APOTEX CORP.

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March 26, 2001

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, Maryland 20857

CITIZEN PETITION

This citizen petition is submitted by Apotex Corp. pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. §§ 10.25(a), 10.30, 314.122, and 314.161.[1] This petition requests that the Food and Drug Administration (FDA) determine that the three day titration dosing schedule for the listed drug Neurontin® capsules was not withdrawn from the labeling for reasons of safety or effectiveness, that the omission of this titration dosing schedule from the labeling of a generic version of Neurontin® capsules would not render the proposed generic drug product less safe or effective than Neurontin® capsules, and therefore that TorPharm's abbreviated new drug application (ANDA) No. 75-360 may reference the discontinued dosage schedule for labeling purposes.

A. Action Requested

Apotex Corp. requests that FDA make a determination that Neurontin®'s sponsor did not discontinue the titration dosage schedule from the drug product's labeling due to safety and effectiveness reasons. Apotex Corp. requests that FDA make a determination that omission of the protected information from the labeling would not render the proposed generic drug product less safe or effective than the currently marketed innovator product. Apotex Corp. further requests that FDA then make a determination that TorPharm's ANDA based on Neurontin® capsules may include the discontinued labeling that was previously FDA-approved.

[1] On October 26, 2000, FDA published a "Draft Guidance for Industry on Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications." 65 Fed. Reg. 64225. Although the draft guidance is consistent with the relief sought, this citizen petition is submitted pursuant to the above-listed statute and regulations, not pursuant to the draft guidance.

B. Statement of Grounds

Background

Apotex Corp. is the U.S. agent for its corporate affiliate, TorPharm Division, Apotex, Inc., one of the largest Canadian generic drug manufacturers. TorPharm is the sponsor of pending ANDA No. 75-360, which references the listed drug Neurontin® capsules. The generic form of Neurontin® capsules is known as gabapentin. TorPharm submitted its ANDA in order to manufacture capsules containing 100mg, 300mg, and 400mg of gabapentin. Gabapentin is an anticonvulsant.

Neurontin® capsules are manufactured by Parke-Davis Pharmaceuticals. The capsule form of Neurontin® received final approval December 30, 1993. On September 29, 1998, Parke-Davis obtained a dosing schedule change, denominated in the "Orange Book" as "D-43," for the immediate initiation of treatment with 900mg/day. The previously approved dosing schedule called for the titration of Neurontin® capsules to 900mg/day over a three-day period. The FDA medical review report for this dosing schedule change does not indicate that the change was made in response to any concerns regarding the safety or efficacy of the titration regimen, indicating support for the conclusion that there were no such concerns (copy attached). The new immediate dosing schedule was granted three-year market exclusivity, 21 U.S.C. § 355(j)(5)(D)(iv), and Parke-Davis deleted the titration dosing schedule from its labeling.

TorPharm submitted its ANDA on December 10, 1998, referencing the previously approved titration dosing schedule for Neurontin® capsules. TorPharm's proposed labeling included (and still includes) the titration schedule. On July 29, 1999, FDA requested that a minor amendment be filed in connection with this ANDA, including a request for an update to the exclusivity statement to indicate that the ANDA product would not be marketed until after the Neurontin® capsule dosing exclusivity expires on September 29, 2001. By letter dated October 12, 1999, Apotex Corp. responded to this request by stating that: "TorPharm labeling does not include the dosing schedule covered by the D-43 exclusivity." Since this date FDA has neither responded to TorPharm nor has it issued a tentative final approval letter, which under FDA practice should have been issued in November 1999.

Referencing Discontinued Labeling

The Drug Price Competition and Patent Term Restoration Act of 1984 (known as the Hatch-Waxman Amendments) created a framework for patent term extensions and non-patent exclusivity periods for brand name drug products and a system for speeding FDA's approval of

generic drug products. One provision of the Hatch-Waxman Amendments requires that an ANDA must provide information to show that the labeling proposed for the generic drug product is the "same as the labeling approved for the listed drug," with minor exceptions not relevant to this petition. 21 U.S.C. § 355(j)(2)(A)(v). While there is no final agency guidance regarding the exact situation presented here, other areas of the statute and regulations demonstrate how FDA deals with similar situations.[2]

When an ANDA references a drug that has been withdrawn from the marketplace, FDA may still approve the ANDA upon a determination that the withdrawal was not for safety or effectiveness reasons. 21 U.S.C. § 355(j)(6); 21 C.F.R. §§ 314.122 and 314.161. Similarly, FDA is also authorized to approve an ANDA that omits in its labeling an indication or other aspect of labeling for the listed drug that is protected by patent or exclusivity. 21 C.F.R. § 314.94(a)(8)(iv). In this circumstance, omission in the ANDA's labeling of protected aspects is allowed if the omission does not render the generic drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use. 21 C.F.R. § 314.127(a)(7).

In conformance with the above referenced provisions, FDA should make a determination that the Neurontin® capsules labeling regarding titration was not withdrawn for safety or effectiveness reasons. FDA should also determine that omission of the currently protected information in the labeling will not render TorPharm's generic drug product less safe or effective than the currently marketed Neurontin® capsules product. Upon such determinations, FDA should allow TorPharm's ANDA to reference the discontinued labeling and allow final approval.

Safety and Effectiveness of the Titration Dosage Schedule

Neurontin®'s titration dosage schedule was discontinued when its sponsor received exclusivity for the immediate dosing schedule, not for safety or effectiveness reasons. As stated in the attached affidavit prepared by Dr. Winston Ortiz, the approved titration schedule was – and is – a conservative and medically sound approach. Dr. Ortiz, a neurologist who participated as a sub-investigator for the investigational studies on Neurontin®, states that the immediate dosage schedule does not provide any safety or efficacy benefit over the titration dosing schedule. In fact, he states that the titration dosing schedule may be a more appropriate approach for starting patients on this product. He also states that omission of the immediate dosing schedule from the labeling would not render the generic product less safe or effective than if that information were included.

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[2] The issue addressed by this petition is not one for which a suitability petition may be filed. 21 C.F.R. § 314.93.

Conclusion

This citizen petition asks that FDA make a determination that the titration dosing schedule was not withdrawn for safety or effectiveness concerns and, therefore, that TorPharm's ANDA can properly reference that dosing schedule for use on a generic drug product's labeling.

C. Environmental Impact

This petition is entitled to a categorical exclusion under 21 C.F.R. § 25.30 and § 25.31.

D. Economic Report

Apotex Corp. will submit an economic analysis upon request.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views upon which the petitioner relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

Marcy Macdonald

Marcy Macdonald
Associate Director, Regulatory Affairs
Apotex Corp.

Attachments

MEMORANDUM

DATE: July 30, 1997

FROM: Deputy Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-235

SUBJECT: Supervisory Review of Supplemental NDA

BACKGROUND

This submission requested changes to the labeling for Neurontin, and contained data that the sponsor felt supported these changes. The requested changes were:

4) a change in the recommended initial dosing regimen to replace the current requirement in labeling of reaching 900 mg/day over 3 days to initial treatment with 900 mg/day.

The following data were submitted to support these changes:

33 PAGES REDACTED

CONTAINED TRADE SECRETS and/or CONFIDENTIAL/ COMMERCIAL INFORMATION

New initial dosing regimen

Finally, the sponsor has requested that the labeling be changed to permit the initial dose to be 900 mg/day, to replace the current recommended initial dosing regimen of 300 mg/day on Day 1, 600 mg/day on Day 2, and 900 mg/day on Day 3.

In support of this change, they have submitted the results of Study 090, which compared the incidence of ADRs, with emphasis on the 4 most common ADRs seen in the earlier studies, with these 2 dosing regimens over the first week of dosing. I am persuaded that initiating treatment with 900 mg/day is likely not to result in significant difficulty, although the sponsor should be asked to submit detailed information about the 3 patients who received the proposed regimen and experienced syncope. (Interestingly, the sponsor points out that the current labeling does not reflect the actual dosing experience gained in the original controlled trials, most of which used a starting dose of 600 mg/day, a dose that did

not result in an unacceptable incidence of ADRs. I have been unable to locate in the file the reason for the slower titration described in labeling that was approved at that time [and which, of course, still persists], other than a statement made by the sponsor in the current submission that suggests it was done to be "conservative").

While the sponsor has not addressed the question of the effect of the new regimen on the ultimate effectiveness of the drug, I am comfortable concluding that no important effect would be expected. Further, I am willing to permit this new initial dosing to apply to both the adjunctive and mono-therapy setting, because the study was performed with Neurontin as adjunctive treatment.

APPEARS THIS WAY
ON ORIGINAL

RECOMMENDATIONS

I recommend that the sponsor be informed that we find the application Approvable, but that the evidence supports Neurontin's use as monotherapy only in newly diagnosed patients. Further, the new initial dosing regimen is acceptable, but additional information needs to be submitted to support the sponsor's proposed statements about the use of higher doses. In addition, detailed information should be submitted about 3 patients in Study 090 who experienced syncope.

/S/

Russell Katz, M.D.

Cc:
NDA 20-235
HFD-120
HFD-120/Katz/Leber/Ware
HFD-710/Sahlroot

APPEARS THIS WAY
ON ORIGINAL

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March 9, 2001

To Whom It May Concern:

I am writing with regards to the safety and efficacy of a three-day titration dosing schedule for Gabapentin. My name is Winston Ortiz. I am a neurologist at Tallahassee Memorial Hospital. I am the Medical Director of the Memory Disorder Clinic and the Co-Medical Director of the Parkinson's Center, both at Tallahassee Memorial Health Care. I work extensively with epileptic patients. I was a sub-investigator for the investigational studies on Gabapentin and, therefore, had the opportunity to evaluate first hand the data regarding Gabapentin's dosing schedule.

Gabapentin is currently marketed by Parke-Davis Pharmaceuticals under the brand name Neurontin®. Neurontin's original dosing schedule called for titration of the capsules to 900 mg per day over a three-day period. This is the dosing schedule that was reviewed by the investigational studies in which I participated. In 1998, a new dosing schedule for Neurontin®, calling for immediate initiation of treatment with 900 mg per day, was approved. Subsequently, the titration dosing schedule was deleted from Neurontin's labeling.

Based on my review of the pertinent data, the titration dosing schedule was not withdrawn due to safety or efficacy concerns. During the original studies of Neurontin®, the safety and efficacy of the titration dosing schedule was demonstrated to the satisfaction of the investigators and the FDA. Titration of Gabapentin was, and remains, a medically sound approach that is conservative but quite appropriate when beginning a patient on this therapy. The new dosing schedule does not provide any additional benefits or safety to the patient. Titration, arguably, is a more prudent approach when beginning a patient on this therapy.

I understand that there is a concern regarding permitting the titration dosing schedule to be displayed on a generic Gabapentin product label. I submit that such concern is unnecessary. A label with the titration dosing schedule is no less safe or effective than a label with the immediate dosing schedule.

Thank you for your considering my observations regarding this important drug.

Sincerely,

Winston R. Ortiz, M.D.

WRO/sbw

Enclosure

WINSTON R. ORTIZ, M.D. EXHIBIT A
January 2000

PERSONAL

Place of Birth: Hato Rey, Puerto Rico
Social Security Number: [redacted]

ADDRESS

[redacted]

TELEPHONE

EDUCATION

PONCE SCHOOL OF MEDICINE
Ponce, Puerto Rico
M.D., May 1987

TULANE UNIVERSITY
New Orleans, LA
B.S. Chemistry, May 1983

POST GRADUATE TRAINING

UNIVERSITY OF MIAMI SCHOOL OF MEDICINE
Miami, FL
Epilepsy/EEG Fellowship
July 1992 - June 1994

VETERAN'S ADMINISTRATION/USC MEDICAL SCHOOL
Los Angeles, CA
Neuromuscular Fellowship
July 1991- June 1992

UNIVERSITY OF MIAMI/JACKSON MEMORIAL HOSPITAL
Miami, FL
Residency in Neurology
July 1988 - June 1991

MEDICAL COLLEGE OF PENNSYLVANIA
Philadelphia, PA
Internship in Internal Medicine
July 1987 - June 1988

CURRENT POSITION	Private practice with Tallahassee Neurological Clinic, P.A. at Tallahassee Memorial Hospital Start Date July 1, 1994 Medical Director or Tallahassee Memorial Health Care Memory Disorder Clinic, Tallahassee, FL Co-Medical Director of Tallahassee Memorial Health Care Parkinson's Center, affiliated with the National Parkinson's Foundation, Tallahassee, FL
MEDICAL LICENSURE	Diplomate of the National Board of Medical Examiners July 1988 Licensure in: Florida ME0057742 (Expiration 1/31/00) DEA #B02342018
CERTIFICATION	Board Certified in American Academy of Psychiatry and Neurology, 1993
PROFESSIONAL ORGANIZATIONS	American Academy of Neurology American Medical Association Association of Clinical Research Professionals Capital Medical Society Florida Medical Association Florida Physician Association
HOSPITAL AFFILIATIONS	Tallahassee Memorial Health Care, Active Tallahassee, FL 32308 Healthsouth Rehabilitation Hospital, Consulting Tallahassee, FL 32308 Jackson Hospital, Consulting Marianna, FL 32447 Doctors Memorial Hospital, Consulting Perry, FL 32347

INVESTIGATIONAL STUDIES

Principal Investigator
- Alzheimer's Disease Prevention Trial with Estrogen

Sub-Investigator with Ricardo Ayala, M.D.:
- Traumatic Brain Injury
- Stroke
- Diabetic Peripheral Neuropathy
- Zonisamide
- Eliprodil in Stroke
- Losigamone
- Lamictal in Absence Seizures
- Lamictal in Complex Partial Seizures
- Alzheimer's Disease

Sub-Investigator with R. Eugene Ramsay, M.D.:
- Felbamate
- Tiagabine
- Gabapentin
- Topiramate
- Vigabatrin
- Lamotrigine
- Vagal Stimulator

SPEAKER BUREAU

Novartis Pharmaceuticals
Parke-Davis Pharmaceuticals
Glaxo-Wellcome Pharmaceuticals
Pfizer Pharmaceuticals

ACADEMIC LECTURES

Chief Resident of Neurology, University of Miami, July 1990 - January 1991

Florida A&M University School of Pharmacy

Florida A&M University School of Physical Therapy

Florida State University, medical students, Program in Medical Science

INVITED LECTURES

Caregiver 101 - Diagnosis and Treatment of Memory Disorders 10/5/98, 1/11/99, 4/20/99

Diagnosis and Treatment of Memory Disorders, Pilot Club, 2/13/99

Nursing Care of the Patient with Alzheimer's Disease, Medical and Nursing Staff, Tallahassee Memorial Hospital, 7/99

REFERENCE ARTICLES

Misra AK, Mishra SK, Ortiz W, "Differential Involvement of Brainstem Pathways due to Fourth Ventricular Epidermoid Cyst: A Case Study" Clin Neruol Neurosurg 1994; May, 96 (2):170-3

REFERENCES

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