

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 21-894

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

21,894

NAME OF APPLICANT / NDA HOLDER

Prestwick Pharmaceutical, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Xenazine

ACTIVE INGREDIENT(S)

Tetrabenazine

STRENGTH(S)

12.5 mg, 25 mg tablets

DOSAGE FORM

oral tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

b. Issue Date of Patent

c. Expiration Date of Patent

d. Name of Patent Owner

Address (of Patent Owner)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

1825 K Street, NW, Suite 1475

City/State

Washington, DC

ZIP Code

20006

FAX Number (if available)

(202) 296-7450

Telephone Number

(202) 296-1400

E-Mail Address (if available)

rickd@prestwickpharma.com

 Richard Dulik, Esq.

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) | Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. | Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



9/19/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Prestwick Pharmaceuticals, Inc., Attention Richard Dulik, Esq., Director of Legal Affairs	
Address 1825 K Street NW, Suite 1475	City/State Washington, DC
ZIP Code 20006	Telephone Number (202) 296-1400
FAX Number (if available) (202) 296-7450	E-Mail Address (if available) rickd@prestwickpharma.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 21-894

SUPPL # N/A

HFD # 120

Trade Name Xenazine

Generic Name tetrabenazine

Applicant Name Prestwick Pharmaceuticals, Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

7

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

Investigation #2

!

YES

!

NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Susan Daugherty
Title: Regulatory Health roject Manager
Date: 7/30/08

Name of Office/Division Director signing form: Russell Katz, M.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Russell Katz
8/8/2008 01:54:17 PM



Prestwick Pharmaceuticals, Inc.
1825 K Street NW, Suite 1475
Washington, DC 20006
202.296.1400
fax 202.296.7450
www.prestwickpharma.com

January 27, 2006

Russell G. Katz, M.D.
Director, Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
c/o Central Document Room
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

Attn: CDR Teresa Wheelous

Re: **NDA No. 21,894**

Sponsor: Prestwick Pharmaceuticals, Inc.
Name of Drug: Tetrabenazine (TBZ) for Huntington's chorea

**Subject: Information Request – Administrative
(Debarment Certification & Financial Disclosure)**

Dear Dr. Katz:

Prestwick Pharmaceuticals, Inc. (Prestwick) is responding to an administrative **“information request”** made by the Division of Neurology Products (Division), Center for Drug Evaluation and Research, Food and Drug Administration. The Division notified Prestwick by two separate **e-mails on January 24, 2006** for this information for the above NDA.

Debarment Certification

Prestwick had originally provided a Debarment Certification that contained the phrase, “... to the best of Prestwick’s knowledge.” A new Debarment Certification is enclosed that fully reflects the language of the Federal Food, Drug, and Cosmetic Act section 306 (k) (1), as follows:

“Prestwick Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.”

1.3.3 Debarment Certification

FDA makes available a separate list of firms or persons debarred pursuant to the debarment provisions of the Federal Food, Drug, and Cosmetic Act located at (http://www.fda.gov/ora/compliance_ref/debar/default.htm). The names of principal investigators involved in clinical research sponsored by Prestwick Pharmaceuticals have been checked against this list to assure that investigators are permitted to conduct clinical investigations for the company.

Principal Investigators:

Principal investigators names checked against the debarment list as of October 25, 2004 from Prestwick-sponsored Phase I, II, or III trials:

1. Karen Anderson, MD
2. Tetsuo Ashizawa, MD
3. Karen Blindauer, MD
4. Amy Cocher, MD
5. Jody Corey-Bloom, MD
6. Andrew Feigin, MD
7. Michael Geschwind, MD
8. Phillip Hanna, MD
9. Donald Higgins, MD
10. Soran Hong, MD
11. Sandra Kostyk, MD, PhD
12. Jean-Paul Macher, MD
13. Martha Nance, MD
14. William Ondo, MD
15. Juan Sanchez-Ramos, MD
16. Kathleen Shannon, MD
17. Claudia Testa, MD, PhD
18. Joanne Wojcieszek, MD
19. Faouzi Saliba, M.D.
20. Philip T. Leese, M.D.
21. Frederick Marshall, MD
22. Francis Walker, MD
23. Justin Richards, MD
24. George Pohl, MD
25. Stanley Fahn, MD
26. Joseph Jankovic, MD

CONFIDENTIAL

Prestwick Pharmaceuticals, Inc.
Tetrabenazine
NDA 21,894

1.3.3 Debarment Certification

Prestwick Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Benjamin P. Lewis, Ph.D., R. Ph., RAC
Vice President, Regulatory Affairs
Prestwick Pharmaceuticals, Inc.

NDA ACTION PACKAGE CHECKLIST

Volume 1

Application Information		
NDA 21-894 IND 63,909		
Drug: Tetrabenazine	Applicant: Prestwick Pharmaceuticals	
RPM: CDR Teresa Wheelous	HFD-120	Phone # 301-796-1161
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):	
❖ Application Classifications:		
• Review priority	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority	
• Chem class (NDAs only)	NME	
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates	3/26/06	
❖ Special programs (indicate all that apply)	<input type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2	
❖ User Fee Information		
• User Fee	<input type="checkbox"/> Paid UF ID number	
• User Fee waiver	<input checked="" type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)	
• User Fee exception	<input checked="" type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)	
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
• Exception for review (Center Director's memo)		
• OC clearance for approval		
A Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	<input checked="" type="checkbox"/> Verified	
Patent		
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified	

Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	
<ul style="list-style-type: none"> Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<input type="checkbox"/> Yes, Application # _____ <input type="checkbox"/> No
D Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	3/15/06
General Information	
E Actions	
<ul style="list-style-type: none"> Proposed action 	<input type="checkbox"/> AP <input type="checkbox"/> TA <input checked="" type="checkbox"/> AE <input type="checkbox"/> NA
<ul style="list-style-type: none"> Previous actions (specify type and date for each action taken) 	
<ul style="list-style-type: none"> Status of advertising (approvals only) 	<input type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
F Public communications	
<ul style="list-style-type: none"> Press Office notified of action (approval only) 	<input type="checkbox"/> Yes <input type="checkbox"/> Not applicable
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	
<ul style="list-style-type: none"> Original applicant-proposed labeling 	
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings) 	9-22-05 DMETS 3-10-06 DMETS
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
H Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> Applicant proposed 	
<ul style="list-style-type: none"> Reviews 	
I Post-marketing commitments	
<ul style="list-style-type: none"> Agency request for post-marketing commitments 	
<ul style="list-style-type: none"> Documentation of discussions and/or agreements relating to post-marketing commitments 	
J Outgoing correspondence (i.e., letters, E-mails, faxes)	
K Memoranda and Telecons	
L Minutes of Meetings	
<ul style="list-style-type: none"> EOP2 meeting (indicate date) 	6-30-04
<ul style="list-style-type: none"> Pre-NDA meeting (indicate date) 	2-01-05
<ul style="list-style-type: none"> Pre-Approval Safety Conference (indicate date; approvals only) 	

• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
Summary Application Review	
M Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	Division Director 3/16/06 Medical Team Leader 3/21/06
Clinical Information	
N Clinical review(s) <i>(indicate date for each review)</i>	Efficacy Reviewer – 3/21/06 Safety Reviewer – 3/24/06
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	
❖ Risk Management Plan review(s) <i>(indicate date/location if incorporated in another rev)</i>	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	
❖ Demographic Worksheet <i>(NME approvals only)</i>	
O Statistical review(s) <i>(indicate date for each review)</i>	
P Biopharmaceutical review(s) <i>(indicate date for each review)</i>	
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>	
Clinical Inspection Review Summary (DSI)	
• Clinical studies	3-06-05
• Bioequivalence studies	
CMC Information	
R CMC review(s) <i>(indicate date for each review)</i>	
❖ Environmental Assessment	
• Categorical Exclusion <i>(indicate review date)</i>	
• Review & FONSI <i>(indicate date of review)</i>	
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Microbiology (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	
❖ Facilities inspection (provide EER report)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ Methods validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested
Nonclinical Pharm/Tox Information	
S Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	3/23/06 – Assoc. Director 3/27/06 – Team Leader 3/30/06 - Reviewer
❖ Nonclinical inspection review summary	
Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	
❖ CAC/ECAC report	



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-894

Prestwick Pharmaceuticals, Inc.
Attention: Martin Stogniew, Ph.D., R.A.C.
Executive Vice President, Chief Technology Officer
1825 K Street N.W., Suite 1475
Washington, DC 20006

Dear Dr. Stogniew:

Please refer to your new drug application (NDA) dated June 13, 2008, received June 16, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xenazine (tetrabenazine) Tablets 12.5 and 25 mg.

We consider this a complete, class 1 response to our March 18, 2008 action letter. Therefore, the user fee goal date is August 16, 2008.

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 reference the waiver granted on March 14, 2007 for the pediatric study requirement for this application.

If you have any question, call me at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Susan Daugherty
Regulatory Health Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Susan B. Daugherty
7/1/2008 01:36:45 PM

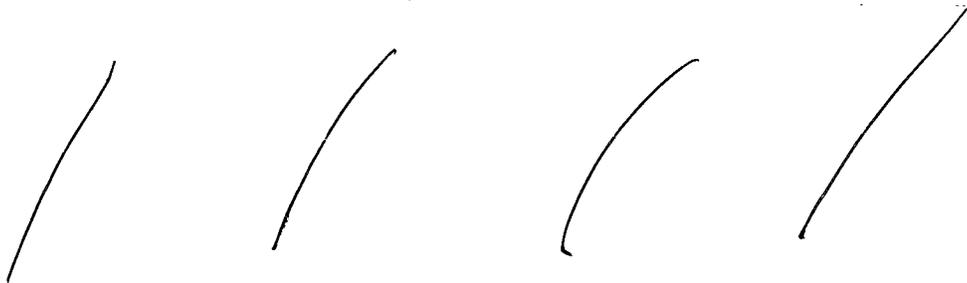
Daugherty, Susan B (CSO)

From: Daugherty, Susan B (CSO)
Sent: Thursday, March 06, 2008 3:28 PM
To: 'Martin Stogniew'
Subject: labeling comments NDA 21-894

Dear Marty,

I am writing to convey comments regarding the container labeling that you submitted in your complete response for NDA 21-894 tetrabenazine on January 18, 2008.

General



Container Label: Xenazine Tablets 12.5 mg and 25 mg (112 count bottle)



Please let me know if you have any questions.

Best Regards,
Susan Daugherty

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/s/

Susan B. Daugherty
3/6/2008 03:33:54 PM



Prestwick Pharmaceuticals, Inc.
1825 K Street NW, Suite 1475
Washington, DC 20006

202.296.1400
fax 202.296.2173
www.prestwickpharma.com

January 18, 2008

Russell G. Katz, M.D.
Director, Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
c/o Central Document Room
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

Attn: Susan Daugherty

Re: **NDA No. 21,894 / Amendment 0067**

Sponsor: Prestwick Pharmaceuticals, Inc.
Name of Drug: Tetrabenazine (TBZ) for Huntington's chorea

Subject: Response to "Approvable" Letter

Dear Dr. Katz:

Per 21 CFR §314.110 (a) (1) Prestwick Pharmaceuticals, Inc. (Prestwick) hereby amends our application in response to the Approvable Letter dated Dec 26, 2007 to the Division of Neurology Products ("Division"), Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA).

The response to the Approvable Letter is located in CTD Section 1.11.3 of this submission.

This following information is enclosed:

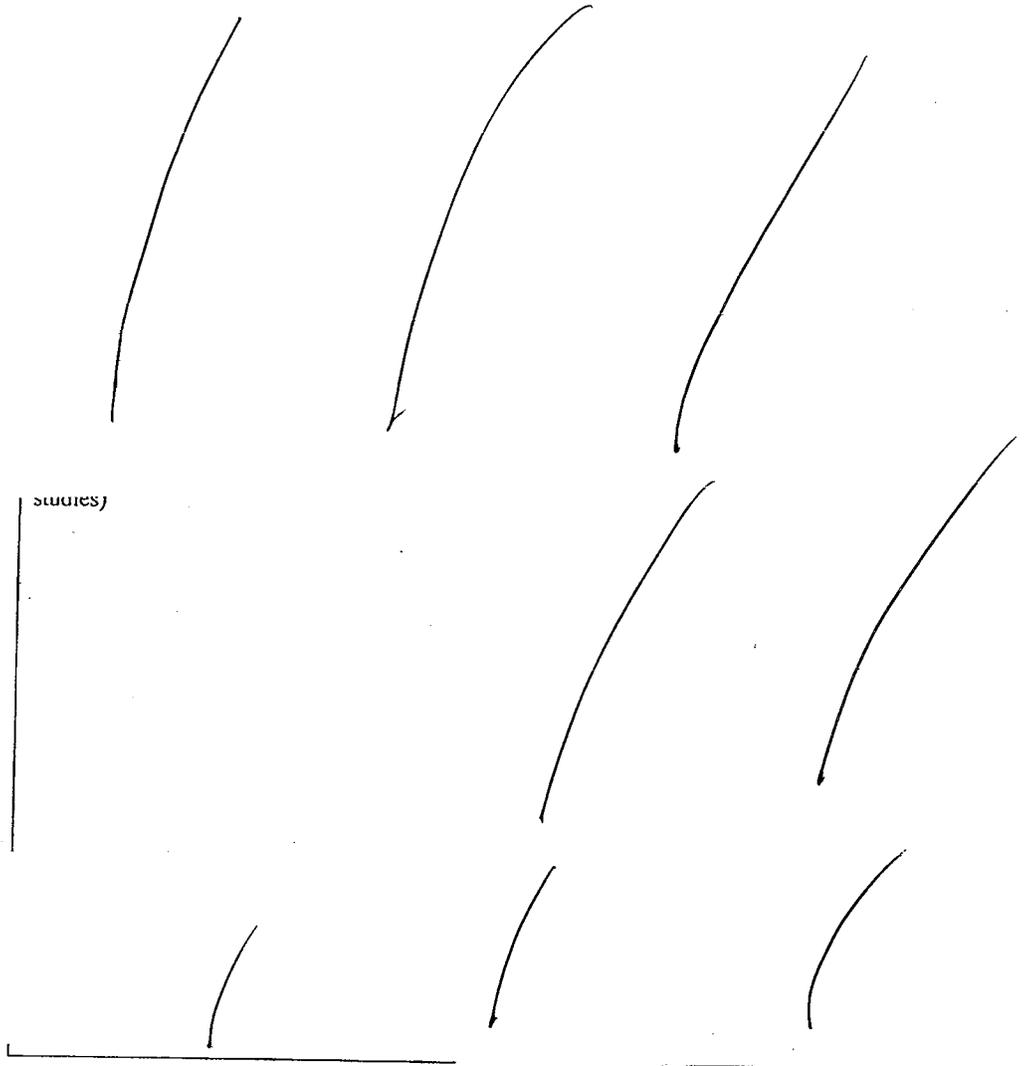
1. Revised Risk Minimization Action Plan (RiskMAP) and draft educational materials. (CTD Section 1.16).
2. Medication Guide
(CTD Section 1.14.1.3)
3. Revised draft package insert.
CTD Section 1.14.1.3



Page 2 – Dr. Russell G. Katz
January 18, 2008

Post-marketing Commitments

The Division has requested dates for submission of final study reports for post-marketing commitments. Prestwick agrees to conduct the following studies and will provide final study reports as follows:





Page 3 – Dr. Russell G. Katz
January 18, 2008

This submission is 1 volume of Module 1 only. A CD-ROM is enclosed that contains the complete submission. The labeling is provided in Microsoft Word with 'track changes.'

If you have any questions, comments or require additional information, please do not hesitate to contact me at benl@prestwickpharma.com; phone 202-296-1400, or fax 202-296-2173 (new).

Sincerely yours,

A handwritten signature in cursive script that reads "Ben P. Lewis".

Benjamin P. Lewis, Ph.D., R.Ph., RAC
Vice President, Regulatory Affairs

Enclosure

Daugherty, Susan B (CSO)

From: Daugherty, Susan B (CSO)
Sent: Wednesday, November 14, 2007 8:25 AM
To: 'Ben Lewis'
Subject: information request tetrabenazine

Good Morning Ben,

Please respond to the following request for information from one of our Medical Reviewers. We appreciate your prompt response.

1. Table 56 of the AC package includes a table summarizing postmarketing reports. Has this information submitted to the NDA?
If yes, please direct the reviewer to the exact date of submission. If not, please submit the above mentioned postmarketing data, including narratives or line listings (including whether the AE was serious or not, TBZ dose, date of onset of AE, treatment received, and outcomes).
2. The AC package states that TBZ has been recently approved in the Netherlands. Please submitted the most recently approved labeling.

Also, can you please provide an update the status of your responses to our previous requests for information?

Many thanks,
Soozee

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/s/

Susan B. Daugherty
11/14/2007 08:28:02 AM

Daugherty, Susan B (CSO)

From: Daugherty, Susan B (CSO)
Sent: Wednesday, November 07, 2007 1:33 PM
To: 'Ben Lewis'
Cc: Daugherty, Susan B (CSO)
Subject: Information request regarding your AC background package

Hi Ben,

Please provide clarification for the following regarding your AC background package:

Your AC package states that there were — unique patients exposed to TBZ in Prestwick-sponsored studies. As per our calculations, there were 111 (54 from 004 who continued as part of stud 007; 27 patients who went from the placebo arm in 004 to active treatment in 007 and 30 patients from study 006). Please clarify the discrepancy.

Best Regards,
Soozee

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/s/

Susan B. Daugherty
11/7/2007 01:36:50 PM

Daugherty, Susan B (CSO)

From: Daugherty, Susan B (CSO)
Sent: Wednesday, November 07, 2007 12:20 PM
To: 'Ben Lewis'
Cc: Daugherty, Susan B (CSO)
Subject: tetrabenazine information request

Dear Ben,

I am forwarding the following request for information from the Clinical Pharmacology Reviewer for the tetrabenazine NDA 21-894:

Please address the following details regarding the hepatic impairment study 203,010 for which the final report was submitted 10/12/07:

1. According to information at the time of the interim report, the study drug expired 6/8/05. This study was completed 12/19/05. Please clarify the study drug (lot and expiration date) that was used to complete the study.
2. Please confirm that the study samples were analyzed within the period for which the samples are stable at -70 C.

In addition, please answer the following 3 questions regarding Study 107,018 (Paroxetine interaction):

1. For the analytical assay for tetrabenazine and its metabolites, how was specificity with respect to interference from paroxetine addressed?
2. For the analytical assay for paroxetine, how was specificity with respect to interference from TBZ and its metabolites addressed?
3. Please provide information regarding the linearity of the calibration curves for the batch runs of the paroxetine assay.

Your prompt response is greatly appreciated.

Best Regards,
Soozee

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/s/

Susan B. Daugherty
11/7/2007 12:23:46 PM



NDA 21-894

INFORMATION REQUEST LETTER

Prestwick Pharmaceuticals, Inc.
Attention: Benjamin Lewis, Ph.D.
Vice President, Regulatory Affairs
1825 K Street N.W., Suite 1475
Washington, DC 20006

Dear Dr. Lewis:

Please refer to your April 5, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xenazine (tetrabenazine) Tablets.

We are reviewing your submission and have the following request for information. We request a prompt written response in order to continue our evaluation of your NDA.

Please submit the following data and analysis results to aid in our regulatory review. We made a similar request for the Chorea scores during our last regulatory review cycle. That correspondence might be a useful reference to better understand this request.

Data:

Please submit Functional Assessment, Total Cognitive and Sedative Effect scores for each patient over time in the following format with dummy numbers for illustration. Submit as SAS xpt files.

Patient ID	Time, days	Dose, mg	Functional Assessment Score	Total Cognitive Score	Sedative effect scores	Gender (is male?)	Age, years	Baseline Chorea	Weight, kg
1	0	0	1	1	0	0	45	15	67
1	1	25	.	3	.	0	45	15	67
1	2	50	2	.	.	0	45	15	67
1	3	50	2	3	5	0	45	15	67

Analysis:

1. Please conduct a dose-response analysis for each of the response measures (scores). Some of these analyses choices might depend on the data signature/trends. One potential approach could be to take the dose closest (current) to the worst score (and another analysis with previous dose) in each patient and perform a logistic regression.

It is likely that you will have questions as you respond to our request. Please call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878 as needed.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-894

Prestwick Pharmaceuticals, Inc.
Attention: Benjamin Lewis, Ph.D.
Senior Director, Regulatory Affairs
1825 K Street N.W., Suite 1475
Washington, DC 20006

Dear Dr. Lewis:

Please refer to your April 4, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xenazine (tetrabenazine) Tablets.

Please further refer to the telephone conversation on August 10, 2007, between representatives from the Division of Neurology Products and you, representing Prestwick Pharmaceuticals in which you were notified that the Division would be taking this application to an Advisory Committee on November 29, 2007.

On August 6, 2007 we received your major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is January 5, 2008.

If you have any questions, call me at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Susan Daugherty
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Susan B. Daugherty
8/15/2007 11:47:53 AM

Daugherty, Susan B (CSO)

From: Daugherty, Susan B (CSO)
Sent: Wednesday, August 15, 2007 11:25 AM
To: 'Ben Lewis'
Cc: Daugherty, Susan B (CSO)
Subject: tetrabenazine clinical information request

Dear Dr. Lewis,

Please respond to the following request for information from the Clinical Reviewers as soon as possible:

Please provide exposure data (in patient-years) for studies 004, 006 and 007, and 011 (chorea & non-chorea studies). If this information has already been submitted, please refer us to its exact location.

Thanks and have a good day,
Susan Daugherty

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/s/

Susan B. Daugherty
8/15/2007 11:31:07 AM

Daugherty, Susan B (CSO)

From: Daugherty, Susan B (CSO)
Sent: Friday, July 20, 2007 11:08 AM
To: 'Ben Lewis'
Subject: Tetrabenazine request for information

Dear Ben,

I am forwarding an additional request for information from the Clinical Reviewer. We would appreciate a response as soon as possible.

For study 004, please provide analyses of Total Chorea Score and Functional Assessment (FA) in patients who developed extrapyramidal symptoms¹ at any time during the study and those who did not develop these adverse events.

Patients with	TBZ (N=54)		Placebo (N=30)	
	EPS N=	No EPS N=	EPS N=	No EPS N=
Total Chorea Score				
Baseline (mean/median/range)				
End (mean/median/range)				
Change from baseline (mean +/- SD)				
Functional Assessment				
Baseline (mean/median/range)				
End (mean/median/range)				
Change from baseline (mean +/- SD)				

¹Include patients who had the following adverse events: akathisia, restlessness, bradykinesia, dystonia, parkinsonism, balance difficulty and stiffness when walking (and any other term that you consider appropriate). Please also conduct a separate analysis excluding the patients with balance difficulty.

Many thanks,
Soozee

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/s/

Susan B. Daugherty
7/20/2007 11:34:23 AM



NDA 21-894

INFORMATION REQUEST LETTER

Prestwick Pharmaceuticals, Inc.
Attention: Benjamin Lewis, Ph.D.
Vice President, Regulatory Affairs
1825 K Street N.W., Suite 1475
Washington, DC 20006

Dear Dr. Lewis:

Please refer to your April 5, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xenazine (tetrabenazine) Tablets.

We are reviewing your submission and have the following request for information. We request a prompt written response in order to continue our evaluation of your NDA.

Please submit the following data and analysis results to aid in our regulatory review. We made a similar request for the Chorea scores during our last regulatory review cycle. That correspondence might be a useful reference to better understand this request.

Data:

Please submit Functional Assessment, Total Cognitive and Sedative Effect scores for each patient over time in the following format with dummy numbers for illustration. Submit as SAS xpt files.

Patient ID	Time, days	Dose, mg	Functional Assessment Score	Total Cognitive Score	Sedative effect scores	Gender (is male?)	Age, years	Baseline Chorea	Weight, kg
1	0	0	1	1	0	0	45	15	67
1	1	25	.	3	.	0	45	15	67
1	2	50	2	.	.	0	45	15	67
1	3	50	2	3	5	0	45	15	67

Analysis:

1. Please conduct a dose-response analysis for each of the response measures (scores). Some of these analyses choices might depend on the data signature/trends. One potential approach could be to take the dose closest (current) to the worst score (and another analysis with previous dose) in each patient and perform a logistic regression.

It is likely that you will have questions as you respond to our request. Please call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878 as needed.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz
7/2/2007 02:35:59 PM

Daugherty, Susan B (CSO)

From: Daugherty, Susan B (CSO)
Sent: Thursday, June 14, 2007 9:24 AM
To: 'Ben Lewis'
Cc: Daugherty, Susan B (CSO)
Subject: tetrabenazine information request

Good Morning Ben,

I am forwarding a request for information from the clinical safety reviewer. We would appreciate a response as soon as possible.

Tetrabenazine - Request of June 14, 2007

1. Please provide Total Chorea Score and dose in patients who developed the following adverse events in studies 004, 007 and 006: Akathisia, parkinsonism, depression, dysphagia and sedation. The following format is suggested:

Table: Total Chorea Scores in patients who had an adverse event of depression in studies 004, 007 and 006

Study/ Pt ID	Onset (relative Day)	Action/AE outcome ¹	Total Chorea Score (dose [mg/day])				
			At baseline	At onset .of AE	At Week 12	At Week 24	At Week 48
004 (n= 8) 447-231	24	Dose ↓- resolved	19 (0)	7 (62.5)	12 (50.0)	-	-
007 (n=24)							
006 (n=9)							

¹ Action/outcome: examples: Dose ↓, No dose↓, medical treatment added/changed/ resolved, did not resolve, partially resolved.

2. Page 165, Vol. 48 of your February 9, 2007 submission states: "Occasionally, clinically significant hyperkinesias were coded as restlessness rather than akathisia, however, appropriate counter-measures including dose reduction was nonetheless employed for these patients."

Please identify these patients. Provide the same information requested under request #1 (if not included already under response #1).

3. Additionally, Vol 48, page 139 of your February 9, 2007 submission states: "To ensure that events coded to anxiety, anxiety aggravated, anxiety attack increased anxiety, restlessness, restlessness aggravated, agitation, nervousness and irritability did not include verbatims that should have been coded as hyperkinesia, all verbatims and patient information for patients with any of these events were reviewed by a neurologist." "Review of these events showed none that should have been coded to akathisia based on the available data (CR Listings 1.27.1, 1.27.2 and 1.27.3 in Appendix 4)."

Please clarify whether the conclusion that akathisia was not miscoded in the Tetrabenazine development program was based on the studies listings or the patient's Case Report Forms, and provide more information about the basis for your conclusion.

4. You compared rates of dysphagia in the Prestwick development program with historical data from CARE-HD. Please provide similar analyses for depression and akathisia.

5. Please provide information on patients who changed the dose of antidepressant medications during study 004, as well of information on patients who initiated or changed the dose of antidepressant medications in studies 006 and 007.

6. Please provide analyses of Total Chorea Score and Functional Assessment (FA) in patients who developed sedation (including somnolence/drowsiness/sleepiness/lethargy) versus those who did not develop this adverse event in study 004. The following format is suggested:

Patients with	TBZ (N=54)		Placebo (N=30)	
	Sedation N=	No sedation N=	Sedation N=	No sedation N=
Total Chorea Score				
Baseline (mean/median/range)				
End (mean/median/range)				
Change from baseline (mean +/- SD)				
Functional Assessment				
Baseline (mean/median/range)				
End (mean/median/range)				
Change from baseline (mean +/- SD)				

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/s/

Susan B. Daugherty
6/14/2007 09:34:49 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-894

Prestwick Pharmaceuticals
Attention: Benjamin P. Lewis, Ph.D., R.Ph., RAC
1825 K Street NW, Suite 1475
Washington D.C. 20006

Dear Dr. Lewis:

We acknowledge receipt on April 5, 2007 of your April 4, 2007 resubmission to your new drug application for Xenazine[®] (tetrabenazine) Tablets.

We consider this a complete, class 2 response to our March 24, 2006 action letter. Therefore, the user fee goal date is October 5, 2007.

We note that you requested a waiver from conducting pediatric studies in your September 23, 2005, submission. In addition, this application was granted orphan status. Orphan drugs are exempt from fulfilling the pediatric use information requirement under 21 CFR 314.55(d). Therefore, we are waiving the requirement for pediatric studies for this application.

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz
5/18/2007 04:13:06 PM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 25, 2006

TIME: 4 PM - 5 PM

LOCATION: White Oak, Building 22, Conference Room 1313

APPLICATION: NDA 21-894, Tetraabenazine for Huntington's Chorea

TYPE OF MEETING: End of Review Meeting

MEETING CHAIR: Dr. Katz

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Dr. Robert Temple – Office Director
Dr. Russell Katz – Division Director
Dr. Marc Walton – Deputy Director
Dr. John Feeney – Group Leader
Dr. Carole Davis – Medical Reviewer, Efficacy
Dr. D. Elizabeth McNeil – Medical Reviewer, Safety
Dr. Marc Stone – Safety Reviewer
Dr. Andrea Powell – Pharmacology / Toxicology Reviewer
Dr. Lois Freed – Pharmacology / Toxicology Supervisor
Dr. Martha Heimann – CMC Team Leader
Dr. Sally Yasuda – Clinical Pharmacology & Biopharmaceutics Reviewer
Dr. Henry Starzman – Orphan Drug Products
Zachary McCall – Orphan Drug Products Pharm D. Intern
Dr. Kevin Cannard – Visiting Fellow
CDR Teresa Wheelous – Sr. Regulatory Management Officer

PRESTWICK ATTENDEES AND TITLES:

Kathleen Clarence-Smith, M.D. – President, R&D, Chief Scientific Officer
Benjamin P. Lewis, Ph.D. – V. P., Regulatory Affairs
Benjamin P. Lewis – Consultant (Pharmacologist)
Jan Farino – Regulatory Affairs
Lucinda Wilson, Senior Project Director

BACKGROUND:

The new drug application for tetraabenazine is dated September 23, 2005, and was received on September 26, 2005. The Agency issued an approvable letter (with labeling) dated March 24, 2006. The Sponsor requested an End of Review Meeting in a March 28, 2006 meeting request, which was granted on April 4, 2006. The Sponsor submitted the meeting package on April 28, 2006 (serial # 0011), which consisted of four questions (reproduced below in italics). A summary of the discussion follows each question. Comments were not sent to the sponsor prior to the meeting.

DISCUSSION QUESTIONS:

1. *In your March 24, 2006 "approvable" letter to Prestwick, you stated that you plan to discuss our NDA at a public meeting of the Peripheral and Central Nervous Systems Drugs Advisory Committee (PCNSAC) and that you would "attempt to arrange this meeting as soon as possible." As of this date, we have not yet been notified that the Division has scheduled this meeting.*

Prestwick is very eager to hear from you about the timing of the advisory committee. We are aware of the May 17, 2006 and September 6 and 7, 2006 meetings of the PCNSAC. Can the Division make accommodations for our discussions at the September 6 and 7 meeting or otherwise schedule a special committee or a subcommittee meeting to deal with the issues listed in the tetrabenazine approvable letter? We respectfully request that you attempt to arrange this meeting as soon as possible as stated in the approvable letter.

Discussion:

The advisory committee schedule is already full through the fall. Given the amount of time needed to identify experts and the fact that the advisory committee meeting calendar is already full, the earliest available time is November 8 or 9, 2006. [N.B. The AC meeting is scheduled for 11/7/06]

2. *Prestwick has reviewed the current membership and specialties of the PCNSAC, and believes that only one member has expertise in movement disorders. We understand that the practice of adding Special Government Employees (SGEs) to certain advisory committees on a one-time basis has been employed on other occasions. We respectfully request that the Division consider adding two or more experts in movement disorders, specifically in Huntington's disease, for inclusion on the PCNSAC to assist in the review and discussion of tetrabenazine.*

Discussion:

The Division is seeking experts that work with both psychometric cognitive scales and Huntington's disease.

3. *Prestwick intends to address all the issues and concerns that were raised in the approvable letter and will submit its response as soon as possible. We understand that upon submission of a complete response the review clock will begin. Prestwick believes that some of the issues and concerns stated in the approvable letter were addressed by Prestwick during the review period. Although, these submissions were acknowledged as being received, they were not reviewed prior to the issuance of the approvable letter (page 1, paragraph 3). These submissions were information requests made by the Division that specifically addressed the Non-clinical and Clinical Pharmacology and Biopharmaceutics areas.*

Since tetrabenazine is an orphan product, and designated as fast track, i.e. it is indicated for the treatment of a severely debilitating symptom of a fatal disease for which no other drug is currently approved, Prestwick respectfully requests that the review period for our complete response be no more than 60-90 days.

Discussion:

- The information required to completely address the approvable letter qualifies for a class 2 resubmission. Class 2 resubmissions have a 6-month review clock.

- The review may be finished before the end of the 6-month clock review clock, but the Division can not commit to reviewing the resubmission in 60 – 90 days from receipt of the response.

4. *We respectfully request further clarification on certain issues that were raised in the approvable letter, as follows:*

- *You stated in the approvable letter (page 2, paragraph 5, line 7) . . . “We also note that there were no patient-rated measures of overall benefit in Study 004.”*

Although there were no patient-rated measures of overall benefit, 75 of 78 eligible patients chose to continue in the long-term Study TBZ 103,007 (“Long-Term Tetra HD”). Similarly, 29 of 30 eligible patients chose to continue in the long-term Study TBZ 103,006 (“Follow Withdrawal”). We believe that by this choice the patients clearly showed they found treatment to be useful.

We respectfully submit that patients treated in the US under Investigator INDs are paying for this treatment (no health insurance reimbursement for a non-approved drug), the price of treatment is high, yet patients are paying for it. Would patients be paying for a treatment that they would perceive as non-beneficial? Or even as harmful?

Discussion:

The Sponsor is reminded that the benefit to the patient cannot be measured by the patient’s willingness to pay for treatment.

- *You stated in the approvable letter (page 2, paragraph 6, line 1) . . . “In particular, among the numerous adverse events seen in association with the use of tetrabenazine, we note Parkinsonism, akathisia, depression, and dysphagia (with associated aspiration pneumonia). Although we acknowledge that the incidence of some of these events in Study 004 is not significantly different from placebo (e.g., Parkinsonism, dysphagia) . . . We acknowledge, of course, that the long-term safety data were collected in an open-label, uncontrolled setting, and also that these can themselves be manifestations of progressive HD. For these reasons a definitive conclusion about causality clearly can not be made at this time. Nonetheless, we are concerned that these events may be drug-related.”*

We fail to understand why an adverse event whose incidence is not different from placebo in Tetra HD, and is therefore not drug-related, would become drug-related in the long-term use of the drug. We do not see the evidence for this statement.

Discussion: DNP agrees that the open-label, long-term experience cannot directly address causality for some adverse events, but, at the same time, the occurrence of these events in the uncontrolled experience, and the possibility that they are drug-related, cannot be ignored.

- *You stated in the approvable letter, (page 3, paragraph 1, line 8) . . . “(In the case of parkinsonism, an article in the literature (Satou T et al. Exp Toxic Pathol 53: 303-*

308, 2001) suggests that there is irreversible damage to the substantia nigra pars compacta in Wistar rats following 7 daily (1 mg/kg) i.p. doses of tetrabenazine.”

However, we have not been able to reproduce these findings in our toxicology studies. In our definitive toxicology studies, there were no clinical signs similar to those reported by Satou et al. Histology also showed no loss of nigral neurons. Irreversible parkinsonism has never been reported in patients who discontinued treatment with tetrabenazine. In the Prestwick-sponsored studies, parkinsonism was never reported during washout from tetrabenazine. For example, parkinsonism was not reported in Study TBZ 103,005 (“Tetra Withdrawal”). In this study, some patients had been treated with tetrabenazine for several years. Following withdrawal of tetrabenazine in Study TBZ 103,004 (“Tetra HD”), no patient had parkinsonism. Thus the Satou findings cannot be reproduced in animals, and there is no evidence of irreversible Parkinsonism following treatment with tetrabenazine in patients (Prestwick-sponsored studies and literature).

Discussion:

- Regarding the neurotoxic potential of tetrabenazine, the Sponsor needs to provide documentation, as requested in the approvable letter, that the histopathology techniques employed in the toxicology studies were adequate to rule out treatment-related neuropathology similar to that reported by Satou et al. (2001).
- The Sponsor was advised that the March 16, 2006 response to a pharmacology/toxicology information request is unacceptable for review based on the quality of the submission (e.g. appendix 38 [a 33 page summary table of clinical signs] is unreadable). It would appear, however, that the original deficiencies may not have been entirely corrected. For example, Table 37 still does not provide a comprehensive summary of clinical signs; the convulsions that occurred in animals #110 and #111 are still not listed.

ADDITIONAL POINTS OF DISCUSSION

Worsening of Disease Symptomatology

- Although not mentioned in the discussion topics, the Division remains especially concerned about the adverse effects of the drug on Huntington’s disease symptoms other than chorea (including cognitive symptoms); these other symptoms appear to worsen while on drug.
- The study #004 substantiates the Sponsor’s claim that tetrabenazine shows efficacy in the treatment of chorea associated with Huntington’s disease. However, nearly all of the secondary endpoints favored the placebo group. Of particular concern is the change in the overall cognitive score, which reached statistical significance. If negative cognitive changes are occurring due to use of the drug, they might be mistakenly ascribed by physicians or family as due to the progression of the disease.

Inspection Report

- As stated in the inspection report, dysphagia reporting at the Baylor site appeared to be inconsistent. The investigator did not appear to report dysphagia systematically. While treatment emergent dysphagia was not always reported, the sponsor will attempt to address this concern.

- The Sponsor plans to submit a new presentation of this data with a different analysis.

Quality of Submission

- The Sponsor was advised to page through the documents/reports prior to submission to ensure that the reports are complete and readable.

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Russell Katz
9/1/2006 08:30:43 AM

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: March 6, 2006

TO: Teresa Wheelous, Regulatory Project Manager
Carole Davis, M.D., Medical Officer
Elizabeth McNeil, M.D., Medical Officer
Russell Katz, M.D., Director
Division of Neurology Products

THROUGH: Constance Lewin, M.D., M.P.H., Acting Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Jose Javier Tavarez, M.S.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-894

SPONSOR: Prestwick Pharmaceuticals, Inc.

DRUG: Tetrabenazine

CHEMICAL CLASSIFICATION: Type 1

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Treatment of Huntington's Chorea

CONSULTATION REQUEST DATE: October 18, 2005

PDUFA GOAL DATE: March 26, 2006

I. BACKGROUND

Clinical investigator inspections were conducted at four clinical sites that performed studies for which the sponsor submitted data in NDA 21-894. The inspections were conducted according to the Compliance Program 7348.811, the Inspection Program for Clinical Investigators. The inspections covered work performed under protocols TBZ 103,004 and TBZ 103,011.

Tetrabenazine is a new molecular entity (NME) product intended for treatment of Huntington's Chorea.

In this NDA, the sponsor has included results of protocols TBZ 103,004 (efficacy study) and 103,011 (long term safety study). Study TBZ 103,004 was a multi-center, randomized, double-blind, placebo-controlled study in two parallel unbalanced (2:1) groups (tetrabenazine titrated to "best dose"; placebo) of HD subjects. The main objective of the study was to demonstrate the efficacy and tolerability of tetrabenazine for the treatment of chorea associated with HD. The study was conducted at 16 sites across the US. A total of 84 subjects were enrolled; 54 were randomized to tetrabenazine, 30 were randomized to placebo. Treatment duration was 12 weeks.

Protocol TBZ 103,011 was a retrospective study designed to assess long-term safety of tetrabenazine used to treat subjects with chorea enrolled in Baylor Protocol H-721. Data was retrieved from a review of patient records for those consecutive patients identified with chorea including HD and treatment with tetrabenazine at Baylor College of Medicine Parkinson's Disease Center and Movement Disorders Clinic between January 1, 1979 and February 29, 2004. A total of 162 chorea subjects have been treated with tetrabenazine at Baylor College since January 1979. Medical records were missing for 17 of these subjects. Thus, a total of 145 subjects (98 with HD, 47 with chorea of other etiologies) were evaluated.

Basis for Sites Selection: Four clinical sites were inspected: Drs. Corey-Bloom, Wojcieszek, Ondo, and Jankovic's sites. These sites enrolled a large number of subjects for protocol TBZ 103,004 or TBZ 103,011. The goals of inspection included validation of submitted data and compliance of study activities with FDA regulations. Among the elements reviewed for compliance were subject record accuracy, informed consent, protocol inclusion/exclusion criteria, adherence to protocol, randomization procedures, and documentation of adverse events.

**APPEARS THIS WAY
ON ORIGINAL**

II. RESULTS (by site):

Clinical Investigator	Location	Protocol	Inspection Date	EIR Received Date	Final Classification
Jody Corey-Bloom, M.D.	UCSD School of Medicine, 9500 Gilman Drive, La Jolla, CA	TBZ 103,004	1/3-10/2006	1/31/2006	NAI
Joanne Wojcieszek, M.D.	Indiana University Outpatient Clinical Research Facility 535 Barnhill Drive Indianapolis, IN	TBZ 103,004	1/4-11/2006	1/23/2006	VAI
William Ondo, M.D.	Baylor College of Medicine, Department of Neurology, 6550 Fannin St. Houston, TX	TBZ 103,004	1/9-11/2006	2/9/2006	VAI
Joseph Jankovic, M.D.	Baylor College of Medicine, Department of Neurology, 6550 Fannin St. Houston, TX	TBZ 103,011	1/11-13/2006	2/21/2006	VAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable

VAI = Minor deviation(s) from regulations. Data acceptable

OAI = Significant deviations from regulations. Data unreliable

Pending = Inspection not completed

- (1) **Jody Corey-Bloom, M.D.** Site #51 – 17 subjects
UCSD School of Medicine
9500 Gilman Drive
La Jolla, CA

- a. What was inspected?

Nine (9) subjects were enrolled into the study TBZ 103,004. The FDA field investigator reviewed the records for all 9 subjects enrolled in the study. The FDA field investigator reviewed the source documents, case report forms and compared these with data listing provided by the sponsor as part of the NDA submission. The inspection encompassed an audit of all subjects' consent forms.

- b. Limitations of inspection: None.

- c. General observations/commentary:

No Form FDA 483, Inspectional Observations, was issued at the close of the inspection. The inspection did not reveal any significant issues regarding the conduct of the study. No underreporting of adverse events noted. Data in

sponsor-provided data listings were supported by data in source documents and case report forms.

Recommendation: Data from this clinical site appear acceptable for use in support of this NDA.

- (2) **Joanne Wojcieszek, M.D.** **Site #45 – 14 subjects**
Indiana University Outpatient Clinical Research Facility
535 Barnhill Drive
Indianapolis, IN

- a. What was inspected?

Eight (8) subjects were enrolled into the study TBZ 103,004. The FDA field investigator reviewed the records for all 8 subjects enrolled in the study. The FDA field investigator reviewed the source documents, case report forms and compared these with the data listing provided by the sponsor as part of the NDA submission. The inspection encompassed an audit of all subjects' consent forms.

- b. Limitations of inspection: None.

- c. General observations/commentary

A two-item FDA 483, Inspectional Observations, was issued noting inadequate drug accountability records, and the failure of the informed consent forms to include a statement regarding confidentiality of the participant's records. No underreporting of adverse events noted. Data in sponsor-provided data listings were supported by data in source documents and case report forms.

Recommendation: Overall, data from this site appear acceptable for use in support of this NDA.

- 3) **William Ondo, M.D.** **Site #7 – 10 subjects**
Baylor College of Medicine
Department of Neurology
6550 Fannin St.
Houston, TX

- a. What was inspected?

Five (5) subjects were enrolled into the study TBZ 103,004. The FDA field investigator reviewed the records for all 5 subjects enrolled in the study. The FDA field investigator reviewed the source documents, case report forms and compared with data listing provided by the sponsor as part of the NDA submission. The inspection encompassed an audit of all subjects' consent forms.

- d. Limitations of inspection: None.
- e. General observations/commentary

A four-item FDA 483, Inspectional Observations, was issued at the close of this inspection, noting the failure to adhere to protocol. Based on the Form FDA 483 and the establishment inspection report (EIR), inspectional findings are as follows:

1. The protocol required adverse events to be recorded throughout the study. Source notes dated 10/29/2003 document that subject 207 “Passed out today – No TBZ taken. Hit head on car door yesterday & cut.” However, this adverse event was not reported to the sponsor.
2. Source notes dated 1/12/2004 document that subject 209 had a dull headache for one week after starting study medication; however, this adverse event was not reported to the sponsor.
3. The protocol required that the clinical investigator immediately notify the Medical Monitor by telephone and by fax of any treatment suspension. Source documents record that subject 207’s treatment was stopped from 10/25/2003 to 10/29/2003; however, the Medical Monitor was not notified of this treatment suspension.
4. The protocol required that subjects taking 5 to 8 tablets per day were to be instructed to reduce the number of tablets to 4 per day for 2 days and then discontinue. Subjects 208, 210, and 211 took 2 tablets for 2 days as reduction to protocol’s active treatment and then discontinued.

Recommendation: Overall, data from this site appear acceptable for use in support of this NDA.

- 4) **Joseph Jankovic, M.D.** **Site – 145 subjects**
Baylor College of Medicine
Department of Neurology
6550 Fannin St.
Houston, TX

- a. What was inspected?

Inspection confirmed the inclusion of 145 subjects in this retrospective study (TBZ 103,011). The FDA field investigator reviewed the records for 25 subjects.

- b. Limitations of inspection: None.
- c. General observations/commentary

No Form FDA 483, Inspectional Observations, was issued at the close of the inspection. However, the clinical investigator did not report the adverse event of increased dysphagia for subjects 414, 347, and 8. The reason given for not reporting these AEs was that they were related to the subject's underlying disease.

Recommendation: Overall, data from this site appear acceptable for use in support of this NDA.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As detailed above, inspection revealed that there were two unreported adverse events and two protocol deviations at Dr. Ondo's site; that at Dr. Jankovic's site, the AE of increased dysphagia for three subjects was not reported; and that at Dr. Wojcieszek's site, an informed-consent document deficiency. At Dr. Corey-Bloom's site, no regulatory deficiencies were noted in the conduct of the study. In general, for the four clinical investigator sites inspected, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol. None of the inspectional findings adversely impact acceptability of the data generated at this sites. Therefore, data from these clinical sites appear acceptable for use in support of NDA 21-894.

Jose Javier Tavarez, M.S.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

Constance Lewin, M.D., M.P.H
Acting Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

DISTRIBUTION:

HFA-224
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HFD-46 Lewin

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

/s/

Constance Lewin
3/6/2006 03:27:15 PM
MEDICAL OFFICER

(A)

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Deliberative Process

Wheelous, Teresa A

From: Ben Lewis [benl@prestwickpharma.com]
Sent: Monday, March 13, 2006 12:30 PM
To: Wheelous, Teresa A
Subject: RE: Your E-mail--CMC Request
Importance: High

Hi Teresa,

Thank you for your note on the CMC requests. Please pass my e-mail to the Reviewing Chemist. I am, in fact, preparing a submission today in response to the CMC questions.

Because some of the questions dealt with a requested change to some of the specifications in the manufacturing process; this required a notification to our "licensor" (Cambridge Laboratories; UK) that these specs were to be changed and with further notification to ~~the licensor~~ that the changes were to be made and have — concurrence on these changes.

I have just received concurrence from Cambridge and — that all the requested specs have been changed and therefore I'm responding the questions from the Reviewing Chemist. I apologize for a delay, however the process took some time; again my apology. Please note that you will receive the submission tomorrow.

Regards, Ben

Benjamin P. Lewis, Ph.D., R.Ph., RAC
Vice President, Regulatory Affairs
Prestwick Pharmaceuticals, Inc.
202-296-1400
benl@prestwickpharma.com

From: Wheelous, Teresa A [mailto:teresa.wheelous@fda.hhs.gov]
Sent: Monday, March 13, 2006 9:23 AM
To: Ben Lewis
Subject:

Ben,

Have the responses to the CMC info requests that were sent in January been provided? If so, what is the submission date?

Thanks,

CDR Teresa Wheelous, R. Ph.
Sr. Regulatory Management Officer
FDA
Division of Neurology
10903 New Hampshire Avenue, Bldg. #22
Silver Spring, MD 20993-0002
(telephone) 301-796-1161

3/14/2006

(fax) 301-796-9842

New email address: teresa.wheelous@fda.hhs.gov

**APPEARS THIS WAY
ON ORIGINAL**

3/14/2006

Wheelous, Teresa A

From: Ben Lewis [benl@prestwickpharma.com]
Sent: Wednesday, March 08, 2006 3:32 PM
To: Davis, Carole; Feeney III, John J
Cc: Wheelous, Teresa A
Subject: Response to Your Questions for NDA 21,894 (Tetrabenazine)

Importance: High

Attachments: TBZ 103,004 - Site Investigator vs Videotaping Total Chorea Scores .pdf; Clinical Relevance of =3 Point Change in Total Chorea Score - Study TBZ 103,004.pdf; Cognitive Impairment in Study TBZ 103,004.pdf; Duration of TBZ Treatment in Study TBZ 103,005.pdf; How to Score the CGI.pdf



TBZ 103,004 - Site Investigato...



Clinical Relevance of =3 Point...



Cognitive pairment in Study .



Duration of TBZ Treatment in S...



How to Score the CGI.pdf (102 ...

Dear Dr. Davis and Dr. Feeney,

The following is in response to your phone call yesterday afternoon regarding NDA 21,894 for tetrabenazine for Huntington's chorea. Your questions are below (total of 6) and a response is provided with a corresponding attachment to each question. Please don't hesitate to contact me for clarification. Regards, Ben Lewis

Q1. *Where is the location of the Operation's Manual for the Tetra HD Study?*

A. The Operation's Manual is located in the paper copy of the NDA submission in Module 5, Volume 24 of 72, pp. 2015 – 2366.

Q2. *Do we have a 1:1 comparison of how the site investigator scored total chorea as compared to the outside reviewer scores?*

A. Please see the attached file:

“TBZ 103,004 – Site Investigator vs Videotaping Total Chorea Scores.pdf”

3. For the Tetra Withdrawal (Tetra WD) Trial, how long had patients been on drug prior to withdrawal?

A. Please see the attached file:

“Duration of TBZ Treatment in Study TBZ 103,005.pdf”

Please note that this file has been sorted 3 different ways, i.e. by treatment sequence groups. However, the duration of treatment prior to enrollment in years is provided on all tables.

Q4. For Study TBZ 103,004 (Tetra HD), there is a change of 3 on the chorea scale, what is the clinical relevance of the change of 3? Please discuss.

A. Please see the attached file:

“Clinical Relevance of ≥ 3 Point Change in Total Chorea Score - Study TBZ 103,004.pdf”

Q5. For the Global Assessment, Clinical Global Impression Scale (CGI), Part 2 what instructions are given to the investigator? What was taken into account?

A. Please see the attached file:

“How to Score the CGI.pdf”

Q6. For Study TBZ 103,004, (Tetra HD) how do you score the cognitive for Part II of the UHDRS, i.e. what is the cognitive assessment score of patients entering the clinical trial for Part II, UHDRS:

“Verbal Fluency Test,”

“Symbol digit Modalities Test,”

“Stroop Interference Test

Color Naming

Word Reading

Interference

A. Please see the attached file:

“Cognitive Impairment in Study TBZ 103,004.pdf”

This file contains:

1. A discussion of the cognitive impairment for Study TBZ 103,004
2. Excerpted Listings of “Baseline Cognitive Assessment,” UHDRS, Part II
3. Instructions to the HSG Investigators and Site Coordinators
4. Literature reference:

Unified Huntington's Disease Rating Scale: Reliability and Consistency. Huntington Study Group. Mov Disord. 1996 Mar;11(2):136-42.

Benjamin P. Lewis, Ph.D., R.Ph., RAC

Vice President, Regulatory Affairs

Prestwick Pharmaceuticals, Inc.

202-296-1400

benl@prestwickpharma.com

Wheelous, Teresa A

From: Ben Lewis [benl@prestwickpharma.com]
Sent: Monday, February 27, 2006 4:49 PM
To: Wheelous, Teresa A
Subject: RE: NDA 21-894 TBZ Clinical info Request 02/27/2006

Importance: High

Attachments: Suicidality narratives for review.doc; Suicidality narratives for review_redacted.doc



Suicidality
narratives for rev...



Suicidality
narratives for rev...

Hi Teresa,

Attached are the narratives for PSRAE referred to section 6.4.7 of the ISS. Please note that there are two attachments which are identical. One is full text and the other is a redacted version. The full text is what you probably want to use for review purposes.

The reason for the redacted version was that it was used internally by an expert panel. The expert panel was charged with reviewing the "blinded" narratives prepared on the 12 identified candidate suicidality cases and with assigning a Columbia Suicidality Classification to each candidate case narrative.

If you have any questions please don't hesitate to contact me by email or phone.

Regards, Ben

Benjamin P. Lewis, Ph.D., R.Ph., RAC

Vice President, Regulatory Affairs

Prestwick Pharmaceuticals, Inc.

202-296-1400

benl@prestwickpharma.com

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transmitted with it are completely deleted from your system. Although this e-mail and its attachments or files have been scanned for the presence of computer viruses, the security of e-mail communication cannot be guaranteed and Prestwick Pharmaceuticals, Inc. and its affiliates, officers, directors and employees will not be liable for any losses as a result of the use of this medium for exchanging electronic messages or the content of any messages, including any viruses contained therein.

From: Wheelous, Teresa A [mailto:teresa.wheelous@fda.hhs.gov]
Sent: Monday, February 27, 2006 12:10 PM
To: Ben Lewis
Subject: NDA 21-894 TBZ Clinical info Request 02/27/2006

Ben,

The following is a clinical request for NDA 21-894 Tetrabenazine:

Please send via email or fax a copy of the 12 narratives for PSRAE referred to in section 6.4.7 of the ISS.

Thank you,

CDR Teresa Wheelous, R. Ph.
Sr. Regulatory Management Officer
FDA
Division of Neurology
10903 New Hampshire Avenue, Bldg. #22
Silver Spring, MD 20993-0002
(telephone) 301-796-1161
(fax) 301-796-9842
New email address: teresa.wheelous@fda.hhs.gov

(B)

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 Deliberative Process

Wheelous, Teresa A

From: Tavarespagan, Jose
Sent: Friday, February 24, 2006 3:29 PM
To: Wheelous, Teresa A
Subject: RE: NDA 21-894 Tetrabenazine Inspections

Teresa,

Inspections were completed. I am working on the clinical inspection summary.

Jose Javier

-----Original Message-----

From: Wheelous, Teresa A
Sent: Friday, February 24, 2006 12:33 PM
To: Tavarespagan, Jose
Cc: Davis, Carole
Subject: NDA 21-894 Tetrabenazine Inspections

Jose,

Do you know the status of the inspections for NDA 21-894 Tetrabenazine?

The due date for this application is March 26, 2006.

Thank you,

CDR Teresa Wheelous, R. Ph.
Sr. Regulatory Management Officer
FDA
Division of Neurology
10903 New Hampshire Avenue, Bldg. #22
Silver Spring, MD 20993-0002
(telephone) 301-796-1161
(fax) 301-796-9842
New email address: teresa.wheelous@fda.hhs.gov

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Deliberative Process

Wheelous, Teresa A

From: Soldatova, Lyudmila
nt: Thursday, February 23, 2006 10:11 AM
to: Wheelous, Teresa A
Cc: Sood, Ramesh
Subject: RE: NDA 21-894 Tetrabenazine CMC Info Requests 2/16/07

Hi Teresa,

Thank you for the information.

Please let me know whether you received responses to the requests/questions for NDA applicant sent by Chhagan Tele in January. If you have any new information from the applicant, please send it to me.

Thanks,

Lyudmila.

-----Original Message-----

From: Wheelous, Teresa A
Sent: Friday, February 17, 2006 7:38 AM
To: Soldatova, Lyudmila
Subject: FW: NDA 21-894 Tetrabenazine CMC Info Requests 2/16/07

fyi

-----Original Message-----

From: Ben Lewis [mailto:benl@prestwickpharma.com]
Sent: Thursday, February 16, 2006 3:20 PM
To: Wheelous, Teresa A
Subject: RE: NDA 21-894 Tetrabenazine CMC Info Requests 2/16/07

Teresa,

Thanks for forwarding the below CMC Information Request. For question # 3, I have already requested notification that _____ the DMF holder, respond to FDA as soon as possible.

Can you tell me how the "Deficiency Comments" were sent to _____ If it were sent by regular mail, they may not have yet received the letter. However, if sent via FedEx they would have it in a few days. Or, if sent via e-mail would be very fast. I will give you 2 email addresses that would get it to _____ immediately. _____

Regards, Ben

Benjamin P. Lewis, Ph.D., R.Ph., RAC

Vice President, Regulatory Affairs

Prestwick Pharmaceuticals, Inc.

202-296-1400

benl@prestwickpharma.com

From: Wheelous, Teresa A [mailto:teresa.wheelous@fda.hhs.gov]
Sent: Thursday, February 16, 2006 9:29 AM
To: Ben Lewis
Subject: NDA 21-894 Tetrabenazine CMC Info Requests 2/16/07

Ben,

The following are CMC information requests for NDA 21-894 Tetrabenazine:

1. Add acceptance criteria for _____ as a part of suitability criteria in the HPLC method for assay and detection of impurities.
2. Provide information on how the drug substance batches to be used in the drug product manufacture will be tested for acceptance at the drug product manufacturing site (by Prestwick).
3. Please be advised that FDA has sent Deficiency Comments to _____ DMF holder of DMF _____ which you are cross-referencing for the Drug Substance information. Please ensure that the DMF holder responds to our comments in timely fashion.

Thank you,
Teresa Wheelous

Wheelous, Teresa A

From: Ben Lewis [benl@prestwickpharma.com]
Sent: Tuesday, February 21, 2006 10:29 AM
To: Wheelous, Teresa A
Subject: RE: Tetrabenazine Final Study Reports

Importance: High

Hi Teresa,

Please pass along to the Medical Reviewer that the INTERIM study reports for TBZ 103,006 and TBZ 103,007 are located in the NDA (# 21,894) at:

007: CTD Module 5.3.5.2.3 (Open-Label Extension Study = Follow-on to Tetra HD)

006: CTD Module 5.3.5.2.4 (Open-Label Extension Study = Follow-on to Tetra WD)

We are in the process of preparing FINAL study reports for each of these studies and are planned to be sent to you by no later than Monday (Feb 27). If you need to discuss, please don't hesitate to contact me.

Regards, Ben

Benjamin P. Lewis, Ph.D., R.Ph., RAC

Vice President, Regulatory Affairs

Prestwick Pharmaceuticals, Inc.

202-296-1400

benl@prestwickpharma.com

From: Wheelous, Teresa A [mailto:teresa.wheelous@fda.hhs.gov]
Sent: Friday, February 17, 2006 3:41 PM
To: Ben Lewis
Subject: Tetrabenazine Final Study Reports

Ben,

The medical reviewer would like to know where to find the final study reports for study 103.006 & 103.007. Let me know where in the electronic submission these study reports are located.

Thanks,

CDR Teresa Wheelous, R. Ph.
Sr. Regulatory Management Officer
FDA
Division of Neurology
10903 New Hampshire Avenue, Bldg. #22
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10

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 Deliberative Process

Wheelous, Teresa A

From: Wheelous, Teresa A
Date: Wednesday, February 15, 2006 2:27 PM
To: 'Ben Lewis'
Subject: DMETS Comments for NDA 21-894

Ben,

The following are DMETS comments regarding NDA 21-894 Tetrabenazine:

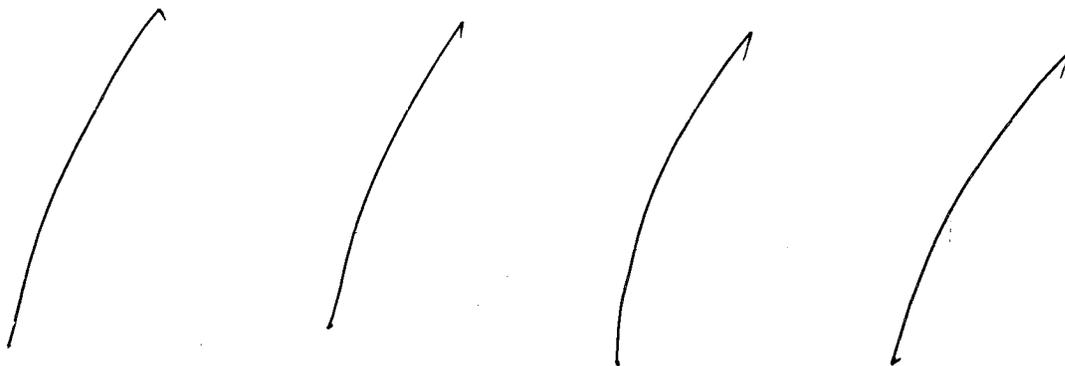
DMETS has no objections to the use of the proprietary name, Xenazine. This is considered a tentative decision and you are notified that this name with its associated labels and labeling must be reevaluated upon submission of the NDA and approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels and insert labeling of Xenazine, DMETS has attempted to focus on safety issues relating to possible medication errors. However, we note that the labels and labeling were submitted in black and white and may not represent the true color of the labels and labeling. Therefore, DMETS cannot assess if there are any safety concerns due to the colors utilized on the labels and labeling. However, upon review of the draft labels and labeling, DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS



C. DDMAC finds the proprietary name, Xenazine, acceptable from a promotional perspective.

Regards,
CDR Teresa Wheelous, R. Ph.
Sr. Regulatory Management Officer
FDA
Division of Neurology
903 New Hampshire Avenue, Bldg. #22
Silver Spring, MD 20993-0002
(telephone) 301-796-1161

(fax) 301-796-9842

New email address: teresa.wheelous@fda.hhs.gov

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**APPEARS THIS WAY
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**APPEARS THIS WAY
ON ORIGINAL**

Wheelous, Teresa A

From: Tele, Chhagan
Sent: Tuesday, February 07, 2006 2:36 PM
To: Wheelous, Teresa A
Cc: Sood, Ramesh; Soldatova, Lyudmila
Subject: NDA 21-894

Hi Teresa,

I will be out of my office from February 13 to March 10, 2006. As soon as you get the response to my IR from the applicant please sent it to Lyudmila Soldatova for the incorporation into the final review.

Thanks,

Chhagan Tele

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ON ORIGINAL**

Wheelous, Teresa A

From: Wheelous, Teresa A
Sent: Monday, January 30, 2006 10:32 AM
To: 'Ben Lewis'
Subject: Tetrabenazine NDA 21-894 Pharm / Tox Question 1/30/06

Ben,

The following is a pharmacology / toxicology question for NDA 21-894:

The report for the 9-month toxicity study in dog states that mid dose male dog #H40641 was a replacement animal that started dosing on Day 5. Therefore, it would appear that the original dog was replaced after 4 or 5 days of treatment. Why was the original dog removed from the study?

Please provide the response to this inquiry as soon as possible.

Thanks,

CDR Teresa Wheelous, R. Ph.
Sr. Regulatory Management Officer
FDA
Division of Neurology
10903 New Hampshire Avenue, Bldg. #22
Silver Spring, MD 20993-0002
(telephone) 301-796-2250
fax) 301-796-9842

Wheelous, Teresa A

From: Wheelous, Teresa A
Sent: Thursday, January 26, 2006 4:55 PM
To: 'Ben Lewis'
Subject: NDA TBZ - Another Clin Pharm Request 1/26/06 #2

Ben,

The following is another Clin Pharm info request for the Tetrabenazine NDA:

Since the QT evaluation has not been sent yet, please add the following:

When calculating the double delta for a given correction ((time matched treatment minus baseline) -(time matched placebo minus baseline)), calculate the mean by time (and plot this), and then give the maximum number from that calculation and give the upper 95% confidence interval. This gives the "maximum mean double delta QTc" for a given correction.

Thanks again,
Teresa

Wheelous, Teresa A

From: Wheelous, Teresa A
nt: Thursday, January 26, 2006 1:40 PM
To: Wheelous, Teresa A
Subject: FW: NDA TBZ Clin. Pharm Question 1/26/06

-----Original Message-----

From: Wheelous, Teresa A
Sent: Thursday, January 26, 2006 1:40 PM
To: 'Ben Lewis'
Subject: NDA TBZ Clin. Pharm Question 1/26/06

Ben,

This is a Clin. Pharm Question for the Tetrabenazine NDA:

Please reconcile the data from the original "mass balance study", the "Schwarz assignments", and the recent mass balance study to account for the metabolites and the metabolic scheme.

Wheelous, Teresa A

From: Wheelous, Teresa A
Sent: Tuesday, January 24, 2006 4:28 PM
To: 'Ben Lewis'
Subject: NDA 21-894 TBZ Debarment Certification

Ben,

The Debarment Certification needs to be revised and resubmitted.

A correctly worded Debarment Certification included with authorized signature is needed
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

*NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,
"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred
under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not
use wording such as "To the best of my knowledge .*

The Debarment Certification uses the wording" to the best of Prestwick's knowledge, ...

Regards,
CDR Teresa Wheelous, R. Ph.
Sr. Regulatory Management Officer
FDA
Division of Neurology
10903 New Hampshire Avenue, Bldg. #22
Silver Spring, MD 20993-0002
(telephone) 301-796-2250
(fax) 301-796-9842

Wheelous, Teresa A

From: Wheelous, Teresa A
nt: Tuesday, January 24, 2006 3:40 PM
ro: 'Ben Lewis'
Subject: Administrative info request

Ben,

Where can I locate the following forms?

Financial Disclosure forms included with authorized signature
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

*Thanks,
Teresa*

Wheelous, Teresa A

From: Wheelous, Teresa A
Sent: Tuesday, January 24, 2006 3:25 PM
To: 'Ben Lewis'
Subject: User Fee Waiver for NDA 21-894 TBZ

Ben,

Please provide the location, in the NDA 21-894, for the user fee exemption for the Tetrabenazine application.

Thanks,
Teresa

Wheelous, Teresa A

From: Wheelous, Teresa A
nt: Tuesday, January 24, 2006 9:57 AM
to: 'Ben Lewis'
Subject: Preclinical Info Requests for NDA 21-894 Tetrabenazine - 1/24/06

Ben,

The following are preclinical information requests for NDA 21-894 tetrabenazine:

Regarding the 26-week (13-week interim kill) study in rat, we have the following requests:

1. The study report for the 26 week study in rat with a 13 week interim kill states that all animals were subjected to "frequent" daily observations and weekly detailed clinical examinations. However, according to the individual animal line listings (Appendix 6) it would appear that, in some cases, animals were observed weekly, not daily, after Week 1. For example, "lethargy" would appear to be recorded only weekly (e.g., high-dose males), whereas "agitation" may have been recorded on a daily basis. Please clarify the schedule for the observation and reporting of clinical signs.
2. There appear to be discrepancies between the data presented in the summary table (Table 1) and the data presented in the individual animal line listings (Appendix 6). For example, according to the summary table, lethargy (mild/marked/unqualified) was observed in high-dose males throughout the dosing period; however, according to the individual animal listings, lethargy was not observed in this dose group beyond Day 28 of dosing. This and similar discrepancies should be addressed.

You need to confirm that the individual line listings are complete for each animal. You also need to provide a new summary table that provides a full delineation of clinical observations by dose group.

3. The day of sacrifice for each animal should be provided. Designation by week is not sufficient.

Please expedite.

Thanks,
Teresa

Wheelous, Teresa A

From: Wheelous, Teresa A
Sent: Tuesday, January 24, 2006 8:46 AM
To: 'Ben Lewis'
Subject: NDA 21-894 Tetrabenazine Clin. Pharm. Info Requests - 1/24/06

Ben,

The following are Clin. Pharm. info requests:

- 1) For the dissolution method, please clarify the spindle speed that was used to generate the data in 0.1 M HCl that are shown on page 27 and page 32 of the most recent (January 18) submission. Also, please provide appendix I, cited on page 26 of the January 18 submission, that describes the methodology used in the dissolution method development. Finally, if the data in 0.1 M HCl were generated at 100 rpm, please justify how the 50 rpm spindle speed was selected for the proposed method. If that is not the case, please clarify.
- 2) Is there any data to show that the proposed dissolution method can discriminate poorly performing tablets?
- 3) From the mass balance study, please clarify what is known about the extent of circulating mono- and bis-dealkyl tetrabenazine, and also whether the components of P16 have been identified.
- 4) Please confirm that in efficacy study 103,004 the plasma samples for TBZ and HTBZ determination were analyzed within the time they were stable under the storage conditions that were used.
- 5) Please clarify how it was determined that intrasubject variability in PK is low.

Thank you,

CDR Teresa Wheelous, R. Ph.
Sr. Regulatory Management Officer
FDA
Division of Neurology
10903 New Hampshire Avenue, Bldg. #22
Silver Spring, MD 20993-0002
(telephone) 301-796-2250
(fax) 301-796-9842

Wheelous, Teresa A

From: Ben Lewis [benl@prestwickpharma.com]
Sent: Friday, January 20, 2006 10:01 AM
To: Wheelous, Teresa A
Subject: RE: NDA 21-894 Tetrabenazine CMC Comments - Question 8 clarification

Teresa: Many thanks. Regards, Ben

Benjamin P. Lewis, Ph.D., R.Ph., RAC

Vice President, Regulatory Affairs

Prestwick Pharmaceuticals, Inc.

202-296-1400

benl@prestwickpharma.com

From: Wheelous, Teresa A [mailto:WHEELOUST@cder.fda.gov]
Sent: Friday, January 20, 2006 8:54 AM
To: Ben Lewis
Subject: NDA 21-894 Tetrabenazine CMC Comments - Question 8 clarification

Ben,

The CMC reviewer sends the following clarification:

Clarification on question 8 is as follow:

The inclusion of the _____ test in the stability protocol, to be performed at the initial time point and annually thereafter, for all future annual batches of 12.5 and 25-mg tablets placed on stability per the commitment in the NDA.

Thanks,

CDR Teresa Wheelous, R. Ph.
Sr. Regulatory Management Officer
FDA

Division of Neurology
10903 New Hampshire Avenue, Bldg. #22
Silver Spring, MD 20993-0002
(Telephone) 301-796-2250
(Fax) 301-796-9842

-----Original Message-----

From: Ben Lewis [mailto:benl@prestwickpharma.com]
Sent: Wednesday, January 18, 2006 4:08 PM
To: Wheelous, Teresa A
Subject: RE: NDA 21-894 Tetrabenazine CMC Comments
Importance: High

Dear Teresa,

Would be so kind to forward to the CMC Reviewer this email in order to get some clarification on question (# 8) of the CMC questions that you sent to me last Wednesday [1/11/06; your e-mail below]. I have prepared responses to all the questions except for question # 8. Once I receive some clarity from the CMC Reviewer, I can prepare a complete response to these questions and send to you.

Many thanks, Ben

8 Include annual testing for _____ or one batch of each strength of the drug product or provide justification for not testing _____ annually

Please clarify if the request to perform the _____ test on at least one batch of 12.5 and 25-mg tablets on an annual basis refers to setting up on stability one batch of each strength and testing for _____ on an annual basis, or to the inclusion of the _____ test in the stability protocol, to be performed at the initial time point and annually thereafter, for all future annual batches of 12.5 and 25-mg tablets placed on stability per the commitment in the NDA.

Benjamin P. Lewis, Ph.D., R.Ph., RAC

Vice President, Regulatory Affairs

Prestwick Pharmaceuticals, Inc.

202-296-1400

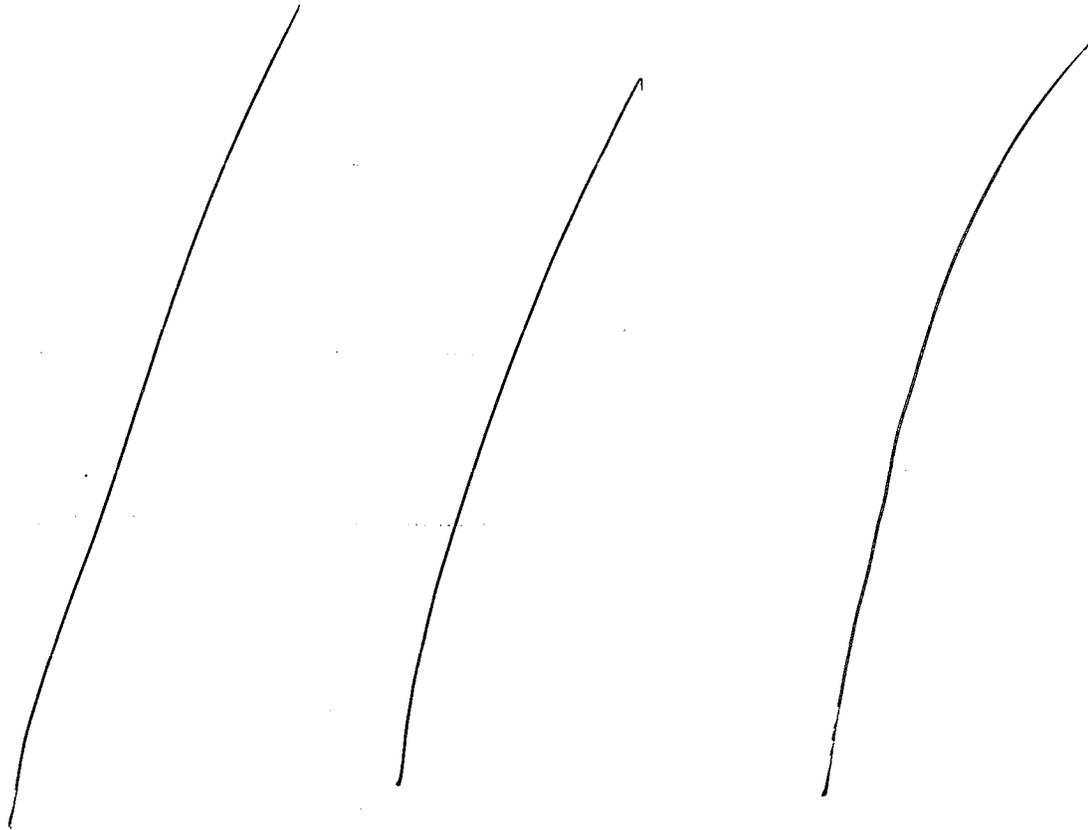
benl@prestwickpharma.com

From: Wheelous, Teresa A [mailto:WHEELOUST@cder.fda.gov]
Sent: Wednesday, January 11, 2006 9:47 AM
To: Ben Lewis
Subject: NDA 21-894 Tetrabenazine CMC Comments

Ben,

The following are CMC information requests for NDA 21-894 Tetrabenazine:

Please send the following comments to the applicant for the Xenazine (tetrabenazine) tablets (NDA 21-894):





Thank you,

*CDR Teresa Wheelous, R. Ph.
Sr. Regulatory Management Officer
FDA
Division of Neurology
10903 New Hampshire Avenue, Bldg. #22
Silver Spring, MD 20993-0002
(telephone) 301-796-2250
(fax) 301-796-9842*

Wheelous, Teresa A

From: Ben Lewis [benl@prestwickpharma.com]
Sent: Thursday, January 12, 2006 1:29 PM
To: Wheelous, Teresa A
Subject: FW: QT Questions from FDA

Importance: High

Attachments: NDA 21-894 TBZ Clin Pharm Info Requests - Jan. 10,2006



NDA 21-894 TBZ
Clin Pharm Info...

RE: Clarification to Clin Pharm Reviewer Information Request of Jan 10, 2006

Hi Teresa,

A Prestwick submission of Dec 23, 2005 (NDA No. 21,894 / Amendment 0009) contained information that would address the Clin Pharm Reviewer questions as provided in your Jan 10, 2006 e-mail; see attached), specifically questions # 4 and # 2.

Could you forward my e-mail to the Clin Pharm Reviewer and also, could the reviewer call me at 202-296-1400 to help clarify the question in order to respond appropriately. Many thanks.

Clin Pharm Question # 4

The Prestwick submission (Amendment 0009) included 15 Figures (Figure 5) which was on the CD as a zip file entitled "ESR TBZ 104,015_Figures. These figures present the change from baseline in HR, QT, QTcI, QTcB and QTcF vs. Concentration of alpha + beta, vs. alpha alone and vs. beta alone. Is this what the Clin Pharm Reviewer is looking for or is he interested in something else. Could you please clarify?

Clin Pharm Question # 2

Also, the results of the CYP2D6 genotyping can be found in listing Listing 27, also present on the CD as a zip file entitled "'ESR TBZ 104,015_Listings". Lastly, our data mgmt colleagues are preparing the SAS transport files outlined in question # 3.

Regards, Ben

Benjamin P. Lewis, Ph.D., R.Ph., RAC

Vice President, Regulatory Affairs

Prestwick Pharmaceuticals, Inc.

202-296-1400

benl@prestwickpharma.com

**APPEARS THIS WAY
ON ORIGINAL**

Wheelous, Teresa A

From: Wheelous, Teresa A
Sent: Tuesday, January 10, 2006 3:00 PM
To: 'Ben Lewis'
Subject: NDA 21-894 TBZ - Another Clin Pharm Info Request

Ben,

Another Clin. Pharm info request:

To support their dissolution method, please send results of dissolution testing in different batches (primary stability, BE study 104012, etc) and from all strengths so that the profiles as well as the raw data, and any other information they have to support their proposed dissolution methodology can be reviewed. Please be clear about the proposed method (including volume of dissolution media) and the specification.

Early next week would be good.

Thanks again,

*CDR Teresa Wheelous, R. Ph.
Sr. Regulatory Management Officer
FDA
Division of Neurology
10903 New Hampshire Avenue, Bldg. #22
Silver Spring, MD 20993-0002
(telephone) 301-796-2250
(fax) 301-796-9842*

Wheelous, Teresa A

From: Wheelous, Teresa A
nt: Tuesday, January 10, 2006 2:16 PM
io: 'Ben Lewis'
Subject: NDA 21-894 TBZ Clin Pharm Info Requests - Jan. 10,2006

Ben

The Clin Pharm reviewer has the following information requests for NDA 21-894 Tetrabenazine:

1. For the Efficacy Study 103004, please send a SAS transport file that lists the last dose taken and the time of the last dose in relation to the plasma concentrations and total daily dose for the data listed in PKLAB2 (the PK results from that study). If you can add those columns onto the PKLAB2 file that would be great.
2. Please send the report/results of the CYP2D6 analysis for the QT study
3. For the QT Study send a SAS transport file including the following columns: subject ID, time, treatment, QT (baseline), QT (treatment), QT (placebo), QT (each correction with a column for each treatment and for placebo), concentration of parent (if applicable) and each metabolite, delta QTc for each treatment (for each correction), and delta QTc for placebo (for each correction), double delta (placebo minus treatment, baseline subtracted), and RR.
4. Finally for the QT study, send concentration QTc plots to include a regression line (slope \pm 95% CI).

As usual, please send this info as soon as possible.

Thank you,

CDR Teresa Wheelous, R. Ph.
Sr. Regulatory Management Officer
FDA
Division of Neurology
10903 New Hampshire Avenue, Bldg. #22
Silver Spring, MD 20993-0002
(telephone) 301-796-1161
(fax) 301-796-9842

MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 1, 2005
TIME: 1:30 PM - 3 PM
LOCATION: WOC2, conference room E
APPLICATION: IND 63909 Tetrabenazine for Huntington's Chorea
TYPE OF MEETING: Pre-NDA Meeting
MEETING CHAIR: Dr. Katz

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Dr. Robert Temple – Office Director
Dr. Russell Katz – Division Director
Dr. John Feeney – Group Leader
Dr. Norman Hershkowitz – Medical Reviewer
Dr. Sharon Yan – Statistical Reviewer
Dr. Ronald Kavanagh – Clinical Pharmacology & Biopharmaceutics Reviewer
Dr. Judith Racoosin – Safety Team Leader
Dr. Marc Stone – Safety Reviewer
CDR Teresa Wheelous – Sr. Regulatory Management Officer

PRESTWICK ATTENDEES AND TITLES:

Kathleen Clarence-Smith, M.D. – President, R&D, Chief Scientific Officer
Christopher O'Brien, M.D. – Chief Medical Officer
Benjamin P. Lewis, Ph.D. – V. P., Regulatory Affairs
_____ - Consultant (Neurologist)
_____ - Consultant (Pharmacologist)
_____ Consultant (Statistician)
_____ - Consultant (Pre-clinical)
Jan Farino – Regulatory Affairs

BACKGROUND:

The Sept. 2, 2004 meeting request was granted on Sept. 15, 2004, and the meeting package was dated and received on November 9, 2004. Subsequently, the Dec. 1, 2004 meeting was rescheduled to February 2, 2005 at the sponsor's request.

DISCUSSION POINTS:

1. Prestwick's NDA for tetrabenazine relies on the findings of two adequate and well-controlled clinical investigations, TBZ 103,004 (Tetra HD Study) and TBZ 103,005 (Tetra Withdrawal Study) to support its claim for the product's efficacy in the _____ of chorea associated with Huntington's disease. **Does the Division have any concerns with this approach that might result in a "refusal to file?"**
- The division noted that the Sponsor does not have the standard two *positive* studies. A thorough explanation as to why the available data is considered adequate will be needed. We usually accept one study when we can't repeat a second study for ethical reasons. It

would be unusual, but it may be enough for filing. The issue may need to go to the advisory panel. Dr. Temple suggested that the Sponsor add an additional short, perhaps 2 day, withdrawal study in patients who are already on the medication.

2. The Clinical Pharmacology and Biopharmaceutics section of the official minutes from the End of Phase 2 meeting suggested that *"The sponsor needs to update the clinical pharmacology section of the labeling. The innovator's (Roche) labeling regarding mass balance data indicated that after IV dosing that only 55% of the dose was recovered after 48 hours, thereby indicating that 45% of the dose was still in the body, most likely as unidentified metabolites. This indicates that a mass balance study is needed."* In a subsequent telephone call on November 23, 2004, FDA informed Prestwick that the Clinical Pharmacology and Biopharmaceutics Division would recommend considering this mass balance study necessary for filing of the application.

Prestwick intends to provide the following data with respect to the metabolism of tetrabenazine:

- A qualitative determination by LC/MS/MS of the metabolites of tetrabenazine in humans as well as in the dog, rabbit, and mouse.
- Effect of tetrabenazine, α -dihydro-tetrabenazine, and β -dihydro-tetrabenazine on the *in vitro* activity of cytochrome P450 isoforms.
- The *in vitro* metabolism of tetrabenazine, α -dihydro-tetrabenazine, and β -dihydro-tetrabenazine by cytochrome P450 isoforms.
- A literature report of the urinary excretion of tetrabenazine and metabolites after intraperitoneal administration to rabbits and dogs and subcutaneous administration to people.
- Prestwick has measured plasma concentrations of tetrabenazine, α -dihydro-tetrabenazine, and β -dihydro-tetrabenazine over time in 45 healthy volunteers.

Prestwick therefore respectfully requests that the Division agree that such a study is not necessary for submission of an NDA. If as a result of review of the application, it becomes clear that there is a reasonable medical or scientific need for the information that would derive from a mass balance study, Prestwick would agree to conduct such a study as a Phase 4 commitment. **Does the Division concur with this approach?**

- The Division asked for clarification if the inter-species metabolism is all the same.
- Nine metabolites have been identified by LC/MS/MS, including three chiral pairs.
- The Division stated that a mass balance study is necessary to completely identify all metabolites. However, this study possibly could be provided during Phase 4.

Carcinogenicity Studies:

Will the lack of reports of *in vivo* lifetime carcinogenicity studies be grounds for the agency to 'refuse to file' Prestwick's NDA?

- This would not be a filing issue.

3. QT/QTc Assessment Issue:

Prestwick has not carried out a definitive clinical investigation on tetrabenazine, (i.e. a 'thorough QT/QTc study') as described in ICH's recently promulgated guidance, "E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs." Prestwick believes, however, that the evidence extant makes it reasonable to defer the conduct of such a study to the post-marketing period. Prestwick believes that these data reasonably establish that tetrabenazine has no clinically significant effect on the duration of the QT interval. **Does the Division agree to defer the conduct of a 'thorough QT/QTc study' to Phase 4?**

- The Division noted that information provided to this point on QT interval effects was extremely limited, consisting of studies at low dosages in healthy volunteers and a report of a negative hERG study. We asked if any more information could be included in the application, specifically whether Prestwick had access to adverse event reports from Canada and Europe.
 - Prestwick replied that they did have adverse event reporting information and that there were no reported incidents of torsade de pointes. They said they would be including this information along with estimates of tetrabenazine usage. They also reported that there were a large number of interpretable electrocardiograms available from the Phase III trials and that this information would also be included in the NDA.
 - The Division did not agree to defer the conduct of a thorough QT study; the need for the study will be a matter of review.
 - The present data, which looks at the Tmax for the parent compound, is problematic: one needs to consider potential effects of metabolites. Moreover, there is limited specific information on metabolites.
 - The Sponsor was queried as to whether there is any other EKG data. The Sponsor noted that they will have post-marketing reports and some EKGs from the first phase 3 trial.
 - In conclusion the answer to this question is that this will be dependent upon what is observed at the time of review. It is possible that it can be deferred.
4. Prestwick intends to submit a paper copy of the NDA (non-electronic). **How many copies does the Division require?**
- Please send 10 desk copies of volume 1 to the project manager.
5. **We are mindful that agency statisticians may want data files and statistical programs in electronic form. We will need the name of a contact person at FDA to define exactly what datasets and programs are needed and in what format.**
- The Sponsor was provided with information on the format for datasets.
 - The electronic version needs to be routed through the EDR.

6. Huntington's disease (HD) is a rare hereditary degenerative disease of the CNS that usually manifests itself in mid-adult life (35-50 years of age) and progresses to death in 12-15 years. The juvenile forms of HD are far rarer than adult expression and manifest chorea as a significant problem far less frequently than in adult forms. We believe that meaningful studies in children are highly impractical because the number of children with clinically significant chorea due to HD is so small and geographically dispersed. Therefore, we request that pediatric studies not be required in accordance with 21 CFR 314.55 (c)(2), "Pediatric use information, *Full waiver*." **Does the Division concur?**

- Yes

7. **Does the Division have any other comments or advice with respect to Prestwick's proposed submission of this NDA?**

- The Safety Team noted that reports of individual adverse events should be extensive, comparable to a case history or hospital discharge summary. In addition to individual reports, the incidence of adverse events should be reported in tabular form. Finally, as their appears to be a small drop in average hemoglobin in treated vs. control subjects, additional relevant information such as red cell indices should be included in the application.
- The Division intends to closely examine the issue of depression observed in the clinical studies.
- The Division noted an error in the method Prestwick used to adjust for baseline differences in chorea scores. Prestwick's statistical consultant was also aware of the error and Prestwick agreed to correct its analysis.
- The Division noted that that it is likely that the application would be presented to the PCNS Advisory Committee.

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

/s/

Russell Katz
1/5/2006 11:11:38 AM

Wheelous, Teresa A

From: Wheelous, Teresa A
nt: Wednesday, January 04, 2006 9:22 AM
to: Wheelous, Teresa A
Subject: FW: A few more 21894 things I need

CDR Teresa Wheelous, R. Ph.
Sr. Regulatory Management Officer
FDA
Division of Neurology
10903 New Hampshire Avenue, Bldg. #22
Silver Spring, MD 20993-0002
(telephone) 301-796-2250
(fax) 301-796-9842

-----Original Message-----

From: Wheelous, Teresa A
Sent: Wednesday, January 04, 2006 9:21 AM
To: Yasuda, Sally
Subject: RE: A few more 21894 things I need

Sally,

You info request has been sent.
Teresa

-----Original Message-----

From: Yasuda, Sally
Sent: Tuesday, January 03, 2006 3:32 PM
To: Wheelous, Teresa A
Subject: A few more 21894 things I need

Hi Teresa,

Happy New Year!

I have a few more things I need if you could please ask the Sponsor:

- 1) age of each subject in the hepatic impairment study TBZ 203,010
- 2) pH solubility profile of tetrabenazine (for the dissolution method consideration)
- 3) The pharmacogenomic study report (including analytical method) to support the CAG repeats for the clinical efficacy studies.

As always - I need it ASAP! - it would be great if they could send by next Monday or sooner!

Thank you very much!

Sally

Wheelous, Teresa A

From: Wheelous, Teresa A
Sent: Wednesday, December 21, 2005 4:22 PM
To: 'Ben Lewis'
Subject: NDA 21-894 Tetrabenazine In Vitro Study Design Information

Ben,

As discussed in a telecon today, 12/21/05, with Dr. Clarence-Smith, the following is the in vitro study design information that we promised to send:

In general, you should take a step-wise approach to understanding the metabolism of TBZ and its metabolites by identifying metabolic pathways (including non-CYP) and determining the contribution of P450. To then characterize methods for identifying the individual CYPs responsible for metabolism of either TBZ or its metabolites, we recommend the use of at least 2 methods. The design of in vitro experiments to characterize the metabolic pathways is outlined in the draft preliminary concept paper "Drug Interaction Studies – Study design, data Analysis, and Implications for Dosing and Labeling"

(http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4079B1_04_Topic2-TabA.pdf) and the you should refer to this for guidance on these studies. We would be happy to review a protocol for the in vitro studies.

In addition, although not discussed today, you should use this draft concept paper to guide your in vitro studies to characterize inhibition and induction of P450s by TBZ and its metabolites, as well as in vitro induction of TBZ or metabolite metabolism by P450s if appropriate.

Regards,
CDR Teresa Wheelous, R. Ph.
Sr. Regulatory Management Officer
FDA
Division of Neurology
10903 New Hampshire Avenue, Bldg. #22
Silver Spring, MD 20993-0002
(telephone) 301-796-2250
(fax) 301-796-9842

Wheelous, Teresa A

From: Wheelous, Teresa A
nt: Tuesday, December 13, 2005 4:02 PM
to: 'Ben Lewis'
Subject: Submission of info requested in the Withdrawal Letter for NDA 21-894 TBZ

Ben,

The Pharmacology / Toxicology reviewer would like to know when the information requested in the withdrawal letter (see below) will be submitted?

Pharmacology / Toxicology:

1. The photo-reduction of many of the literature reports presented in module 4, volumes 24-27 has resulted in text that is frequently too small to review (e.g., 4.3.4: Bagchi 1983, and 4.3.23: Darchen 1988A). Although not all of the references are affected, many are. The most expeditious solution to this problem would be for you to simply submit a "desk copy" of the literature references in their original size. Please submit this "desk copy" as soon as possible.
2. The study reports for the 4 and 26 week toxicity studies in rat (4.2.3.2.2.2: 19371 and 4.2.3.2.2.3: 20730, respectively) do not contain summaries or discussions of unscheduled deaths (i.e., animals found dead or subject to a moribund/humane sacrifice or accidental deaths). You should provide a summary table for each of the two studies that contains the treatment group, animal number, circumstances of the early death/sacrifice, date of death (with regard to initiation of treatment), and cause of death when possible.

**APPEARS THIS WAY
ON ORIGINAL**

Thank you,
CDR Teresa Wheelous, R. Ph.
Sr. Regulatory Management Officer
FDA

Division of Neurology
10903 New Hampshire Avenue, Bldg. #22
Silver Spring, MD 20993-0002
(telephone) 301-796-2250
(fax) 301-796-9842

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-894

Prestwick Pharmaceuticals, Inc.
Attention: Benjamin Lewis, Ph.D.
Senior Director, Regulatory Affairs
1825 K Street N.W., Suite 1475
Washington, DC 20006

Dear Dr. Lewis:

Please refer to your September 23, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tetrabenazine 12.5mg and 25 mg tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on November 26, 2005 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

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

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Russell Katz
12/14/2005 08:00:30 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-894

Prestwick Pharmaceuticals, Inc.
Attention: Benjamin Lewis, Ph.D.
Senior Director, Regulatory Affairs
1825 K Street N.W., Suite 1475
Washington, DC 20006

Dear Dr. Lewis:

We have received your June 13, 2005 correspondence on June 14, 2005 notifying us that you are withdrawing your new drug application (NDA) for (Tetrabenazine) Tablets 12.5mg and 25 mg prior to its filing date.

In accordance with 21 CFR 314.65, this application is withdrawn as of June 14, 2005.

If you decide to resubmit this application, this withdrawal will not prejudice any future decisions on filing. You may reference information contained in this withdrawn application in any resubmission. However, because we retain only the archival copy of a withdrawn application in our files, you should resubmit appropriate review copies of all information. Retain the above NDA number for the resubmitted application but obtain a new user fee identification number. The new user fee identification number must be on the User Fee Cover Sheet in the resubmitted application. Submit the check for the appropriate user fee to the following address:

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

For courier delivery, write the NDA number, the FDA Post Office box number (P.O. Box 360909), and the user fee identification number are the check and deliver it to the following address:

Food and drug Administration (360909)
Mellon Client Service Center, Room 670
500 Ross Street
Pittsburgh, PA 15262-0001

In addition, the resubmitted application should address the following deficiencies identified before receipt of your withdrawal request:

CLINICAL

As discussed in our teleconference on June 1, 2005, we have found a number of deficiencies in the module that contains the ISS of this withdrawn NDA. We ask that if you resubmit the NDA you revise the submission to address such deficiencies.

- There should be an attempt to synthesize information from a variety of sources in the discussion of potential drug causality in adverse events. This is particularly important with regard to already-identified significant events such as depression, suicide, Parkinsonism, orthostatic blood pressure changes, CNS changes (e.g. somnolence), etc, but may also include analyses of serious adverse events as well as those resulting in withdrawal or death. Because of the paucity of formal controlled studies, data from the post-marketing and the open label data base should be included in these discussions. Such sections should include a thorough discussion of potential causality by drug by examining drug/placebo incidences in the controlled study as well as a comparison of incidences in open label and post marketing experience with rates expected in the studied (Huntington's) population.
- This module should be relatively self contained and easily navigable. The data should be presented in a fashion that does not require the reader to persistently refer back to the original study reports. For example, in the discussion of cardiac interval data, complete cardiac interval tables should be presented. There should be a description as to how these tables were derived and a thorough examination of the data using central tendencies and outlier analyses.
- Because of this division's recent experience examining the issue of suicidality in pediatric patients on antidepressants, a guide to assist sponsors in examining treatment emergent signals for this adverse event has been created and is attached to this letter. Because of tetrabenazine's mood altering effects, we ask you to address this issue, using these techniques, and submit your results in the revised ISS.
- Also included with this letter is a general outline and description as to what is expected in an ISS. This was distributed to you by Dr. Hershkowitz at the previous pre-NDA meeting on 2/1/05. You should ascertain that all the elements contained in this outline are included in your revised submission.

Although not filing issues, we have the following comments and information requests:

Pharmacology / Toxicology:

1. The photo-reduction of many of the literature reports presented in module 4, volumes 24-27 has resulted in text that is frequently too small to review (e.g., 4.3.4: Bagchi 1983, and 4.3.23: Darchen 1988A). Although not all of the references are affected, many are. The most expeditious solution to this problem would be for you to simply submit a "desk copy" of the literature references in their original size. Please submit this "desk copy" as soon as possible.
2. The study reports for the 4 and 26 week toxicity studies in rat (4.2.3.2.2.2: — 9371 and 4.2.3.2.2.3 — 20730, respectively) do not contain summaries or discussions of unscheduled deaths (i.e., animals found dead or subject to a moribund/humane sacrifice or accidental deaths). You should provide a summary table for each of the two studies that contains the treatment group, animal number, circumstances of the early death/sacrifice, date of death (with regard to initiation of treatment), and cause of death when possible.

Page 3

If you have any questions, call CDR Teresa Wheelous, Sr. Regulatory Management Officer, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

**Appendix A:
A description of ISS Organization**

- The ISS should clearly state what safety assessments were carried out in each study included in the ISS. A tabular presentation of schedule of events might be helpful.
- All deaths that occurred in the clinical development program or found during a literature search and from various commercial and non-commercial databases (ex AERS) should be described in a single section and individual deaths should be listed in a table.
- All non-fatal serious adverse events, regardless of assigned causality, that occurred during the clinical development program or were reported from secondary sources (i.e. literature and/or post marketing reports) should be described in a single section. Serious adverse events may, in addition to signs, symptoms, and diagnosable events, include changes in laboratory parameters, vital signs, ECG, or other parameters of sufficient magnitude to meet the regulatory definition of a serious adverse event [21 CFR 312.32(a); 314.80(a)].
- Dropouts due to adverse events should be clearly described in a single section of the ISS. CRF/narratives should be provided for all dropouts. An overall profile of these patients by reason for dropping out (e.g. adverse events, treatment failures, lost to follow up) should be provided. For the more common adverse events associated with dropouts, the ISS should present the incidence of these adverse events, preferably in a table. Investigator causality assessment can be described but should be justified. The ISS should also describe any dose-response, time dependency of the dropout, drug-demographic, drug-disease, and drug-drug interactions. With respect to rarer events that could represent an important adverse event, the ISS should critically assess whether any of these may represent treatment-induced injury. Finally the ISS should consider these events individually with narratives and reference to other data as appropriate.
- The ISS should contain a section entitled "Other Significant Adverse Events." This section should describe significant safety findings such as marked hematological or other lab abnormalities not meeting the definition of serious, any events that led to an adverse dropout or any other intervention such as dose reduction or significant additional concomitant therapy (an expansion of the adverse dropout concept) and potentially important abnormalities not meeting the above definition of serious and not leading to death or modification of therapy (e.g., a single seizure, syncopal episode, orthostatic symptoms). Those adverse events that did not lead to discontinuation but otherwise meet the definition described above should be described in this section.
- If preclinical pharmacology/toxicology, post-marketing and/or literature reports provide insight into possible safety signals with the investigational drug product the ISS should describe any findings relative to these signals. This is especially important for new chemical entities. Similarly, if there are particular safety concerns evident from other drug products that are members of the same pharmacological class as the investigational drug product, the ISS should describe a thorough safety analysis of these concerns.
- The ISS should contain a section entitled "Common Adverse Events". You should include a table (or tables) that present the best overall display of commonly occurring adverse events, generally those occurring at a rate of 1% or more (but lower rates can be presented for very large data bases). This table or tables will be the basis for the ADR table in labeling, which may, however, use a higher cut off if this does not lose important information, and will eliminate ADRs that are equally common on drug and placebo. This table or tables should compare the incidence of common adverse events between cohorts regardless of the investigator's assignment of causality from the pooled studies. You should justify any decision for not including a particular study in the pooled adverse event incidence tables. For development programs with a significant amount of severe adverse events it would be helpful to include a table that compares the incidence of severe adverse events between cohorts from the pooled studies.
- For adverse events that seem clearly drug related (i.e., consistent difference from control across studies, evidence of dose response etc.) you should provide the following additional analysis as appropriate:

1. exploration for dose dependency, exploration of time to onset (for those that show a delay in onset)
 2. exploration of adaptation (for common, troublesome events such as somnolence, nausea)
 3. explorations of demographic interactions, explorations of drug-disease and drug-drug interactions (if there is a strong signal for an interaction, or a good rationale for expecting an interaction)
 4. selective exploration of individual cases in an attempt to better characterize the events.
- For each trial described in the ISS you should include a brief discussion on how adverse events were captured (i.e. checklist, open-ended questions on follow up visits etc.). The frequency of assessments should also be described.
 - For each trial described in the ISS you should clearly state which translation dictionary (MedDRA, COSTART) was used to categorize verbatim adverse event terms.
 - The ISS should include a discussion of the less common adverse events of significant concern seen across all studies in the clinical development program. Since the overall database is typically very heterogeneous, it is unlikely to lend itself to meaningful estimations of rates or assessments of causality. Thus it may be sufficient to group these events by incidence and by body system. For example, it may be useful to categorize less common adverse events in order of decreasing frequency within certain ranges: e.g. $\leq 1\%$, between 0.1% and 1% ; $\leq 0.1\%$.
 - The ISS should clearly provide an overview of what laboratory testing (chemistry, hematology, and urinalysis) was carried out in each study. It is best to summarize the overall approach, rather than provide detailed comments about laboratory testing for each study. The ISS should also describe any discrepancies between planned analyses and those actually conducted, as well as the procedures used to evaluate abnormal values. Provide a summary table identifying the numbers of patients exposed to test drug who had baseline laboratory values and follow-up assessments.
 - The ISS should include an integrated discussion of significant laboratory findings from the clinical development program. Controlled comparisons generally provide the best data for deciding whether there is a signal of an effect of a drug on a laboratory test. However placebo-controlled trials are generally short term, and unsuitable for assessing late-developing abnormalities, so that longer term data need to be therefore examined also. If there is no concomitant control in the long term studies the comparison may need to be with similar populations outside the NDA. The ISS should explain which studies were pooled relative to the evaluation of laboratory findings and why they were selected.
 - The ISS should generally include three standard approaches to the analysis of laboratory data. The first two analyses are based on comparative trial data. The third analysis should focus on all patients in the phase 2-3 experience. Analyses are intended to be descriptive and should not be thought of as hypothesis testing. P-values or confidence intervals can provide some evidence of the strength of the finding, but unless the trials are designed for hypothesis testing (rarely the case), these should be thought of as descriptive. The analysis of all laboratory findings should include a comparative description of mean or median changes from baseline across treatment groups. The ISS should include a discussion on individual patients whose laboratory values deviate substantially from the reference range and describe what criteria were used to identify outliers. Additional analyses may be appropriate for certain laboratory findings, including analyses for dose dependency, time dependency, and also drug-demographic, drug-disease, and drug-drug interactions. The ISS should discuss the rationale for additional explorations, the methods used, and the results and interpretations.
 - The ISS should include an evaluation of vital sign assessment using a similar approach as described for laboratory data (i.e., description of vital sign assessment in each study, measures of central tendencies, analysis focused on shifts from normal to abnormal, discussion of outliers etc).
 - The ISS should include an evaluation of ECG findings using a similar approach as described for laboratory data (i.e., description of ECG assessments in each study, measures of central tendencies, analysis focused on shifts from normal to abnormal, discussion of outliers etc). Particular attention should be given to ECG findings where the timing of the assessment was done at or near the time of maximum concentration for the drug product (generally during phase I or phase II studies) in order to assess QT prolongation effects. A brief discussion on any preclinical cardiac findings would be helpful in orienting the reviewer to any potential concerns.

- The ISS should include a discussion of the impact of immunogenicity (if applicable) on safety, efficacy and/or clinical pharmacology and pharmacokinetics.
- The ISS should include a brief discussion of human carcinogenicity data if available. A systematic discussion of all human tumors reported during drug development can provide useful safety information, particularly in the case of drugs or biologics that have positive genotoxicity or animal carcinogenicity findings, or those that are known immune modulators.
- The ISS should include a summary of any studies designed to evaluate a specific safety concern(s). These studies may include:
 1. studies to assess whether a drug has safety concerns common to its pharmacological class
 2. studies in topical products to assess cumulative irritancy, contact sensitizing potential, photosensitivity, and photoallergenicity
 3. studies to characterize the effect on the QT interval (part of most modern development efforts)
 4. studies intended to demonstrate a safety advantage over therapeutic alternatives
- The ISS should contain a discussion of abuse potential and any apparent withdrawal symptoms seen during the clinical development program. This discussion should contain a summary of findings from any non-clinical and clinical abuse liability studies (if done), problems in medication accounting encountered while monitoring the investigational supply of medication, chemistry and pharmacology issues that relate to abuse potential, and relevant adverse events and epidemiologic data. The ISS should describe any adverse events that emerge after discontinuation of the drug in order to determine whether they may indicate a withdrawal phenomenon. If studies evaluated the potential for withdrawal phenomena, the ISS should indicate whether there was a prospective or post-hoc assessment of withdrawal emergent signs and symptoms (during drug taper or following discontinuation) and discuss the implications of the approach used on the reliability of the findings.
- The ISS should include a discussion of all pregnancies that occur during the clinical development program. A brief description of each pregnancy should include outcome, duration on therapy, use of drug relative to trimester.
- The ISS should summarize all overdose experience with the investigational drug/biologic in humans. The summary should include a description of the constellation of signs and symptoms that might be associated with overdose. A description of phase I or phase II safety findings in subjects exposed to doses higher than planned for marketing should be included. Patients with certain physiological differences that would compromise their ability to clear the drug (e.g. renal impairment, limited CYP450 2D6 activity for a drug cleared by this isozyme) may provide relevant data to the clinical implications of overdose.
- The ISS should include relevant findings from U.S. and foreign post-marketing experience if available.
- The ISS should include a clear description of all patient exposures from the entire clinical development program. The exposure summary should describe various demographic subsets such as race, gender and age. Additionally the summary should include a clear description of dose and duration of exposure. Tables and graphs may be helpful in describing the data sources for the ISS. If applicable the ISS should describe any secondary sources of safety data (ex. studies not conducted under the IND and not meeting the standards for inclusion as primary, post marketing data, and/or literature reports). Secondary sources should be briefly described. Original articles and study reports should be provided.
- The ISS should briefly describe the findings from any preclinical studies that were conducted in order to explore certain potential adverse events, using preclinical models based either on a drug's pharmacology or on clinical findings that emerged early in clinical development. For example, for a drug anticipated to cause QT prolongation because of its drug class or because QT prolongation was seen in phase I studies, were there any preclinical (in-vitro) studies done to evaluate this potential.
- The ISS should include a discussion of any in vitro and in vivo studies done to evaluate how a drug is metabolized and excreted. Issues to be included should include the following:
 1. The enzymatic pathways responsible for clearance of the drug and the effects of inhibition of those pathways, notably CYP450 enzymes and p-glycoproteins.

2. The effect of the drug on CYP450 enzymes (inhibition, induction) and the effects of the drug on the PK of model compounds.
 3. The major potential safety consequences of drug-drug interactions.
- The ISS should describe the general methodology used to construct the integrated safety review. This discussion should include a rationale for pooling safety data (if done) and the method employed. For example a justification for pooling safety data may include an argument that a larger data base will permit explorations of possible drug-demographic or drug-disease interactions in subgroups of the population or pooling data from different studies can improve the precision of an incidence estimate (i.e., narrow the confidence intervals by enlarging the sample size). In pooling safety data, usually the numerator events and denominators for the selected studies are simply combined. If other more formal weighting methods are used (e.g., weighting studies on the basis of study size or inversely to their variance) the ISS should justify why and how it was done. Information on baseline risk factors of concern should be retrievable from the case report tabulations.
 - Since adverse reaction rates may differ considerably from one patient population to another and may change over time the ISS should explore factors that may affect the safety profile of a drug. For example the ISS could explore common drug related predictive factors, such as dose, plasma level, duration of treatment and concomitant medications, and patient related predictive factors such as age, sex, race, concomitant illnesses. In general, these explorations are meaningful only for adverse reactions that appear to be drug-related. The ISS may present these explorations using the following subheadings: exploration of dose-dependency for adverse findings, explorations for time dependency for adverse findings, exploration for drug-demographic interactions, exploration for drug-disease interactions and exploration for drug drug interactions. It may be helpful to link individual safety observations with other on-therapy data such as dose, duration of treatment, concomitant therapy, other adverse effects, lab data or effectiveness results.

**APPENDIX B:
ADVICE FOR THE PHARMACEUTICAL INDUSTRY IN EXPLORING THEIR PLACEBO-
CONTROLLED CLINICAL TRIALS DATABASES FOR SUICIDALITY AND PREPARING
DATA SETS FOR ANALYSIS BY FDA**

[Draft: 7-21-05]

Given the finding of a signal for an increased risk of suicidality (suicidal ideation and behavior) in pediatric patients exposed to various antidepressants in placebo-controlled trials, and possible signals for treatment-emergent suicidality for antidepressants and other drugs in adult trials, including nonpsychiatric drugs and indications, there is interest in re-examining data from trials of a broader range of drugs and indications. In exploring these clinical trials databases, we recommend that similar methods to those used in evaluating the pediatric antidepressant data be utilized. We have outlined in this guidance document an approach that we recommend for these exploratory efforts.

Clinical Trials to Include in the Suicidality Exploration

Precisely which trials to include will depend in part on the study designs used in the indications of interest. In general, however, we recommend that the explorations be limited to double-blind, randomized, placebo-controlled trials which have been completed. Duration of the trials should not be a limiting factor, however, we recommend that only trials with at least 20 patients or subjects per treatment arm be included. Before beginning the exploration, we ask that you provide a list of the trials that you intend to include, and also a list of the RCTs that you have chosen not to include, along with a brief explanation for their exclusion.

Once there is agreement with FDA on which trials to include in the exploration, we ask that you provide certain descriptive information about these trials. We ask that you provide this information in table format at the same time that you submit a dataset with the suicidality data (see later). Attached to this document is the information that should be included in the requested tables.

Search for “Possibly Suicide-Related” Adverse Events and Preparation of Narrative Summaries

Time Frame for “Possibly Suicide-Related” Adverse Events

This search should be strictly limited to adverse events that occurred during the double-blind phase of treatment, or within 1 day of stopping randomized treatment. Adverse events should not be included if they occurred prior to randomization or more than 1 day after discontinuing from randomized treatment. The end of trials with a tapering period should be set to be at the beginning of the tapering period. Events occurring more than 1 day after discontinuing from randomized treatment should be excluded even if discontinuation occurred before the nominal endpoint of the trial. For example, if a patient either discontinued of his or her own volition or was asked to discontinue by the investigator after 2 weeks of randomized treatment in a trial of 8 weeks duration, and the patient then experienced a “possibly suicide related” adverse event 2 days after stopping, that event should not be included.

Generally, events that are preexisting at baseline are not counted as treatment emergent if they recur during the course of a trial. However, in the requested analysis, suicidality-related events that occur during the course of the double-blind phase or within 1 day of beginning taper, switching or stopping treatment should be counted, even if they occur in a patient who had such events at some prior time. The rationale for this rule is that it is generally very difficult to determine for the quality of data available in most of these trials whether suicidality occurring during the context of these trials is new or a continuation of some prior event.

Search Strategies for Possibly Suicide-Related Adverse Events (PSRAEs)

The following search strategies should be employed to identify adverse events of possible interest with regard to suicidality:

- The following text strings should be used in searches of (1) all preferred terms; (2) all verbatim terms; and, (3) any comment fields:

“accident-”, “attempt”, “burn”, “cut”, “drown”, “gas”, “gun”, “hang”, “hung”, “immolat”, “injur-”, “jump”, “monoxide”, “mutilat-”, “overdos-”, “self damag-”, “self harm”, “self inflict”, “self injur-”, “shoot”, “slash”, “suic-”, “poison”, “asphyxiation”, “suffocation”, “firearm” should be included. All events identified by this search should be included among the PSRAEs, unless they can be considered false positives.

Note: Any terms identified by this search because the text string was a substring of an unrelated word should be excluded (for example, the text string “cut” might identify the word “acute”). These terms might be characterized as “false positives” in the sense that the verbatim term was selected because one of the text strings occurred within that term but the term had no relevance to suicidality. Although we request that such terms be excluded, we ask that you prepare a table listing all such false positives, as follows:

<u>Study #</u>	<u>Patient #</u>	<u>Treatment Assignment</u>	<u>Term in Which Text String Occurred</u>
----------------	------------------	-----------------------------	---

The patients in this table will have as many rows as they have potential events.

- All deaths and other serious adverse events (SAEs) should be included among the PSRAEs.
- All PSRAEs identified by these 2 search strategies (and not excluded as “false positives”) should have narrative summaries prepared, as described in the following section.

Preparation of Narrative Summaries for “Possibly Suicide-Related” Adverse Events

A complete set of narrative summaries should be prepared and collected for all PSRAEs that were not otherwise excluded as false positives. In some cases, narratives will have already been prepared, e.g., deaths and SAEs. Many of these may be acceptable, however, some may need to be re-written if important information is missing (see below). In other cases, however, sponsors will need to prepare narrative summaries by searching CRFs for any information that might be considered possibly relevant to suicidality. They should also utilize other relevant sources of information, e.g., hospital records, results of consults, questionnaire responses, etc, in preparing these narrative summaries. Depending on how much information is available, narrative

summaries may be longer than 1 page, however, in no case, should more than 1 narrative summary be included on a single page. Following is the type of information that should be included in the original narrative summaries:

- Patient ID number
- Trial number
- Treatment group
- Dose at time of event (mg)
- Recent dose change – elaborate on timing and amount of dose change
- Sex
- Age
- Diagnosis
- History of suicidal thoughts
- History of suicide attempt
- History of self harm
- Adverse event Preferred term
- Adverse event Verbatim term
- Serious adverse event (y/n)
- Number of days on drug at time of event
- Treatment was discontinued following event (y/n)
- Patient had an emergency department visit and was discharged (y/n)
- Patient was hospitalized (y/n)
- Patient died (y/n) – if yes, elaborate on cause of death
- Associated treatment emergent adverse events
- Concurrent psychosocial stressors
- Psychiatric comorbidities
- Concomitant medications
- Other pertinent information (e.g., family history of psychiatric disorders)-

Other relevant information for preparing narrative summaries:

-Patients may be identified as having events of interest in one or more of the above searches, and they may have more than one event of interest. In no case, however, should there be more than one narrative summary per patient. In cases where there is more than one event for a given patient, each different event should be clearly demarcated in the narrative.

-Only events occurring during the “exposure window” defined as during the double-blind phase (including the first day after abrupt discontinuation or the first day of taper, if tapering is utilized) should be included in the narrative summary, i.e., sponsors should not include any prerandomization events or events occurring more than 1 day after stopping randomized treatment or during the tapering period.

-As noted, sponsor should not exclude events of interest on the basis of a judgment that they might not represent “treatment-emergent” events; we feel this judgment is too difficult to make and we prefer to simply include all potentially relevant events, regardless of whether or not similar thoughts or behaviors may have occurred prior to treatment.

The narrative summaries do not need to be submitted to FDA. However, we may at some point request a random sample of the summaries to audit your classification process.

Classification of “Possibly Suicide-Related” Adverse Events

Once the narrative summaries for “possibly suicide-related” adverse events are prepared and collected, we ask that you accomplish a rational classification of these events using the approach that was well-characterized by the Columbia group for the pediatric suicidality narratives. This approach was described in detail by Dr. Kelly Posner at the September 13 and 14, 2004 advisory committee meeting. The details are provided in her slides for that meeting (available on FDA’s website), in the transcript for that meeting, and in other reviews, etc. pertinent to pediatric suicidality and available on FDA’s website [Slides http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4065S1_06_FDA-Posner.ppt and Briefing Document, transcripts, etc. <http://www.fda.gov/ohrms/dockets/ac/cder04.html#PsychopharmacologicDrugs>

The categories of interest from FDA’s standpoint are as follows:

- Completed suicide (code 1)
- Suicide attempt (code 2)
- Preparatory acts toward imminent suicidal behavior (code 3)
- Suicidal ideation (code 4)
- Self-injurious behavior, intent unknown (code 5)
- Not enough information (code 6a for fatal and 6b for nonfatal)
- Self-injurious behavior, no suicidal intent (code 7)
- Other: accident; psychiatric; medical (code 8)

Those individuals who classify the narratives must have the appropriate expertise and training to accomplish this task. Thus, this task could be accomplished by seeking the help of an outside contractor who has this expertise. However, it is also possible that a sponsor may have internal expertise to accomplish this classification. Even in the latter instance, you may consider at least obtaining training of your internal staff from an outside contractor. Such training might help to increase the reliability of the classifications for subsequent meta-analyses of the data across programs.

Prior to their rational classification, the narratives must be blinded to details that might bias their assessments. The details of appropriate blinding of the narratives can also be obtained in the transcript from the advisory committee meeting referred to above, and the materials available on FDA’s website pertinent to that meeting. We request that you block out the following information that could reveal treatment assignment:

- Identifying patient information, identity of study drug, and patient's randomized drug assignment
- All identifying information regarding the sponsor, the clinical trial number, and the location of the trial
- All years with the exception of years in remote history
- Study drug start and stop dates (month, day, and year)
- All medications, both prescription and non-prescription, whether taken before, during, or after the study; non-pharmaceutical substances (e.g., alcohol, tobacco) should not be blocked out
- Names of medications involved in overdoses; the number of pills consumed should not be blocked out

- Indications for medications started during or after the study
- Indications for study drug

Data Submission

In order to perform additional analyses investigating the relationship between exposure to the drug of interest and PSRAEs among the patients of interest, we would appreciate your submitting the following variables as outlined in the next table. As noted, we are requesting information from placebo controlled trials only. Please do not submit data from active control only studies, uncontrolled extensions of placebo controlled studies, or combination drug studies. We would expect that you will provide us with a SAS transport file.

Variable name	Type	Description	Coding notes
SOURCE	Character	First few letters of your drug name	
TRIAL	Character	Trial ID	
INDICATION	Character	Indication that is focus of the trial	
CTPID	Character	Patient ID within each trial	
UNIQUEID	Character	A unique ID for every patient	
AGE	Numeric	Patient age	In years
AGECAT	Numeric	Age category	1=5-17 y 2=18-24 y 3=25-64 y 4=65 y or more
GENDER	Numeric	Patient gender	1=female 2=male
RACE	Numeric	Patient race	1=White Caucasian 2=African-American 3=Hispanic 4=Asian 5=Other . = Missing
RANTXCAT	Numeric	Treatment category (assuming drugs can be categorized by class)	1= 2= 3= 6=placebo
SETTING	Numeric	Setting of trial	1=inpatient 2=outpatient 3=both
LOCATION	Numeric	Location of trial	1=North America 2=Non-North America
TXARM	Numeric	Randomized treatment	1=drug 2=placebo 3=active control No missing values are allowed in this variable.

Variable name	Type	Description	Coding notes
TXACTIVE	Character	Name of drug used as active control	Leave patients in other treatment arms blank
SCALE	Character	Primary scale used to rate indication that is focus of the trial (this variable is required only for depression trials)	This should be a text field. As noted, please submit an electronic copy of whatever instrument was used for the primary protocol-specified endpoint(s).
SCOREA	Numeric	Score of primary scale at baseline (this variable is required only for depression trials)	No missing values are allowed in this variable.
SCOREB	Numeric	Score of primary scale at end of trial (this variable is required only for depression trials)	No missing values are allowed in this variable.
RESPONSE	Numeric	Response status (this variable is required only for depression trials)	0=non-responder 1=responder ¹ .= Missing
EVENT	Numeric	This variable contains the code for the first suicidality event. If a patient had more than one event in the desired "exposure window", then the most severe event should be listed. Severity is decided based on the following order of codes: 1>2>3>4>5>6a>6b. Every patient in every trial will be classified on this variable. For the majority of patients who are not identified as having a "possibly suicide-related AE", the classification will be 0 (no event). Similarly, those patients who have "possibly suicide-related AEs" that are coded as 7 or 8 will also be classified for this variable as 0 (no event), because we will not be using codes 7 or 8 in our analyses. Patients with event codes 1	0=no event 1=completed suicide 2=suicide attempt 3=preparatory acts toward imminent suicidal behavior 4=suicidal ideation 5=self-injurious behavior, intent unknown 6a= not enough information, fatal 6b= not enough information, non-fatal No missing values are allowed in this variable.

¹ Please specify the criteria used to define patients as responders

Variable name	Type	Description	Coding notes
		through 6 for SRE's will be classified with their most severe event code.	
EVENTDAY	Numeric	The number of days to the first most severe suicidal event, counting from the day of the first dose.	For patients without events, this variable should contain days until end of trial or until premature discontinuation For patients with more than one event, this variable should contain days until the first most severe event that is listed under the variable "EVENT" No missing values are allowed in this variable.
DISCONT	Numeric	The patient discontinued before the end of the controlled portion of the trial	0=No 1=Yes No missing values are allowed in this variable
HXSUIATT	Numeric	The subject had a history of suicide attempt prior to entering the RCT as defined by: HAMD item 3=4 or relevant screen in other questionnaires used at baseline (this variable is required only for depression trials)	0=No 1=Yes . = Missing or no information available
HXSUIID	Numeric	The subject had a history of suicidal ideation prior to entering the RCT as defined by: HAMD item 3=3, MADRS item 10 >=3, or relevant screen in other questionnaires used at baseline (this variable is required only for depression trials)	0=No 1=Yes . = Missing or no information available

Attachment

For each trial included in the analysis, please provide a summary of important study characteristics in tabular form as shown in Tables 1 and 2 below. Many of the column headings are self-explanatory. However, the following headings merit clarification:

- **Number of Patients:** number of patients randomized to the drug and placebo treatment groups.
- **DB TX Duration:** the nominal duration of the analyzed double-blind treatment phase.
- **Protocol Dose:** the protocol-specified daily target dose expressed as a range for flexible dose studies and as individual doses for fixed dose trials.

Note: The following headings apply only to depression trials:

- **Extensive DX Screening:** indicate yes if the study required confirmation of the diagnostic entry criteria by two or more independent raters. Otherwise, indicate no.
- **Exclude TX Resistant:** indicate yes if a study exclusion criterion was a history of treatment resistance or poor response of the index illness to previous treatment. Otherwise, indicate no.
- **Exclude Bipolar D/O:** indicate yes if a study exclusion criterion was a history or presence of bipolar disorder or mania in the patient. Otherwise, indicate no.
- **Exclude Family H/O Bipolar Disorder:** indicate yes if a study exclusion criterion was any family history of bipolar disorder or mania. Otherwise, indicate no.

TABLE 1: BASIC STUDY DESIGN							
Drug	Study	Indication	Age Range (years)	Number of Patients		DB TX Duration (weeks)	Protocol Dose (mg/day)
				Drug	Placebo		
XYZ	123	MDD	18 to 60	120	119	6	120 to 160
	456	MDD	55 to 85	148	148	8	120, 140, 160
	789	OCD	18 to 65	119	110	12	120, 140
	1111	OCD	18 to 70	71	69	13	120 to 160

TABLE 2: SCREENING AND KEY EXCLUSIONARY CRITERIA									
Drug	Study	Indication	Extensive DX Screen	Placebo Lead-In	Exclude TX Resistant	Excl. Current Suicide Risk	Excl. H/O Suicide Attempt	Excl. Bipolar D/O	Excl. Family H/O Bipolar Disorder
XYZ	123	MDD	No	Yes	No	Yes	No	Yes	No
	456	MDD	Yes	Yes	No	No	No	Yes	Yes
	789	OCD	Yes	Yes	Yes	Yes	No	Yes	Yes
	1111	OCD	No	No	No	Yes	No	Yes	Yes

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

/s/

Russell Katz
8/12/05 08:29:11 AM

Wheelous, Teresa A

From: Wheelous, Teresa A
nt: Monday, December 12, 2005 8:02 AM
io: 'Ben Lewis'
Subject: Tetrabenazine Status of Info Request & new info request

Ben,

The Clinical Pharmacology reviewer would like to know the status of the last information request. That info is necessary for her to continue her review, so please expedite.

Additionally, she has the following info request:

Also, for the efficacy study 103,005 provide a SAS transport file with the PK data for the 10 subjects that completed the PK data (in the format that I described before), that would include subject, date, study day, time after dose, concentrations of each analyte, and TBZ dose (total daily dose as well as dosing regimen). Also provide the PK parameters for each subject analyzed for the baseline day of that study.

Thank you,

CDR Teresa Wheelous, R. Ph.
Sr. Regulatory Management Officer
FDA
Division of Neurology
10903 New Hampshire Avenue, Bldg. #22
Silver Spring, MD 20993-0002
(telephone) 301-796-2250
x) 301-796-9842

Wheelous, Teresa A

From: Wheelous, Teresa A
Sent: Tuesday, December 06, 2005 9:01 AM
To: 'Ben Lewis'
Subject: Tetrabenazine Clin Pharm Reviewer Information Request - Analytical Study Report for Digoxin

Ben,
The clinical pharmacology reviewer for TBZ has the following information request:

For the tetrabenazine NDA, please send the Analytical study report (and method validation) for digoxin for study 203-009 (the P-glycoprotein digoxin study). Also from that study I would like to have race and smoking status of study subjects. I would also like to have demographic information on race from the hepatic impairment study. Please provide this information (especially the study report and validation) by Monday December 12.

Thank you very much,

*CDR Teresa Wheelous, R. Ph.
Sr. Regulatory Management Officer
FDA
Division of Neurology
10903 New Hampshire Avenue, Bldg. #22
Silver Spring, MD 20993-0002
(telephone) 301-796-11651
(fax) 301-796-9842*

Wheelous, Teresa A

From: Wheelous, Teresa A
nt: Friday, December 02, 2005 3:34 PM
o: 'Ben Lewis'
Subject: RE: Clin Pharm Request

Ben,

Yes, please send a desk copy to me.

Thank you,

Teresa

-----Original Message-----

From: Ben Lewis [mailto:benl@prestwickpharma.com]
Sent: Friday, December 02, 2005 1:09 PM
To: Wheelous, Teresa A
Subject: RE: Clin Pharm Request
Importance: High

Teresa,

This is in response to your e-mail that "the Clin Pharm reviewer would like this information as quickly as possible." I want to respond back to you as soon as possible with this information; I believe that it's very important to keep the momentum of the review moving.

I'm currently in the process gathering all the data and also have been on the phone this morning with both the laboratory and our partner in the UK who conducted the mass balance [¹⁴C] study in humans and who is also preparing the final report. I'm projecting that I should have all the data compiled and to you toward the end of next week.

Do you want me to send to you a "desk copy" (for the Clin Pharm reviewer) because of the ASAP request; and also send an official submission to the file (1 archive copy; and 1 copy for Clin Pharm reviewer)? Please let me know.

Regards, Ben

Benjamin P. Lewis, Ph.D., R.Ph., RAC

Vice President, Regulatory Affairs

Prestwick Pharmaceuticals, Inc.

202-296-1400

benl@prestwickpharma.com

From: Wheelous, Teresa A [mailto:WHEELOUST@cder.fda.gov]
Sent: Friday, December 02, 2005 8:20 AM
To: Ben Lewis
Subject: RE:

Ben,

The Clin Pharm reviewer would like this information as quickly as possible. When do you think that the info will be available?

Teresa

-----Original Message-----

From: Ben Lewis [mailto:benl@prestwickpharma.com]
Sent: Monday, November 28, 2005 6:14 PM
To: Wheelous, Teresa A
Subject: RE:

Teresa,

Thanks for sending comments. Regards, Ben

Benjamin P. Lewis, Ph.D., R.Ph., RAC

Vice President, Regulatory Affairs

Wheelous, Teresa A

From: Wheelous, Teresa A
Sent: Monday, November 28, 2005 10:18 AM
To: 'Ben.Lewis'
Cc: Wheelous, Teresa A

Ben,

The clinical pharmacology & Biopharmaceutics reviewer for NDA 21-894 Tetrabenazine has the following information request:

Study 104,012 (BE study)

1. How were the study samples stored (by analytical site) and what was the time frame for analysis (dates of analysis)?
2. Please send an electronic data set with subject, sequence, period, analyte, treatment, dose, concentration, and time (SAS transport file) where the data are presented vertically, not horizontally.
3. Please send figures showing plasma concentration vs time curve for 1) alpha-HTBZ vs beta-HTBZ for each treatment, and 2) treatment A vs treatment B for each enantiomer. Please show arithmetic mean.

Study 103,003 (Food Effect)

1. How were the study samples stored (by analytical site) and what was the time frame for analysis (dates of analysis)?
2. Please send an electronic data set with subject, sequence, period, analyte, treatment, dose, concentration, and time, with data presented vertically, not horizontally.

Study 1700114 (Dose Proportionality)

1. Please send legible representative chromatograms from the plasma samples.
2. Please provide dates of the sample analysis.
3. The low QC samples from run 5 for TBZ (and 4&5 for HTBZ) should have resulted in those runs being rejected. Were samples from those runs re-assayed? Which samples (which subjects) were those?
4. Please provide the smoking status by subject in this study (it was not included in appendix 2.2).
5. Please send an electronic data set with subject, sequence, period, analyte, treatment, dose, concentration, and time, with the data presented vertically, not horizontally.

Study 203010 – Hepatic Impairment – Please send an electronic data set with subject, analyte, subtype, time, dose, and concentration presented vertically.

Study 203,009 (PgP Study) – Please include time, study day, and subject along with concentration data for each analyte in an electronic data set arranged vertically, not horizontally.

Other PK datasets – For any other PK data set not mentioned above, please include time, study day, subject as appropriate along with concentration data for each analyte in an electronic data set arranged vertically, not horizontally.

Dose proportionality

Since the peaks from study 1700114 could not be resolved into the two enantiomers, it will be difficult to get

meaningful data on dose proportionality from that study. Please integrate the available human PK data from the submission to describe dose proportionality.

Metabolism in Humans

Please provide a discussion of Tables 1 and 2 from the Final Report of HFL1627. Please explain the values for relative abundance (e.g. for human I & II what do the values of 145/100% represent?). Similarly, for #VII and VIII, what does the value of 15% represent? Please explain in detail for each metabolite shown in Table 2. Has the pharmacology of any of the metabolites other than HTBZ enantiomers been evaluated?

Mass balance –

We are aware that a mass balance study has recently been conducted in humans. Please send the report for this study ASAP so it can be reviewed in this submission.

Labeling – It would be very helpful to have the proposed labeling as a word document.

Thank you,

*CDR Teresa Wheelous, R. Ph.
Sr. Regulatory Management Officer
FDA
Division of Neurology
10903 New Hampshire Avenue, Bldg. #22
Silver Spring, MD 20993-0002
(telephone) 301-796-2250
(fax) 301-796-9842*

Wheelous, Teresa A

From: Yasuda, Sally
Sent: Tuesday, November 22, 2005 2:49 PM
To: Wheelous, Teresa A
Cc: Uppoor, Ramana S
Subject: Information needed for 21894 tetrabenazine from OCPB

Attachments: Information needed from Sponsor.doc



Information needed
from Sponso...

Hi Teresa,

Please send this information request to the Sponsor as soon as possible. Please aks them to provide the information by December 2.

Thanks,

Sally

Wheelous, Teresa A

From: Wheelous, Teresa A
Sent: Tuesday, November 22, 2005 11:00 AM
To: 'Ben Lewis'
Subject: RE: NDA 21-894 Request for Contact Info

Thank you

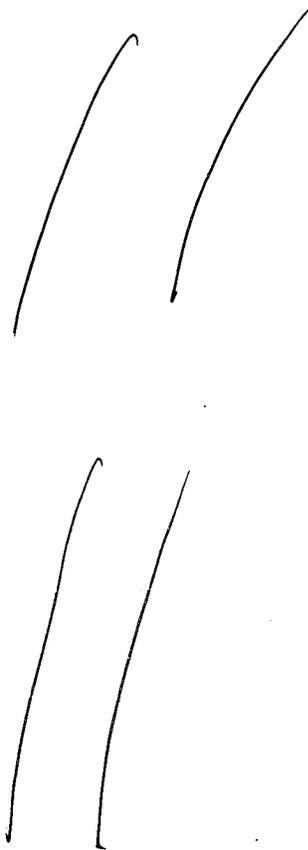
Message-----

From: Ben Lewis [mailto:benl@prestwickpharma.com]
Sent: Friday, November 18, 2005 8:07 PM
To: Wheelous, Teresa A
Subject: RE: NDA 21-894 Request for Contact Info
Importance: High

Teresa: As requested, contact information for information. Regards, Ben

and Don't hesitate to contact me if you need additional

Contact Information:



Commercial Director

Benjamin P. Lewis, Ph.D., R.Ph., RAC

Vice President, Regulatory Affairs

Prestwick Pharmaceuticals, Inc.

202-296-1400

benl@prestwickpharma.com

From: Wheelous, Teresa A [mailto:WHEELOUST@cder.fda.gov]

Sent: Friday, November 18, 2005 9:14 AM

To: Ben Lewis

Subject: NDA 21-894 Request for Contact Info

Ben,

Please provide the following contact information:

Please provide contact information for _____ and _____. This contact information should include a contact person at the facility or US Agent with name, telephone, and fax number.

Thank you,

CDR Teresa Wheelous, R. Ph.

Sr. Regulatory Management Officer

FDA

Division of Neurology

10903 New Hampshire Avenue, Bldg. #22

Silver Spring, MD 20993-0002

(telephone) 301-796-2250

(fax) 301-796-9842

MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 30, 2004
TIME: 2:30 PM
LOCATION: WOC2, conference room E
APPLICATION: IND 63909 Tetrabenazine for Huntington's Chorea
TYPE OF MEETING: End of Phase 2
MEETING CHAIR: Dr. Katz

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Dr. Russell Katz – Division Director
Dr. John Feeney – Group Leader
Dr. Norman Hershkowitz – Medical Reviewer
Dr. Lois Freed – Pharmacology / toxicology Team Leader
Dr. Linda Fossom – Pharmacology / Toxicology Reviewer
Dr. Sharon Yan – Statistical Reviewer
Dr. Ronald Kavanagh – Clinical Pharmacology & Biopharmaceutics Reviewer
Dr. Henry Startzman – Orphan Drugs Reviewer
CDR Teresa Wheelous – Sr. Regulatory Management Officer

PRESTWICK ATTENDEES AND TITLES:

Kathleen Clarence-Smith, M.D. – President, R&D, Chief Scientific Officer
Christopher O'Brien, M.D. – Chief Medical Officer
Benjamin P. Lewis, Ph.D. – V. P., Regulatory Affairs
_____ Consultant (Neurologist)
_____ - Consultant (Pharmacologist)
_____ - Consultant (Statistician)
_____ - Consultant (Pre-clinical)
Jan Farino – Regulatory Affairs

BACKGROUND:

The meeting request dated 4/14/04 was granted on April 28, 2004. The meeting package is dated 5/24/04

MEETING OBJECTIVES:

To discuss the following:

1. Tetra HD Study: double-blind, randomized, placebo-controlled trial. Two parallel unbalanced groups of HD patients (54 on tetrabenazine, 30 placebo). During the first 7 weeks titrate dose by 12.5 mg increments until efficacy, tolerability or 100mg/day is reached. Maintenance from week 7 – week 12, and then an open label extension.
2. Clinical Safety database
3. Pre-clinical studies

4. QTc information

DISCUSSION POINTS:

CLINICAL

Given the clinical information provided, does the study meet the “substantial evidence of efficacy” in the meaning of the Act?

- The division discussed weaknesses in the TetraHD study that mitigate its use alone as a single study to earn a claim for chorea associated with Huntington’s disease. Because of this the Sponsor will be required to submit two pivotal studies. These problems include the following:
 - Some degree of inadvertent unblinding may occur in the study as a result of the advent of adverse events that results from the fact that the study calls for the titration of tetrabenazine to a maximum tolerated dose. Because of this, the division had previously recommended that chorea analysis be performed through a video record by a blinded investigator who did not participate in patient care. This is being done, but not as a primary endpoint.
 - The between-group difference on the primary endpoint is rather modest even though the p value is substantial.
 - The between-group difference on the secondary global endpoint is also modest.
 - Some functional scales showed no benefit.
- The second phase III trial (TBZ 103,004) was discussed.
 - In view of the above a second study would be required for approval.
 - Apparently recruitment has been slow in this study because patients are unwilling to withdraw from tetrabenazine for too long a period. The division noted that an amendment for a reduction in the required numbers, power permitting, may be acceptable.
 - Some concern was expressed by the division that a 3 day primary endpoint measure may be a little short because of the issue of potential rebound. The Sponsor noted that data on day 5 of withdrawal indicates no rebound. This should be analyzed and discussed in the final submission.

Does the clinical safety database support submission of an NDA for tetrabenazine for the treatment of chorea associated with HD?

- Safety issues were discussed.
 - The Division expressed concern for the high incidence of depression (8 vs 0; drug vs Placebo) and the single reported case of a suspected suicide. Moreover the high incidence of insomnia (12 vs 0) may be related to depression. Added to the divisions’ concern is the fact that the treatment is only symptomatic. The Sponsor will have to convince the Division that this is not a problem.

- The Sponsor noted that the changes in the HAM D scale were very small.
- The division noted that antidepressant use was allowed in the TetraHD study. The Sponsor, in analysis of depression, should examine the pattern of antidepressant use in the different groups.
- With regard to the issue of depression this division feels it is very important to identify a dose that is well tolerated. Depression is a serious problem. Perhaps an additional small detailed study can accomplish this or a detailed analysis of the present ongoing studies.
- Careful QT evaluation was not possible in the TetraHD study because of the artifact resulting from the choreiform movements. As a result the Sponsor has submitted a brief draft proposal for QT analysis in normal subjects.
 - The principal concern regarding this study was that the dose examined (25 mg) was lower than the maximal potential dose studied in the ongoing studies (100 mg). The Sponsor noted that they were unable to achieve higher doses because of drug intolerance, resulting predominantly from sedation.
 - One potential solution to the problem discussed by the Sponsor and Division was to perform a single dose study, if it can be shown that patient's exposure to both parent and metabolic products are in excess to that which will be expected at the highest dose studied in the pivotal studies.
 - The Sponsor was advised to consult with their experts regarding this issue.
 - The Division's Clinical Pharmacologist also raised the issue that radiolabel mass balance studies appear to indicate there may be a number of unidentified metabolites. The issue of these metabolites should also be addressed in regard to the QT study.
- The Sponsor notes that a total of 540 patients have been studied in other INDs with very few lost to follow up.

PRECLINICAL

Are the pre-clinical studies sufficient for approval of an NDA for tetrabenazine for the treatment of chorea associated with HD?

- Segment 1 study is needed but can be provided as a Phase 4 commitment.
- Carcinogenicity has not been conducted, and is ordinarily provided prior to approval. The division will have to get back to the sponsor about the possibility of conducting carcinogenicity studies as a Phase 4 commitment.

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS

- The sponsor needs to update the clinical pharmacology section of labeling. The innovator's labeling regarding mass balance data indicated that after IV dosing that only 55% of the dose was recovered after 48 hours, thereby indicating that 45% of the dose was still in the body, most likely as unidentified metabolites. This indicates that a mass balance study is needed.

- The sponsor should not start the hepatic impairment study or analysis until tetrabenazine's metabolism is understood.
- The sponsor was advised to examine the literature as a start to address the risk of effects on other transporters or drug-drug interactions via transporters.

**APPEARS THIS WAY
ON ORIGINAL**

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? NO
If yes, explain:
- Does another drug have orphan drug exclusivity for the same indication? NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? N/A
If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).
- Is the application affected by the Application Integrity Policy (AIP)? NO
If yes, explain.
- If yes, has OC/DMPQ been notified of the submission? N/A
- Does the submission contain an accurate comprehensive index? YES
- Was form 356h included with an authorized signature? YES
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES
If no, explain:
- If an electronic NDA, does it follow the Guidance? Paper submission
If an electronic NDA, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?
Additional comments:
- If in Common Technical Document format, does it follow the guidance? Yes
- Is it an electronic CTD? All paper, with an electronic follow up in eCTD format
If an electronic CTD, all certifications must be in paper and require a signature.

Which parts of the application were submitted in electronic format?

Administrative & prescribing Info, Summary, Quality, Safety, Clinical study reports, i.e. -Complete eCTD submission (certifications have been submitted in paper).

Additional comments:

- Patent information submitted on form FDA 3542a? YES
- Exclusivity requested? NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.
NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"
- Financial Disclosure forms included with authorized signature? - missing FDA form 3455
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
- List referenced IND numbers: 63,909
- End-of-Phase 2 Meeting(s)? Date(s) 6/30/04 NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 2/1/05 NO
If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A
- Has DOTCDP been notified of the OTC switch application? N/A

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? N/A

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 22, 2005

BACKGROUND:

Tetrabenazine is approved in other countries, under the name of Nitoman, for movement disorders.

The original NDA submission is dated April 22, 2005. However, after a telephone conversation with the Division on June 1, 2005, the sponsor decided to withdraw the application to address deficiencies in the Integrated Summary of Safety (ISS). An Agency letter, dated August 12, 2005, acknowledged the withdrawal and provided recommendations for addressing the inadequacies in the ISS. The September 23, 2005 is the resubmitted application.

ATTENDEES:

- Dr. Russell Katz – Division Director
- Dr. John Feeney – Group Leader
- Dr. Carole Davis – Efficacy Clinical Reviewer
- Dr. Norman Hershkowitz – RTF Clinical Reviewer
- Dr. Elizabeth McNeil – Safety Clinical Reviewer
- Dr. Andrea Powell – Pharmacology / Toxicology Reviewer
- Dr. Lois Freed – Pharmacology / Toxicology Supervisor
- Dr. Martha Heimann – CMC Team Leader
- Dr. Jose Tavarezpagan – DSI Reviewer

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Dr. Carole Davis – Efficacy Clinical Reviewer
Secondary Medical:	Dr. Elizabeth McNeil – Safety Clinical Reviewer
Statistical:	Dr. Tristan Massie
Pharmacology:	Dr. Andrea Powell
Chemistry:	Dr. Chhagan Tele
Biopharmaceutical:	Sally Yasuda, Pharm. D.
DSI:	Jose Tavarezpagan
Regulatory Project Management:	Teresa Wheelous
Other Consults:	

Per reviewers, are all parts in English or English translation? NO
If no, explain:

CLINICAL FILE X REFUSE TO FILE

- Clinical site inspection needed: YES
- Advisory Committee Meeting needed? YES, date if known

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A

CLINICAL MICROBIOLOGY NA _____

STATISTICS FILE X

BIOPHARMACEUTICS FILE _____ REFUSE TO FILE _____

- Biopharm. inspection needed: NO

PHARMACOLOGY NA _____ FILE X REFUSE TO FILE _____

- GLP inspection needed: YES NO

CHEMISTRY FILE _____ REFUSE TO FILE _____

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

 X The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

 X No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

Regulatory Project Manager, HFD-120

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, YES NO
ORP?

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

N/A

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). NO

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). NO

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise N/A

made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9).

10. Are there certifications for each of the patents listed for the listed drug(s)? N/A

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.) N/A

___ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

___ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

___ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

___ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must subsequently submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].

___ 21 CFR 314.50(i)(1)(ii): No relevant patents.

___ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent 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 as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

___ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

_____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

N/A

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

N/A

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

N/A

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4): N/A

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND # _____ NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

N/A