

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 21-894

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-894

NDA APPROVAL

Prestwick Pharmaceuticals, Inc.
Attention: Martin Stogniew
Vice President, Regulatory Affairs
1825 K Street N.W., Suite 1475
Washington, DC 20006

Dear Dr. Stogniew:

Please refer to your new drug application (NDA) dated September 23, 2005, received September 23, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xenazine[®] (tetrabenazine) Tablets 12.5 and 25 mg.

We acknowledge receipt of your submissions dated June 16, July 1, 7, 8, 22, and August 5, 2008.

- The June 16, 2008, submission constituted a complete response to our March 18, 2008, action letter.

This new drug application provides for the use of Xenazine[®] (tetrabenazine) Tablets for the chorea of Huntington'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 enclosed agreed-upon labeling text.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(O)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing

studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the following unexpected serious risks: the potential for carcinogenicity, the potential effects on reproduction, the potential for neurotoxicity, and the inhibitory effect of tetrabenazine and its alpha and beta metabolites on CYP2B6.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to identify these unexpected serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following studies.

1. Complete the ongoing 2-year carcinogenicity study in male rats to identify the unexpected serious risk of carcinogenicity.

Final Report Submission: by March 2009

2. Conduct a 2-year carcinogenicity study in female rats to identify the unexpected serious risk of carcinogenicity.

Protocol Submission: by September 2009

Study Start Date: by January 2010

Final Report Submission: by January 2013

3. Conduct a nonclinical toxicity study of fertility and early embryonic development (to implantation) to identify the unexpected serious risk of adverse effects on reproduction.

Protocol Submission: by September 2008

Study Start Date: by January 2009

Final Report Submission: by September 2009

4. Submit *in vivo* metabolism data in the animal species used in the nonclinical studies of tetrabenazine, particularly the reproductive toxicology and the carcinogenicity studies.

Final Report Submission: by October 2008

5. Conduct a neurotoxicity study of tetrabenazine using methodology and a multiple dose regimen similar to Satou T et al. *Exp Toxicol Pathol* 53(4):303-308, 2001. Consideration should be given to including a group in which tetrabenazine is administered i.p. as in Satou et al. (2001) in order to facilitate comparisons between studies. Ideally, tetrabenazine should be tested at several dose levels with the high dose being a maximum tolerated dose.

Protocol Submission: by September 2008

Study Start Date: by January 2009
Final Report Submission: by January 2010

6. Conduct an *in vitro* metabolism study to characterize the potential serious safety risk of the inhibitory effect of tetrabenazine, α -HTBZ, and β -HTBZ on CYP2B6.

Protocol Submission: by September 2008
Study Start Date: by January 2009
Final Report Submission: by April 2009

Submit the protocols to your IND 63,909, with a cross-reference letter to this NDA 21-894. Submit all final reports to your NDA 21-894. Use the following designators to prominently label all submissions, including supplements, relating to these postmarketing studies as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

You are required to report periodically to FDA on the status of the postmarketing studies described above pursuant to sections 505(o)(3)(E)(ii) and 506B of the FDCA, as well as 21 CFR 314.70. Under section 505(o)(3)(E)(ii), you are also required to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue associated with tetrabenazine.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Title IX, Subtitle A, Section 901 of FDAAA amended the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if the Secretary determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). This provision took effect on March 25, 2008.

In accordance with 505-1 of the FDCA, we have determined that a REMS is necessary for Xenazine (tetrabenazine) Tablets, 12.5 and 25 mg, to ensure that the benefits of the drug outweigh the risks of depression and suicidality.

Your proposed REMS, submitted on January 18, 2008 and resubmitted June 16, 2008, and appended to this letter, is approved. The REMS consists of a Medication Guide, communication plan, a timetable for assessments, and assessments of the REMS.

Use the following designator to prominently label all submissions, including supplements, relating to this REMS:

NEW SUPPLEMENT NDA 21-894 PROPOSED REMS MODIFICATION
NEW SUPPLEMENT NDA 21-894 REMS ASSESSMENT

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert, Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 21-894.**"

Submit final printed container labels that are identical to the enclosed immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Container Labels for approved NDA 21-894.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration

HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

REPORTING REQUIREMENTS

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 Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

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

Enclosure: Labeling and REMS