CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-894

CHEMISTRY REVIEW(S)

Xenazine
(tetrabenazine)
Tablets

NDA 21-894

Division Director Review - 2
Chemistry, Manufacturing, and Controls

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

Indication: Treatment of Chorea associated with Huntington's Disease

Xenazine (tetrabenazine) immediate release tablets will be provided in two strengths, 12.5 mg (white, cylindrical biplanar tablet) and 25 mg (Yellowish-buff, cylindrical biplanar tablet), and supplied in [redacted] bottles with child-resistant caps, 112 count, with 36 month expiration at room temperature.

Review of the original application resulted in an Approvable letter issued on 24-MARCH-2006, which contained two CMC deficiencies, one for a pending recommendation from the Office of Compliance and a second for an unresolved issue regarding drug substance. Approvable was recommended in the CMC Division Director memorandum of 21-MARCH-2006.

In the resubmission of 04-APR-2007, the applicant provided satisfactory responses to the CMC deficiencies in the action letter. First, an Overall "Acceptable" Recommendation was issued by the Office of Compliance on 06-JUL-2006. Second, a revised optical rotation acceptance criterion for drug substance was proposed and accepted.

Subsequently, the applicant reported several CMC changes to the drug product manufacturing that included addition of an alternate manufacturing, packaging, labeling, and control facility. This technology transfer was deemed acceptable, the drug product met the specification, and an Overall "Acceptable" Recommendation was issued by the Office of Compliance on 03-AUG-2007.

Overall Conclusion:

From a CMC perspective, the application is recommended for **approval**, pending agreement on product labeling.

Blair A. Fraser, Ph.D.
Director
DPA I/ONDQA

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/s/

Blair Fraser
11/9/2007 06:11:25 AM
CHEMIST

CHEMISTRY REVIEW

NDA 21-894

Xenazine (tetrabenazine) Tablets
Prestwick Pharmaceuticals, Inc.

Division of Neurology Products
Review of Chemistry, Manufacturing, and Controls

Chhagan G. Tele, Ph.D.
Lyudmila N. Soldatova, Ph.D.
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

Table of Contents

Chemistry Assessment Section

Chemistry Review Data Sheet

1. NDA 21-894

2. REVIEW #: 2

3. REVIEW DATE: September 21, 2007

4. REVIEWERS: Chhagan G. Tele, Ph.D.
   Lyudmila N. Soldatova, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Review #1	21-MAR-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission (incomplete)	09-FEB-2007
Resubmission (complete)	04-APR-2007
Amendment	10-APR-2007
Amendment	12-JUN-2007
Amendment, Alternate DP Manufacturing Site [redacted]	26-JUN-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Prestwick Pharmaceuticals, Inc.
Address:	1825 K Street, NW, Suite 1475, Washington, DC 20006
Representative:	Benjamin P. Lewis, Vice President, Regulatory Affairs
Telephone:	(202) 296-1400

8. DRUG PRODUCT NAME/CODE/TYPE:

   a) Proprietary Name: Xenazine
   b) Non-Proprietary Name (USAN): Tetrabenazine
   c) Code Name/# (ONDC only): N/A
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: 1
      - Submission Priority: P

Chemistry Assessment Section

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: For the treatment of Chorea Associated with Huntington's Disease

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 12.5 mg and 25 mg

13. ROUTE OF ADMINISTRATION: Oral

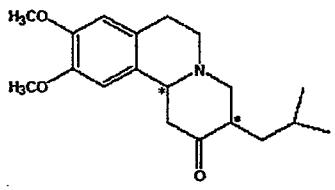
14. Rx/OTC DISPENSED: __X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
___X_Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

INN:	Tetrabenazine
Chemical Name:	*cis rac* – 1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-3-(2-methylpropyl)-2H-benzo[a]quinolizin-2-one
Chemical Formula:	$C_{19}H_{27}NO_3$
Molecular Weight:	317.4
CAS registry #:	58-46-8
Structure:	



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
~~	II	~~~	Tetrabenazine	1	Inadequate Inadequate Adequate	16 -FEB-06 18-MAY-2006 24-JUL-2007 (Dr. L. Soldatova)	Drug Substance

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	63,909	Commercial IND (HD)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		N/A
EES	Acceptable	03-AUG-07	S. Ferguson
Pharm/Tox	Approvable		Andrea M. Powell, Ph.D.
Biopharm	Approvable		Sally U. Yasuda, MS, Pharm.D.
LNC	N/A		
Methods Validation	Under the ONDQA Method Validation Program Procedures, none of the test methods qualify for evaluation by FDA method validation laboratory.		
DMETS			
EA	Acceptable, categorical exclusion granted as per information from Prestwick in this NDA		Chhagan G. Tele, Ph.D.
Microbiology	N/A	N/A	N/A

Chemistry Assessment Section

The Chemistry Review for NDA 21-894

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the Chemistry, Manufacturing, and Controls (CMC) standpoint, NDA 21-894 for Xenazine (tetrabenazine) Tablets is recommended **APPROVAL**. The approval is based on the acceptable CMC information for drug substance and drug product, and on overall acceptable recommendation on establishments from the Office of Compliance.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None as per this review.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

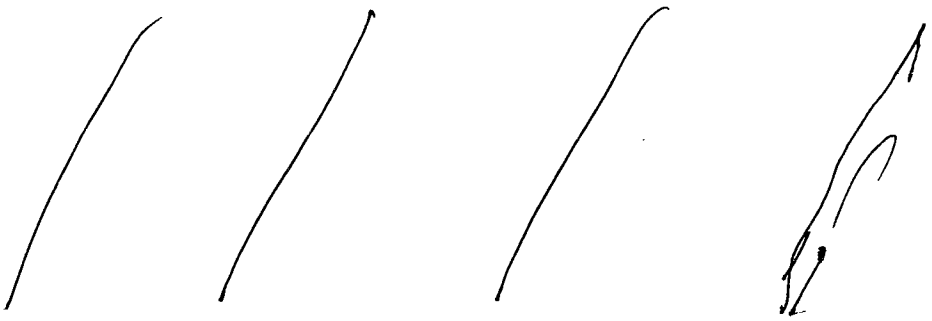
BACKGROUND

Tetrabenazine is a dopamine-depleting agent that has been used for the management of hyperkinetic movement disorders and shown to deplete monoamines selectively in the central nervous system (CNS). The applicant submitted an original IND 63,909 (Phase 3) for tetrabenazine for the treatment of Huntington's chorea and was allowed to proceed on 07-MAY-03. The disease is characterized by a symptomatic triad of chorea, dementia, and personality disorder. Huntington Disease (HD) is a neurodegenerative disorder, characterized by progressive inexorable loss of nerve cells. Onset usually occurs around the age of 40 years. Tetrabenazine was originally developed by Hoffmann-LaRoche in the late 1950s and 1960s as part of an antihelminthic program. Currently, it is available in several foreign countries (Australia, Canada, Denmark, Ireland, Israel, New Zealand, Portugal, and United Kingdom) for various hyperkinetic movement disorders that include Huntington's chorea. It is also noted that [redacted]. There is currently no FDA-approved treatment for the chorea symptoms of HD and no therapy is known to prevent the progression of neurodegeneration. FDA's Office of Orphan Product Development granted "orphan" designation for tetrabenazine to Prestwick on 15-JAN-2004 for the indication of treatment of Huntington Disease. FDA's Division of Neurology Products granted "fast track" designation to Prestwick on 23-APR-2004 under the Fast Track Drug Development Program with priority review for the specific indication of chorea associated with HD.

DRUG PRODUCT*

Xenazine (tetrabenazine) tablets are indicated for the treatment of Chorea Associated with Huntington's Disease. Xenazine is a conventional tablet dosage form (Xenazine Tablets, 12.5 mg and 25 mg) manufactured by [redacted] (original NDA: [redacted]) and will be distributed by Prestwick

Pharmaceuticals, Inc. Washington, DC. Each tablet contains 12.5 mg and 25 mg of tetrabenazine. The excipients used in the 12.5 mg and 25 mg tablet formulations are lactose ( ), maize starch, talc, and magnesium stearate . Iron oxide (Yellow) is also used in the formulation of 25 mg tablets (yellow in color) to discriminate from 12.5 mg tablets (white in color). These excipients are commonly used in tablet formulations for their respective functions. All excipients used in the 12.5 mg and 25 mg tablets are of compendial (USP or NF) quality. The commercial manufacturing process (Batch size) for Xenazine tablets



The specifications for tablets included Description, Identification (HPLC and UV), Tetrabenazine content (HPLC), Degradation Products (HPLC), Dissolution (UV), Content Uniformity (HPLC), . The batch analysis was provided for three batches of 12.5 mg and four batches of 25 mg strengths of Xenazine tablets. The release and stability specifications for the drug product are identical. Acceptable validated analytical methods are provided in the submission.

These batches of drug product were manufactured at the commercial manufacturing site,) at the commercial scale using commercial method. The applicant provided Certificates of Analysis (CoAs) of all of these batches. A typical drug product batch size consists of approximately units of each strength. Xenazine tablets will be marketed only into bottles with child resistant caps. The bottle size is 112 counts for both strengths.

The original NDA provided 24 months long term (stability updated for 36 months, 14-MAR-06) and 6 months accelerated stability data for three primary batches of 12.5 mg and four primary batches of 25 mg strengths, of Xenazine tablets. In addition, the applicant provided 60-months long term and 6 months accelerated stability data for three supportive batches of 25 mg strength.

*The applicant submitted amendment (26-JUN-07) for the addition of s site as an alternate manufacturing, packager, labeler, and control for 12.5 mg and 25 mg Xenazine (tetrabenazine) tablets. The excipients and unit formula for 12.5 mg or 25 mg tetrabenazine tablets manufactured at are the same as those manufactured by however, the quality

standard for the [redacted] has been changed from USP to Ph. Eur. The formulation development of 12.5 mg and 25 mg tetrabenazine tablets at [redacted] remained unchanged from the formulation at [redacted] will manufacture tetrabenazine tablets at a 1.7 larger scale [redacted] using equipment of the same class, with minor processing changes as compared to [redacted] The 12.5 mg and 25 mg tetrabenazine tablets contained no overage of tetrabenazine. The container closure system is similar to the container closure system used to package tablets manufactured at [redacted] The tests and acceptance criteria for the 12.5 mg and 25 mg tetrabenazine tablets manufactured at [redacted] remained unchanged from those used to release the tablets manufactured at [redacted] The 6-month long-term and accelerated stability data for three commercial size batches of each strength, 12.5 mg and 25 mg Xenazine tablets manufactured at [redacted] Site is provided. There is essentially no change in the tetrabenazine assay and no increase in the amount of degradation products. Dissolution profiles comparing tablets manufactured at [redacted] and [redacted] are provided and are comparable. Data showed that all stability parameters are well within their respective acceptance criteria after 6 months at 25° C/60% RH and 40° C/75% RH and comparable with batches manufactured at [redacted]

DRUG SUBSTANCE

The drug substance, tetrabenazine, does not have a monograph in US Pharmacopoeia. For information regarding chemistry, manufacturing and controls (CMC) of the drug substance, tetrabenazine, [redacted] DMF [redacted] is cross-referenced. A letter of Authorization to reference DMF [redacted] dated 6/08/2006, is provided. Prestwick Pharmaceuticals Inc. provided significant CMC information on the drug substance in the NDA submission. The drug substance, tetrabenazine, is manufactured by [redacted] according to the process and controls described in their DMF [redacted] and supplied to the applicant. The DMF [redacted] was reviewed by Dr. Lyudmila Soldatova, and, originally, was found inadequate (Review #1 dated 2/16/06). Current status of [redacted] DMF is adequate (Review #3 dated July 24, 2007; by Dr. Lyudmila Soldatova). Tetrabenazine is a white to slightly yellow powder; it has two stereo centers, C3 and C11b and four isomers, RS, SR (*trans*) and SS, RR (*cis*) are possible [redacted] . The acceptable batch analysis data for drug substance batches produced by [redacted] were submitted in the NDA.

B. Description of How the Drug Product is Intended to be Used

Xenazine (tetrabenazine) tablets will be marketed only into bottles. The bottle sizes are [redacted] /112 counts for both strengths. The maximum recommended total daily dose is 100 mg/day. Prestwick provided 24 months of stability data at 25° C/60% RH and 6 months stability data at 40° C/75% RH for registration batches of each strength, 12.5 mg and 25 mg tetrabenazine tablets manufactured at [redacted] The applicant submitted amendment (26-JUN-07) for the addition of Fournier [redacted] site as an alternate manufacturing, packager, labeler, and control for 12.5 mg and 25 mg Xenazine (tetrabenazine) tablets. In support of proposed alternate manufacturing site, 6-month long-term and accelerated stability data for three commercial size batches of each strength, 12.5 mg and 25 mg Xenazine tablets is provided. The applicant has requested a 36 month expiration period (shelf life) for all strengths packaged in bottles and it is granted.

The storage conditions for the drug product were recommended as "Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature]. Dispense in tight container (USP).

The applicant makes the usual post-approval stability commitments with regards to stability studies indicating that the first three production batches for each strength and container/closure system will continue according to the approved stability protocols through the expiration dating period.

This application qualifies for categorical exclusion from environmental assessment under the provisions in 21 CFR § 25.31(a).

The Office of Compliance has found all manufacturing, testing, and packaging sites for drug substance and drug product acceptable.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-894 for Xenazine tablets is recommended **Approval** status from CMC standpoint.

III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS.

B. Endorsement Block

Chemists Names:	Chhagan G. Tele, Ph.D. (Drug Product) Lyudmila N. Soldatova, Ph.D. (Drug Substance)
Chemistry Branch Chief:	Ramesh K. Sood, Ph.D.
Chemistry Project Manager Name:	Scott N. Goldie, Ph.D.
Clinical Project Manager Name:	Teresa A. Wheelous, Pharm.D.

C. CC Block

See DFS.

17 Page(s) Withheld

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_____ Deliberative Process

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/s/

Chhagan Tele
10/3/2007 12:56:25 PM
CHEMIST

Lyudmila Soldatova
10/3/2007 05:03:45 PM
CHEMIST

Ramesh Sood
10/4/2007 02:54:22 PM
CHEMIST

NDA 21-894

Xenazine (tetrabenazine) Tablets

Prestwick Pharmaceuticals, INC.

Chhagan G. Tele, Ph.D.
Lyudmila N. Soldatova, Ph.D.

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-894

2. REVIEW #: 1

3. REVIEW DATE: March 10, 2006

4. REVIEWERS: Chhagan G. Tele, Ph.D.
Lyudmila N. Soldatova, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	23-SEP-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Prestwick Pharmaceuticals, Inc.
Address:	1825 K Street, NW, Suite 1475, Washington, DC 20006
Representative:	Benjamin P. Lewis, Vice President, Regulatory Affairs
Telephone:	(202) 296-1400

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Xenazine
b) Non-Proprietary Name (USAN): Tetrabenazine
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: For the treatment of Chorea Associated with Huntington's Disease

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 12.5 mg and 25 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
___X_Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

INN: Tetrabenazine

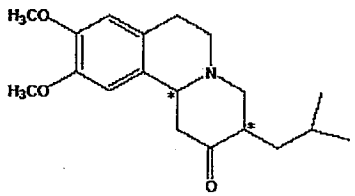
Chemical Name: *cis rac* – 1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-3-(2-methylpropyl)-2H-benzo[a]quinolizin-2-one

Chemical Formula: $C_{19}H_{27}NO_3$

Molecular Weight: 317.4

CAS registry #: 58-46-8

Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	Tetrabenazine	1	Inadequate	16 -FEB-06	Drug Substance

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review

4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	63,909	Commercial IND (HD)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		N/A
EES	Pending		
Pharm/Tox	Pending		Andrea M. Powell, PhD
Biopharm	Acceptable		Sally U. Yasuda, MS, PharmD
LNC	N/A		
Methods Validation	Pending		To be forwarded once specifications and methods finalized
DMETS			
EA	Acceptable, categorical exclusion granted as per information from Prestwick in this NDA		Chhagan G. Tele, Ph.D. (HFD-130)
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 21-894

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 21-894 for Xenazine (tetrabenazine) Tablets is recommended APPROVABLE from the CMC standpoint. The approval from CMC standpoint is contingent on adequate responses to the CMC deficiencies outlined in this review, and on the overall recommendation on establishment from the Office of Compliance. Based on the stability data, 24 month expiry could be granted for Xenazine Tablets.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None as per this review.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

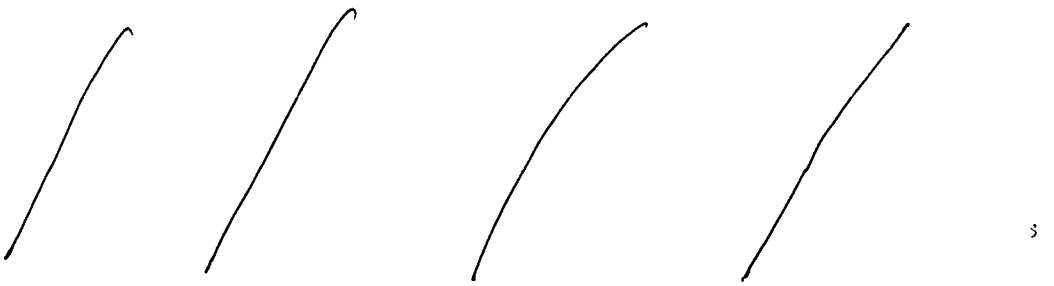
BACKGROUND

Tetrabenazine is a dopamine-depleting agent that has been used for the management of hyperkinetic movement disorders and shown to deplete monoamines selectively in the central nervous system (CNS). The applicant submitted an original IND 63,909 (Phase 3) for tetrabenazine for the treatment of Huntington's chorea and was allowed to proceed on 07-MAY-03. The disease is characterized by a symptomatic triad of chorea, dementia, and personality disorder. Huntington Disease (HD) is a neurodegenerative disorder, characterized by progressive inexorable loss of nerve cells. Onset usually occurs around the age of 40 years. Tetrabenazine was originally developed by Hoffmann-LaRoche in the late 1950s and 1960s as part of an antihelminthic program. Currently, it is available in several foreign countries (Australia, Canada, Denmark, Ireland, Israel, New Zealand, Portugal, and United Kingdom) for various hyperkinetic movement disorders that include Huntington's chorea. It is also noted that [redacted] There is currently no FDA-approved treatment for the chorea symptoms of HD and no therapy is known to prevent the progression of neurodegeneration. FDA's Office of Orphan Product Development granted "orphan" designation for tetrabenazine to Prestwick on 15-JAN-2004 for the indication of treatment of Huntington Disease. FDA's Division of Neuropharmacological Drug Products granted "fast track" designation to Prestwick on 23-APR-2004 under the Fast Track Drug Development Program with priority review for the specific indication of chorea associated with HD.

DRUG PRODUCT

Xenazine (tetrabenazine) tablets are indicated for the treatment of Chorea Associated with Huntington's Disease. Xenazine is a conventional tablet dosage form (Xenazine Tablets, 12.5 mg and 25 mg) manufactured by [redacted] and will be distributed by Prestwick Pharmaceuticals, Inc. Washington, DC. Each tablet contains 12.5 mg

and 25 mg of tetrabenazine. The excipients used in the 12.5 mg and 25 mg tablet formulations are lactose [redacted] maize starch, [redacted], talc, and magnesium stearate [redacted] Iron oxide (Yellow [redacted] is also used in the formulation of 25 mg tablets (yellow in color) to discriminate from 12.5 mg tablets (white in color). These excipients are commonly used in tablet formulations for their respective functions. All excipients used in the 12.5 mg and 25 mg tablets are of compendial (USP or NF) quality. The commercial manufacturing process (Batch size [redacted] for Xenazine tablets [redacted]



The specifications for tablets included Description, Identification (HPLC and UV), Tetrabenazine content (HPLC), Degradation Products (HPLC), Dissolution (UV), Content Uniformity (HPLC), [redacted] The batch analysis was provided for three batches of 12.5 mg and four batches of 25 mg strengths of Xenazine tablets. The release and stability specifications for the drug product are identical. Acceptable validated analytical methods are provided in the submission.

These batches of drug product were manufactured at the commercial manufacturing site, [redacted] at the commercial scale using commercial method. The applicant provided Certificates of Analysis (CoAs) of all of these batches. A typical drug product batch size consists of approximately [redacted] units of each strength. Xenazine tablets will be marketed only into bottles with [redacted] child resistant caps. The bottle size is [redacted] /112 counts for both strengths.

The original NDA provided 24 months long term and 6 months accelerated stability data for three primary batches of 12.5 mg and four primary batches of 25 mg strengths, of Xenazine tablets. In addition, the applicant provided 60-months long term and 6 months accelerated stability data for three supportive batches of 25 mg strength.

DRUG SUBSTANCE

The drug substance, tetrabenazine, does not have a monograph in US Pharmacopoeia. For information regarding chemistry, manufacturing and controls (CMC) of the drug substance, tetrabenazine, [redacted] DMF # [redacted] is cross-referenced. A letter of Authorization to reference DMF [redacted], dated 3/31/2005, was provided. Prestwick Pharmaceuticals Inc. provided significant CMC information on the drug substance in the NDA submission. The drug substance, tetrabenazine, is manufactured by [redacted] according to the process and controls described in their DMF [redacted] and supplied to the applicant. The DMF [redacted] was reviewed by Dr. Lyudmila Soldatova, and, originally, was found inadequate (Review #1 dated 2/16/06). Tetrabenazine is a white to slightly yellow powder; it has two stereo centers, C3 and C11b and four

isomers, RS, SR (*trans*) and SS, RR (*cis*) are possible.

Specifications for drug substance and batch analysis data for drug substance batches produced by were submitted in the NDA. Deficiencies were found in the specifications and in the batch analysis, which are reported in this review.

B. Description of How the Drug Product is Intended to be Used

Xenazine (tetrabenazine) tablets will be marketed only into bottles. The bottle sizes are 112 counts for both strengths. The maximum recommended total daily dose is 100 mg/day. Prestwick provided 24 months of stability data at 25° C/60% RH and 6 months stability data at 40° C/75% RH for registration batches of each strength, 12.5 mg and 25 mg tetrabenazine tablets. The applicant has requested a expiration period (shelf life) for all strengths packaged in bottles.

The storage conditions for the drug product were recommended as "Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature].

The applicant makes the usual post-approval stability commitments with regards to stability studies indicating that the first three production batches for each strength and container/closure system will continue according to the approved stability protocols through the expiration dating period.

This application qualifies for categorical exclusion from environmental assessment under the provisions in 21 CFR § 25.31(a).

The recommendation from the Office of Compliance regarding several manufacturing, testing, and packaging sites for drug product is pending at this time. Manufacturing site for drug substance was found acceptable.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-894 for Xenazine tablets is recommended **Approvable** status from CMC standpoint.

III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS.

B. Endorsement Block

Chemists Names: Chhagan G. Tele, Ph.D.
Lyudmila N. Soldatova, Ph.D.
Chemistry Branch Chief: Ramesh K. Sood, Ph.D.
Chemistry Project Manager Name: Scott N. Goldie, Ph.D.
Clinical Project Manager Name: Teresa A. Wheelous, Pharm.D.

C. CC Block

See DFS.

APPEARS THIS WAY
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_____ Draft Labeling

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/s/

Lyudmila Soldatova
3/21/2006 10:44:45 AM
CHEMIST

Chhagan Tele
3/21/2006 11:03:54 AM
CHEMIST

Ramesh Sood
3/21/2006 11:10:57 AM
CHEMIST

MEMORANDUM

To: NDA 21-894
From: Chi-wan Chen, Acting Director, Division of Pre-Marketing Assessment I
Date: March 21, 2006
Subject: Executive Summary for NDA 21-894

Introduction: Xenazine (tetrabenazine) Tablets are indicated for the treatment of chorea associated with Huntington's Disease (HD). The agency has granted "orphan drug" designation for tetrabenazine to Prestwick on 15-JAN-2004 for the indication of treatment of Huntington Disease. FDA's Division of Neurological Products granted "fast track" designation to this NDA on 23-APR-2004 under the Fast Track Drug Development Program with priority review for the specific indication of chorea associated with HD.

Drug Substance: The drug substance, tetrabenazine, is manufactured by according to the process and controls described in their DMF ; nd supplied to the applicant. Tetrabenazine is a white to slightly yellow powder; it has two stereo centers, C3 and C11b, and four isomers RS, SR (*trans*) and SS, RR (*cis*), are possible.

The quality of the drug substance will be controlled through well-controlled manufacturing process and drug substance specification.

Drug Product: Xenazine is a conventional immediate release tablet dosage form available in 12.5 mg and 25 mg strengths. The tablets are manufactured using . The tablets are packaged into bottles with child-resistant caps. The 25 mg tablets are scored on one side and the applicant has justified the scoring based on the fact that the dosing regimen will be 12.5 mg in the morning and noon, and 25 mg at night. This way the patient will not need tablets of two different strengths to accommodate this possible dosing regimen. The recommended storage conditions for the drug product are at room temperature. A 36-month expiration date was requested by the applicant based on real time stability data and the request has been granted.

Recommended action: An overall approvable action is expected for this NDA. An approvable action is also recommended from CMC perspective. The approvable recommendation is based on (1) a pending recommendation from the Office of Compliance for three facilities and (2) an unresolved deficiency in the cross-referenced DMF for the drug substance. Two of the three facilities are undergoing inspection at the time of writing this memorandum and a recommendation from the OC is expected prior to PDUFA date; but the inspection of the third facility will not be completed prior to the PDUFA date. The DMF for the drug substance is deficient because of an unresolved issue regarding the control of

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/s/

Chi Wan Chen
3/21/2006 05:45:28 PM
CHEMIST