CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-894

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	July 15, 2008
To:	Russell Katz, M.D., Director Division of Neurology Products (DNP)
Thru:	Claudia Karwoski, Pharm.D., Acting Director Division of Risk Management (DRISK)
From:	**OSE Tetrabenazine Risk Management Team** Scientific Lead: Mary Willy, PhD., Senior Risk Management Analyst Acting Team Leader, DRISK Team Members: Mary Dempsey, Risk Management Program Coordinator, DRISK Jodi Duckhorn, MA, Patient Information and Research Team Leader, DRISK Charlene M. Flowers, R.Ph, Safety Evaluator, DAEA Cindy Kortepeter, Pharm.D., Safety Evaluator Team Leader, DAEA Laura Pincock, Pharm. D., Safety Evaluator, DMEDP Kellie Taylor, PharmD, MPH, DMEDP Team Leader
Subject:	Review of Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	Tetrabenazine (Xenazine)
Application Type/Number:	21-894
Applicant/Sponsor:	Prestwick Pharmaceuticals, Inc
OSE RCM #:	2007-757

CONTENTS

EXECUTIVE SUMMARY

Tetrabenazine is a drug being considered for approval with an indication for treating chorea associated with Huntington's Disease (HD). The Sponsor had originally proposed a Risk Minimization Action Plan (RiskMAP) that called for restricted distribution of the drug during the dosing titration phase to minimize adverse events. Following discussion at a December 2007 Peripheral and Central Nervous System (PCNS) Advisory Committee Meeting, the Sponsor submitted a revised RiskMAP that included targeted education and outreach of the providers, patient and caregivers to minimize adverse events including depression and suicidality.

The Sponsor was sent an approvable letter on March 18, 2008 because they had outstanding risk management issues that could not be resolved before the due date. On March 25, 2008 Title IX, Subtitle A of the Food and Drug Administrations Amendments Act of 2007 (FDAAA) went into effect. Because it was anticipated that the Sponsor would not resubmit the Tetrabenazine RiskMAP before March 25, 2008, the approvable letter informed the Sponsor that the RiskMAP would need to be resubmitted as a Risk Evaluation and Mitigation Strategy (REMS). On May 6, 2008, the Sponsor was sent an information request outlining the requirements of the REMS submission. A proposed REMS was submitted as part of Complete Response to the approvable letter, on June 13, July 1 and July 8, 2008.

We find the proposed REMS, which consists of a Medication Guide, a Communication Plan, and a timetable for assessment of the REMS, to be acceptable to mitigate the risk of serious depression and suicidality and to assist healthcare providers and their patients with the complicated dose initiation instructions. The survey instrument and methodology for the prescriber and patient surveys will be submitted for FDA review at least two months before it is administered in the field.

1 BACKGROUND

1.1 INTRODUCTION

The current application for tetrabenazine was submitted by Prestwick Pharmaceuticals to the Division of Neurology Products (DNP) for review in April 2007. The proposed indication is for the treatment of chorea associated with HD. Tetrabenazine is available in 12.5 and 25 mg tablets and is supposed to be titrated slowly to minimize the serious adverse events. The suggested starting dose is 25 mg a day (12.5 mg BID); the dose is to be increased each week until the 100 mg daily dose is reached or symptoms improve. Tetrabenazine has been found to be efficacious, but has a number of safety concerns including, and most importantly, depression and suicidality.

The PCNS Advisory Committee met on December 6, 2007 to discuss the efficacy and safety of this drug. In preparation for the meeting, OSE completed a review of the sponsor's proposed RiskMAP.[1] After hearing the presentations and completing a discussion of the data presented, the committee agreed that the adverse events associated with the drug were not sufficient to justify not approving the drug.[2]

---

[1] Risk Management Proposal Review, OSE Tetrabenazine Risk Management Team; November 27, 2007.

[2] Minutes from December 6, 2008 Peripheral and Central Nervous System Drugs Advisory Committee Meeting: http://www.fda.gov/ohrms/dockets/ac/07/minutes/2007-4328m1-Final.pdf

1.2 REGULATORY HISTORY

The first new drug application for tetrabenazine (NDA 21-894) was withdrawn at the request of the sponsor prior to the filing date. The application was withdrawn as of June 14, 2005. The next new drug application for tetrabenazine was submitted in September 2005. The Sponsor received the first approvable letter in March 2006. The Sponsor resubmission in February 2007 was not considered a complete response to the March 2006 approvable letter. There were deficiencies that still needed to be addressed and they were outlined in the agency letter of March 2007. The Sponsor resubmission of April 2007 was considered a Complete Response to the March 2006 approvable letter. In August 2007 the agency received a major amendment to the application which extended the goal date to January 5, 2008.

The Complete Response included a proposal for a [redacted]

Following the December 2007 Advisory Committee, the Agency communicated concerns about restrictive components of the proposed RiskMAP plan, [redacted] The Agency emphasized the importance of good communication between the provider and patient and the need for very good education of all stakeholders (providers, patients and caregivers). In addition, the sponsor was instructed on the need to have the educational materials completed before marketing the drug.

On December 26, 2007 the sponsor received a second approvable letter that included a request for: 1) a revised RiskMAP that included an education program for physicians, patients and families addressing adequate dosing and the risk of depression, suicidality, and other important adverse effects of tetrabenazine, 2) a medication guide and 3) draft package insert.[3] The RiskMAP was to be in place before tetrabenazine was marketed. As part of the revised plan, the sponsor was told to submit a draft of the educational materials and a plan for how they plan to identify tetrabenzine prescribers and potential prescribers, and how they will transmit educational materials to prescribers and patients.

The Sponsor submitted a revised RiskMAP on January 18, 2008 which was considered a complete response to the agency's December 2007 letter. The Sponsor also submitted educational materials in February and March 2008.

The Sponsor was sent a third approvable letter on March 18, 2008 because they had outstanding risk management issues that could not be resolved before the due date. On March 25, 2008 Title IX, Subtitle A of the FDAAA went into effect. Because it was anticipated that the Sponsor would not resubmit the Tetrabenazine RiskMAP before March 25, 2008, the approvable letter informed the Sponsor that the RiskMAP would need to be resubmitted as a Risk Evaluation and Mitigation Strategy (REMS). On May 6, 2008, the Sponsor was sent an information request outlining the requirements of the REMS submission with a REMS template attachment for their reference. Submissions on June 13, July 1 and July 8, 2008. included the final REMS and the final educational materials.

2 METHODS AND MATERIALS

2.1 DATA AND INFORMATION SOURCES

[3] Approvable Letter, tetrabenazine (NDA-21-894), December 26, 2007.

1) Approvable Letter, tetrabenazine (NDA-894); March 26, 2006
2) Response to FDA Approvable Letter, with revised Tetrabenazine Risk Minimization Action Plan, submitted February 2007
3) Clinical Review, Lourdes Villalba, M.D.; November 9, 2007
4) Approvable Letter, tetrabenazine (NDA-894); December 26, 2007
5) Response to FDA Approvable Letter, with Revised Tetrabenazine Risk Minimization Action Plan, submitted January 18, 2008
6) Addendum to RiskMAP, March 7, 2008
7) Approvable Letter, tetrabenazine (NDA-894); March 18, 2008
8) Revised Tetrabenazine Educational materials, submitted March through May 2008
9) Information request letter: Risk Evaluation and Mitigation Strategy Requirements, May 6, 2008.
10) Response to FDA Approvable Letter, with revised Tetrabenazine Risk Evaluation and Mitigation Strategy, submitted June 13, July 1 and July 8, 2008.

2.2 ANALYSIS TECHNIQUES

The submission was reviewed for responsiveness to FDA communications. Conformance with the Food and Drug Administration Amendments Act of 2007 was also determined.[4]

3 RESULTS OF REVIEW

3.1 SAFETY CONCERNS

As described in more detail in our November 2007 review the safety concerns for tetrabenazine include: akathisia, restlessness, and agitation, parkinsonism, sedation, and depression/suicidality. Of these adverse events, depression (and suicidality) is most concerning. Although depression is recognized to be associated with HD, in the tetrabenazine studies there were more treated than placebo patients with depression. Most importantly, some of the patients had serious adverse events: one patient committed suicide, one attempted suicide, and three had suicidal ideation. Another concern is the risk of drug-drug interactions with strong CYP2D6 inhibitors.

The previously proposed RiskMAP and the current proposed REMS address the risk of depression and suicidality as well as the risk of drug-drug interactions through education of HCPs and patients about the serious risks of tetrabenazine and about proper dose titration of tetrabenazine to minimize those risks.

3.2 PROPOSED RISKMAP

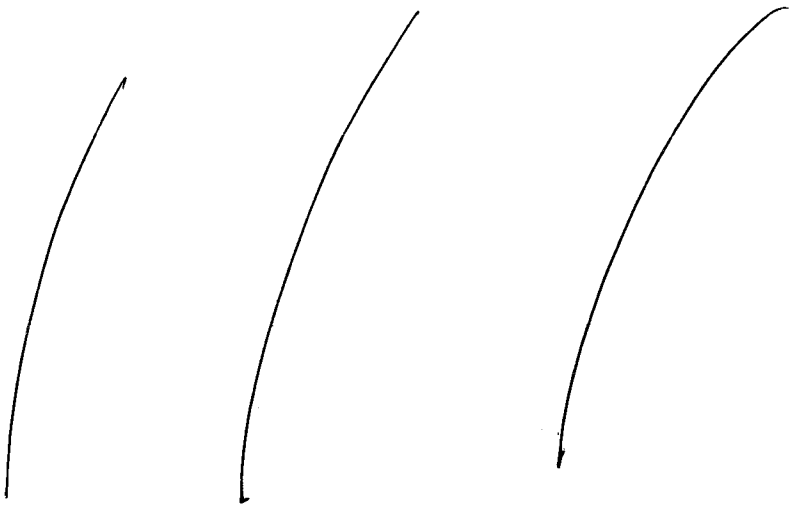
[4] Food and Drug Administration Amendments Act of 2007. http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110

1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process



3.3 CONVERSION OF RISKMAP TO REMS

3.3.1 CONSIDERATION OF A REMS

The Food and Drugs Amendments Act of 2007 lays requires certain criteria be considered when determining if a REMS is needed to ensure the benefits of a drug outweigh its risks. For tetrabenzine the following summary was developed by DNP.

1. **The estimated size of the population likely to use the drug:** While it is not possible to estimate the size of the population likely to use tetrabenazine, the number of patients affected with Huntington's disease in the United States is approximately 30,000.
2. **The seriousness of the disease or condition being treated by the drug:** tetrabenazine will be approved to treat the chorea of Huntington's disease, a serious medical condition. Chorea, a motor disorder characterized by involuntary movements, can impact a patient's ability to carry out activities of daily living. It also can be a contributor to falls, associated injuries, and institutionalization.
3. **The expected benefit of the drug with repect to such a disease or condition:** tetrabenazine has been shown to reduce the chorea of Huntington's disease.
4. **The expected or actual duration of treatment with the drug:** We expect that tetrabenazine would be chronic therapy for patients for whom it is effective without intolerable side effects.
5. **The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug:** Known serious risks associated with use of tetrabenazine include the occurrence of depression and suicidality, and neuroleptic malignant syndrome (NMS). In a controlled clinical trial in Huntington's disease, depression occurred in 19% of 54 tetrabenazine -treated patients as compared to 0% of 30 patients on placebo treatment. One patient committed suicide and one had suicidal ideation in the tetrabenazine -treated group, and no patient had such events in the placebo-treated group. Although no cases of NMS occurred in the controlled clinical trial with tetrabenazine, cases of NMS have been reported in the foreign postmarketing setting

prior to US approval. Other important risks associated with tetrabenazine include but are not limited to akathisia, Parkinsonism, and QT prolongation. Akathisia and Parkinsonism may be difficult to distinguish from the underlying disease. In the controlled trial mentioned above, akathisia was observed in 19% of patients randomized to tetrabenazine and no patients randomized to placebo. Parkinsonism and other extrapyramidal events were observed in 15% of patients randomized to tetrabenazine and no patients randomized to placebo. tetrabenazine causes a small increase (about 8 msec) in the corrected QT (QTc) interval. QT prolongation can lead to development of torsade de pointes-type ventricular tachycardia with the risk increasing as the degree of prolongation increases.

6. **Whether the drug is a new molecular entity**: tetrabenazine is a new molecular entity (NME).

3.3.2 PROPOSED REMS ELEMENTS

The Sponsor submitted a proposed REMS document that was based on a template that was sent to them by DNP. The REMS document included the following:

Medication Guide that will be dispensed with each tetrabenazine prescription. Three (3) Medication Guides will be attached to each Xenazine package. The package will also include a prominent notice to include a Medication Guide with each prescription in the event that less than a full bottle of Xenazine is prescribed. The "Dear Pharmacist" letter will include instructions to provide the Medication Guide with each prescription. Ten Medication Guides will be included with the "Dear Pharmacist" letter. Medication Guides will be available via sales and/or clinical representatives, the product website or through the Sponsor toll-free medical information line.

Communication Plan: The Sponsor will implement a communication plan to healthcare providers to support implementation of this REMS. The audience is healthcare professionals (HCPs)—especially neurologists and movement disorder specialists and pharmacists. The Sponsor will provide physicians and pharmacists with the educational materials listed below that describe the key risks and benefits of tetrabenazine:

a. Prescriber materials:
   i. Xenazine® Package Insert (PI)
   ii. Dear Healthcare Professional Letter
   iii. Xenazine® Medication Guide
   iv. Prescribing Xenazine®: A Healthcare Professional Guide
   v. Patient/Caregiver Counseling Guide
   vi. Initial Dosing Plan
b. Pharmacist materials
   i. Dear Pharmacist Letter
   ii. Xenazine® Package Insert (PI)
   iii. Xenazine® Medication Guide
   iv. Prescribing Xenazine®: A Healthcare Professional Guide

A Pharmacy Management Systems will be developed as a point of sale clinical alert data to inform dispensing pharmacists and pharmacy technicians of the significant known risks of tetrabenazine. The Sponsor will seek to include appropriate drug-drug interaction information, dosing guidelines and other clinical alerts. Ongoing Healthcare Professional Education will also use several educational vehicles to continue educating and updating Healthcare Professionals about tetrabenazine and the REMS.

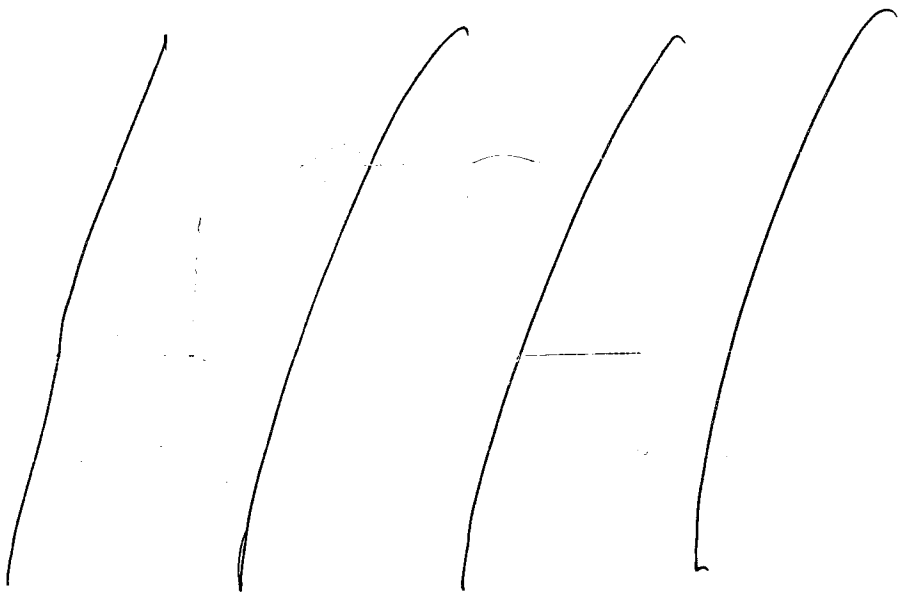
Materials will be distributed:

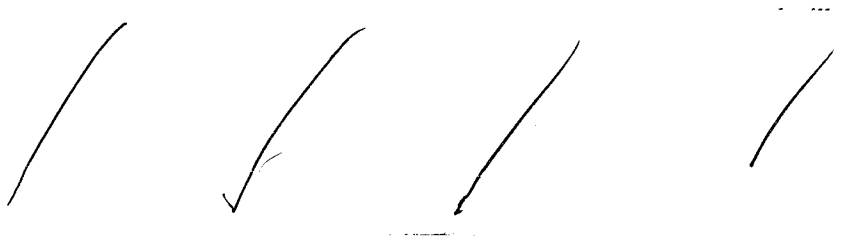
a. At the time of tetrabenazine availability, the Dear Healthcare Professional Letter will be sent by mass mailing to targeted medical specialists. The mailing will also include a copy of the PI, the *Prescribing Xenazine®: A Healthcare Professional Guide*, the patient Medication Guide, the *Patient/Caregiver Counseling Guide* and the Initial Dosing Plan. Additional materials will be available via sales and/or clinical representatives, the product website or through the Sponsor toll-free medical information line.
b. At the time of tetrabenazine availability, a letter will be sent by mass mailing to all. The mailing will also include a copy of the PI and the *Prescribing Xenazine®: A Healthcare Professional Guide*. Pharmacists will also be provided with 10 copies of the Medication Guide. The pharmacist can obtain additional educational materials from the Sponsor toll-free medical information line or the product website.
c. In order to ensure that healthcare professionals remain informed of the tetrabenazine REMS, the Dear Healthcare Professional letter and the Dear Pharmacist letter will be updated annually and sent to all neurologists, movement disorder specialists and pharmacists. These annual mailings will include the most current PI, *Prescribing Xenazine®: A Healthcare Professional Guide*, *Patient/Caregiver Counseling Guide,* and Medication Guide.

Elements To Assure Safe Use: Tetrabenazine has been shown to be effective but is associated with risk of depression and suicidality. Tetrabenazine can be approved without any elements to assure safe use.

Implementation System: Because tetrabenazine can be approved without any elements to assure safe use, an implementation system is not required.

Information Needed for Assessments: Results of the two surveys to be conducted by the Sponsor will be designed to monitor the effectiveness of the interventions in educating prescribers on the proper use of tetrabenazine therapy, compliance with the titration and dosing guidelines contained in the labeling, and occurrence of targeted adverse events and their management by the prescriber.





4 DISCUSSION

The Sponsor has submitted a REMS to address concerns about proper drug titration, treatment-emergent depression and drug-drug interactions. The REMS includes a Medication Guide for patients, a communication (educational) plan, and an assessment component. The REMS is nearly identical to the proposed RiskMAP submitted earlier this year. There were minor changes made to include changes in the name of the educational materials and the expectation that prescribers will provide patients and/or caregivers with a *Patient/Caregiver Counseling Guide* (previously _____ and an initial dosing plan to help during the titration phase.

The one outstanding issue is the survey component which was not submitted with the REMS because there was inadequate time for the Sponsor to fully develop these prior to approval. While DRISK would have preferred that the survey methodology and survey instruments be included in the final REMS, this would have further delayed approval of this orphan product. The REMS obligates the company to submit the survey instrument and methodology for prescribers, patients, nd caregivers to the FDA for review and comment at least 2 months before it is administered.

5 CONCLUSION

We find the proposed REMS to be acceptable at this time. The Medication Guide and educational plan that is proposed should help inform providers, patients, and caregivers so that tetrabenazine is titrated properly and serious adverse events are minimized

6 RECOMMENDATIONS

- Please consult DRISK when the information on the evaluation methods, sample size, follow-up of non-responders, and copies of draft surveys are submitted.

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

/s/

Mary Dempsey
7/15/2008 07:52:41 AM
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
7/15/2008 08:47:54 AM
DRUG SAFETY OFFICE REVIEWER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	March 6, 2008
To:	Russell Katz, M.D., Director Division of Neurology Products
Through:	Kellie Taylor, Pharm.D., M.P.H., Team Leader Denise Toyer, Pharm.D., Deputy Director Carol Holquist, R.Ph., Director Division of Medication Errors and Technical Support
From:	Laura Pincock, R.Ph., Pharm.D., Safety Evaluator
Subject:	Labeling Review for Xenazine
Drug Name(s):	Xenazine (Tetrabenazine Tablets)
Submission Number:	NDA #: 21-894
Application Type/Number:	
Applicant/sponsor:	Prestwick Pharmaceuticals, Inc.
OSE RCM #:	2008-162

CONTENTS

EXECUTIVE SUMMARY

The results of the Label and Labeling Risk Assessment found that the presentation of information and design of the proposed carton and container labels appears to be vulnerable to confusion that could lead to medication errors. Specifically, the concerns surround the poor readability of text on the container label and the separation of the proprietary name from the established name by intervening matter. Additionally, measures should be taken to ensure that every patient receives a Medication Guide. DMETS believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Neurology Products (DNP) to evaluate the revised labeling of Xenazine for the potential to contribute to medication errors. The revised labeling includes container labels, package insert labeling, and a Medication Guide.

1.2 REGULATORY HISTORY

Xenazine was first approved in the U.K. in 1971 for the treatment of chorea and other movement disorders; it is currently approved in several European countries for the same indication under the proprietary name Xenazine. In the U.S., there are no currently approved drugs to treat chorea associated with Huntington's Disease, although some anti-psychotic drugs are used off-label.

DMETS has completed three previous reviews for this product. The first two reviews of the proposed name, Xenazine, in OSE Review #05-0120 and #05-0120-1, dated 9/22/2005 and 3/10/2006, DMETS had no objections to the use of the proprietary name. Additionally, label and labeling changes were recommended in these reviews.

The third review that DMETS completed was a final review of the proposed name, Xenazine, in OSE Review # 2007-2216, dated December 18, 2007, in which DMETS had no objections to the use of the proprietary name.

The Sponsor has also submitted a revised Risk Minimization Action Plan. The Applicant indicates the RiskMAP is to address the risks of depression and to promote appropriate titration and dosing. The RiskMAP is still a matter of ongoing review in the Division of Risk Management (DRISK).

Tetrabenazine was discussed at a FDA Advisory Committee Meeting on December 6, 2007. The Advisory Panel voted unanimously to recommend the approval of tetrabenazine.

1.3 PRODUCT INFORMATION

Tetrabenazine is a monoamine depletory agent for oral administration. It is proposed to be indicated in the treatment of chorea associated with Huntington's Disease. The starting daily dose is 12.5 mg per day given once in the morning. After one week, the dose should be increased to 25 mg per day given as 12.5 mg twice a day. Xenazine should be titrated up slowly at weekly intervals by 12.5 mg to allow the identification of a dose that reduces chorea and is well tolerated. If a dose of 37.5 mg to 50 mg per day is needed, it should be given in a three times a day regimen. The maximum recommended single dose is 25 mg. If adverse events such as akathisia, restlessness, parkinsonism, depression, insomnia, anxiety or intolerable sedation occur, titration should be stopped and the dose should be reduced. If the adverse event does not resolve, consideration should be given to withdrawing Xenazine treatment or initiating other specific treatment (e.g., antidepressants). Patients who require doses greater than 50 mg per day

should be genotyped for CYP2D6. In CYP2D6 poor metabolizers (patients who do not express CYP2D6), the maximum single dose is 25 mg and the maximum daily dose is 50 mg. In CYP2D6 extensive and intermediate metabolizers (patients who express CYP2D6), the maximum daily dose may be titrated up past 50 mg. Doses above 50 mg per day should be given in a three times a day regimen. The maximum recommended single dose is 37.5 mg, and the maximum recommended daily dose is 100 mg. Xenazine is supplied in bottles of 112 tablets and is stored at room temperature.

2 METHODS AND MATERIALS

This section describe the methods and materials used by DMETS medication error staff to conduct a label, labeling, and/or packaging risk assessment. The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. DMETS defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The carton and container labels communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because DMETS staff analyze reported misuse of drugs, DMETS staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. DMETS uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Sponsor submitted on January 18, 2008 and March 3, 2008 the following labels and insert labeling for DMETS review (see Appendix A for images):

- Container Label: 12.5 mg and 25 mg Xenazine Tablets (112 tablet bottle)
- Medication Guide Labeling (no image)
- Package Insert Labeling (no image)

3 RESULTS

3.1 LABEL AND LABELING RISK ASSESSMENT

Review of the package, container labels, and insert labeling identified several potential sources of medication error. Specifically important information that must be conveyed with respect to the proper

---

[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

use of the product, expression of net quantity, the intervening graphic on the principal display panel of the container label, and information contained in the Medication Guide labeling.

The proposed packaging f

4 DISCUSSION

5 CONCLUSIONS AND RECOMMENDATIONS

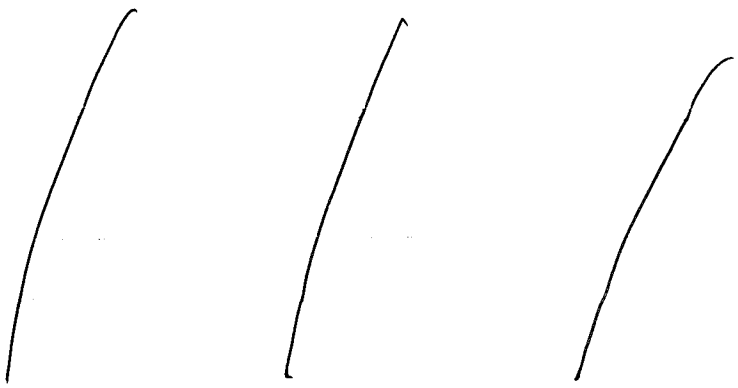
The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed package and container labels introduces vulnerability to confusion that could lead to medication errors. DMETS believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

5.1 COMMENTS TO THE DIVISION

Based upon our assessment of the labels and labeling, and the review of post-marketing medication error reports, DMETS has identified areas needed of improvement. We have provided recommendations in section 5.2 and request this information be forwarded to the Applicant. DMETS would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed.

Please copy DMETS on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Daniel Brounstein, Project Manager, at 301-796-0764 or Cheryl Campbell at 301-796-0723.

5.2 COMMENTS TO THE APPLICANT



1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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

/s/

Laura Pincock
3/6/2008 12:47:10 PM
DRUG SAFETY OFFICE REVIEWER

Kellie Taylor
3/6/2008 12:57:34 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
3/6/2008 02:40:31 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/6/2008 03:10:45 PM
DRUG SAFETY OFFICE REVIEWER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	February 25, 2008
To:	Russell Katz, M.D., Director Division of Neurology Products
Through:	Jodi Duckhorn, M.A., Team Leader Patient Labeling and Education Team Division of Risk Management
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Specialist Patient Labeling and Education Team Division of Risk Management
Subject:	DRISK Review of Patient Labeling (Medication Guide)
Drug Name(s):	Xenazine (tetrabenazine) Tablets
Application Type/Number:	NDA# 21-894
Applicant/sponsor:	Prestwick Pharmaceuticals
OSE RCM #:	2008-160

1 INTRODUCTION

Xenazine (tetrabenazine) tablets is a New Molecular entity and has been granted orphan drug status. Prestwick Phamaceuticals submitted a New Drug Application (NDA#21-894) in September 2005. The sponsor received an approvable letter in March 2006. The current application, submitted in April 2007, is a complete response to the approvable letter and included efficacy and safety information. The Agency took an Approvable action on December 26, 2008 in response to the sponsor's complete response. In the Approvable letter, the Agency notified the sponsor of the determination that Xenazine poses a serious and significant public health concern related to depression and suicidality. In part, the letter states: "This concern requires development and distribution of a Medication Guide under 21 CFR 208 in order to prevent serious adverse effects, inform patients of information concerning risks that could affect their decision to use or continue to use the drug, and/or assure effective use of the drug."

The sponsor submitted a major amendment on January 18, 2008 which has been determined to be a class 1 resubmission for Xenazine (tetrabenazine) for a 3rd review cycle. The submission contains a new Medication Guide, a revised RiskMAP, patient and physician education materials, revised container labeling, and a revised Package Insert.

The Patient Labeling and Education Team has been requested to review the Medication Guide that has been developed for this product.

2 MATERIAL REVIEWED

- Xenazine (tetrabenazine) tablets proposed Medication Guide (MG) as revised by the review division February 19, 2008.
- Xenazine (tetrabenazine) tablets proposed Professional Information (PI) as revised by the review division on February 21, 2008.

3 DISCUSSION

The purpose of Medication Guides is to enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft Medication Guide (MG) submitted by the sponsor has a Flesch Kinkaid grade level of 8.4, and a Flesch Reading Ease score of 59.1. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). Our revised MG has a Flesch Kinkaid grade level of 7.8 and a Flesch Reading Ease score of 60.0%.

In our review of the MG, we have:

- simplified wording where possible,
- made it consistent with the Professional Information,
- removed unnecessary or redundant information
- ensured that the Medication Guide meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

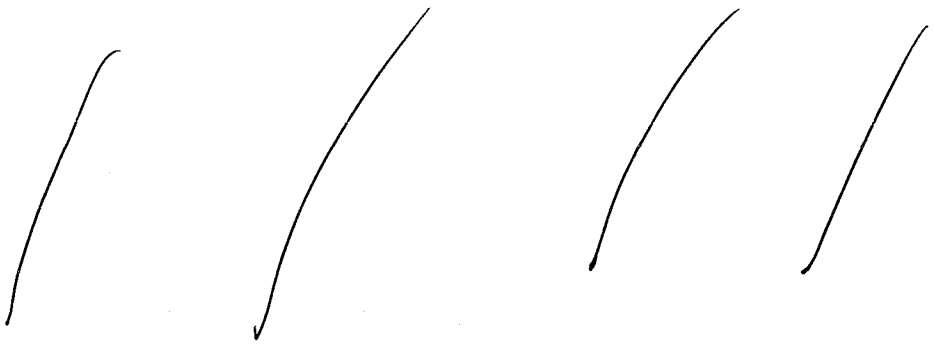
In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

4 CONCLUSIONS AND RECOMMENDATIONS



Please let us know if you have any questions.

15 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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

/s/

Sharon Mills
2/25/2008 03:35:46 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
2/25/2008 03:40:45 PM
CSO

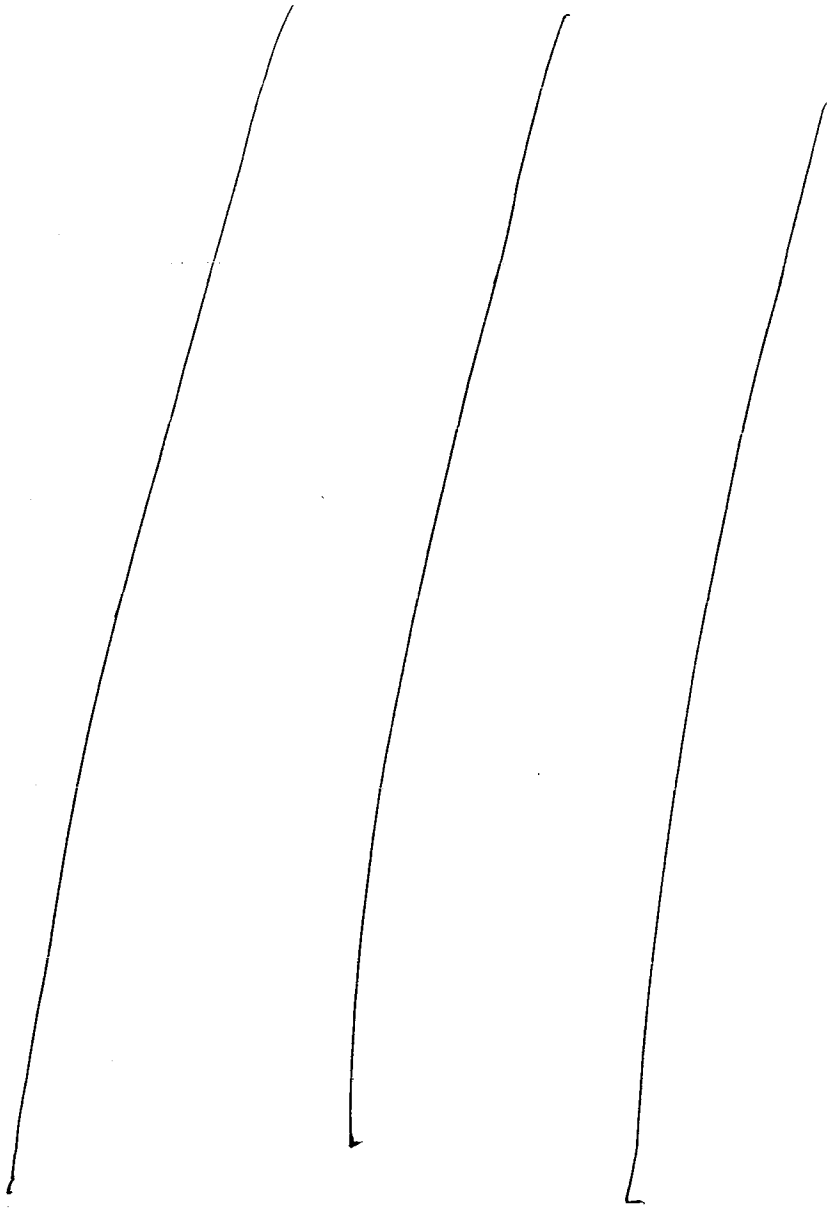
Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	November 27, 2007
To:	Russell Katz, M.D., Director Division of Neurology Products (DNP)
Thru:	Gerald Dal Pan, MD, MHS, Director Office of Surveillance and Epidemiology (OSE)
From:	**OSE Tetrabenazine Risk Management Team** Jeanine Best, MSN,RN,PNP, Senior Drug Risk Management Analyst, OSE-IO Mary Dempsey, Risk Management Program Coordinator, OSE-IO Jodi Duckhorn, MA, Patient Information and Research Team Leader, DSRCS Charlene M. Flowers, R.Ph, Safety Evaluator, DDRE Claudia B. Karwoski, Pharm.D., Risk Management Team Leader, OSE-IO Cindy Kortepeter, Pharm.D., Safety Evaluator Team Leader, DDRE Laura Pincock, Pharm. D., Safety Evaluator, DMETS Kellie Taylor, PharmD, MPH, DMETS Team Leader Joyce Weaver, Pharm.D. BCPS,Senior Drug Risk Management Analyst, OSE-IO Mary Willy, Ph.D., Senior Drug Risk Management Analyst, OSE-IO
Subject:	Risk Management Proposal Review
Drug Name(s):	Tetrabenazine (Xenazine)
Application Type/Number:	21-894
Applicant/Sponsor:	Prestwick Pharmaceuticals, Inc
OSE RCM #:	2007-757

CONTENTS

EXECUTIVE SUMMARY

Tetrabenazine is a drug being considered for approval with an indication for treating chorea associated with Huntington's Disease (HD). The Sponsor has proposed a risk minimization action plan (RiskMAP) that



7 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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

/s/

Mary Dempsey
11/27/2007 09:12:14 AM
DRUG SAFETY OFFICE REVIEWER

Gerald DalPan
11/27/2007 10:21:33 AM
MEDICAL OFFICER