (Original, Duplicate), HFD-655 (S Nerurkar, S Shrivastava), Drug File, Division File.

BIOEQUIVALENCY COMMENTS

ANDA: 75-350

APPLICANT: Purepac Pharmaceuticals, Inc.

DRUG PRODUCT:

Gabapentin capsules, 100, 300 and 400 mg strengths

The Division of Bioequivalence has completed its review and has following comments:

1. Please acknowledge that the following dissolution testing specifications have been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of 0.06 N HCl, at 37 °C using USP Apparatus 2 (Paddle) at 50 r.p.m. The test product should meet the following specifications:

Not less than $\frac{1}{2}$ (Q) of the labeled amount of the drug in the dosage form is dissolved in 20 minutes.

2. Please note that you have used expired lots in the dissolution study. In future, you are advised to avoid the use of expired lots in the study.

Please also 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,



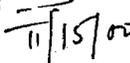
Dale Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-350
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Secretary - Bio Drug File
HFD-655/ SShrivastava

X:NEW\FIRMSNZ\Purepac\ltrs&rev\75350o.N00
Printed in final on 11/13/00

Endorsements: (Final with Dates)

HFD-650/ SShrivastava 

HFD-655/ SNerurkar 

HFD-617/ Steven Mazzella

HFD-650/ D. Conner 

11/15/00
11/29/00

 11/20/2000

BIOEQUIVALENCY - ACCEPTABLE

1. Amendment (DIS)

All Strengths
Outcome: AC

WINBIO COMMENTS:

APPEARS THIS WAY
ON ORIGINAL

Gabapentin Capsules 100, 300, 400 mg
ANDA #75-350
Reviewer: S.P. Shrivastava
WP #75350o.101

Purepac Pharm. Co.
Elizabeth, NJ
Submitted:
January 30, 2001

REVIEW OF AN AMENDMENT

The firm had submitted single dose fasting and nonfasting studies, and dissolution data in 0.1 N and 0.06 N HCl media (3/30/98, 11/10/00). The application was acceptable (see review, SShrivastava, 8/26/98, 11/29/00). In this amendment the firm has responded to the FDA letter dated 11/30/00.

FDA COMMENTS AND FIRM'S RESPONSE

Comment #1

Please acknowledge that the following dissolution testing specifications have been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of 0.06 N HCl, at 37 °C using USP Apparatus 2 (Paddle) at 50 r.p.m. 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.

Response

The firm has incorporated the recommended dissolution method in their Finished Product and Stability Specification sheets, and revised the sheets for each product to reflect such changes.

Conclusion

The response is acceptable.

Comment #2

Please note that you have used expired lots in the dissolution study. In future, you are advised to avoid the use of expired lots in the study.

Response

The firm recognizes the use of expired lots in dissolution study. Although the firm had used expired lots in second dissolution study, drug substance appeared to be stable for longer periods, and no loss

in the labeled amount of the active moiety was observed. Lots showed —, % dissolution at 45 minutes by a specific HPLC method. In future, Purepac will try to avoid the use of expired lots for data generation.

Conclusion

The response is acceptable.



S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

for RD INITIALED S Nerurkar
FT INITIALED S Nerurkar Moharival Date 2/13/01
Concur: De Salvaite Date: 2/27/2001

for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

SPS/sps/1-30-01/75350o.101
cc: ANDA #75350 (Original, Duplicate), HFD-655 (S Nerurkar, S Shrivastava), Drug File,
Division File.

BIOEQUIVALENCY COMMENTS

ANDA: 75-350

APPLICANT: Purepac Pharmaceuticals, Inc.

DRUG PRODUCT:

Gabapentin capsules, 100, 300 and 400 mg strengths

The Division of Bioequivalence has completed its review and has no further questions at this time.

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 0.06 N HCl, at 37°C using USP Apparatus 2 (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,



fr

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-350
ANDA DUPLICATE
DIVISION FILE
HFD-655/ SShrivastava

X:NEW\FIRMSNZ\Purepac\ltrs&rev\75350o.101
Printed in final on 1/12/01

Endorsements: (Final with Dates)

HFD-655/ SShrivastava

HFD-655/ S Nerurkar *MM 2/13/01* *2/13/01*

HFD-650/ Steven Mazzella

HFD-650/ D. Conner *for due 2/27/2001*

BIOEQUIVALENCY - ACCEPTABLE

1. Amendment

All Strengths
Outcome: AC

WINBIO COMMENTS:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-350

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION/MEETING

LuAnn Erlich was contacted regarding their faxed correspondence dated June 4, 1997 regarding bioequivalence requirements for gabapentin capsules. After discussion with Nick Fleischer, the following comments were provided.

Currently, there is no guidance for this product. Patent expires in 2008.

Since there is no food effects, a non-fasting study is not required.

Since there is non-linearity in the bioavailability of this product, bioequivalence studies will be required for the 100 mg and 400 mg strengths. A waiver may be considered for the 300 mg strength, if they are proportionally formulated and the dissolution testing is acceptable.

4/16/98

A meeting was held to discuss requirements for gabapentin. Ms Erlich was informed that a food study on the 400 mg is now necessary and the fasting study should be done on the 400 mg strength. Waivers for the lowest strength may be requested if formulated proportionally similar and in-vitro testing performed is acceptable.

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DATE
6/10/97

AADA NUMBER

IND NUMBER

TELECON
Bio97-130

INITIATED BY	MADE
<input checked="" type="checkbox"/> APPLICANT/	<input type="checkbox"/> BY
SPONSOR	TELE.

<input type="checkbox"/> FDA	<input type="checkbox"/> IN
PERSON	

**APPEARS THIS WAY
ON ORIGINAL**

PRODUCT NAME Gabapentin
FIRM NAME Apotex
NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD LuAnn Erlich Director, Pharmaceutical Sciences
TELEPHONE NUMBER (847) 541-1141 X27
SIGNATURE L. Sanchez, Pharm.D.

5.1

RECORD OF TELEPHONE CONVERSATION

<p>I called Joan Janulis regarding a request by the firm for a meeting to discuss the gabapentin exclusivity, D-43. I let her know that we will defer meeting with them regarding this issue at this time. I told her that meetings on this topic will be held by the Center in mid to late October. She asked whether their firm would get an approvable letter since she heard from the PM that all other parts of the application are OK. I told her that this option is being looked into by the Office.</p>	DATE September 29, 1999
	ANDA NUMBER 75-350
	IND NUMBER
	TELECON
	INITIATED BY MADE APPLICANT/ X BY SPONSOR TELE.
	X FDA IN PERSON
	PRODUCT NAME Gabapentin
	FIRM NAME Purepac Pharmaceutical Co.
	NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Joan Janulis Director Regulatory Affairs
	TELEPHONE NUMBER (908) 659-2430
SIGNATURE Charlie Hoppes	

Handwritten initials

Charlie Hoppes 9/29/99

File in archive

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. *Russell Katz 1/16/03*
Director
Division of Neuropharmacological Drug Products
HFD-120

THRU: Rosemary Roberts, M.D. *Rosemary Roberts 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:

7 page(s) of draft
labeling has been
removed from this
portion of the review.

MEMORANDUM

RECORD OF TELEPHONE CONVERSATION

<p>I telephone Joan Janulis of Purepac and requested the following; revise storage temperature on container and insert labeling to: Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature].</p> <p>Ms. Janulis will provide a commitment to revise the storage temperature as stated above at the time of next printing.</p>	<p>DATE September 3, 2003</p>
	<p>ANDA NUMBER 75-350</p>
	<p>IND NUMBER</p>
	<p align="center">TELECON</p>
	<p>INITIATED BY</p>
	<p>SPONSOR</p> <p align="center">FDA X</p>
	<p>PRODUCT NAME Gabapentin Capsules</p>
	<p>FIRM NAME Purepac</p>
	<p>NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Joan Janulis</p>
	<p>TELEPHONE NUMBER 908-659-2430</p>
<p>SIGNATURE <i>M. Bell</i></p>	

V:\FIRMSNZ\PUREPAC\TELECONS\telecon090303.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 75-350

CORRESPONDENCE

ANDA 75-350

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

APR 23 1998

|||||

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.

NAME OF DRUG: Gabapentin Capsules, 100 mg, 300 mg and 400 mg

DATE OF APPLICATION: March 30, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 30, 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.

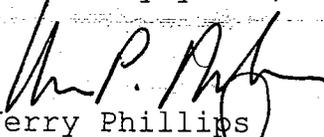
We will correspond with you further after we have had the opportunity to review the application.

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 75-350
DUP/Jacket
Division File
Field Copy
HFD-610/J.Phillips
HFD-92
HFD-615/M.Bennett

Endorsement: HFD-615/PRickman, Chief, RSB  4/20/98 date
HFD-615, GDavis, CSO  4/20/98 date
HFD-645, BARNwine, Sup. Chem. _____ date
WP File x:\new\firmnsz\purepac\ltrs&rev\75350.ack
FT/mjl/4/16/98
ANDA Acknowledgment Letter!

A Trusted Name For Over Half A Century



ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

PATENT AMENDMENT

NAI
MD 5/19/98

UPS OVERNIGHT COURIER

May 7, 1998

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW COURIER

RE: ANDA #75-350, Gabapentin Capsules, 100 mg, 300 mg, and 400 mg

Dear Mr. Sporn:

Reference is made to our March 30, 1998 submission of an Abbreviated New Drug Application, ANDA #75-350 for Gabapentin Capsules, 100 mg, 300 mg, and 400 mg. Further reference is made to our April 30, 1998 amendment in accordance with 21 CFR 314.95(b) in which Purepac certified that Warner Lambert Co., the holder of U.S. Patent 4,894,476, and Parke Davis Pharmaceutical Research (A Division of Warner Lambert Co.), the holder of the application for the listed drug, were sent notice of patent certification.

As required by 21 CFR 314.95(e), Purepac Pharmaceutical Co. is providing, as documentation of receipt of notice, copies of the certified mail return receipts from Warner Lambert Company and Parke Davis Pharmaceutical Research, dated May 4, 1998 and April 30, 1998; respectively.

If there are any questions concerning this amendment, please contact the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

[Signature]
Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

Sporn
5-18

RECEIVED

MAY 08 1998

GENERIC DRUGS

JJ:cp

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

*NAI
AA 9/12/03*

NEW CORRESP

ELECTRONIC SUBMISSION ESD

NC

JPS OVERNIGHT COURIER

May 11, 1998

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RECEIVED
MAY 11 1998
GENERIC DRUGS

RE: ANDA #75-350, Gabapentin Capsules, 100 mg, 300 mg, and 400 mg

Dear Mr. Sporn:

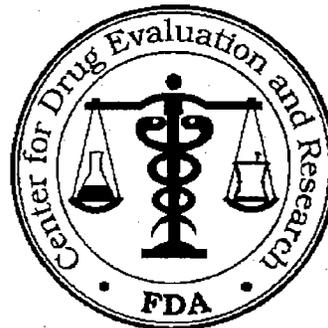
Reference is made to our March 30, 1998 submission of an Abbreviated New Drug Application, ANDA #75-350, for Gabapentin Capsules, 100 mg, 300 mg, and 400 mg. Further reference is made to the agency's April 23, 1998 letter received by Purepac on April 27, 1998) acknowledging the receipt of this application on March 30, 1998.

In accordance with the Office of Generic Drugs' letter to "All ANDA Applicants", dated March 23, 1998, Purepac is hereby submitting the Bioavailability/bioequivalence and Chemistry, Manufacturing and Controls electronic submission documents (ESDs). The diskettes, submitted in duplicate, contain the information/data files for the BA/BE or CMC review part, as applicable. Therefore, a total of 4 diskettes (1 original and 1 duplicate disk for each review part) are enclosed. Purepac is submitting these Electronic Submission Documents within the 45 day grace period permitted from the agency's receipt of our paper submission as stated in the March 23 letter from OGD.

MAJOR AMENDMENT

ANDA 75-350

OCT 30 1998



OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Purepac Pharmaceutical Co.

PHONE: 908-659-2430

ATTN: Joan Janulis, R.A.C.

FAX: 908-659-2440

FROM: Kassandra Sherrod

PROJECT MANAGER (301) 827-5849

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated March 30, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Gabapentin Capsules, 100 mg, 300 mg and 400 mg.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (6 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

C.M.C. Labeling and Bioequivalence comments are attached.
Prms 10/30/98

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

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Redacted 5 page(s)

of trade secret and/or

confidential commercial

information from

10/30/98 FAXED LETTER

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

UPS OVERNIGHT COURIER

MAJOR AMENDMENT

January 11, 1999

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT

N/AC

RE: ANDA #75-350, Gabapentin Capsules, 100 mg, 300 mg and 400 mg

Dear Mr. Sporn:

Reference is made to our March 30, 1998 submission of an Abbreviated New Drug Application for Gabapentin Capsules, 100 mg, 300 mg and 400 mg ANDA #75-350. Further reference is made to your Major Chemistry deficiency letter dated October 30, 1998, which also included labeling and bioequivalence comments. Your comments are provided in bold type, followed by our firm's response.

A. Chemistry Deficiencies

Agency Comment

- 1. Please be aware that the application cannot be approved until deficiencies regarding DMF # _____ have been addressed satisfactorily by the DMF holder.**

Purepac's Response



JAN 12 1999

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information from

PUREPAC'S 1/11/99 LETTER

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07201
908-527-9100
Fax: 908-527-0649

ANDA ORIG AMENDMENT

AC

~~AC~~

NAE
2/17/99

MAJOR AMENDMENT

ELECTRONIC SUBMISSION DOCUMENTS

UPS OVERNIGHT COURIER

February 17, 1999

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-350, Gabapentin Capsules, 100 mg, 300 mg, and 400 mg

Dear Mr. Sporn:

Reference is made to our March 30, 1998 submission of an Abbreviated New Drug Application for Gabapentin Capsules, 100 mg, 300 mg and 400 mg ANDA #75-350. Further reference is made to our firm's Major Amendment, submitted January 11, 1999, in response to the Agency's deficiency letter dated October 30, 1998.

In accordance with the Office of Generic Drugs' letter to "All ANDA Applicants", dated March 23, 1998, Purepac is hereby submitting the Major Amendment Chemistry, Manufacturing and Controls electronic submission documents (ESDs). The diskettes, submitted in duplicate, contain the information/data files for the CMC review part including the pertinent revisions, as noted in our paper copy submission (exceptions are noted on the following page). Please note that there were no changes to the Bioavailability/Bioequivalence review section (BA/BE ESDs).

RECEIVED

FEB 18 1999

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information from

PUREPAC'S 2/17/99 LETTER

MAJOR AMENDMENT, ELECTRONIC SUBMISSION DOCUMENTS

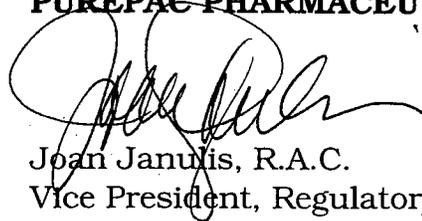
RE: ANDA #75-350, GABAPENTIN CAPSULES, 100 MG, 300 MG, AND 400 MG

PAGE 4 OF 4

If there are any questions concerning this correspondence, please contact the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.



Joan Janulis, R.A.C.

Vice President, Regulatory Affairs

Enclosures

JJ:cp

A Trusted Name For Over Half A Century



ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

ANDA ORIG AMENDMENT
AC

**MAJOR AMENDMENT
ELECTRONIC SUBMISSION DOCUMENTS**

RESUBMISSION

UPS OVERNIGHT COURIER

March 29, 1999

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-350, Gabapentin Capsules, 100 mg, 300 mg, and 400 mg

Dear Mr. Sporn:

Reference is made to our firm's Major Amendment for Gabapentin Capsules, 100 mg, 300 mg and 400 mg, ANDA #75-350, submitted January 11, 1999, in response to the Agency's deficiency letter dated October 30, 1998. Further reference is made to the Chemistry, Manufacturing and Controls electronic submission documents (ESDs) submitted on February 17, 1999.

On February 16 and February 19, Cathy Petrock, of Purepac, spoke with Jon Clark, of OGD, regarding the difficulties that we encountered in preparing the February 17th electronic submission document (ESD) amendment referenced above. Mr. Clark intimated that the problems Purepac has discovered may necessitate a new EVA version. He then requested that Purepac resubmit the February 17th ESD amendment. This should be performed by renaming the original ANDA ESD and subsequently making the necessary changes that are detailed in the paper amendment.

RECEIVED

MAR 30 1999

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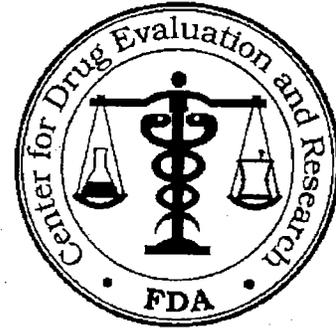
information from

PUREPAC'S 3/29/99 LETTER

FACSIMILE AMENDMENT

JUL 12 1999

ANDA 75-350



OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Purepac Pharmaceutical Co.
ATTN: Joan Janulis, R.A.C.

PHONE: 908-659-2430
FAX: 908-659-2440

FROM: Kassandra Sherrod

PROJECT MANAGER (301) 827-5849

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated March 30, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Gabapentin Capsules, 100 mg, 300 mg and 400 mg.

Reference is also made to your amendment(s) dated January 11 and February 17, 1999.

Attached are 1 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301-827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. Further if a major deficiency is cited in the bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT.

SPECIAL INSTRUCTIONS:

f.s. Chemistry deficiencies

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

X:\new\ogdadmin\macros\faxfax.frm

JUL 12 1999

5.1

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-350

APPLICANT: Purepac Pharmaceutical Co.

DRUG PRODUCT: GABAPENTIN Capsules, 100 mg, 300 mg and 400 mg

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

Please address the following issue regarding you response concerning _____, and

_____ :

--	--

_____ policy to be in accordance with this recommendation.

B. In addition, please note and acknowledge the following:

We ask that you provide a list of _____ used in the

Sincerely yours,

Florence S. Fang

FS

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research



*noted
for
7/14/99*

PUREPAC PHARMACEUTICAL Co.
FAX NO. (908) 659-2440

TELEFAX / MEMORANDUM

TO: Kassandra Sherrod

FAX NO. 301-827-4337

FROM: *Carl Hedrick for*
Joan Janulis

SUBJECT: Facsimile Amendment

DATE: July 13, 1999

CC: NO. PAGES INCLUDING THIS COVER SHEET: 8

ORIG AMENDMENT

N/FA

The information contained in this message is intended only for the personal and confidential use of the recipient(s) named above. If the reader of this message is not the intended recipient or an agent responsible for delivering it to the intended recipient, you are hereby notified that you have received this document in error and that any review, dissemination or copying of this message is strictly prohibited. If you have received this communication in error, please notify us immediately by telephone (908-527-9100) and return the original message to us by mail. Thank you.

Following please find a Facsimile Amendment dated July 13, 1999. Hard copy to follow via overnight mail.

A Trusted Name For Over Half A Century



ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

UPS OVERNIGHT COURIER

FACSIMILE AMENDMENT

July 13, 1999

NDA ORIG AMENDMENT
N/FA

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-350, Gabapentin Capsules, 100 mg, 300 mg and 400 mg

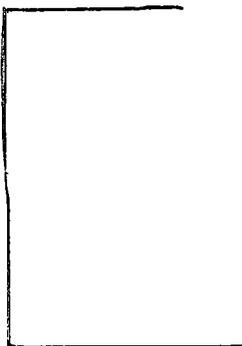
Dear Mr. Sporn:

Reference is made to our March 30, 1998 submission of an Abbreviated New Drug Application for Gabapentin Capsules, 100 mg, 300 mg and 400 mg, ANDA #75-350. Further reference is made to your Minor Chemistry deficiency letter dated July 12, 1999. Your comments are provided in bold type, followed by our response.

Chemistry Deficiencies

Agency Comment

A. Please address the following issue regarding you response concerning
_____ and _____



Redacted 2 page(s)

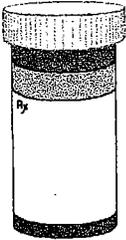
of trade secret and/or

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information from

PUREPAC'S 7/13/99 LETTER

Fax Cover Sheet



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

Date: July 28, 1999

To: Ms. Joan Janulis of Purepac

Phone: 908-659-2430 Fax: 908-659-2440

From: Koung Lee

Phone: (301) 827-5830 Fax: (301) 443-3847

Number of Pages: 3
(Including Cover Sheet)

Comments:

Attached Labeling comments for ANDA 75-350

*This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, this communication is not authorized. If you have received this document in error, immediately notify us by telephone and return it to us at the above address by mail. Thank you.

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

ANDA Number: 75-350 Date of Submission: January 11, 1999

Applicant's Name: Purepac Pharmaceutical Co.

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

Labeling Deficiencies:

1. GENERAL

AA-1
Kan...

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.

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".

b. ADVERSE REACTIONS

Add the following subsection (——— after "Special Senses" 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.

c. DOSAGE AND ADMINISTRATION

i. The second sentence of the first paragraph should read as "...pediatric patients below the age of — years —"

ii. Replace "



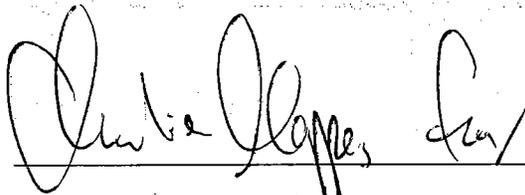
" with "The starting dose is 300 mg three times a day." in the third paragraph.

Please revise your labeling, as instructed above, and submit final printed, or if you 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.



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



ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

FACSIMILE AMENDMENT

UPS OVERNIGHT COURIER

August 2, 1999

Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

NC to
Fax

RE: ANDA 75-350, Gabapentin Capsules, 100 mg, 300 mg and 400 mg

Dear Mr. Sporn:

Reference is made to the agency's correspondence dated July 28, 1999, detailing labeling deficiencies in the referenced Abbreviated New Drug Application. These deficiencies have been excerpted from your correspondence and presented with our responses in the text that follows:

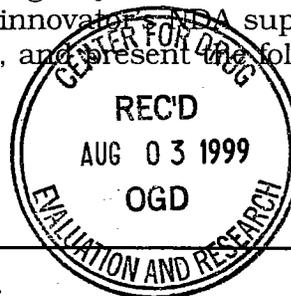
Agency Comment:

1. GENERAL

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.

Purepac's Response:

We respectfully decline the request to certify in accordance with the above comment as we do not intend to adopt the text of the innovator's labeling that is covered by D-43 exclusivity. Our proposed insert labeling retains the starting dose regimen (titration to a dose of 900 mg/day over a three day period) that was in place prior to the approval of the innovator's NDA supplement # S-011. We believe that this action is appropriate, and present the following in support of our position:



The relevant regulation:

21 CFR 314.127 (a) (7) states that the agency shall refuse to approve an abbreviated new drug application under the following circumstances:

- *Information submitted in the abbreviated new drug application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the application except for changes required because of differences approved in a petition under §314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers or because aspects of the listed drug's labeling are protected by patent, or by exclusivity, and such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use.*

The difference in labeling qualifies for approval under the regulation:

Our proposed labeling differs from the labeling of the listed drug with respect to an aspect that is covered by exclusivity, thus fulfilling the first criterion that must be satisfied to support approval of the associated application.

The difference in labeling will not render the proposed product less safe or effective for all non-protected conditions of use:

We have retained the instructions to titrate to a dose of 900 mg/day over a three day period, where the innovator has eliminated this restriction and supported its elimination with a clinical study. A copy of the approval package for NDA supplement S-011 is appended as **Attachment 1** of this amendment. The following information contained in the approval package clearly supports our maintenance of the original starting dose regimen from a safety and efficacy standpoint:

- 1) In support of the labeling change covered in supplement S-011, Parke Davis conducted a study comparing the tolerability of the approved and proposed dosing regimens. Tolerability was measured in terms of the rate of occurrence of four specific adverse reactions. The medical review concluded that initiation of treatment with 900 mg/day "is not likely to result in significant difficulty". The review document further stated that no information could be located in the file stating the reason for the slower titration in the approved (original) labeling other than a statement to the effect that it was done to be "conservative".
- 2) The medical review summary specifically stated that the sponsor has not addressed the effect of the new regimen on the ultimate effectiveness of the drug. However, the reviewer was "comfortable" concluding that no important effect would be expected.

The information contained in the approval package for NDA supplement S-011 clearly supports the absence of a safety and/or efficacy concern associated with our maintenance of the original starting dose regimen. An amended exclusivity statement referencing D-43 exclusivity and our elimination of the protected aspect from our labeling is appended as **Attachment 2** of this amendment.

Agency Comment:

2. INSERT
 - a. CLINICAL PHARMACOLOGY
(Etc... Full text omitted)
 - b. ADVERSE REACTIONS
(Etc... Full text omitted)
 - c. DOSAGE AND ADMINISTRATION
(Etc... Full text omitted)

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

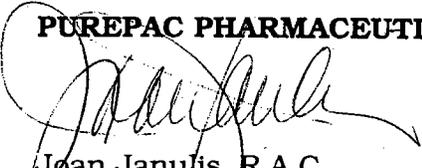
Purepac's Response:

Purepac has amended our package insert labeling as requested, with the exception of the text under comment c. ii regarding elimination of the titration requirement. A side-by-side comparison of our amended labeling and the proposed labeling from our last submission is included as **Attachment 3** of this amendment. Twelve (12) final printed copies of our package insert labeling are included in **Attachment 4**.

This completes our Facsimile Amendment in response to your labeling review letter dated July 28, 1999. Purepac Pharmaceutical Co. trusts that this submission is complete and in order. We look forward to the tentative approval of this Abbreviated New Drug Application.

Sincerely,

PUREPAC PHARMACEUTICAL CO.


Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

A Trusted Name For Over Half A Century

PUREPAC

ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

CORRESPONDENCE TO FILE

(CMC and Labeling Information)

ORIG AMENDMENT
N/FA

UPS OVERNIGHT COURIER

March 23, 2000

Mr. Gary Buehler, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-350, Gabapentin Capsules, 100 mg, 300 mg and 400 mg

Dear Mr. Buehler:

Reference is made to our March 30, 1998 submission of an Abbreviated New Drug Application for Gabapentin Capsules, 100 mg, 300 mg and 400 mg, ANDA #75-350. Further reference is made to the Agency's February 23, 2000 Fax Chemistry, Labeling and Bioequivalence deficiency letter regarding Purepac's ANDA for Gabapentin Tablets, 600 mg and 800 mg, ANDA #75-694. In that letter (copies of relevant pages are provided in Section 1 of this correspondence), our firm was asked to also submit our response to the Agency's comment 4, to our pending application for Gabapentin Capsules, ANDA #75-350.



Purepac Pharmaceutical Co. is a subsidiary of Faulding Inc.

Redacted 5 page(s)

of trade secret and/or

confidential commercial

information from

PUREPAC'S 3/23/00 LETTER



ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

PATENT AMENDMENT

UPS OVERNIGHT COURIER

May 9, 2000

NAE [initials]
a/r/03

NEW CORRESP
NC

Mr. Gary Buehler, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-350, Gabapentin Capsules, 100 mg, 300 mg and 400 mg

Dear Mr. Buehler:

Pursuant to the May 9, 2000 verbal request of Mr. Gregg Davis of your Regulatory Support Branch, appended is a copy of the patent infringement complaint filed by Warner-Lambert Company in response to Purepac's ANDA submission and paragraph IV certification for Gabapentin Capsules, 100 mg, 300 mg and 400 mg.

Should you have any questions or require further information, please do not hesitate to contact me at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs



A Trusted Name For Over Half A Century



ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

MAE
a/r/03

PATENT AMENDMENT

UPS OVERNIGHT COURIER

May 25, 2000

NEW CORRESP

NC

Mr. Gary Buehler, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-350, Gabapentin Capsules, 100 mg, 300 mg, and 400 mg

Dear Mr. Buehler:

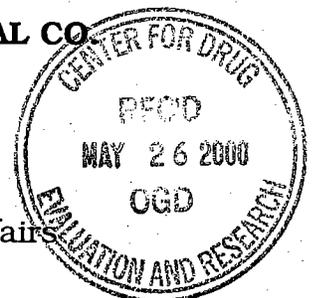
Reference is made to our March 30, 1998 submission of an Abbreviated New Drug Application, ANDA #75-350 for Gabapentin Capsules, 100 mg, 300 mg, and 400 mg. Further reference is made to the current patent information, published in "The Orange Book", relating to the listed drug product Neurontin® Capsules. Purepac Pharmaceutical Co. is hereby providing an additional Patent Certification with respect to recently issued U.S. Patent 6054482.

If there are any questions concerning this amendment, please contact the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs



JJ:cch



ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

MAP
TJ 9/12/00

PATENT AMENDMENT

UPS OVERNIGHT COURIER

NEW CORRESP

October 9, 2000

NC

Mr. Gary Buehler, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-350, Gabapentin Capsules, 100 mg, 300 mg, and 400 mg

Dear Mr. Buehler:

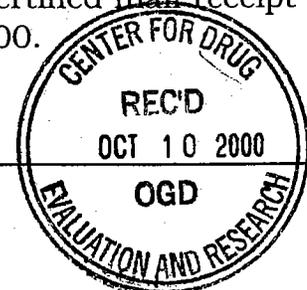
Reference is made to Purepac's Abbreviated New Drug Application for Gabapentin Capsules, 100 mg, 300 mg and 400 mg which was submitted to the agency on March 30, 1998. Further reference is made to our Patent Amendment dated May 25, 2000, that contained a paragraph IV certification regarding U.S. patent **6,054,482**. The subject patent issued subsequent to our original ANDA submission.

This correspondence and its enclosures are intended to fulfill the requirements set forth in 21 CFR 314.95 and 314.107(f)(2) regarding documentation of notice receipt and initiation of patent infringement litigation by the patent holder and holder of the approved application. Enclosed please find the following:

314.95(e)

- 1) Documentation confirming receipt of notice by the NDA holder, Parke Davis:**

Included in Section 1 of this Amendment is a copy of a certified mail receipt verifying that Parke Davis received notice on June 14, 2000.



GABAPENTIN CAPSULES, 100 MG, 300 MG AND 400 MG

2) Documentation confirming receipt of notice by the patent holder, Gödecke Aktiengesellschaft:

In lieu of a certified mail return receipt, we are enclosing a copy of the patent infringement complaint filed by plaintiffs, Pfizer Inc., Warner Lambert Company and Gödecke Aktiengesellschaft. (Please refer to Section 2 of this amendment.) The complaint was filed in the U.S. District Court for the District of New Jersey on **July 20, 2000**. Please be advised that Purepac provided notice to the patent holder located in Berlin, Germany, via Certified Mail, but has not received the return receipt as of the date of this correspondence. The patent infringement complaint naming the patent holder (Gödecke) as plaintiff verifies that notice was received. However, in the absence of a document listing the actual date of receipt, we ask that the agency utilize the date of the complaint for the regulatory determinations outlined in the statute and regulations. In the event that the Certified Mail Return Receipt becomes available to Purepac while our application is pending, we will further amend the application to provide a copy of the document.

314.107(f)(2)

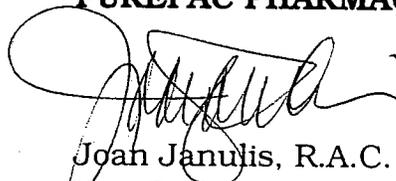
Notification of Patent Infringement Litigation

Purepac Pharmaceutical Co. certifies that an action for patent infringement (**Civil Action #00-CV3522**) was filed by plaintiff's Pfizer Inc., Warner-Lambert Company and Gödecke Aktiengesellschaft in response to Purepac's paragraph IV certification re: U.S. patent 6,054,482.

If there are any questions concerning this amendment, please contact the undersigned at (908) 659-2430.

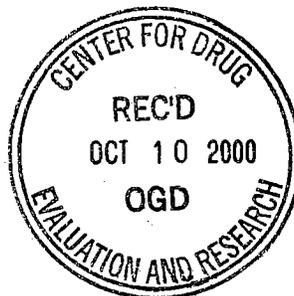
Sincerely,

PUREPAC PHARMACEUTICAL CO.



Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ:cch





Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

BIOEQUIVALENCE TELEPHONE AMENDMENT

Bioequivalence Information

UPS OVERNIGHT COURIER

November 10, 2000

Mr. Gary Buehler, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-350, Gabapentin Capsules, 100 mg, 300 mg & 400 mg

Dear Mr. Buehler:

Reference is made to our March 30, 1998 submission of an Abbreviated New Drug Application for Gabapentin Capsules, 100 mg, 300 mg & 400 mg, ANDA #75-350. Further reference is made to the October 31, 2000 telephone conversation between Ms. Krista Scardina, Project Manager in the Division of Bioequivalence, and Elizabeth Trowbridge, of Purepac, regarding the subject application. In accordance with the agency's request, Purepac is providing comparative dissolution profiles for the test batches manufactured in support of our application and the reference drug products, utilizing the following conditions:

Medium: 0.06 N HCl, 900 mL
Apparatus 2: 50 rpm

In conjunction with this submission, Purepac is providing a copy of this amendment to our local district office. The required Field Copy Certification is included in this submission.

BIOEQUIVALENCE TELEPHONE AMENDMENT**ANDA #75-350****Gabapentin Capsules, 100 mg, 300 mg & 400 mg****page 2 of 2**

This concludes our **BIOEQUIVALENCE TELEPHONE AMENDMENT** in response to the Agency's October 31, 2000 request. Purepac Pharmaceutical Co. trusts that you will find this amendment complete and in order, and looks forward to the approval of our Abbreviated New Drug Application. If you have any questions regarding this submission, please do not hesitate to call the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Elizabeth Trowbridge / for

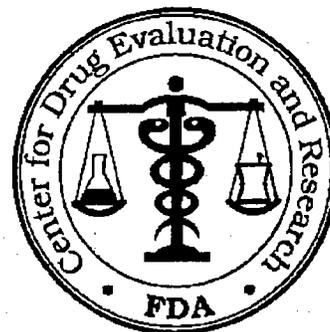
Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ/bt
Enclosures

MINOR AMENDMENT

ANDA 75-350

NOV 30 2000



OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Purepac Pharmaceutical Co.

TEL: 908-659-2430

ATTN: Joan Janulis

FAX: 908-659-2440

FROM: Kassandra Sherrod

PROJECT MANAGER: 301-827-5849

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated March 30, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Gabapentin Capsules, 100 mg, 300 mg, 400 mg.

Reference is also made to your amendment(s) dated: May 20, 1998; January 11, February 17, March 29, July 13, August 2, 1999; and March 23, 2000.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry and bioequivalence deficiencies and comments

1/29

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

NOV 30 2000

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-350 APPLICANT: Purepac Pharmaceutical Company

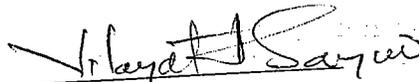
DRUG PRODUCT: Gabapentin Capsules, 100 mg, 300 and 400 mg

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

1. Please be aware that the application cannot be approved until deficiencies regarding DMF # _____ have been addressed satisfactorily by the DMF holder. Please do not respond until the DMF holder has notified you that a response has been sent to the Agency.
2. The Agency has become aware that more than one polymorphic form exists for the Gabapentin drug substance. This information was not provided in your ANDA. Please provide evidence that the appropriate controls are in place regarding this issue. It is also recommended that a polymorph specification be set for the drug substance. In addition, please assess the potential for interconversion of the polymorphic forms during the manufacture and storage of the drug product.

Sincerely yours,



Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research



A Trusted Name For Over Half A Century



ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

AMENDMENT

CMC Information

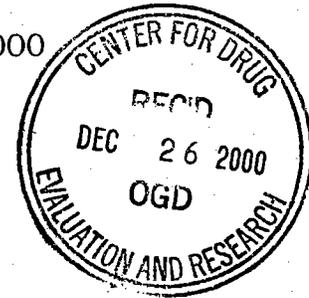
UPS OVERNIGHT COURIER

December 22, 2000

Mr. Gary Buehler, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

N/A



RE: ANDA #75-350, Gabapentin Capsules, 100 mg, 300 mg & 400 mg

Dear Mr. Buehler:

Reference is made to our March 30, 1998 submission of an Abbreviated New Drug Application for Gabapentin Capsules, 100 mg, 300 mg & 400 mg, ANDA #75-350.

Purepac is submitting this amendment in order to add a new regulatory test and test specification for Gabapentin active drug substance. This new regulatory test will be used to determine the _____ content in the Gabapentin active drug substance used in the manufacture of our finished drug products. The specification is as follows:

Test/Method	Specification
_____	_____

Purepac hereby commits to utilizing Gabapentin active drug substance which contains _____ in the manufacture of all commercial batches of the finished drug product. Active drug substance that does not meet this specification will not be used in commercial manufacture.



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AMENDMENT

ANDA #75-350

Gabapentin Capsules, 100 mg, 300 mg & 400 mg
page 2 of 2

Accordingly, Purepac has developed In-house Method _____

This amendment contains the following information in support of this additional test:

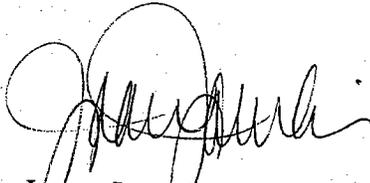
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In conjunction with this submission, a copy of this amendment has been provided to the local district office. The required Field Copy Certification is also included in this amendment.

If you have any questions concerning this submission, please do not hesitate to contact the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.



Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ/cah
Enclosures



ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

BIOEQUIVALENCE AMENDMENT
(Bioequivalence and CMC Information)

UPS OVERNIGHT COURIER

NEW CORRESP
NC/BIO

January 30, 2001

Mr. Gary Buehler, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-350, Gabapentin Capsules, 100 mg, 300 mg and 400 mg

Dear Mr. Buehler:

Reference is made to our March 30, 1998 submission of an Abbreviated New Drug Application for Gabapentin Capsules, 100 mg, 300 mg and 400 mg, ANDA #75-350. Further reference is made to your Bioequivalence letter dated November 30, 2000. Your comments are provided in bold type, followed by our firm's response.



BIOEQUIVALENCE AMENDMENT

ANDA #75-350

Gabapentin Capsules, 100 mg, 300 mg and 400 mg

Page 2 of 3

Agency Comment

1. Please acknowledge that the following dissolution testing specifications have been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of 0.06 N HCl, at 37°C using USP Apparatus 2 (Paddle) at 50 r.p.m. The test product should meet the following specifications:

Not less than \sim % (Q) of the labeled amount of the drug in the dosage form is dissolved in 20 minutes.

Purepac's Response

Purepac acknowledges that the FDA recommended dissolution testing conditions and specifications, as noted above, have been incorporated into our stability and quality control programs. The finished product and stability specification sheets have been revised to reflect the referenced requirements and are included in Section 1 of this amendment.

Agency Comment

2. Please note that you have used expired lots in the dissolution study. In future, you are advised to avoid the use of expired lots in the study.

Purepac's Response

Purepac acknowledges that the most recently (October 31, 2000) requested dissolution profiles were generated on test batches and reference drug product lots that have exceeded their expiration dating periods.

Please note that on October 30, 1998, we received confirmation of our originally proposed dissolution conditions and specification from the Division of Bioequivalence. Purepac recognizes that initial bioequivalence comments are preliminary, however, since Purepac has not manufactured any additional batches of the product, the subsequent request required the generation of profiles using expired batches. In the future, Purepac will avoid the use of expired lots for data generation whenever possible.

BIOEQUIVALENCE AMENDMENT

ANDA #75-350

Gabapentin Capsules, 100 mg, 300 mg and 400 mg

Page 3 of 3

In conjunction with this submission, Purepac is providing a copy of this Bioequivalence Amendment to our local district office. The required Field Copy Certification is included in Section 2.

This concludes our **BIOEQUIVALENCE AMENDMENT** in response to your letter of November 30, 2000. Purepac Pharmaceutical Co. trusts that you will find this amendment complete and in order, and looks forward to the approval of our Abbreviated New Drug Application. If you have any questions regarding this submission, please do not hesitate to call the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Elizabeth Trowsbridge / for

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ/cah
Enclosures



ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

LABELING AMENDMENT

UPS OVERNIGHT COURIER

February 28, 2001

ORIG AMENDMENT

N/A F

Mr. Gary Buehler, Acting Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Food & Drug Administration
Document Control Room
MPN II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-350, Gabapentin Capsules, 100 mg, 300 mg, and 400 mg

Dear Mr. Buehler:

Reference is made to our March 30, 1998 submission of an Abbreviated New Drug Application for Gabapentin Capsules, 100 mg, 300 mg, and 400 mg, ANDA #75-350.

Purepac Pharmaceutical Co. is amending the above-referenced application to provide revised package insert labeling as per Parke Davis' letter dated October 12, 2000 for Neurontin® Capsules, Tablets, and Oral Suspension, which was obtained from the Office of Generic Drugs Labeling Review Branch web site.

Enclosed please find twelve (12) copies of final printed insert labeling for your review. Also included in this submission is a side-by-side comparison of our proposed insert and that of the listed drug's with all differences annotated and explained. If this meets with your approval please consider this as final printed insert labeling.



ANDA 75-350

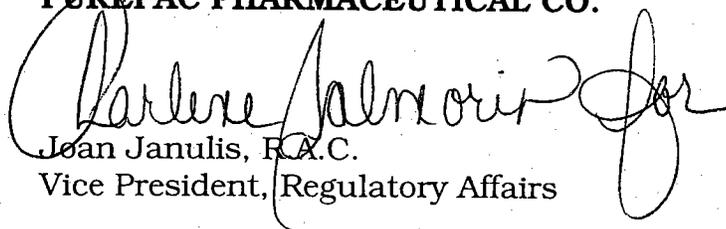
Gabapentin Capsules, 100 mg, 300 mg, and 400 mg

Page 2 of 2

Purepac Pharmaceutical Co. looks forward to your review of this amendment.

Sincerely,

PUREPAC PHARMACEUTICAL CO.



Jean Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ/cs

Enclosures

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

Am
ORIG AMENDMENT

MINOR AMENDMENT
(CMC and Bio-equivalence Information)

UPS OVERNIGHT COURIER

April 24, 2001

Mr. Gary Buehler, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-350, Gabapentin Capsules, 100 mg, 300 mg and 400 mg

Dear Mr. Buehler:

Reference is made to our March 30, 1998 submission of an Abbreviated New Drug Application for Gabapentin Capsules, 100 mg, 300 mg and 400 mg, ANDA #75-350. Further reference is made to your Minor Chemistry deficiency letter dated November 30, 2000. Your comments are provided in bold type, followed by our firm's response.



ML
4-24-01

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information from

4/24/01 PUREPAC LETTER

MINOR AMENDMENT

ANDA #75-350

Gabapentin Capsules, 100 mg, 300 mg and 400 mg

Page 5 of 5

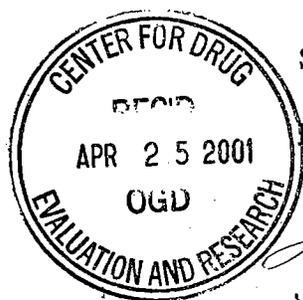
-
2. **Please note that you have used expired lots in the dissolution study. In future, you are advised to avoid the use of expired lots in the study.**

Purepac's Response

Purepac acknowledges that in future, will avoid the use of expired lots in the study.

In conjunction with this submission, Purepac is providing a copy of this amendment to our local district office. The required Field Copy Certification is included in Section 4.

This concludes our **MINOR AMENDMENT** in response to your letter of November 30, 2000. Purepac Pharmaceutical Co. trusts that you will find this amendment complete and in order, and looks forward to the approval of our Abbreviated New Drug Application. If you have any questions regarding this submission, please do not hesitate to call the undersigned at (908) 659-2430.



Sincerely,

PUREPAC PHARMACEUTICAL CO.

J. Janulis
Joan Janulis, R.A.C.

Vice President, Regulatory Affairs

JJ/cch
Enclosures

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

CORRESPONDENCE

UPS OVERNIGHT COURIER

NC

NEW CORRESP

May 7, 2001

Mr. Gary Buehler, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-350, Gabapentin Capsules, 100 mg, 300 mg and 400 mg

Dear Mr. Buehler:

Reference is made to the Exclusivity Statement (NCE) provided in our March 30, 1998 submission of an Abbreviated New Drug Application for Gabapentin Capsules, 100 mg, 300 mg and 400 mg, ANDA #75-350.

Via this Correspondence, Purepac is providing an additional Exclusivity Statement addressing marketing exclusivity for a new indication (I-311) of the reference listed drug, Neurontin® Capsules.

Purepac Pharmaceutical Co. trusts that the information provided will be useful to the Agency in approval process of our Abbreviated New Drug Application. If you have any questions regarding this submission, please do not hesitate to call the undersigned at (908) 659-2430.

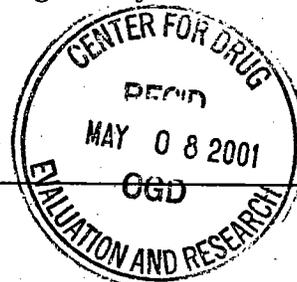
Sincerely,

PUREPAC PHARMACEUTICAL CO.



Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ
Enclosures



A Trusted Name For Over Half A Century



ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

*N.A.C.
M/S 12-26-01
Item will be addressed
via central document
01-609*

NC

NEW CORRESP

December 14, 2001

BY FAX AND UPS

Mr. Gary J. Buehler
Director, Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855

Re: ANDA 75-350; Gabapentin Capsules
Purepac Pharmaceutical Co.

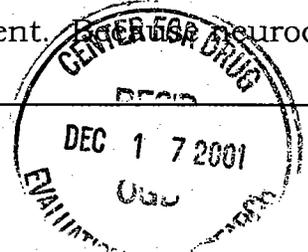
GENERAL CORRESPONDENCE

Dear Mr. Buehler:

This is a confidential submission to the file of our above-identified Abbreviated New Drug Application (ANDA).

In light of Purepac's understanding of FDA's current position and its actions in other cases, Purepac respectfully requests your office to reconsider the matter raised in our previous letter dated March 5, 1999 (Attachment 1). In that letter, Purepac requested that FDA require Torpharm, Inc. to amend its gabapentin ANDA paragraph IV certification against U.S. Patent No. 5,084,479 ("the '479 patent") to a "little (viii) statement" of inapplicable use.

The '479 patent claims a method of treating neurodegenerative diseases by the administration of gabapentin. As Torpharm has admitted in publicly filed court documents, Torpharm filed a paragraph IV certification to the '479 patent. Under the applicable law and regulations, Torpharm cannot file a paragraph IV certification to the '479 patent.



Purepac Pharmaceutical Co. is a subsidiary of Faulding Inc.

Gary J. Buehler
December 14, 2001
Page 2

disease treatment is not an approved indication for the reference listed drug Neurontin®, Torpharm cannot include this indication in its labeling. Therefore, Torpharm should have filed a statement of inapplicable use with respect to the '479 patent. See 21 U.S.C. §355(j)(2)(A)(viii) and 21 CFR 314.94(a)(12)(III)(A). Purepac, on the other hand, properly included a "little (viii) statement" of inapplicable use regarding the '479 patent in our ANDA.

Torpharm's improper paragraph IV certification against the '479 patent could jeopardize Purepac's entitlement to generic market exclusivity. Purepac is entitled to exclusivity on gabapentin because it was the first ANDA applicant to certify paragraph IV on the other two listed gabapentin patents. The '479 patent should not be subject to any paragraph IV certification because it is a patent claiming an unapproved use for the drug. However, Torpharm's improper Paragraph IV certification on this patent could erroneously lead to an argument by Torpharm that it is somehow entitled to exclusivity for its certification on the '479 Patent--a patent for which a "little (viii) statement" of inapplicable use must be filed. FDA should not allow Torpharm the opportunity to improperly interfere with Purepac's right to generic exclusivity.

FDA's response to our initial letter (Attachment 2) did not squarely address the improper Torpharm certification. The agency referred to the patent listing regulations, which are not relevant to the certification issue. It is Purepac's understanding from public statements by FDA personnel that FDA's position is to require a "little (viii) statement" from applicants in situations similar to the one in gabapentin involving Torpharm. It has also come to our attention that FDA has contacted generic applicants who have made inappropriate paragraph IV certifications against method of use patents claiming unapproved uses, and has required those applicants to amend to

Gary J. Buehler
December 14, 2001
Page 3

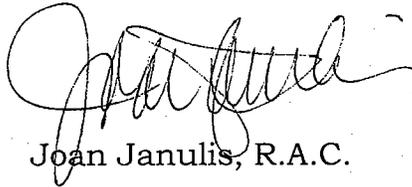
"little (viii) statements." Purepac believes this is the appropriate path for FDA to follow in the case of gabapentin and one that is consistent with FDA's treatment of other similarly situated ANDA applications.

Purepac's request for reconsideration is timely. Purepac has moved for summary judgment in our paragraph IV litigation, and there has been a recent district court decision of non-infringement on the '479 patent in Torpharm's paragraph IV case. An appeal of this latter ruling is pending, and a decision can be expected in the near future. To insure that the FDA does not prejudice Purepac's right to exclusivity in this case, it is imperative that FDA require Torpharm to properly certify with a "little (viii) statement" against the '479 patent.

We look forward to your prompt action and are available for a meeting or other further communications on this matter.

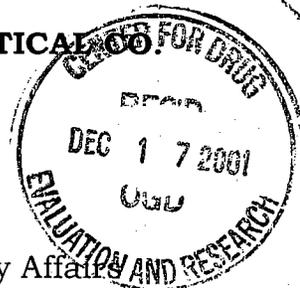
Sincerely yours,

PUREPAC PHARMACEUTICALS



Joan Janulis, R.A.C.

Vice President, Regulatory Affairs



ATTACHMENT 1



Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

March 5, 1999

Doug Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Dear Mr. Sporn,

We wish to bring to your attention, a matter concerning our abbreviated new drug application (ANDA) for Gabapentin Capsules, 100 mg, 300 mg and 400 mg (ANDA #75-350), and its potential effect on the period of marketing exclusivity to which Purepac is entitled as the first sponsor to submit a substantially complete ANDA containing a paragraph IV patent certification.

On March 30, 1998, Purepac submitted an ANDA for Gabapentin Capsules, 100 mg, 300 mg and 400 mg. The reference listed drug is Neurontin® Capsules, a product of Parke-Davis (a Division of Warner-Lambert Company). FDA's publication entitled "Approved Drugs Product with Therapeutic Equivalence Evaluations", 18th Edition, lists three patents which purportedly claim the reference listed drug or use of such drug. The following table summarizes these patents and the corresponding certifications contained within our ANDA:

U. S. Patent Number	Claim	Expiration Date	Purepac Certification
4,087,544	Treatment of epilepsy	January 16, 2000	Paragraph III
4,894,476	Gabapentin Monohydrate	May 2, 2008	Paragraph IV
5,084,479	Treatment of neurodegenerative diseases	January 2, 2010	Statement of nonapplicability 505(j)(2)(A)(viii)

It is important to note that the '479 patent is a method of use patent covering an indication which is not present in the innovator's approved labeling. Accordingly, generic applicants cannot seek approval of this indication through an ANDA submission. Because our labeling cannot and does not reference the indication claimed in the '479 patent, we filed a statement of nonapplicability, commonly known as a "little eight" statement with respect to this patent. Our actions were in accord with 21 CFR 314.94(a)(12)(iii)(A), which reads as follows:

If patent information is submitted under section 505(b) or (c) of the act and §314.53 for a patent claiming a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, a statement explaining that the method of use patent does not claim any of the proposed indications.

Shortly after we received notice of ANDA filing acceptance, OGD's Regulatory Support Branch confirmed that Purepac submitted the first substantially complete application for Gabapentin Capsules, 100 mg, 300 mg and 400 mg containing a paragraph IV certification. In accordance with OGD's June 30, 1998 guidance entitled "180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug and Cosmetic Act", and the interim rule promulgated on November 2, 1998, Purepac is entitled to a 180 day period of marketing exclusivity commencing on the date which the agency receives notice of the first commercial marketing of our product, or the date of a court decision holding that the patent which is the subject of the paragraph IV certification is invalid or not infringed, whichever is earlier. The agency and the courts have decided that the latter "litigation trigger" need not be activated by the first applicant. Marketing exclusivity may commence upon a final, non-appealable court ruling in favor of another sponsor who has subsequently filed a paragraph IV certification with respect to a listed patent.

Our concern lies with a patent certification contained in a subsequent ANDA for Gabapentin Capsules filed by Torpharm, Inc. Based on information present in publicly available court documents, (refer to Attachment 1 for a copy of the infringement complaint which Warner-Lambert filed against Torpharm) it appears that Torpharm made an improper certification with respect to the '479 patent, by failing to file a statement of non-applicability ("little eight" statement) as required by 21 CFR 314.94(a)(12)(iii)(A). Instead Torpharm filed a paragraph IV certification. This error appears to have been missed during the ANDA filing acceptance process.

The details known to Purepac from publicly available documents surrounding Torpharm's certification are as follows:

Torpharm, via its U.S. agent, Apotex Corp., filed an ANDA for Gabapentin Capsules, 100 mg, 300 mg and 400 mg prior to May 19, 1998, but after Purepac filed its ANDA for Gabapentin Capsules. Like Purepac, Torpharm filed a paragraph IV certification with respect to the '476 patent (Gabapentin monohydrate) and a paragraph III certification with respect to the '544 patent (treatment of epilepsy). However, unlike Purepac, Torpharm filed a paragraph IV certification with respect to the '479 patent (treatment of neurodegenerative diseases), despite the fact that the firm is unable to seek approval of the corresponding method of use under an Abbreviated New Drug Application. As stated above, the labeling of the reference listed drug, Neurontin®, does not cover treatment of neurodegenerative diseases, thus an applicant seeking approval for such use must file an NDA rather than an ANDA. Torpharm's certification with respect to the '479 patent is contrary to 21 CFR 314.94(a)(12)(iii)(A), and the language contained in the preamble to the cited regulation (Federal Register, Vol. 59, No. 190, October 3, 1994, page 50347), which reads as follows:

FDA does not intend §314.94(a)(12)(i)(A)(4) to authorize certifications with respect to patents that claim a use for the listed drug for which the applicant is not seeking approval. The statute requires patent certifications only if the patent "claims a use for [the] listed drug for which the applicant is seeking approval * * *" (section 505(j)(2)(A)(vii) of the act). The statute requires an applicant to make a patent statement when a method of use patent "does not claim a use for which the applicant is seeking approval * * *" (section 505 (j)(2)(A)(viii) of the act.) The proposed rule recognized this distinction. FDA stated that if a patent claims a method of using the listed drug, and labeling for the ANDA applicant's proposed drug product does not contain any indications covered by the method of use patent, the ANDA applicant "should not submit a certification under §314.94(a)(12)(i)(A) for such a patent" (54 FR 28872 at 28886). The preamble also indicated that if the labeling for the ANDA applicant's product did contain an indication that was claimed by a patent, the applicant should make a certification under §314.94(a)(12)(i)(A). (Id.)

Thus, the two provisions cited by the comment are not overlapping, and an applicant does not have the option of making a certification under §314.94(a)(12)(i)(A)(4) in lieu of, or in addition to, a statement under §314.94(a)(12)(iii).

Based on the plain language of the regulations and the preamble, Torpharm should not have filed a paragraph IV certification with respect to the '479 patent.

Torpharm's certification, as it currently is believed to exist, could conceivably be argued by Torpharm or other ANDA applicant as threatening a premature triggering of Purepac's marketing exclusivity. Warner-Lambert has sued Torpharm for infringement of the '476 and '479 patents. Warner-Lambert has also sued Purepac for infringement of the '476 and '479 patents. Entry of a final, non-appealable judgment of non-infringement in Warner-Lambert's action against Purepac to the '479 patent cannot serve as a vehicle for triggering marketing exclusivity because Purepac did not and could not file a paragraph IV certification with respect to this patent. Torpharm, however, by improperly filing a paragraph IV certification with respect to the '479 patent, may call into question whether its success in establishing non-infringement of the '479 patent could prematurely trigger Purepac's exclusivity. Torpharm filed a motion for summary judgment of noninfringement regarding the '479 patent. This motion is independent of the '476 patent, which is also the subject of ongoing litigation between Warner Lambert and Torpharm. It is conceivable that a court could render a ruling of noninfringement in favor of Torpharm, given that their labeling cannot make reference to the method of use covered under the '479 patent.

If Torpharm wins its summary judgment motion, Warner-Lambert could appeal this decision (even though it only resolves one claim in the case) and Torpharm may obtain a final, non-appealable decision of non-infringement. If the agency does not take action to correct Torpharm's improper certification as to the '479 patent, a final decision of non-infringement could conceivably be argued to start Purepac's period of marketing exclusivity and cause it to elapse before Purepac has received tentative or final approval to market a generic version of Gabapentin Capsules. (We note that the controlling patent for treatment of epilepsy does not expire until January 16, 2000.) This would result in an absurd outcome.

We believe that upon careful review of the Torpharm patent certification, you will determine that the ANDA was filed with an improper certification for the method of use ('479) patent. Since this is a unique situation, we believe that

there is a high likelihood of an inadvertent oversight of the corresponding regulation.

In summary, the issues resulting from the situation outlined in this letter are as follows:

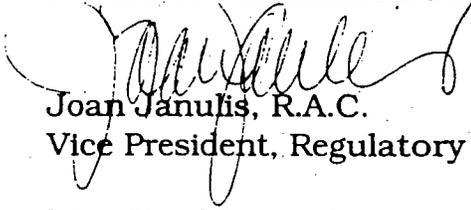
- The Torpharm application appears to have been accepted in error, due to the inclusion of an improper patent certification as to the '479 patent.
- The possibility exists that Torpharm's improper patent certification could be argued to curtail or vitiate Purepac's entitlement to exclusivity.
- If the agency does not rectify the matter promptly, the situation could become confounded and the outcome, uncertain.

In light of these issues, we request that the agency take the following action:

- a) Confirm that Purepac correctly filed a statement of non-applicability ("little eight" statement) regarding the '479 patent.
- b) Confirm that a paragraph IV certification with respect to the '479 patent is improper.
- c) Confirm that by virtue of Purepac's "first to file" status regarding the '476 patent and adherence to FDA requirements regarding the '479 patent (treatment of neurodegenerative disease) Purepac's entitlement to marketing exclusivity for Gabapentin Capsules cannot be triggered by an improper paragraph IV certification filed by Torpharm or any other applicant with regard to the '479 patent.

We appreciate your prompt attention to this matter, and look forward to your response. Should you have any questions concerning the information which we have provided, please do not hesitate to contact me at (908) 659-2430.

Sincerely,
PUREPAC PHARMACEUTICAL CO.


Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

cc: Elizabeth H. Dickinson, Office of the Chief Counsel, FDA
Andrew Berdon, General Counsel, Purepac

A Trusted Name For Over Half A Century



DUPLICATE

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

January 10, 2002

BY FAX AND UPS

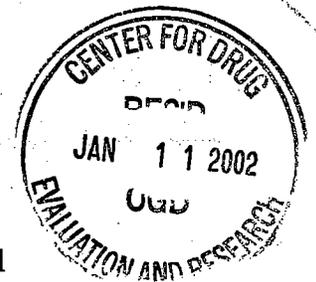
NEW CORRESP
NC

Mr. Gary J. Buehler
Director, Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855

Re: ANDA 75-350; Gabapentin Capsules
ANDA 75-694; Gabapentin Tablets
Purepac Pharmaceutical Co.

GENERAL CORRESPONDENCE

Dear Mr. Buehler:



This confidential submission to the files of our above-identified Abbreviated New Drug Applications is a supplement to our previous letter of December 14, 2001 (copy enclosed as **Attachment 1**), regarding Torpharm's improper paragraph IV certification against U.S. Patent No. 5,084,479 ("the '479 patent") listed in the Orange Book for the drug gabapentin.

This matter has now taken on significantly greater urgency, in light of FDA's recently-announced decision to grant **shared** 180-day generic market exclusivity to two ANDA applicants, where each applicant is the first generic drug company to file a paragraph IV certification against a different listed patent for the same drug.

Shared exclusivity may be a proper approach to address an exclusivity standoff, as described in FDA's letters of November 16, 2001 to Genpharm, Inc. and Andrx Pharmaceuticals, Inc. However, shared exclusivity also creates the potential for abuse. Specifically, a subsequent ANDA applicant for a given drug (who is not the first applicant to file a paragraph IV certification with respect to an Orange Book patent claiming the drug) can assert a supposed right to a share of exclusivity by filing a spurious paragraph IV certification against a separate listed patent claiming a method of using the drug that is not approved



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by FDA, even for the reference drug. A paragraph IV certification against an unapproved method of use patent in this context, although clearly improper, could spawn unnecessary controversies.

While FDA may not have intended the new shared exclusivity policy to produce this unwarranted result, it has actually occurred in the case of gabapentin, as reiterated below. Prompt clarification from the agency is urgently needed.

Purepac is the first ANDA applicant to file paragraph IV certifications against the two Orange Book patents which purport to claim the reference drug Neurontin® (U.S. Patent Nos. 4,894,476 and 6,054,482).¹ The third Orange Book patent is the '479 patent, which claims treatment of neurodegenerative diseases, including stroke, Alzheimer's disease, Huntington's disease, Amyotrophic Lateral Sclerosis and Parkinson's disease. As found by the court in the action entitled Warner-Lambert Company v. Apotex, Inc. and Torpharm Inc., (N.D. Ill. No. 98 C 4293, Sept. 14, 2001), 2001 WL 1104618 ** 1-2 (copy enclosed as **Attachment 2**), "the FDA has not approved gabapentin for any of the uses claimed in the '479 patent."

As explained in our December 14th letter, the Hatch-Waxman Amendments, 21 U.S.C. §355(j)(2)(A)(viii), and FDA regulation 21 C.F.R. §314.94(a)(12)(iii) require an ANDA applicant to file a statement of inapplicable use with respect to a patent covering a use for which the applicant is not seeking approval. This is confirmed by FDA's response to comment 46 in the preamble to the final ANDA patent and exclusivity regulations: "[a]n applicant does not have the option of making a certification under §314.94(a)(12)(I)(A)(4) in lieu of, or in addition to, a statement under §314.94(a)(12)(iii)." 59 Fed. Reg. 50338, 50347 (Oct. 3, 1994).

Thus, ANDA applicants for gabapentin have **no choice**. They cannot certify non-infringement of a patent for a use that they are barred from including in their labeling. They are mandated by law to submit a "little (viii)" statement of inapplicable use concerning the '479 patent.

Purepac properly did so. Torpharm did not. Instead, Torpharm ignored the plain language of the above-cited statute and regulation and, as found by the court in the above-cited decision, submitted a paragraph IV certification of

¹ Purepac is the first-to-file a paragraph IV certification on both the capsule and tablet dosage forms of the drug.

Mr. Gary J. Buehler
January 10, 2002
Page 3

non-infringement against the '479 patent in its ANDA for gabapentin capsules. See Warner -Lambert v. Apotex, * 2.² Based on this clearly inappropriate certification, and in the wake of FDA's implementation of shared exclusivity, Torpharm can now maintain that it should be granted a share of Purepac's exclusivity period for gabapentin.

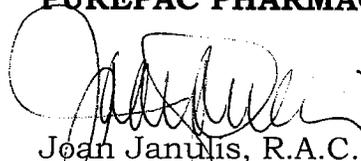
Manifestly, FDA should enforce its own regulation and direct Torpharm, as well as all other ANDA applicants for gabapentin who have filed paragraph IV certifications against the '479 patent, to amend their certifications to "little (viii)" statements of inapplicable use.³ To allow this situation to continue unaddressed will obviously jeopardize Purepac's justly earned market exclusivity entitlement for gabapentin.

Taking such action at this time will also permit FDA to prevent similar future misuses of the shared exclusivity policy. The policy should be amended to exclude applicants who have filed improper paragraph IV certifications against unapproved method of use patents from receiving any share of 180-day exclusivity.

To amplify our position on this issue, and to answer any questions you may have, we request a meeting with you and members of your staff as promptly as possible.

Sincerely yours,

PUREPAC PHARMACEUTICAL CO.



Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

² Since our letter of December 14, Torpharm has also filed an ANDA for gabapentin tablets in which it submitted the same certification against this patent. Thus, this correspondence is being submitted to both our capsule and tablet ANDAs for gabapentin. Moreover, at least one other ANDA applicant for gabapentin, Zenith, has submitted an improper paragraph IV certification against the '479 patent. See Pfizer Inc. and Warner-Lambert Company v. Zenith Laboratories, Inc., et al. (D.N.J. No. 01-CV-1538), complaint, para. 23 (copy enclosed as **Attachment 3**).

³ FDA need not attempt to construe the '479 patent claims to take such action. Orange Book use codes U-125 and U-258 pertaining to the '479 patent are entitled "treatment of neurodegenerative diseases," based on information supplied by the patentee. The only approved indication for Neurontin® is "adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy."

ATTACHMENT 1



A Trusted Name For Over Half A Century

FILE COPY

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

December 14, 2001

BY FAX AND UPS

Mr. Gary J. Buehler
Director, Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855

Re: ANDA 75-350; Gabapentin Capsules
Purepac Pharmaceutical Co.

GENERAL CORRESPONDENCE

Dear Mr. Buehler:

This is a confidential submission to the file of our above-identified Abbreviated New Drug Application (ANDA).

In light of Purepac's understanding of FDA's current position and its actions in other cases, Purepac respectfully requests your office to reconsider the matter raised in our previous letter dated March 5, 1999 (Attachment 1). In that letter, Purepac requested that FDA require Torpharm, Inc. to amend its gabapentin ANDA paragraph IV certification against U.S. Patent No. 5,084,479 ("the '479 patent") to a "little (viii) statement" of inapplicable use.

The '479 patent claims a method of treating neurodegenerative diseases by the administration of gabapentin. As Torpharm has admitted in publicly filed court documents, Torpharm filed a paragraph IV certification to the '479 patent. Under the applicable law and regulations, Torpharm cannot file a paragraph IV certification to the '479 patent. Because neurodegenerative



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disease treatment is not an approved indication for the reference listed drug Neurontin®, Torpharm cannot include this indication in its labeling. Therefore, Torpharm should have filed a statement of inapplicable use with respect to the '479 patent. See 21 U.S.C. §355(j)(2)(A)(viii) and 21 CFR 314.94(a)(12)(III)(A). Purepac, on the other hand, properly included a "little (viii) statement" of inapplicable use regarding the '479 patent in our ANDA.

Torpharm's improper paragraph IV certification against the '479 patent could jeopardize Purepac's entitlement to generic market exclusivity. Purepac is entitled to exclusivity on gabapentin because it was the first ANDA applicant to certify paragraph IV on the other two listed gabapentin patents. The '479 patent should not be subject to any paragraph IV certification because it is a patent claiming an unapproved use for the drug. However, Torpharm's improper Paragraph IV certification on this patent could erroneously lead to an argument by Torpharm that it is somehow entitled to exclusivity for its certification on the '479 Patent--a patent for which a "little (viii) statement" of inapplicable use must be filed. FDA should not allow Torpharm the opportunity to improperly interfere with Purepac's right to generic exclusivity.

FDA's response to our initial letter (Attachment 2) did not squarely address the improper Torpharm certification. The agency referred to the patent listing regulations, which are not relevant to the certification issue. It is Purepac's understanding from public statements by FDA personnel that FDA's position is to require a "little (viii) statement" from applicants in situations similar to the one in gabapentin involving Torpharm. It has also come to our attention that FDA has contacted generic applicants who have made inappropriate paragraph IV certifications against method of use patents claiming unapproved uses, and has required those applicants to amend to

Gary J. Buehler
December 14, 2001
Page 3

"little (viii) statements." Purepac believes this is the appropriate path for FDA to follow in the case of gabapentin and one that is consistent with FDA's treatment of other similarly situated ANDA applications.

Purepac's request for reconsideration is timely. Purepac has moved for summary judgment in our paragraph IV litigation, and there has been a recent district court decision of non-infringement on the '479 patent in Torpharm's paragraph IV case. An appeal of this latter ruling is pending, and a decision can be expected in the near future. To insure that the FDA does not prejudice Purepac's right to exclusivity in this case, it is imperative that FDA require Torpharm to properly certify with a "little (viii) statement" against the '479 patent.

We look forward to your prompt action and are available for a meeting or other further communications on this matter.

Sincerely yours,

PUREPAC PHARMACEUTICAL CO.



Joan Janulis, R.A.C.

Vice President, Regulatory Affairs



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 75-350 (Gabapentin Capsules)
ANDA 75-694 (Gabapentin Tablets)

APR 8 2002

Please file in latest
open archival
volume
75-350

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

Sent by Facsimile and U.S. Mail

Reference Number: OGD # 01-609

Dear Ms. Janulis:

This letter addresses issues raised in your December 14, 2001, and January 10, 2002, letters to the Office of Generic Drugs (OGD). Purepac Pharmaceuticals submitted in its ANDAs a statement pursuant to section 505(j)(2)(A)(viii) of the Federal Food, Drug, and Cosmetic Act (Act) (section viii statement) with respect to U.S. Patent No. 5,084,479 (the '479 patent). This patent is listed for the reference listed drugs (RLD), Neurontin® (Gabapentin) Capsules and Tablets, NDAs 20-235 and 20-882, in *Approved Drug Products with Therapeutic Equivalence Evaluations*, (Orange Book). It is identified as a use patent. Its use (U-258) is listed in the Orange Book as "Treatment of Neurodegenerative diseases".

Your letters claim that Torpharm submitted an improper paragraph IV certification pursuant to section 505(j)(2)(A)(vii)(IV) for the '479 patent, and that Torpharm should be required to amend its patent certification to a section viii statement. The agency has reviewed the issues raised in your letters, and determined that ANDA applicants referencing Neurontin® may not submit section viii statements to the '479 patent; they must submit a certification under section 505(j)(2)(A)(vii) (III) or (IV) of the Act. Therefore, Purepac must change its section viii statement for this patent to a paragraph III or IV certification.

The basic issue in this matter is what is the correct approach under section 505(j)(2)(A) when an ANDA applicant does not believe a listed use patent actually claims the approved innovator product, as asserted by the NDA holder. Torpharm believes the '479 patent does not claim the approved use for Neurontin (for which use Torpharm seeks approval) and it submitted a paragraph IV certification; Purepac submitted a section viii statement to the same patent, for the same reasons. Torpharm's approach was correct.

Purepac Pharmaceutical Co.
Gabapentin
Patent Certification

The Act establishes a specific mechanism whereby disputes over patent protection for an innovator drug product may be resolved. This may not be circumvented by an ANDA applicant's own assessment of the claims of a patent and inappropriate use of the section viii statement. In this case, Torpharm properly used the patent certification process to challenge whether a listed patent claims the approved innovator drug.

Patent Listing

The Act requires the NDA applicant to file, and FDA to publish,

the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application **or which claims a method of using such drug** and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.

Section 505(b)(1) (emphasis added).

The agency requires that NDA sponsors submit for listing only patents covering approved uses of the drug, or uses for which the applicant is seeking approval. The requirement that a use patent submitted to FDA cover an approved use is set out at 21 C.F.R. § 314.53(b), which states: "For patents that claim a method of use, the applicant shall submit information only on those patents that claim indications or other conditions of use of a pending or approved application." The regulations require the NDA sponsor to state the type of patent and, if the patent covers a use of the drug, to submit a signed declaration that the drug covers a method of use for the pending or approved product. 21 C.F.R. § 314.53(c)(1) and (2). FDA regulations do not specifically require the NDA sponsor to identify which approved indication(s) the patent covers, but sponsors regularly provide information identifying the use protected by the patent. FDA publishes this information in the Patent and Exclusivity section of the Orange Book by annotating the use patent listings.

Patent Certifications

The Act provides that an ANDA applicant submit

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;

section 505(j)(2)(A)(vii).

Section viii Statements

The omission of a patent certification under section 505(j)(2)(A)(vii) to a timely filed patent is appropriate in only one circumstance. Section 505(j)(2)(A)(viii) states that a sponsor may submit "if with respect to the listed drug referred to in clause (I) information was filed under subsection (b) or (c) 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." The regulations at 21 CFR § 314.94(a)(12)(iii) further state "if patent information is submitted under section 505(b) or (c) of the act and § 314.53 for a patent claiming a method of using the listed drug, and the labeling of the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, [the ANDA applicant must submit] a statement explaining that the method of use patent does not claim any of the proposed indications."

Neurontin®, the '479 Patent and ANDA Patent Certifications

Neurontin® is approved by FDA only for use "as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy." You assert that the '479 patent, which is described in the Orange Book as covering the use of gabapentin in "[t]reating neuro[de]generative diseases," does not claim the approved use of Neurontin® because epilepsy is not a use claimed in the '479 patent. Therefore, even if the Purepac generic gabapentin product is labeled for the same approved use as Neurontin®, the Purepac product will not infringe the '479 patent.¹

Your letter argues that FDA should permit Purepac to 1) ignore Warner-Lambert's assessment of the scope of the '479 patent, 2) make its own assessment of the patent protection, and 3) file a section viii statement if it believes the patent doesn't cover the innovator product. FDA has considered and rejected the interpretation you propose, as have the courts. Specifically, the agency rejected an approach that would "allow the generic applicant complete discretion to interpret the scope of any relevant use patent," opting instead for a combination of innovator patent certifications (now "declarations") and required ANDA patent certifications. FDA described the approach it adopted as the one that "more fairly implements Congress' intent that patent owners receive preapproval notice of potentially infringing products." 54 Fed. Reg. 28872, 28909 (July 10, 1989). See also 59 Fed. Reg. 50338, 50347 (Oct. 10, 1994). In a recent case challenging FDA's approach to section viii statements on similar facts, the court found the ANDA applicant's

¹ Because this is the only approved indication for Neurontin®, all ANDA applicants must submit labeling that includes this use.

argument "unpersuasive," rejecting the approach that would have made the ANDA applicant "the final arbiter of whether or not a method of use patent covers the use for which it is seeking approval" (quoting Bristol Opp'n at 20). *Mylan Pharmaceuticals, Inc. v. Thompson, et al.*, 139 F. Supp. 2d 1, 18 and n.14 (D.C.C. 2001), *rev'd on other grounds*, 268 F.3d 1323 (Fed. Cir. 2001).

A section viii statement is appropriate when – and only when – generic drug labeling is "carved out" (omits an indication or protected labeling) to avoid infringement of a listed patent. This approach permits approval of ANDAs as appropriate when some of an innovator's market protections have expired, while protecting the paragraph IV certification process for resolving patent disputes. The information submitted by the NDA sponsor regarding protected uses is referred to by ANDA applicants and FDA in determining when, and with what labeling, an ANDA may be approved. FDA may approve an ANDA if at least one of the approved indications for the listed drug no longer has applicable patent protection. 21 C.F.R. 314.94(a)(8)(iv). For example, if an innovator product has three indications, two of which are no longer protected, FDA may be able to approve a generic drug with labeling for only those two indications, and which omits the protected third indication. If the protected labeling cannot be carved out of the generic product's labeling, a section viii statement is not appropriate.

Purepac is not proposing to omit information related to the approved use from the generic gabapentin labeling.² It is seeking approval for the same indication approved for Neurontin®. Warner-Lambert has submitted the '479 patent as claiming the approved use for Neurontin®. Although Purepac believes this patent does not correspond to the approved labeling, Warner-Lambert has submitted an adequate declaration stating that it does. If Purepac disagrees with Warner-Lambert about whether the use patent claims the labeling for which Purepac now seeks approval, the appropriate course is for Purepac to submit a paragraph IV certification and, if sued for patent infringement, resolve the issue in court. Torpharm did just that, and in so doing followed the correct regulatory course.

As your letter notes, on September 14, 2001, a district court found that the '479 patent does not claim the approved use of Neurontin®. *Warner-Lambert Co. v. Apotex Corp., Apotex, Inc., and Torpharm*, (N.D. Ill. No. 98 C 4293, Sept. 14, 2001). The court made this determination after Torpharm submitted a paragraph IV certification. Torpharm defended the resulting lawsuit by claiming that its ANDA for gabapentin does not infringe the '479 patent even though it bears labeling for the same use as Neurontin®, because the '479 patent does not claim the approved use for Neurontin®. Purepac now claims that the conclusion reached in that lawsuit is affirmation of its view that Torpharm's paragraph IV certification was not correct. To the contrary, the conclusion that the '479 patent did not claim the approved use of Neurontin® was reached through the process Purepac should have followed with its own ANDA for gabapentin.³

² There are other aspects of labeling for Neurontin® that are protected by exclusivity and patent. However, they are not at issue in this matter.

³ As described above, a patent that only covers the use of a drug not approved in the NDA should not be submitted to FDA for listing in the Orange Book. However, FDA will neither second-guess an NDA

Purepac Pharmaceutical Co.
Gabapentin
Patent Certification

Therefore, to be eligible for final approval, Purepac must submit an amended patent certification to its pending ANDA for gabapentin. Questions regarding 180-day exclusivity under section 505(j)(5)(B)(iv) for ANDAs referencing Neurontin® will be resolved at a later date.

If you have further questions regarding this issue, please contact Cecelia Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs, at (301) 827-5845.

Sincerely,



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

holder who has submitted a use patent accompanied by a correct declaration under 21 C.F.R. § 314.53(c), nor permit the use of a section viii statement as a substitute for a paragraph IV certification.

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

PATENT AMENDMENT

UPS OVERNIGHT COURIER

November 1, 2002

*MAZ
TAT
a/2/02*

**NEW CORRESP
NC**

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-350, Gabapentin Capsules, 100 mg, 300 mg, and 400 mg

Dear Mr. Buehler:

Reference is made to Purepac's ANDA #75-350 for Gabapentin Capsules, 100 mg, 300 mg, and 400 mg which was submitted to the agency on March 30, 1998. Further reference is made to our Patent Amendment dated October 9, 2000 which contained documentation of notice receipt regarding our paragraph IV certification for U.S. Patent 6,054,482 (noted hereafter as the '482 patent).

By way of the present Patent Amendment, Purepac respectfully requests that the agency revise the expiration date for the 30 month stay on the approval of our application from January 20, 2003 to December 14, 2002. Based on the absence of a return receipt for the notice letter that was sent to the patent holder, Godeke Aktiengesellschaft, the expiration date for the 30 month stay was computed using the date of the resulting patent infringement complaint as the start date. Purepac requested this action in our Patent Amendment dated October 9, 2000, while reserving the opportunity to seek an earlier expiration date in the event that we were able to produce a return receipt at a later date. We have exhausted all efforts to obtain a return receipt or other documentation confirming the date that Godeke received the notice letter. In lieu of this documentation, our request for assignment of the earlier expiration date is based on the following:

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NOV 04 2002

OGD / CDER

GABAPENTIN CAPSULES, 100 mg, 300 mg & 400 mg

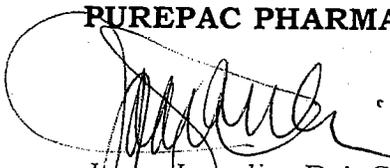
Page 2 of 2

- 1) Godeke Aktiengesellschaft (the holder of the '482 patent) is a wholly-owned subsidiary of Warner Lambert (now Pfizer). This is confirmed on page 2, paragraph 4 of the patent infringement complaint naming Purepac and Faulding Inc. as defendants. Further, as indicated on the complaint both Godeke Aktiengesellschaft and Warner Lambert sued Purepac. A copy of the complaint document is contained in **Section 1** of this Amendment.
- 2) Warner Lambert and Parke Davis were collectively provided notice of our Paragraph IV certification on the '482 patent on June 13, 2000. A copy of the notice letter and the corresponding Certified Mail Receipt are included in **Section 2** of this Amendment. The return receipt confirms that the parties received the notice letter on **June 14, 2000**. Since the patent infringement complaint against Purepac was collectively filed by Godeke and its parent, Warner Lambert, the 30 month stay should not run longer than the date that the parent company and co-plaintiff received the notice letter.
- 3) Purepac repeatedly attempted to obtain documentation confirming delivery of the notice letter to Godeke, located in Berlin, Germany, without success. We are mindful of the fact that the tracking of notice letters to foreign entities has been an issue for our industry. In light of this situation and the information presented in points 1 and 2 above, Purepac believes that our firm would be unduly disadvantaged by the overly conservative computation of the 30 month stay that we originally proposed.

Purepac Pharmaceutical Co. appreciates your attention to this matter and looks forward to your timely response. If there are any questions concerning this amendment, please contact the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.



Joan Janulis, R.A.C.

Vice President, Regulatory Affairs

JJ:bt

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NOV 04 2002
OGD / CDER

A Trusted Name For Over Half A Century



Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-659-2440

AMENDMENT - FINAL APPROVAL REQUESTED

CMC and Exclusivity Information

UPS OVERNIGHT COURIER

November 15, 2002

Ms. Nancy Rolli, Pre-Approval Program Manager
Newark District
U.S. Food and Drug Administration
North Brunswick Resident Post
120 North Center Drive
North Brunswick, NJ 08902

RE: ANDA #75-350, Gabapentin Capsules, 100 mg, 300 mg, and 400 mg

Dear Ms. Rolli:

In accordance with 21 CFR 314.96(b), Purepac Pharmaceutical Co. hereby submits a Field Copy of our Amendment for ANDA #75-350, Gabapentin Capsules, 100 mg, 300 mg, and 400 mg.

Purepac Pharmaceutical Co. certifies that this Field Copy is a true copy of the technical section contained in the Archival and Review Copies of the Amendment.

If you have any questions regarding this submission, please do not hesitate to contact the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

A handwritten signature in black ink, appearing to read "Joan Janulis", is written over the typed name.

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

RECEIVED

NOV 18 2002

OGD/CDER

Dillahunt, Michelle

From: Dillahunt, Michelle
Sent: Tuesday, December 10, 2002 12:08 PM
To: 'joan.janulis@us.faulding.com'
Subject: ANDA 75-350, 75-694 (Gabapentin Tablets and Capsules-Purepac)
Importance: High

From: FDA, CDER, Office of Generic Drugs

To: ANDA Gabapentin Applicant:

With this transmission, the Office of Generic Drugs is providing text for use in revising the package insert labeling for gabapentin tablets, gabapentin capsules and gabapentin oral solution. This text represents our current thinking on the subject, which we believe is consistent with the "Best Pharmaceuticals Act

for Children" recently passed by Congress.

Please revise your insert to be in accord with the labeling presented in the text. Then prepare and submit 12 copies of the final printed insert labeling. You should also submit final printed container labels and address all exclusivities listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") if you have not previously done so. In addition, please

provide a side-by-side comparison of your proposed labeling with the enclosed gabapentin text with all differences annotated and explained.

Your submission should be designated as a minor amendment. We request that you send copies of your cover letter to the attention of Lillie Golson, Acting Team

Leader, Labeling Review Branch and to Robert L. West, Deputy Director, Office of Generic Drugs, Metro Park North II, 7500 Standish Place, Rockville Maryland 20855.

Should you have any questions about the text, please contact Lillie Golson at (301) 827-5846.



A Trusted Name For Over Half A Century

ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

**MINOR AMENDMENT
(LABELING)**

UPS OVERNIGHT COURIER

December 11, 2002

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Food & Drug Administration
Document Control Room, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

N/AF

RE: ANDA 75-350, Gabapentin Capsules, 100 mg, 300 mg and 400 mg

Dear Mr. Buehler:

Reference is made to our March 30, 1998 submission of an Abbreviated New Drug Application for Gabapentin Capsules, 100 mg, 300 mg and 400 mg, ANDA # 75-350. Further reference is made to your electronic mail dated December 10, 2002, requesting additional labeling revisions.

Purepac Pharmaceutical Co. is amending the above-referenced application to provide for a revised package insert as requested in the referenced agency correspondence.

Contained in Section 1 are twelve (12) copies of our revised final printed insert labeling for your review. Contained in Section 2 are twelve (12) final printed container labels for your review. Furthermore, Section 3 contains a side-by-side comparison of our proposed package insert with the Gabapentin text, supplied to us by the agency, with all differences annotated and explained. If this meets with your approval, please consider this as final printed labeling.

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OGD / CDER

MINOR AMENDMENT

ANDA 75-350

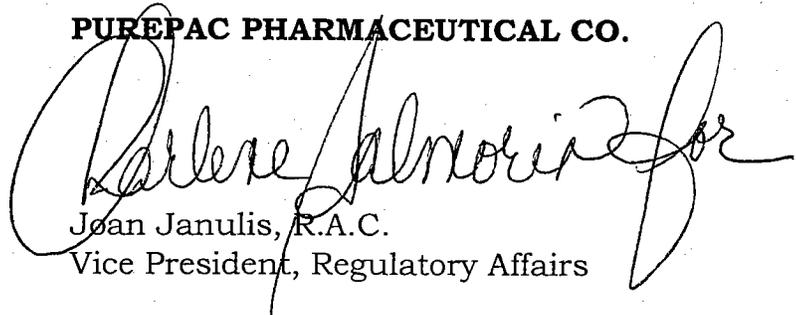
Gabapentin Capsules, 100 mg, 300 mg and 400 mg

Page 2 of 2

Purepac Pharmaceutical Co. looks forward to your review of this amendment.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

A large, stylized handwritten signature in black ink, appearing to read "Joan Janulis".

Joan Janulis, R.A.C.

Vice President, Regulatory Affairs

JJ/fp
Enclosures

111
W. Park

ANDA 75-350 (Capsules, 100 mg, 300 mg and 400 mg) ✓
ANDA 75-694 (Tablets, 600 mg and 800 mg)

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

Dear Madam,

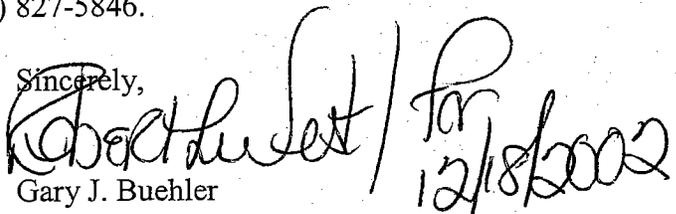
You have pending before the Food and Drug Administration an abbreviated new drug application (ANDA) for gabapentin capsules and tablets referencing Neurontin. As you may be aware, on Monday, December 16, 2002, Judge Huvelle of the U.S. District Court for the District of Columbia issued a decision regarding 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,

 for 12/18/2002

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

cc: 75-350
75-694
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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V:\firmsnz\purepac\trs&rev\75694-gabapentinfollowup.doc

F\T by cll/12/18/02

**APPEARS THIS WAY
ON ORIGINAL**

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Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-659-2440

NEW CORRESP
NC
MAR 11/12/03

December 30, 2002

BY FAX AND FIRST CLASS MAIL

Gary J. Buehler
Director, Office of Generic Drugs (HFD-600)
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Re: Purepac Pharmaceutical Co.;
ANDAs ~~75-350~~ 75-694: Gabapentin Capsules and Tablets;
Comments in Response to Letter of December 18, 2002

Dear Mr. Buehler:

Purepac Pharmaceutical Co. hereby submits its comments on the issues raised in your letter of December 18, 2002, namely: (i) how FDA should implement Judge Huvelle's Memorandum Opinion dated December 16, 2002 in the case of *Purepac v. Thompson* regarding the propriety of a section viii statement on the '479 patent, which claims a method of using gabapentin for the treatment of neurodegenerative diseases; (ii) the related issue of gabapentin ANDA applicants maintaining a paragraph IV certification to that patent; and (iii) implications for 180-day exclusivity.

Purepac's comments (supplementing those previously provided in letters from our counsel dated December 17 and December 23, 2002 to FDA Chief Counsel Daniel Troy) are summarized as follows:

- The above issues on which FDA seeks input must be resolved in accordance with pertinent provisions of the Hatch-Waxman Amendments and FDA's regulations, and consistent with precedential FDA implementation of 180-day generic market exclusivity that rewards the first ANDA applicant to file a paragraph IV certification against specific listed patents. Critically, these issues must also be resolved upon the particular facts relating to the ANDAs for gabapentin filed by Purepac, TorPharm, Inc. and other applicants.
- Based on Judge Huvelle's correct decision, all ANDA applicants for gabapentin should be required to file a section viii statement for the '479 patent because the patent claims an unapproved use for which an ANDA applicant is barred from seeking approval.

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JAN 03 2003

OGD / CDER
Final Draft

- FDA's decision on 180-day exclusivity for gabapentin should be awarded to Purepac under its "patent-based" exclusivity rule. Under this rule, Purepac is eligible for 180-days of generic market exclusivity as a result of its undisputed status as the first ANDA applicant to file Paragraph IV certifications with respect to the '476 and '482 patents listed by Warner-Lambert in the Orange Book.
- Even if FDA were to consider allowing other generic gabapentin applicants, such as TorPharm, to maintain a Paragraph IV certification in the face of Judge Huvelle's decision, the "patent-based" rule, and Purepac's exclusivity, remain intact because there is no exclusivity standoff between two applicants whose respective first-to-file positions block the approval of each other's ANDA.

Purepac's comments are amplified below.

I. FDA Must Follow the Statute, Its Regulations, and Its Precedents

It is axiomatic that in deciding the subject issues, FDA must follow pertinent provisions of the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act, the agency's own regulations interpreting these provisions, and precedential FDA decisions made in implementing 180-day generic market exclusivity. These decisions include the patent-based exclusivity principles articulated by the agency in its August 2, 1999 cisplatin decision, in its November 16, 2001 letter addressing exclusivity with respect to the 10 mg and 20 mg dosage strengths of omeprazole, and, we are informed, in a March 28, 2002 letter addressing contentions by Reddy Cheminor Inc. regarding exclusivity for the 40 mg dosage strength of omeprazole.

It is just as important for FDA to base its decision upon the objective facts relating to the ANDAs that have been submitted for gabapentin. These facts include the particular listed patents for gabapentin, the coverage of those patents as declared by the patent owner Warner-Lambert, the statements addressing those patents made by particular ANDA applicants, and pertinent first-to-file dates. Making a decision on the basis of other subjective considerations, or purported "equitable" arguments by applicants such as TorPharm, would clearly be improper. Moreover, basing a decision on some general policy consideration not supported by the statute or regulations, or not advanced to date by FDA, would contravene the Administrative Procedure Act and invite further judicial review.

II. Implementation of Judge Huvelle's Decision

A. The '479 Patent Claims an Unapproved Use of Gabapentin, and Must Be Addressed Via a Section viii Statement

As you know, in *Purepac Pharmaceutical Co. v. Tommy G. Thompson, et al.*, Judge Ellen Segal Huvelle of the U.S. District Court for the District of Columbia very recently held that

it was proper for Purepac to file a section viii statement of inapplicable use with respect to the '479 patent claiming an unapproved use of gabapentin. Memorandum Opinion ("Mem. Op.") at 21-22, 31-32. The Court ruled that a section viii statement for this patent is appropriate because: (a) the patent owner, Warner-Lambert, informed FDA that the '479 patent claims an unapproved use of gabapentin (treatment of neurodegenerative diseases), for which generic applicants cannot seek approval, and (b) FDA, in reliance on this information, created an unapproved use code for this patent. Mem Op. at 24-25, 31-32. Purepac maintains that this decision is correct on the facts and the law.

FDA should implement Judge Huvelle's decision by requiring every ANDA applicant for gabapentin to submit a section viii statement for the '479 patent (or amend their applications to do so). This is self-evident from the fact that the use covered by this patent, treatment of neurodegenerative diseases, has not been approved by FDA for the reference listed drug Neurontin®. By virtue of its unapproved status, such use is barred from inclusion in proposed labeling for any generic gabapentin drug product. 21 U.S.C. §§ 355 (a), 355 (j)(2)(A)(v). A patent certification can **only** be made for a method-of-use patent when an ANDA applicant seeks approval, and proposes to label its drug for, the use claimed in the patent:

An abbreviated application for a new drug shall contain... a certification... which claims a use for such listed drug for which the applicant is seeking approval under this subsection...

21 U.S.C. § 355(j)(2)(A)(vii) (emphasis supplied).

Accordingly, no ANDA can include a paragraph IV certification against the '479 patent because a generic applicant cannot seek approval for, and hence cannot propose to label its gabapentin product for, the unapproved use claimed by that patent.

Instead, the mechanism prescribed by Congress for addressing a patent claiming a method of use for which the ANDA applicant does not seek approval is a section viii statement:

An abbreviated application for a new drug shall contain . . . 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.

21 U.S.C. § 355 (j)(2)(A)(viii).

It follows that a **section viii statement is the sole appropriate way** for each ANDA applicant for gabapentin to address the '479 patent, because each applicant is barred by law from seeking approval of gabapentin for the use covered by this patent.

B. There Is No Option for a Paragraph IV Certification Against the '479 Patent

FDA has maintained a long-standing position that a paragraph IV certification and a section viii statement “are not overlapping,” and that an ANDA applicant “does not have the option” of making a paragraph IV certification “in lieu of, or in addition to,” a section viii statement (59 Fed. Reg. 50338, 50447, Oct. 3, 1994). FDA publicly reiterated this position at an agency-drug industry workshop on September 20, 2000. The mutually exclusive “seeking approval/not seeking approval” language of paragraph IV and section viii provides ample statutory support for this position. Since Judge Huvelle ruled that a section viii statement is proper for the '479 patent, an ANDA applicant **must** submit a section viii statement as to this patent.

Nor can another applicant, such as TorPharm, be permitted to address the '479 patent by a paragraph IV certification, while Purepac maintains its section viii statement. Where there is only one approved use in the labeling of the reference listed drug, and an Orange Book patent claims an unapproved use of the drug, the only proper way to address such a patent is by a section viii statement. Here, there is only one approved use of gabapentin (treatment of epilepsy), which is not covered by the '479 patent. **In this situation**, each and every ANDA applicant, including TorPharm, **has no choice** but to file a section viii statement as to this unapproved use patent.¹

Allowing TorPharm to benefit from its simultaneous recourse to the paragraph IV route and the section viii filing route would reward a firm for circumventing FDA's regulations in an obvious attempt to secure a share of exclusivity. Such precedent would undoubtedly encourage future ANDA applicants to mirror this strategy for other drugs, and would create a result that is contrary to the intent of the Hatch-Waxman Amendments.

III. Purepac Is Eligible for 180-Day Generic Market Exclusivity for Both Gabapentin Capsules and Tablets

In her December 16th decision, Judge Huvelle found that Purepac filed its ANDA for gabapentin capsules prior to TorPharm (Mem. Op. at 14-15). FDA records will confirm that: (a) Purepac's ANDA 75-350 for gabapentin capsules contains the first-filed paragraph IV certification against the '476 and '482 patents (the remaining listed Orange Book patents for gabapentin), and (b) Purepac's ANDA 75-694 for gabapentin tablets also contains the first-filed paragraph IV certification against those patents.

¹ It should be noted that TorPharm improperly submitted an ANDA containing both a section viii statement and a paragraph IV certification with respect to the '479 patent. Thus, TorPharm need only withdraw its paragraph IV certification to meet the requirement of addressing the '479 patent with a section viii statement.

As the first ANDA applicant to file a paragraph IV certification against the '476 and '482 patents, Purepac is eligible for an award of 180-day generic market exclusivity for gabapentin capsules and tablets. This eligibility is supported by Hatch-Waxman, 21 U.S.C. § 355(j)(5)(B)(iv), FDA regulation 21 C.F.R. § 314.107(c), and FDA's precedential decisions confirming the rule of patent-based exclusivity (the August 2, 1999 cisplatin decision, the November 16, 2001 omeprazole letter, and, we understand, the March 28, 2002 omeprazole letter).

As FDA stated in the November 16, 2001 omeprazole letter in affirming eligibility for 180-day exclusivity on a patent-by-patent basis:

In an August 2, 1999, response to petitions from two generic drug firms addressing this issue with respect to approval of ANDAs for cisplatin, FDA stated that these regulations must be interpreted, at least in the situation with cisplatin, to base eligibility for 180-day exclusivity on who filed the first paragraph IV certification for each listed patent. (Docket No. 99P-1271/PSA1 and PSA2). Therefore, multiple applicants may be eligible for periods of exclusivity for a single drug product. Based upon statements in the petition response, and FDA's actions in approving ANDAs for cisplatin, the agency's approach has been to use a patent-based analysis in determining eligibility or exclusivity. In other words, the first applicant with a paragraph IV certification for each listed patent has been separately eligible for 180-day exclusivity based on that patent.

FDA letter to Andrx Pharmaceuticals, Inc., Nov. 16, 2001, at 2 (emphasis supplied).

Applying patent-based exclusivity to the four Orange Book patents listed for gabapentin: (i) the expired '544 patent is immaterial; (ii) the '479 patent must be addressed by a section viii statement; and (iii) Purepac is the first paragraph IV filer on the '476 and '482 patents. Indisputably, Purepac is eligible for 180-day exclusivity for gabapentin.²

IV. Shared Exclusivity Cannot Apply, Because There Is No Exclusivity Standoff

Even were FDA inclined to permit TorPharm or other applicants to retain a paragraph IV certification for the '479 patent (which the agency should not), the agency is barred from awarding any "shared" exclusivity for gabapentin. This is self-evident from the explicit terms of

² While TorPharm has claimed that Purepac's exclusivity with respect to its first-filed status on the '476 patent was triggered by a court decision against Warner-Lambert, evidence of TorPharm's submission of a copy of a final judgment in that matter to FDA was absent from the Administrative Record submitted in the recent *Purepac v. Thompson* litigation.

FDA's patent-based interpretation of 180-day generic market exclusivity set forth in FDA's omeprazole letter of November 16, 2002 (and, according to our information, the agency's further explanation set forth in the March 28, 2002 omeprazole letter). These letters make clear that patent-based exclusivity is the rule, and shared exclusivity is the exception, invoked only where necessary to avoid an "absurd result." Thus, shared exclusivity will only apply if there is an "exclusivity standoff" between two ANDA applicants, each of whom blocks the other's approval by virtue of being "first-to-file" a paragraph IV certification against different listed patents. (FDA Omeprazole Letter of Nov. 16, 2001 at 3-4, 6).

Here, there is no exclusivity standoff. Judge Huvelle has determined: (i) Purepac filed its ANDAs with paragraph IV certifications against the '476 and '482 patents and a section viii statement for the '479 patent, **before** TorPharm filed its ANDA with paragraph IV certifications against these and the '479 patent (Mem. Op. at 14-15). FDA's records will confirm this. Thus, Purepac's application was **first-in-time**, and did **not** include a paragraph IV certification against the '479 patent. Put another way, TorPharm's ANDA has a subsequent paragraph IV certification that could not block Purepac's prior section viii statement.

The only conceivable argument that TorPharm could put forth is that its paragraph IV certification on the '479 patent blocks the approval of subsequent applications containing the same certification against that patent. (This argument, of course, becomes moot if FDA abides by its long-standing position that a paragraph IV certification and a section viii statement are mutually exclusive, and discards the relevance of TorPharm's and other applicants' paragraph IV certifications against the '479 patent).

In sum, Purepac is entitled to a 180-day generic market exclusivity period for gabapentin capsules and tablets, based on Purepac's "first-to-file" status on the '476 and '482 patents. Thus, the most that TorPharm and other gabapentin applicants are entitled to at this juncture is tentative approval of their ANDAs. Final approval of all other gabapentin ANDAs must await a pertinent triggering event, and expiration of Purepac's 180-day exclusivity period based on the '476 and '482 patents.

V. No "Equitable" or "Policy" Consideration Can Change the Result

At oral argument before Judge Huvelle, FDA intimated that some "equitable considerations" might persuade FDA to approve TorPharm's ANDA at this time (see Mem. Op. at 16, note 16; 33). Presumably, the agency was referring to TorPharm's arguments that it relied upon FDA's advice that a paragraph IV certification was proper for the '479 patent, and that it is prepared to launch its gabapentin product.

No such considerations can properly override Purepac's approval and exclusivity positions in these comments, which are based on the controlling statute, regulations and FDA precedents. The statute guarantees exclusivity for first filers. This is an important incentive to encourage and effect the rapid market entry of generic drugs. FDA cannot read exclusivity out

of the statute just because a subsequent filer says it is willing to launch at risk. The benefit of first-to-file status, and the efforts of the first filer itself, are the engines that encourage early market formation. As in the case of *Mova Pharmaceutical Corp. v. Shalala*, 140 F.3d 1060 (D.C. Cir. 1998), Mylan's willingness to market did not justify denial of exclusivity to Mova, the first-to-file applicant which was still involved in paragraph IV litigation.

Moreover, TorPharm's arguments are specious. TorPharm itself has argued to the U.S. Court of Appeals for the Federal Circuit that a section viii statement is the right way to address the '479 patent (Mem. Op. at 25, note 23), belying whatever reliance it may have had upon whatever it may have been told by the agency. As for a "policy" desire to have a generic gabapentin product on the market at the earliest possible time, such a desire must be channeled through the governing statutory exclusivity incentive created by Congress to foster early generic challenges to blocking patents, which in this case has been rightfully earned by Purepac.

Indeed, Purepac has not only satisfied the "first-to-file" criterion, but remains engaged in four-year old paragraph IV litigation with respect to each of the patents listed in the Orange Book for gabapentin -- including the '479 patent -- to bring its generic gabapentin products to the American public at the earliest possible time, consistent with Hatch-Waxman. By providing a dual trigger for 180-day exclusivity, either (i) launch by first filer or (ii) court decision, 21 U.S.C. § 355 (j)(5)(B)(iv) recognizes the right of the first filer to control its launch date. Congress clearly intended to allow the first filer to take into consideration, and if it desires protect itself from, the effect of an "at risk" launch. Purepac moved over a year ago for summary judgment in its paragraph IV actions concerning all three patents. Furthermore, Purepac has not taken any action that would cause it to benefit financially from a launch delay.

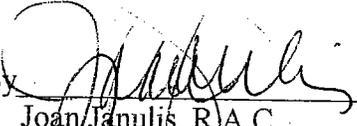
Finally, any "launch at risk" by TorPharm before its own paragraph IV litigation is concluded will undoubtedly be challenged by Warner-Lambert via an immediate motion for temporary restraining order and preliminary injunction, thereby rendering early generic market entry theoretical at best.

If FDA is prepared to take any action regarding the issues at hand that deviates from the positions set forth in these comments, we request that your office send us an advance letter setting forth the legal and factual basis for the action, to permit Purepac to protect its rights.

Sincerely yours,

PUREPAC PHARMACEUTICAL CO.

By


Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

Food and Drug Administration
Rockville MD 20857

JAN 28 2003

Dear ANDA Applicant for Gabapentin:

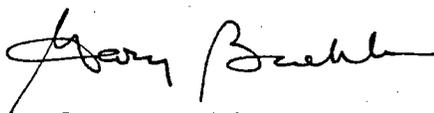
This is in reference to your abbreviated new drug application (ANDA) submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Gabapentin Capsules, Tablets, or Oral Solution.

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
- /C. Parise
- /R. West
- /G. Davis
- /P. Rickman
- /D. Hare
- /R. Hassall
- /T. Ames

G. Buehler
1/28/03

GCF-1/E. Dickinson

GCF-1/K. Schifter

Endorsed: 1/28/03/E. Dickinson, C. Parise, R. West

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LETTER OUT



ANDAs 75-360 Torpharm (Gabapentin Capsules, 100 mg, 300 mg and 400 mg) and
ANDAs 75-350 Purepac (Gabapentin Capsules, 100 mg, 300 mg and 400 mg)

Food and Drug Administration
Rockville MD 20857

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

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 Aktiengesellschaft (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.

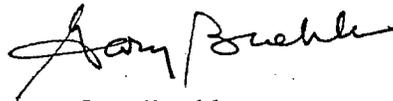
Judge Huvelle's finding that Purepac's section viii statement was appropriate **because the '479 patent does not claim a use for which Purepac – or Torpharm – was seeking approval** was fatal to any claim Torpharm had to exclusivity. It is possible the court could have found a different basis for permitting 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. Raubichuck, 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 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 75-827/TEVA
ANDA 76-120/Geneva

Oral Solution ANDA:

HFD-600/C.Parise
/G.Buehler
/R.West
/G.Davis
/P.Rickman
/D.Hare
/R.Hassall
/T.Ames

G Buehler
1/28/03

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

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V:\firmsnz\torpharm\ltrs&rev\75360.479pat.doc

LETTER OUT

A Trusted Name For Over Half A Century



ORIGINAL

Handwritten notes:
B. Jones
WAT
2/28/03

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-659-2440

PATENT AMENDMENT

'L NEW CORRESP

Handwritten: NC

UPS OVERNIGHT COURIER

February 10, 2003

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-350, Gabapentin Capsules, 100 mg, 300 mg, and 400 mg

Dear Mr. Buehler:

Reference is made to your letter of January 28, 2003 regarding the removal of U.S. Patent No. 5,084,479 from Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book). Pursuant to the noted action and the directive contained in your letter, Purepac Pharmaceutical Co. hereby requests the withdrawal of our section viii statement as to this patent. This statement was contained in Section III of original ANDA submission dated March 30, 1998.

Should you have any questions regarding the contents of this communication, please do not hesitate to contact the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

RECEIVED

FEB 12 2003

OGD / CDER

ANDA 75-350

JUN 30 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 (Act) for Gabapentin Capsules, 100 mg, 300 mg, and 400 mg.

Reference is also made to our Approvable letter dated April 25, 2002 and to your amendments dated November 15 and December 11, 2002.

The application is deficient and, therefore, not approvable under 21 CFR 314.125 (b)(13) because the Center for Drug Evaluation and Research (CDER) is unable to find that the methods used in, and the facilities and controls used for, the manufacture, processing, packaging, or holding of Gabapentin Capsules, 100 mg, 300 mg, and 400 mg by Purepac Pharmaceutical Co. Elizabeth, NJ comply with current good manufacturing practice (cGMP) regulations.

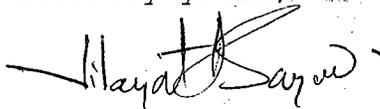
Our conclusion is based upon the findings revealed during an inspection of Purepac Pharmaceutical Co., conducted in November/December 2002, and January 2003, by representatives of the United States Food and Drug Administration and the cGMP Warning Letter issued on February 28, 2003. Upon review of this report and the inspectional observations noted during this inspection, we have received a recommendation from our Division of Manufacturing and Product Quality (DMPQ), Office of Compliance, to withhold approval of your abbreviated application.

Until such time that you can demonstrate to the Agency that the problems have been corrected and the Agency's concerns are otherwise satisfied, your application cannot be approved.

You should amend this application when the cGMP-related issues have been satisfactorily resolved. Your amendment to the application submitted in response to this not approvable letter will be considered a MINOR AMENDMENT provided that the amendment contains no significant additional information necessary to remedy the cGMP problems, and includes a statement from a responsible corporate official certifying that your facilities have been found to be in compliance with cGMPs and have been cleared for approval of the drug product by representatives of the local FDA District Office. If, as a result of follow-up inspections related to the ongoing evaluation of this or other applications, it is necessary for you to significantly revise your procedures, controls or practices to correct the deficiencies, then the amendment will be considered to represent a MAJOR AMENDMENT. Your amendment should be plainly marked as such in your cover letter.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw this application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,



4/1/03.

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-350
ANDA 75-350/DUP
Division File
Field Copy
HFD-324

Endorsements:

HFD-645/K. Bernard/ *K Bernard 3/25/03*
HFD-645/B. Arnwine/3/24/03 *(B) Arnwine 3/31/03*
HFD-617/N. Park/ *Mann 3/27/03*

V:\FIRMSAM\PUREPAC\LTRS&REV\75350cGMP
Drafted and F/T by: EW 3/25/03

*Robert West
6/30/2003*

NOT APPROVABLE - MINOR- CGMP



ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-659-2440

AMENDMENT - FINAL APPROVAL REQUESTED

UPS OVERNIGHT COURIER

August 25, 2003

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

RE: ANDA #75-350, Gabapentin Capsules, 100 mg, 300 mg, and 400 mg

Dear Mr. Buehler:

Reference is made to our March 30, 1998 submission of an Abbreviated New Drug Application, ANDA #75-350 for Gabapentin Capsules, 100 mg, 300 mg, and 400 mg. Further reference is made to the telephone conversation that took place on August 21, 2003, between Ms. Nicole Park, Project Manager at OGD and Janak Jadeja at Purepac. In this telephone conversation, Ms. Park indicated that OGD has confirmed cGMP clearance for this application and accordingly, Purepac should submit an amendment requesting final approval.

Therefore, via this amendment, Purepac requests the Agency to grant final approval for Gabapentin Capsules, 100 mg, 300 mg, and 400 mg, ANDA #75-350.

CMC update:



RECEIVED

AUG 26 2003

OGD/CDER

AMENDMENT

ANDA #75-350

Gabapentin Capsules 100 mg, 300 mg, and 400 mg

Page 2 of 2

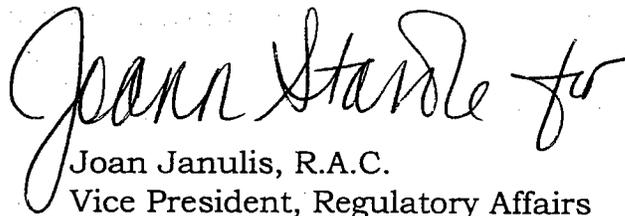
In conjunction with this submission, Purepac is providing a Field Copy of this amendment to our local District Office in accordance with 21 CFR 314.71 (b). The required Field Copy Certification is contained in Section 2 of this amendment.

Please be advised that there are no additional changes to the application to report at this point in time.

Purepac Pharmaceutical Co. appreciates your timely attention to this amendment and looks forward to the final approval of our application. If there are any questions concerning this amendment, please contact the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.


Joan Janulis, R.A.C.
Vice President, Regulatory Affairs



ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-659-2440

**AMENDMENT
(LABELING)**

NEW CORRESP

NC

UPS OVERNIGHT COURIER

September 3, 2003

*NAI
9/12/03*

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Food & Drug Administration
Document Control Room
MPN II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-350, Gabapentin Capsules, 100 mg, 300 mg, & 400 mg

Dear Mr. Buehler:

Reference is made to our March 30, 1998 submission of an Abbreviated New Drug Application for Gabapentin Capsules, ANDA #75-350. Further reference is made to today's telephone conversation between Ms. Michelle Dilahunt of the Labeling Review Branch and Ms. Joan Janulis of Purepac.

Purepac Pharmaceutical Co. hereby commits to revising the storage temperature statement, which appears on the container labels and package insert for Gabapentin Capsules, at the time of next printing. As per Ms. Dilahunt's request, the statement will be revised to read: "Store at 20° - 25°C (68° - 77°F) [see USP Controlled Room Temperature]." The revised components will be submitted in our annual report submission with all changes described in full.

RECEIVED

SEP 04 2003

OGD/CDER

ANDA 75-350

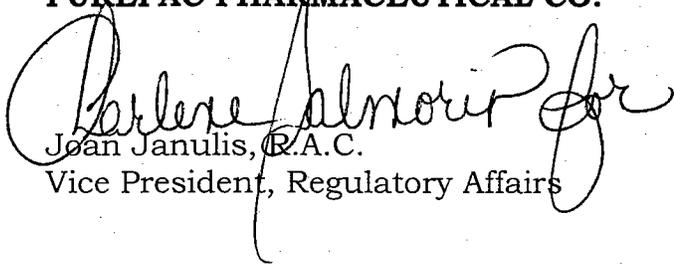
Gabapentin Capsules, 100 mg, 300 mg, & 400 mg

Page 2 of 2

Purepac Pharmaceutical Co. appreciates your timely attention to this amendment and looks forward to the final approval of our application. If you have any questions pertaining to this amendment, please contact the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.


Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ/cs