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RESEARCH**

APPLICATION NUMBER:

21829

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-829

Schwarz BioSciences, Inc.
Attention: David Dobrowski
Director, Regulatory Affairs
P.O. Box 110167
Research Triangle Park, NC 27709

Dear Mr. Dobrowski:

Please refer to your new drug application (NDA) dated January 19, 2005, received January 28, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act submitted under 505(b) for Neupro (rotigotine) 2mg/24 hr., 4 mg/24 hr., and 6 mg/24hr.transdermal system.

We acknowledge receipt of your submissions dated:

February 23, 2006	March 16, 2006	April 24, 2006
August 25, 2006	August 31, 2006	October 2, 2006
November 7, 2006	December 7, 2006	January 10, 2007
January 24, 2007	February 5, 2007	April 4, 2007
May 4, 2007	May 8, 2007	

The November 7, 2006 submission constituted a complete response to our February 28, 2006 action letter.

This new drug application provides for the use of Neupro (rotigotine) transdermal system for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease.

We have completed our review of this application, as amended and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these

submissions “**FPL for approved NDA 21-829.**” Approval of these submissions by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

We remind you of your postmarketing study commitments in your submission dated May 4, 2007. These commitments are listed below.

1. Description of Commitment

To complete your thorough QTc study characterizing the effects of rotigotine on cardiac repolarization in humans and submit the final study report.

Protocol Submission: to IND 47,852 on December 13, 2005
Study Start: by January 6, 2006
Final Report Submission: by July 31, 2007

2. Description of Commitment

To complete the echocardiographic study in patients with Parkinson’s disease comparing the effects of different dopamine agonists, including rotigotine, on echocardiographic measures. This study will help determine if rotigotine is associated with the cardiac valvulopathy seen with some other dopamine agonists.

Protocol Submission: by June 30, 2007
Study Start: by April 2007
Interim Report Submission: September 2009
Final Report Submission: September 2011

3. Description of Commitment

To complete a fixed-dose dose-response study of rotigotine in patients with advanced Parkinson's disease that incorporates monitoring of laboratory parameters related primarily to hematopoiesis and renal function, including iron, transferrin, ferritin, reticulocyte count, red cell morphology, erythropoietin, erythrocyte sedimentation rate, C-reactive protein, haptoglobin and urine hemoglobin as well as hemoglobin; hematocrit; red cell indices; absolute and differential white cell counts; BUN, creatinine, serum electrolytes (including bicarbonate), albumin and globulin. This study will include continued detailed monitoring during post-treatment washout in order to assess rate of recovery from any reduction of renal function, hemoglobin or albumin. Measurement of red cell volume and creatinine clearance should be performed before initiating treatment, at the end of treatment and the end of post-treatment washout. These data will help to further characterize the previously noted changes in hematologic and renal measures and, importantly, to determine if, in those patients in whom these changes occur, the changes are reversible upon discontinuation of treatment.

Protocol Submission: by June 30, 2007
Study Start: by August 2007
Final Report Submission: by February 2010

4. Description of Commitment

To conduct an in vivo micronucleus assay by the subcutaneous route.

Protocol Submission: to NDA 21-829 on August 25, 2006
Study Start: by September 2006
Final Report Submission: by June 30, 2007

5. Description of Commitment

To conduct embryo-fetal development studies in mouse.

Protocol Submission: to NDA 21-829 on August 25, 2006
Study Start: by October 2006
Final Report Submission: by September 30, 2007

6. Description of Commitment

To conduct an embryo-fetal development study in rabbit.

Protocol Submission: to NDA 21-829 on August 25, 2006
Study Start: by October 2006
Final Report Submission: by September 30, 2007

7. Description of Commitment

To conduct a local tissue distribution study to compare tissue distribution of drug-related material at the site of application following subcutaneous and dermal administration.

Protocol Submission: by June 30, 2007
Study Start: by August 2007
Final Report Submission: by December 31, 2007

If local tissue exposure to drug-related material following subcutaneous administration (route used in the completed 2-year carcinogenicity studies) is not essentially the same as that following dermal administration, then a 2-year dermal carcinogenicity study in one species will be conducted.

Protocol Submission: by March 2008
Study Start: by May 2008
Final Report Submission: by September 30, 2011

8. Description of Commitment

To conduct an in vitro binding assay to assess the affinity of the metabolite, rotigotine sulfate, at the serotonin 5HT_{2B} receptor.

Protocol Submission: by July 2007
Study Start: by September 2007
Final Report Submission: by February 28, 2008

Additional Nonclinical Comments

1. You have provided protocols for the embryo-fetal development studies in mouse and rabbit that are to be conducted Phase 4. The study protocols describe standard embryo-fetal studies; however, concurrence cannot be provided on dose selection since no dose-range finding data were provided. Doses should be selected based on data from valid dose-ranging studies in each species, preferably collected by the laboratory conducting the pivotal studies. In each pivotal study, rotigotine should be tested at doses up to a clear maximum tolerated (or maximum feasible) dose.
2. If a 2-year carcinogenicity is conducted Phase 4, it is recommended that the study be conducted using a clinical formulation containing the----- t at or above the proposed limit -----) in order to provide additional assurance of safety.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence.**"

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Neurology Products and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call CDR Teresa Wheelous, Sr. Regulatory Project Manager, at (301) 796-1161.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Office Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Package Insert and Patient Package Insert

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Robert Temple
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