

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021825Orig1s000

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo
NDA 21825, FERRIPROX (deferiprone) tablets, 500 mg
Date: 12-OCT-2011

Introduction

FERRIPROX (deferiprone) tablets are immediate-release, film-coated tablets supplied in one strength (500 mg). FERRIPROX is indicated for the treatment of patients with excessive body iron stores due to chronic transfusion therapy. The dose is 25-33 mg/kg body weight, taken orally three times daily for a total dose of 75-^{(b) (4)} mg/kg body weight. The maximum safe dose is ^{(b) (4)} mg/kg body weight/day.

ONDQA recommends approval of this NDA. There are no outstanding CMC deficiencies for this NDA.

Administrative

The current submission is a Class 2 Resubmission to the Agency's 30-NOV-2009 Complete Response action. The Chemistry, Manufacturing and Controls assessment for the current cycle is captured in Chemistry Review #3 (dated 26-SEP-2011), the ONDQA Biopharmaceutics Review (dated 16-SEP-2011), and the ONDQA Biopharmaceutics Memorandum (25-SEP-2011). Primary CMC review of drug substance and drug product information, as well as biopharmaceutics information, confirm an approval recommendation, and all primary reviews confirm that there are no outstanding CMC deficiencies.

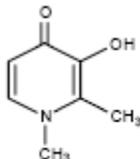
At the time of primary review completion, an overall recommendation from the Office of Compliance was still pending. An overall acceptable recommendation was issued by the Office of Compliance on 07-OCT-2011. This pending issue is now resolved.

This NDA is recommended for approval from a Chemistry, Manufacturing and Controls standpoint.

Insert the following language into the approval letter: "Based on the stability data provided in your application, the drug product is granted a 24-month expiry when stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F)."

Drug Substance (Deferiprone)

Chemical Name: 1,2-dimethyl-3-hydroxypyrid-4-one



Deferiprone is a new chemical entity. Deferiprone is a bidentate iron chelator that preferentially binds ferric ions into a 3:1 (deferiprone: iron) complex at low pH. Bulk drug substance is a white to pink crystalline powder. (b) (4)

(b) (4) Deferiprone is highly soluble in water at pH 1-7.5 and has high permeability, thus is a BCS class 1 drug. Structural elucidation studies show the material is prepared (b) (4)

Manufacture is by a (b) (4)

(b) (4). Manufacture and control of bulk process at each proposed site is described in Apotex, Inc.'s type II DM 10867. During the CMC review, the DMF was reviewed and was found adequate to support approval of this application.

The CMC review grants a re-test period of (b) (4) for the Apotex Pharmachem and (b) (4) sites, and a retest period of (b) (4) for the (b) (4) site when stored under controlled room temperature. This is in agreement with what the Applicant proposes, and not additional action is needed.

Drug Product (Deferiprone Tablets, 500 mg)

The drug product is a scored tablet manufactured (b) (4). All excipients used in the formulation are compendial and are conventional for solid oral dosage forms. The release specification includes testing for identity, average tablet weight, dissolution, content uniformity/assay, and degradants (unspecified and total). The CMC review confirms that the tests are adequate to establish identify, purity and strength of the drug product. The methods for assay and related substances were revised after NDA submission. Descriptions of the analytical methods are complete and provided in sufficient detail. Representative spectra and chromatograms have been provided. Validation studies for the non-compendial methods are complete and establish the methods as adequate for the intended use.

The proposed commercial presentation is 100 tablets in a 120cc round, white HDPE bottle. There is no carton for the bottle. Suppliers and materials of construction for each packaging component are identified and an acceptance specification for each component is provided. All Type III DMFs for the component suppliers and their materials of construction were evaluated as acceptable to support this NDA.

The CMC review grants a 24-month expiration dating period when stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

Insert the following language into the approval letter:

“Based on the stability data provided in your application, the drug product is granted a 24-month expiry when stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).”

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

/s/

RICHARD T LOSTRITTO
10/12/2011

NDA 21-825

Ferriprox®

ApoPharma, Inc.

William M. Adams

Review Branch I

Division of New Drug Quality Assessment I

Office of New Drug Quality Assessment

For the Division of Hematology Products

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CMC Review Data Sheet

CMC Review Data Sheet

1. **NDA 21-825**
2. **REVIEW 03**
3. **REVIEW DATE:** 26 Sep 2011
4. **REVIEWER:** William Adams
5. **PREVIOUS DOCUMENTS:**

<i>Document</i>	<i>Darrts Submit Date</i>
Amendment N-002 (CMC RU, tablets & solution)	12 Mar 2007
CMC IQA	27 Mar 2007
<i>Amendment (EA submission; not in Darrts or EDR)</i>	<i>30 Aug 2007</i>
Amendment N-004 (resubmission of CMC RU, tablets & solution)	26 Sep 2007
Amendment N-006 (CMC RU, tablets)	21 Dec 2007
IR letter (CMC only)	28 Feb 2008
CMC Review 01	21 Mar 2008
Amendment N-008 (partial response to IR)	27 Mar 2008
DR Letter (CMC)	27 Mar 2008
Amendment N-009 (intent to respond to DR letter)	12 Jun 2008
Amendment N-010 (non-CMC & labeling)	27 Jun 2008
Amendment N-012 (complete CMC response to IR letter)	29 Sep 2008
Amendment N-013 (complete CMC response to DR letter)	30 Oct 2008
Amendment N-015 (new NDA; clinical and labeling)	29 Jan 2009
Amendment N-016 (draft labels & labeling)	17 Feb 2009
Amendment N-017 (request trade name review)	25 Feb 2009
<i>Amendment N-020 (CMC information; not in EDR)</i>	<i>18 Mar 2009</i>
Correspondence (denial of trade name)	24 Mar 2009
74-Day Letter (multi-discipline)	31 Mar 2009
<i>Amendment N-021 (response to 74-day letter; not in EDR)</i>	<i>07 May 2009</i>
Amendment N-024 (request for trade name reconsideration)	15 Jun 2009
Amendment N-026 (biostat & labeling)	09 Jul 2009
Amendment N-028 (minor CMC revisions)	06 Aug 2009
Correspondence (proprietary name granted)	11 Sep 2009
CMC Review 02	20 Oct 2009
Complete Response letter (clinical, clinpharm, CMC, labeling, EES)	30 Nov 2009
General Advice (labeling comments)	02 Dec 2009

6. **SUBMISSION(S) BEING REVIEWED:**

<i>Document</i>	<i>Darrts Submit Date</i>
Amendment N-058 (partial response - CMC & draft labeling)*	25 Feb 2011
Amendment N-059 (complete response; class 2 resubmission)	14 Apr 2011
Amendment N-060 (draft trade name & package insert)	29 Apr 2011
IR letter (labeling)	03 Jun 2011

CMC Review Data Sheet

Amendment N-063 (draft container labels)	07 Jun 2011
Amendment N-064 (draft container labels)	14 Jun 2011
IR letter (CMC only)	16 Jun 2011
Amendment N-068 (proprietary name)	27 Jul 2011
Correspondence (proprietary name granted)	28 Jul 2011
IR Letter (CMC only)	10 Aug 2011
Amendment N-075 (clinical & labeling)	06 Sep 2011
IR Letter (CMC only)	19 Sep 2011
<i>Email Partial Response to 09/19/11 IR Letter</i>	<i>19 Sep 2011</i>
<i>Minutes for 09/20/11 Tcon (not yet entered into Dartrts)</i>	<i>21 Sep 2011</i>
<i>Email Complete Response to 09/19/11 IR Letter</i>	<i>22 Sep 2011</i>
Amendment N-077 (multidiscipline response to multiple IR letters)	22 Sep 2011
<i>Email Response to Biopharm Comment**</i>	<i>23 Sep 2011</i>
Amendment N-078 (revised release/stability specification)	26 Sep 2011
* Response to General Advice letter dated 02 Dec 2009 (labeling) and partial response (CMC Questions 1-15) to Complete Response letter dated 30 Nov 2009	
** After discussion between Biopharm and the applicant, the Dissolution criterion was finalized in the 09/23/11 Amendment.	

7. NAME & ADDRESS OF APPLICANT:

Name: ApoPharma, Inc.
 Address: 200 Barmac Drive
 Toronto, Ontario, Canada M9L 2Z7
 Ms Lynda Sutton, Chief Regulatory Officer
 Representative: Cato Research Ltd.
 4364 south Alston Avenue
 Durham, NC 27713-2220
 Telephone: 919-361-2286

8. Drug Product NAME/CODE/TYPE:

- a) Proprietary Name: Ferriprox®
- b) Non-Proprietary Name (USAN): Deferiprone
- c) Code Name/# (ONDQA only): L1, CP20, APO-66, PL1, DN-180-01-AF
- d) Chem. Type/Submission Priority (ONDQA only): 1S

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

10. PHARMACOLOGICAL CATEGORY: Metal Chelator

11. DOSAGE FORM: Immediate Release, Film-Coated Tablet

12. STRENGTH/POTENCY: 500 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

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

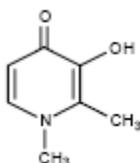
CMC Review Data Sheet

SPOTS product – Form Completed

Not a SPOTS product

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

Chemical Name 1,2-dimethyl-3-hydroxypyrid-4-one
 Molecular Formula C₇H₉NO₂
 Molecular Weight 139.15
 Molecular Structure



17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYP E	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS ³
10867	II	Apotex	API	1	Adequate	09/16/11	Review by W.Adams

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)

³ Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
IND 45,724	ApoPharma	Ferriprox	active		

CMC Review Data Sheet

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	REVIEWER	DATE	STATUS/ CONCLUSION	COMMENTS
Biometrics	Q.Xu	09/16/11	Adequate	
Clinical	G.Shashaty	09/16/11	Adequate	
NonClinical	Y.Chopra	Pending Darrrts		
ClinPham	J.Grillo	09/16/11	Adequate	
EES	DMPQ		Pending	GMP inspection of DP mfg & control site started 09/19/11
Biopharm	T.M.Chen	Pending Darrrts	Adequate	
ODS/DMEPA	L.Holmes	07/11/11	Adequate	
EA	W.Adams	---	---	Categorical Exclusion granted in CMC Review 01
Maternal Health	L.Sahin	08/16/11	Adequate	

Executive Summary Section

The CMC Review for NDA 201532

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC standpoint, this application is recommended for approval pending the receipt of an overall acceptable recommendation from the Office of Compliance. The submission is complete and all other CMC review issues have been resolved.

Insert the following language into the action letter: Based on the stability data provided in your application, the drug product is granted a 24-month expiry when stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

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

None

II. Summary of CMC Assessments

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

Proposed in this application is Ferriprox® (deferiprone) 500 mg oral tablets in a 100-count bottle. Ferriprox® is currently marketed in Europe and Australia. The application has been granted orphan drug and fast track status, and was accepted as a rolling submission. (b) (4)

Subsequent amendments included CMC reviewable units for drug substance and drug product. The application has also been updated to include an additional drug substance supplier.

Drug Substance

Deferiprone (3-hydroxy-1,2-dimethylpyridin-4-one) is a bidentate iron chelator that preferentially binds ferric ions into a 3:1 (deferiprone: iron) complex at low pH. Bulk drug substance is a white to pink crystalline powder. (b) (4)

Deferiprone is highly soluble in water at pH 1-7.5 and has high permeability, thus is a BCS class 1 drug. Structure elucidation studies show the material is prepared (b) (4)

Executive Summary Section

Manufacture is by [REDACTED] (b) (4)

[REDACTED]. Manufacture and control of bulk process at each proposed site is described in Apotex, Inc.'s type II DM 10867. A letter of authorization to this file is provided. The DMF has been reviewed and found adequate to support approval of this application.

Drug substance specifications for release from the manufacturer site and for acceptance at the single drug product manufacturing site differ in some of the non-chromatographic analytical methods, but the tests and criteria are identical. Testing is to be performed at each of these four sites or by contract laboratories. Testing is for identity, melting range, residue on ignition, heavy metals, water content, assay, residual solvents, related compounds (specified, unspecified and total impurities), bulk density, tapped density, particle size and [REDACTED] (b) (4). The HPLC methods for assay and related substances were revised after NDA submission. Each analytical method has been described completely and in sufficient detail. Acceptable method validation studies have been submitted for each non-compendial analytical method at their site of use.

The proposed acceptance criteria for residual solvents, total impurities and water content are supported by batch analysis data. The proposed limits for specified impurity [REDACTED] (b) (4) and [REDACTED] (b) (4) are justified based on referenced safety studies. The proposed criteria for particle size, tapped density and bulk density are established to assure efficient tablet manufacture. Criteria for the other tests are justified based on data observed to date. Batch analysis data is provided for commercial-scale lots representing material manufactured since 1993 and at each of the proposed manufacturing sites.

Since there are no USP reference standards for this drug, samples taken from specified commercial lots without further processing are designated as the primary and secondary reference standard materials. These materials have been characterized and were used in the structure elucidation studies.

Packaging for storage and shipment is [REDACTED] (b) (4). Descriptions and specifications for each packaging component and material of construction used at each of the manufacturing site are provided. Letters of authorization to the type III DMFs for the packaging component suppliers and their materials of construction have been provided.

The primary stability studies are performed on multiple commercial-scale lots from each of the manufacturers stored in the proposed shipping container. Data is provided for storage at ICH long term conditions for 12-60 months; at ICH accelerated conditions for 6 months; and for exposure to UV and fluorescent light. Testing is for appearance, identity, assay, related substances and water content. Identity, appearance, assay and related substances did not change over time and no new impurities were detected. Water content increased slightly at high relative humidity. Supportive studies of drug substance with protective packaging for extended exposure to room temperature and short term exposure to high heat, high humidity and light show the same stability trends as the primary studies. Stress and forced degradation studies of unprotected

Executive Summary Section

solid and aqueous solutions show the drug molecule is slightly sensitive to (b) (4). Degradants from these studies are not identified. The applicant proposes a retest period of (b) (4) for the Apotex Pharmachem and (b) (4) sites, and a (b) (4) retest period for the (b) (4) site with a label storage statement is USP CRT. The post approval stability protocol and commitment to continue the stability studies is acceptable.

Drug Product

Ferriprox® is a white to off white, capsule-shaped, immediate release, film-coated tablet containing 500 mg deferiprone. The tablet is imprinted with “APO” over “500” with a functional score on one side and plain on the other. The scoring is intended to facilitate breaking the tablet into two equal halves.

Drug product development and investigational formulations for 100 mg, 250 mg and 500 mg tablets are summarized. The difference between the phase 3 and the commercial tablets is the (b) (4). A Quality by Design approach was not used and a design space for the manufacturing process steps has not been developed. Tablet divisibility is adequately addressed by studies using developmental lots; by process validation studies addressing blend uniformity; and by data from the supportive stability studies. Development of the dissolution method is addressed in studies using developmental and clinical lots. An acceptable dissolution criterion has been proposed based on submitted drug release profile data.

Unit and batch formulations are provided. The excipients are Microcrystalline Cellulose, Magnesium Stearate, and Colloidal Silicon Dioxide in the cores; and Hypromellose (b) (4), Polyethylene Glycol (b) (4) and Titanium Dioxide in the film coating. All excipients are USP/NF grade materials. Dry excipients are purchased from major suppliers and each has an internet website. No excipient is novel or of human origin. (b) (4) Excipient specifications are the current USP/NF monograph for each material. (b) (4) is prepared at the tablet manufacturing site. Certificates of analysis for the excipients lots used in the stability and 3 biolots are provided. Contract laboratories for excipient testing may be used.

Tablet manufacture, control, packaging, release testing, and stability testing are performed at Apotex, Inc. (Etobicoke, Canada). Tablets may be packaged and labeled at Apotex, Inc. (Toronto, Canada). The tablet manufacture process is (b) (4). The manufacturing process, process parameters and in-process controls are acceptable and are described in sufficient detail. A narrative description and process flow diagram are included. Tablet (b) (4) is not proposed. Executed batch records and supporting analytical information are provided for the clinical and stability batches.

The release specification includes testing for identity, average tablet weight, dissolution, content uniformity/assay, and degradants (unspecified and total). The tests are adequate to establish identity, purity and strength of the drug product. The methods for assay and related substances were revised after NDA submission. Descriptions of the analytical methods are complete and

Executive Summary Section

provided in sufficient detail. Representative spectra and chromatograms have been provided. Validation studies for the non-compendial methods are complete and establish the methods as adequate for the intended use.

The proposed acceptance criteria are justified based on batch analysis data submitted for batches used in clinical and stability studies, and safety information. The absence of testing for residual moisture content and microbial limits is justified based on historical batch analysis data.

The proposed reference standards are (b) (4) and the drug substance standards.

The proposed commercial presentation is 100 tablets in a 120cc round, white HDPE bottle with a (b) (4) child resistant closure having a silver foil/foam cap liner; an aluminum foil (b) (4) induction innerseal; and an extended content label (ECL). The ECL is a patient information leaflet which may be removed or re-applied to the bottle by the patient. The innerseal is constructed with a "Lift N'Peel" tab for easy removal. There is no carton for the bottle. Suppliers and materials of construction for each packaging component are identified and an acceptance specification for each component is provided. Letters for authorization for the type III DMFs for the component suppliers and their materials of construction are provided.

Primary stability studies are performed on commercial-scale white tablets in the proposed 100-count package and in a 1000-count version of the same package stored at ICH long term conditions for 12-60 months, ICH intermediate conditions for 60 months and ICH accelerated conditions for 6 months. The lots were tested for identity, appearance, assay, degradants, and 1-point dissolution. Some lots were also tested for microbial limits after 60 months. The results show no change in test values over time, no microbial limits failures at release and no formation of new degradants. Supportive stability studies were performed on pink tablets stored in 100-count and 1000-count packages at 25-30°C/ambient RH, ICH accelerated and light stress conditions for 36 months, 6 months, and 3 months, respectively. The results from all studies show no change in test values over time and the formation of no new degradants. Since multiple drug substance sources are proposed, the approved expiry period is to be based on the studies for tablets manufactured with each drug substance supplier. The application is to be approved with an initial expiry period of 24 months with storage at controlled room temperature. The post approval stability protocol and commitment are acceptable.

The applicant has requested a categorical exclusion from the environmental assessment requirements under 21 CFR 25.31(b) in that the amount of drug introduced into the environment is less than 1 ppb per year. A calculation of expected introduction concentration is included. The request is considered to be justified.

Draft container label and patient information leaflet are provided. The proposed trade name, established name, storage condition statement and other CMC information are acceptable. Final revisions to the CMC information in the patient information leaflet have already been requested.

The Overall EES Conclusion was Pending dated 11 Jul 2011. GMP inspection of the drug product manufacturing site is pending. All sites were re-submitted in the current review clock

Executive Summary Section

for confirmation of cGMP status, and an updated overall recommendation has not yet been received.

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

Deferiprone formulated as Ferriprox® is indicated for the treatment of patients with excessive body iron stores due to chronic transfusion therapy. The dose is 25-33 mg/Kg body weight taken orally three times daily for a total dose of 75-^{(b) (4)} mg/Kg body weight. The maximum safe dose is ^{(b) (4)} mg/Kg body weight/day. Doses are to be rounded to the nearest half tablet.

C. Basis for Approvability or Not-Approval Recommendation

The proposed application is considered to be adequate for APPROVAL from the CMC perspective, pending the receipt of an overall acceptable recommendation from the Office of Compliance. Complete and acceptable CMC information has been provided.

III. Administrative**A. Reviewer's Signature: (See appended electronic signature page)**

William M. Adams
DNDQA I/CMC Reviewer

B. Endorsement Block: (See appended electronic signature page)

Sarah Pope Miksinski, Ph.D.
DNDQA I/Branch Chief

C. CC Block: (entered electronically in Dartrts)

DNDQA I/PMQ/T.V.Lambert
DNDQA I/CMC Lead/J.Brown
DMIHP/RPM/M.Miller

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/s/

WILLIAM M ADAMS
09/26/2011

SARAH P MIKSINSKI
09/27/2011

NDA 21-825

Ferriprox

ApoPharma, Inc.

William M. Adams
Office of New Drug Quality Assurance (ONDQA)

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Chemistry Review Data Sheet

1. NDA 21-825
2. REVIEW #2
3. REVIEW DATE: 19 Oct 2009
4. REVIEWER: William Adams
5. PREVIOUS DOCUMENTS:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (N-001, CMC RU)	12 Mar 2007
Amendment (N-002, BP RU)	28 Mar 2007
Amendment	26 Jul 2007
Amendment (EA submission)	30 Aug 2007
Amendment (N-003, response to 072607 comments)	24 Sep 2007
Amendment (N-004, CMC RU)	21 Dec 2007
IR letter	28 Feb 2008
DR letter	27 Mar 2008
Filing Letter	06 Apr 2009
Meeting	13 Apr 2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
IR letter (CMC only)	28 Feb 2008
Amendment (N-006, partial response to IR letter)	27 Mar 2008
DR Letter (multi-discipline)	27 Mar 2008
Amendment (N-007, intent to respond to DR letter)	12 Jun 2008
Amendment (N-010, complete CMC response to IR letter)	29 Sep 2008
Amendment (N-011, complete CMC response to DR letter)	29 Oct 2008
Amendment (N-015, request trade name review)	24 Feb 2009
Amendment (N-016, transfer regulatory responsibility to Cato Research)	24 Feb 2009
74-Day Letter (multi-discipline)	31 Mar 2009
Amendment (N-019, response to 74-day letter & meeting comments)	06 May 2009
Amendment (N-022, request for trade name reconsideration)	15 May 2009

7. NAME & ADDRESS OF APPLICANT:

Name: ApoPharma, Inc.
 200 Barmac Drive
 Toronto, Ontario, Canada M9L 2Z7

Chemistry Review Data Sheet

Representative: Lynda Sutton, Chief Regulatory Officer
Cato Research, Ltd.
4364 South Alston Avenue
Durham, SC 27713-2220

Telephone: (919) 361-2286

8. DRUG PRODUCT NAME/CODE/TYPE:

- (a) Proprietary Name: Ferriprox®
- (b) Non-Proprietary Name (USAN): Deferiprone
- (c) Code Name/# (ONDC only): L1, CP20, APO-66, PL1, DN-180-01-AF
- (d) Chem. Type/Submission Priority (ONDC only)
Chem. Type:
Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOLOGICAL CATEGORY: Metal Chelator

11. DOSAGE FORM: Film Coated Tablet

12. STRENGTH/POTENCY: 500 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

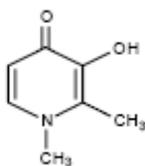
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

XX Not a SPOTS product

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

Chemical Name: 1,2-dimethyl-3-hydroxypyrid-4-one
Molecular Formula: C₇H₉NO₂
Molecular Weight: 139.15 daltons
Molecular Structure



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
10867	II	Apotex, Inc	Drug substance	1	Inadequate	IR 02/29/08	Reviewed by M.Adams

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 45,724	submitted July 1994	Deferiprone

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Clinical		10/19/09	G.Shastaty
follow-uo EES	withhold	10/19/09	OC
NonClin		09/24/09	D.Bailey
Clinpharm		09/24/09	P.Hepp
Methods Validation	package submitted		
OPDRA			
EA	acceptable	NDA Review #1	W.Adams, CMC

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 21-825

The Executive Summary

I. RECOMMENDATIONS

A. RECOMMENDATION & CONCLUSION ON APPROVABILITY

From a CMC standpoint, this application cannot be approved until the following deficiencies are adequately addressed:

1. The regulatory methods have not been appropriately described and validated at each of the proposed drug substance and drug product manufacturing sites.
2. The storage condition statement for bulk drug substance should be revised to reflect the results of the stability studies.
3. The dissolution criterion should be revised to reflect the submitted drug release profile data.
4. Inadequate drug product stability data has been submitted to support the proposed expiry period.
5. CMC information in the proposed Patient Information Leaflet should be revised.
6. Type I DMF 10,867 for bulk drug substance has been reviewed and found deficient to support approval of the NDA. A deficiency letter has been issued to the holder.-

Section III of this review provides draft comments for the action letter which detail the specific deficiencies. Also, the overall EES recommendation for this application is Withhold dated 10/19/09.

B. RECOMMENDATION ON PHASE 4 (Post-Marketing) COMMITMENTS, AGREEMENTS and/or RISK MANAGEMENT STEPS, if Approvable

None

II. SUMMARY OF CHEMISTRY ASSESSMENTS

A. DESCRIPTION OF THE DRUG PRODUCT(S) & DRUG SUBSTANCE(S)

Proposed in this application is Ferriprox® (deferiprone) 500 mg oral, film-coated tablets in a 100-count bottle. Ferriprox® is currently marketed in Europe and Australia. The application has been granted orphan drug and fast track status, and is being accepted as a rolling submission. (b) (4)

. Subsequent amendments have provided partial CMC reviewable units for drug substance and drug product, and have updated the application to include another drug substance supplier.

DRUG SUBSTANCE

Deferiprone (3-hydroxy-1,2-dimethylpyridin-4-one) is a bidentate iron chelator that preferentially binds ferric ions into a 3:1 (deferiprone: iron) complex at low pH. Bulk drug substance is a white to pink crystalline powder. (b) (4)

Deferiprone is highly soluble in water at pH 1-7.5 and has high permeability, thus is a BCS class 1 drug. Structure elucidation studies show the material is prepared (b) (4)

The drug is manufactured by (b) (4)

. The manufacturing process are described in Apotex, Inc.'s type II DM 10867. A letter of authorization to this file is provided. The DMF has been reviewed and found inadequate to support approval of this application. An IR letter with comments and requests is being sent.

Executive Summary Section

Specifications for release from the manufacturers and for acceptance at the drug product manufacturing site differ in some of the analytical methods, but the tests and criteria are identical. Testing is to be performed at each of these four sites or by contract laboratories. Testing is for identity (IR, UV), melting range, residual solvents, heavy metals, water content, assay (HPLC), residual solvents (headspace GC), related compounds (b) (4), unidentified impurities and total impurities by HPLC, bulk density, tapped density, particle size and (U) (), (UV). The methods for assay and related substances were recently revised. Each analytical method is described in detail, but further revisions have been requested. Method validation studies have not been submitted for each of the manufacturing sites.

Batch analysis data is provided for 40 commercial-scale lots representing material manufactured since 1993 and at each of the three manufacturing sites. The proposed criteria for residual solvents, total impurities and water content are supported by batch analysis data. The proposed limits for the identified impurity (b) (4) and (b) (4) are justified based on referenced safety studies. The proposed criteria for particle size, tapped density and bulk density are established to assure efficient tablet manufacture. Criteria for the other tests are justified based on data observed to date.

Since there are no USP reference standards for this drug, samples taken from specific commercial lots without further processing are designated as the primary and secondary reference standard materials. These materials have been characterized and were used in the structure elucidation studies.

Packaging for storage and shipment is (b) (4). Descriptions and specifications for each packaging component and material of construction used at each of the three manufacturing sites are provided. Letters of authorization to the type III DMFs for the packaging component suppliers and their materials of construction have been requested.

The primary stability studies are performed on multiple commercial-scale lots from each of the manufacturers stored in the proposed shipping container. Data is provided for storage at ICH long term conditions for 12-60 months; at ICH accelerated conditions for 6 months; and with exposure to UV and fluorescent light for 6 months. Testing is for appearance, identity, assay, related substances and water content. Identity, appearance, assay and related substances did not change over time and no new impurities were detected. Water content increased slightly at high relative humidity. Supportive studies of drug substance with protective packaging for extended exposure to room temperature and short term exposure to high heat, high humidity and light show the same stability trends as the primary studies. Stress and forced degradation studies of unprotected solid and aqueous solutions show the drug molecule is slightly sensitive to (b) (4). Degradants from these studies are not identified. The applicant proposes a storage condition of 15-30 C with a retest period of (b) (4) for the Apotex Pharmachem and (b) (4) sites, and a (b) (4) retest period for the (b) (4) site. A revised storage statement to reflect the current definition of USP CRT and additional stability study data have been requested. The post approval stability protocol and commitment to continue the stability studies is acceptable.

DRUG PRODUCT

Feriprox® is white to off white capsule-shaped immediate release tablet (caplet) containing 500 mg deferiprone with a non-functional film coating. The caplet is imprinted with "APO" bisect "500" on one side and plain on the other. The bisect is intended to facilitate splitting the caplet into 2 equal halves.

The drug product development process and investigational formulations for 100 mg, 250 mg and 500 mg tablets are summarized. The difference between the phase 3 and the commercial tablets is (b) (4). A QbD approach is not used and a design space for the manufacturing process steps has not been developed. Tablet divisibility is adequately addressed by studies using developmental lots; by process validation studies addressing blend uniformity; and by data from the supportive stability studies. Development of the dissolution method is addressed in studies using developmental and clinical lots. A revised dissolution criterion has been proposed by the reviewer based on submitted drug release profile data.

Unit and batch formulations are provided. The excipients are microcrystalline cellulose, magnesium stearate, and colloidal silicon dioxide in the cores and hypromellose (b) (4), polyethylene glycol (b) (4), and titanium dioxide in the film coating. All excipients are USP/NF grade materials. Dry excipients are purchased from major suppliers and each has an internet website. No excipient is novel or of human origin. (b) (4). Excipient specifications are the current USP/NF monograph for each material. (U) () for the film coating is prepared at the tablet manufacturing site. Certificates of analysis for the excipients lots used in the stability and 3 biolots are provided. Contract laboratories for excipient testing are identified.

Executive Summary Section

A single drug product manufacturer is identified as Apotex - Etobicoke. The tablet manufacture process is (b) (4). The manufacturing process, process parameters and in-process controls are described in detail and a process flow diagram is included. A procedure for tablet reprocessing is not proposed. Executed batch records and supporting information are provided for clinical and stability batches.

The tablet release specification includes testing for identity (HPLC retention time, color test (b) (4)), average tablet weight, dissolution (UV assay), content uniformity/assay (HPLC), and degradants (largest unknown and total by HPLC). The tests are adequate to establish identity, purity and strength of the drug product. The methods for assay and related substances were recently revised. Each analytical method is described in detail, but further revisions have been requested. Representative spectra and chromatograms have been provided. Complete method validation studies have been requested.

The proposed criteria are justified based on batch analysis data submitted for 40 clinical and stability, and safety information. The criteria are supported by the submitted batch analysis data. The absence of testing for water content and microbial limits is justified based on historical data.

The proposed reference standards are (b) (4) and the drug substance standards.

The market package is 100 caplets in a 120cc round white HDPE bottle with a (b) (4) child resistant closure, aluminum foil (b) (4) induction innerseal and silver foil/foam liner. The innerseal is constructed with a "Lift N'Peel" tab for easy removal. The suppliers and materials of construction for each packaging component are identified and an acceptance specification for each component is provided. Letters for authorization for the type III DMFs for the component suppliers and their materials of construction are requested.

Primary stability studies are performed on commercial-scale white tablets in the proposed 100 count package and a 1000-count version of the same package stored at ICH long term conditions for 36-60 month, ICH intermediate conditions for 60 months and ICH accelerated conditions for 6 months. The lots were tested for identity, appearance, assay, degradants, and 1-point dissolution. Some lots were also tested for microbial limits after 60 months. The results show no change in test values over time, no microbial limits failures and no new degradants were observed. Supportive stability studies were performed on pink tablets stored in 100-count and 1000-count packages at 25-30°C/ambient RH, ICH accelerated and light stress conditions for 36 months, 6 months, and 3 months, respectively. The results show no change in test values over time and no new degradants were observed. The applicant proposes a (b) (4) expiry period with storage at less than 30°C. The applicant has been requested to provide additional stability studies to support the expiry period for drug product made with drug substance from each of the proposed suppliers. The post approval stability protocol for is acceptable.

A draft carton label and patient information leaflet are provided. The established name is acceptable. Revisions to the CMC information in the patient information leaflet have been requested.

The applicant has requested a categorical exclusion from the environmental assessment requirements under 21 CFR 25.31(b) in that the amount of drug introduced into the environment is less than 1 ppb per year. A calculation if expected introduction concentration is included. The request is considered to be justified.

The Overall EES Conclusion is Withhold dated 19 Oct 2009. The drug product manufacturing site is the subject of a warning letter and an import embargo for GMP issues.

An information request letter with comments regarding the submitted CMC reviewable units and the subsequent amendments is to be sent to the applicant.

B. DESCRIPTION OF HOW THE DRUG PRODUCT IS INTENDED TO BE USED

Deferiprone formulated as Ferriprox® is indicated for the treatment of patients with excessive body iron stores due to chronic transfusion therapy. The dose is 25-33 mg/Kg body weight taken orally three times daily for a total dose of 75- (b) (4) mg/Kg body weight. The maximum safe dose is (b) (4) mg/Kg body weight/day. Doses are to be rounded to the nearest half tablet.

C. BASIS FOR APPROVABILITY OR NOT APPROVAL RECOMMENDATION

The proposed application cannot be approved based on inadequate responses to the IR and DR letters. Additional comments are included in this review. Drug substance comments address the method descriptions and validations

Executive Summary Section

studies; and the stability studies. The drug product comments address the dissolution criterion; the method validation studies; and the stability studies.

III. ADMINISTRATIVE**A. REVIEWER'S SIGNATURE**

William M. Adams/DPMA III/CMC Reviewer

B. ENDORSEMENT BLOCK

E.Leutzinger/DPMA III/PAL
S.Pope Miksinski/DPMA III/Branch V Chief
D.Mesmer/ONDQA/PM
Hyon-Zu Lee/DMIHP/PM

C. CC BLOCK

R.Lostritto/DPMA III/Director

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-21825	----- ORIG-1	----- AOPHARMA INC	----- FERRIPROX (DEFERIPRONE)

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

/s/

WILLIAM M ADAMS
10/20/2009

Sarah Pope Miksinski
10/20/2009



NDA 21-825

Ferriprox

ApoPharma, Inc.

William M. Adams
Office of New Drug Quality Assurance (ONDQA)

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Chemistry Review Data Sheet

1. NDA 21-825
2. REVIEW #1
3. REVIEW DATE: 19 Mar 2008
4. REVIEWER: William Adams
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (N-000)	12 Mar 2007
Amendment (N-001)	28 Mar 2007
Amendment	26 Jul 2007
Amendment (N-003)	24 Sep 2007
Amendment (N-004)	21 Dec 2007

7. NAME & ADDRESS OF APPLICANT:

Name: ApoPharma, Inc.

200 Barmac Drive
Toronto, Ontario, Canada M9L 2Z7
Lynda Sutton, Chief Regulatory Officer
Cato Research, Ltd.

Representative: 4364 South Alston Avenue
Durham, SC 27713-2220

Telephone: (919) 361-2286

8. DRUG PRODUCT NAME/CODE/TYPE:

- (a) Proprietary Name: Ferriprox®
- (b) Non-Proprietary Name (USAN): Deferiprone
- (c) Code Name/# (ONDC only): L1, CP20, APO-66, PL1, DN-180-01-AF
- (d) Chem. Type/Submission Priority (ONDC only)
Chem. Type:
Submission Priority: Standard

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)
10. PHARMACOLOGICAL CATEGORY: Metal Chelator
11. DOSAGE FORM: Film Coated Tablet
12. STRENGTH/POTENCY: 500 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

XX Not a SPOTS product

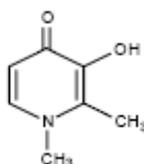
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 1,2-dimethyl-3-hydroxypyrid-4-one

Molecular Formula C₇H₉NO₂

Molecular Weight 139.15 daltons

Molecular Structure



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
10867	II	Apotex, Inc	Drug substance	1	Inadequate	IR 02/29/08	

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")



CHEMISTRY REVIEW



Chemistry Review Data Sheet

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 45,724	submitted July 1994	Deferiprone

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Clinical	Pending		G.Shastaty
EES	Acceptable	01/31/08	OC
Pharm/Tox	Deficiencies	06/27/07	D.Bailey
Biopharm	Pending		P.Hepp
LNC			
Methods Validation	Package submitted		
OPDRA			
EA	Acceptable	CMC Review #1	W.Adams, CMC

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 21-825

The Executive Summary

I. RECOMMENDATIONS

A. RECOMMENDATION & CONCLUSION ON APPROVABILITY

The proposed application is APPROVABLE with respect to CMC information.

B. RECOMMENDATION ON PHASE 4 (Post-Marketing) COMMITMENTS, AGREEMENTS and/or RISK MANAGEMENT STEPS, if Approvable

None

II. SUMMARY OF CHEMISTRY ASSESSMENTS

A. DESCRIPTION OF THE DRUG PRODUCT(S) & DRUG SUBSTANCE(S)

Proposed in this application is Ferriprox® (deferiprone) 500 mg oral, film-coated tablets in a 100-count bottle. Ferriprox® is currently marketed in Europe and Australia. The application has been granted orphan drug and fast track status, and is being accepted as a rolling submission. (b) (4)

Subsequent amendments have provided partial CMC reviewable units for drug substance and drug product, and have updated the application to include another drug substance supplier.

DRUG SUBSTANCE

Deferiprone (3-hydroxy-1,2-dimethylpyridin-4-one) is a bidentate iron chelator that preferentially binds ferric ions into a 3:1 (deferiprone:iron) complex at low pH. Bulk drug substance is a white to pink crystalline powder. (b) (4)

Deferiprone is highly soluble in water at pH 1-7.5 and has high permeability, thus is a BCS class 1 drug. Structure elucidation studies show the material is prepared (b) (4)

The drug is manufactured by (b) (4)

The manufacturing process are described in Apotex, Inc.'s type II DM 10867. A letter of authorization to this file is provided. The DMF has been reviewed and found inadequate to support approval of this application. An IR letter with comments and requests has been sent to the holder on 29 Feb 2008.

Specifications for release from the manufacturers and for acceptance at the drug product manufacturing site differ in some of the analytical methods, but the tests and criteria are identical. Testing is to be performed at each of these four sites. Information regarding contract testing by contract labs has been requested. Testing is for identity (IR, UV), melting range, residua on ignition, heavy metals, water content, assay (HPLC), residual solvents (headspace GC), related compounds ((b) (4) unidentified impurities and total impurities by HPLC), bulk density, tapped density, particle size and (b) (4) (UV). Each analytical method is described in detail and validated per USP <1225>. Tests and methods are acceptable except for minor details. The method validation studies fail to meet the current USP <1225> requirements for ruggedness and robustness; revised studies have been requested.

Batch analysis data is provided for 40 commercial-scale lots representing material manufactured since 1993 and at each of the three manufacturing sites. The data fails to support the proposed criteria for residual solvents, total impurities and water content. Revision of these specifications has been requested. The proposed limits for the identified impurity (b) (4) and (b) (4) are justified based on referenced safety studies. The proposed criteria for particle size, tapped density and bulk density are established to assure efficient tablet manufacture. The

Executive Summary Section

proposed criterion for dissolution is justified based on profiles from developmental and clinical lots; additional profile data has been requested. Criteria for the other tests are justified based on data observed to date.

Since there are no USP reference standards for this drug, samples taken from specific commercial lots without further processing are designated as the primary and secondary reference standard materials. These materials have been characterized and were used in the structure elucidation studies.

Packaging for storage and shipment is (b) (4). Descriptions and specifications for each packaging component and material of construction used at each of the three manufacturing sites are provided. Letters of authorization to the type III DMFs for the packaging component suppliers and their materials of construction have been requested.

The primary stability studies are performed on multiple commercial-scale lots from each of the manufacturers stored in the proposed shipping container. Data is provided for storage at ICH long term conditions for 9-60 months; at ICH accelerated conditions for 6 months; and with exposure to UV and fluorescent light for 6 months. Testing is for appearance, identity, assay, related substances and water content. Identity, appearance, assay and related substances did not change over time and no new impurities were detected. Water content increased slightly at high relative humidity. Supportive studies of drug substance with protective packaging for extended exposure to room temperature and short term exposure to high heat, high humidity and light show the same stability trends as the primary studies. Stress and forced degradation studies of unprotected solid and aqueous solutions show the drug molecule is slightly sensitive to (b) (4). Degradants from these studies are not identified. The applicant proposes a storage condition of 15-30 C with a retest period of (b) (4) for the Apotex Pharmachem and (b) (4) sites, and a (b) (4) retest period for the (b) (4) site. Additional stability study data has been requested. The post approval stability protocol and commitment to continue the stability studies is acceptable. Clarification has been requested regarding the post approval sampling scheme for the three sites.

DRUG PRODUCT

Ferriprox® is white to off white capsule-shaped immediate release tablet (caplet) containing 500 mg deferiprone with a non-functional film coating. The caplet is imprinted with "APO" bisect "500" on one side and plain on the other. The bisect is intended to facilitate splitting the caplet into 2 equal halves.

The drug product development process and investigational formulations for 100 mg, 250 mg and 500 mg tablets are summarized. The difference between the phase 3 and the commercial tablets is (b) (4). A QbD approach is not used and a design space for the manufacturing process steps has not been developed. Tablet divisibility is adequately addressed by studies using developmental lots; by process validation studies addressing blend uniformity; and by data from the supportive stability studies. Development of the dissolution method is addressed in studies using developmental and clinical lots. Additional dissolution profile data is requested for the lots used in the phase 3 clinical and stability studies.

Unit and batch formulations are provided. The excipients are microcrystalline cellulose, magnesium stearate, and colloidal silicon dioxide in the cores and hypromellose (b) (4), polyethylene glycol (b) (4) and titanium dioxide in the film coating. All excipients are USP/NF grade materials. Dry excipients are purchased from major suppliers and each has an internet website. No excipient is novel or of human origin. (b) (4)

Excipient specifications are the current USP/NF monograph for each material. (b) (4) for the film coating is prepared at the tablet manufacturing site. Certificates of analysis for the excipients lots used in the stability and 3 biolots are provided. Additional information regarding tests for physico-chemical attributes to differentiate specific grades of excipients has been requested. Clarification regarding the use of contract labs for excipient testing is requested.

A single drug product manufacturer is identified as Apotex - Etobicoke. The tablet manufacture process is (b) (4). The manufacturing process, process parameters and in-process controls are described in detail and a process flow diagram is included. A procedure for tablet reprocessing is not proposed. Executed batch records and supporting information are provided for clinical and stability batches.

The tablet release specification includes testing for identity (HPLC retention time, color test (b) (4)), average tablet weight, dissolution (UV assay), content uniformity/assay (HPLC), and degradants (largest unknown and total by HPLC). The tests are adequate to establish identity, purity and strength of the drug product. Each analytical method is described in sufficient detail. Representative spectra and chromatograms have

Executive Summary Section

been requested. Each method had been validated per USP <1225>, however none of the studies meets the current requirements for ruggedness or robustness. Revised studies are requested.

The proposed criteria are justified based on batch analysis data submitted for 40 clinical and stability, and safety information. Statistical evaluation of the batch analysis data show that the criteria for total degradants is not supported. A revised criterion is proposed. The other criteria are supported by the submitted data. The absence of testing for (b)(4) microbial limits is justified based on historical data.

The proposed reference standards are (b)(4) and the drug substance standards.

The market package is 100 caplets in a 120cc round white HDPE bottle with a (b)(4) child resistant closure, aluminum foil (b)(4) induction innerseal and silver foil/foam liner. The innerseal is constructed with a "Lift N'Peel" tab for easy removal. The suppliers and materials of construction for each packaging component are identified and acceptance specification for the components are provided. Letters for authorization for the type III DMFs for the component suppliers and their materials of construction are requested.

Primary stability studies are performed on commercial-scale white tablets in the proposed 100 count package and a 1000-count version of the same package stored at ICH long term conditions for 36-60 month, ICH intermediate conditions for 60 months and ICH accelerated conditions for 6 months. The lots were tested for identity, appearance, assay, degradants, and 1-point dissolution. Some lots were also tested for microbial limits after 60 months. The results show no change in test values over time, no microbial limits failures and no new degradants were observed. Supportive stability studies were performed on pink tablets stored in 100-count and 1000-count packages at 25-30°C/ambient RH, ICH accelerated and light stress conditions for 36 months, 6 months, and 3 months, respectively. The results show no change in test values over time and no new degradants were observed. The applicant proposes a (b)(4) expiry period with storage at less than 30°C. The applicant has been requested to either revise the label storage statement to use the USP controlled room temperature statement or to provide additional stability studies to support the upper and lower storage temperature limits. The post approval stability protocol for is acceptable.

A draft carton label and patient information leaflet are provided. The established name and the CMC information in these labels are sufficient to meet the requirements of 21 CFR 201.57

The applicant has requested a categorical exclusion from the environmental assessment requirements under 21 CFR 25.31(b) in that the amount of drug introduced into the environment is less than 1 ppb per year. A calculation if expected introduction concentration is included. The request is considered to be justified.

An information request letter with comments regarding the initially submitted CMC reviewable unit and the subsequent amendments was sent to the applicant on 29 Feb 2008. Additional comments are provided in this review for inclusion in the DR letter.

B. DESCRIPTION OF HOW THE DRUG PRODUCT IS INTENDED TO BE USED

Deferiprone formulated as Ferriprox® is indicated for the treatment of patients with excessive body iron stores due to chronic transfusion therapy. The dose is 25-33 mg/Kg body weight taken orally three times daily for a total dose of 75-(b)(4) mg/Kg body weight. The maximum safe dose is (b)(4) mg/Kg body weight/day. Doses are to be rounded to the nearest half tablet.

C. BASIS FOR APPROVABILITY OR NOT APPROVAL RECOMMENDATION

The proposed application is APPROVABLE in that a response to comments in the information request letter dated 29 Feb 2008 with preliminary comments is pending. Additional comments are included in this review. Drug substance comments address the use of contract labs; the release specifications; the method validations studies; and the stability studies. The drug product comments address the use of contract labs; the excipient specifications; the release specification including the dissolution criterion; the method validation studies; certificates of analysis for packaging components and materials; and the stability studies.

III. ADMINSTRATIVE

A. REVIEWER'S SIGNATURE

Executive Summary Section

William M. Adams

B. ENDORSEMENT BLOCK

M.Adams/ONDQA
R.Harapanhalli/DPMA III/Chief Branch V
L.Mullins Athey/PM/ONDQA
Hyon-Zu Lee/PM/DMIHP

C. CC BLOCK

Rik Lostritto/ONDQA/Dir DPMA III

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this page is the manifestation of the electronic signature.**

/s/

Mike Adams
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CHEMIST

Richard Lostritto
3/21/2008 03:42:53 PM
CHEMIST
I am signing for Ravi Harapanhalli

Initial Quality Assessment
Pre-Marketing Assessment and Manufacturing Science Division III
Branch V

Office of New Drug Quality Assessment
Division of Medical Imaging and Hematology Products (HFD-160)

OND Division:	Medical Imaging and Hematology Products
NDA #	21-825
Applicant:	ApoPharma Incorporation
Stamp Date:	March 13, 2007
PDUFA date:	September 13, 2007
Trademark:	Ferriprox
Established Name:	Deferiprone
Dosage Form:	Film coated tablet and solution
Route of Administration:	Oral
Indication:	Treatment of chronic iron overload in patients with transfusion-dependent anemias
Pharmaceutical Assess. Lead:	Ali Al-Hakim, Ph.D.
ONDQA Fileability:	YES <input checked="" type="checkbox"/> NO <input type="checkbox"/>
Comments for 74-day Letter:	YES <input type="checkbox"/> NO <input type="checkbox"/>

Summary, Critical Issues and Comments

- A. Summary**
- B. Review, Comments and Recommendations**
- C. Critical Issues for review and Recommendation**
- D. Comments for the 74th day Letter**
- E. Recommendation for fileability**
- F. Fileability template**

A. Summary

Deferiprone (3-hydroxy-1,2-dimethylpyridin-4-one) is formulated as Ferriprox 500 mg immediate release film-coated tablets, and 100 mg/mL solution to facilitate the administration of the active ingredient to iron overloaded thalassemia patients who have difficulty with swallowing tablets. Deferiprone is iron chelator that preferentially binds trivalent iron cations (Fe^{3+}) in a 3:1 (deferiprone:iron) complex. It is rapidly absorbed after oral administration, and shows little binding to plasma proteins. The low molecular weight, uncharged deferiprone readily enters cells, and the deferiprone:iron complex is readily eliminated from them. Most of the ingested drug is excreted in urine, predominantly as a pharmacologically inactive glucuronide, and the remainder as unchanged deferiprone or the chelation complex. The elimination half-life of deferiprone is 2-3 hours.

Deferiprone formulated as Ferriprox® is indicated for the treatment of patients with excessive body iron stores due to chronic transfusion therapy.

B. Review, Comments and Recommendations

Drug Substance

Deferiprone is a white to pinkish white crystalline powder and is slightly soluble in methanol (~8 mg/mL) and ethanol (~3 mg/mL), very slightly soluble in acetone and sparingly soluble in deionized water (about 13 mg/mL). There are no polymorphic forms for Deferiprone. Deferiprone is a 3-hydroxy-1,2-dimethylpyridin-4-one is prepared by (b) (4)

(b) (4)

The applicant reported that all the CMC information for the drug substance is provided in Drug Master File (DMF) # 10867. Therefore, the DMF should be reviewed and evaluated with respect to the manufacturing key issues which are considered critical for the drug substance manufacturing process. (b) (4)

Additionally, validation process with respect to (b) (4) within the facility should be evaluated with respect to consistency of particle size distribution for various and the absence of polymorphism. See tables below for the drug substance specifications from the above facilities.

There are other concerns that need to be assessed which include (b) (4). Justification for the presence of (b) (4) and proposed limit should be evaluated taking into consideration the nature of the manufacturing process capability and the proposed limit for (b) (4) as a potential impurity. Impurity profile of the API and justification for deleting (b) (4) impurity from drug substance specifications need to be evaluated.

Assessment and subsequent evaluation should be performed with respect to any significant differences between the two drug substance manufacturing sites (Apotex Pharmachem Inc and (b) (4)) including release and stability batches. The sponsor reported that identical CMC information is provided in the DMF and that the same specifications are used to test and release the deferiprone drug substance, independent of its manufacturing site and that stability test data for (b) (4)

(b) (4), exhibit comparable trends to the initial lots and annual lots produced at Apotex Pharmachem Inc

Stability test data should be evaluated regarding the proposed retest period of (b) (4) for deferiprone drug substance stored at 15 - 30°C in the proposed container (b) (4)

Table 2.3.S.4.1-2 Testing specifications of deferiprone at Apotex Inc. - Etobicoke site

Test	Method	Acceptance criteria
Appearance	G-74	(b) (4)
Identification A	RM3078-01	
Heavy Metals	USP <231> Method II	
(b) (4)	(b) (4)	
Residue on Ignition	USP <281>	
Melting Range	USP <741>*	
(b) (4)	(b) (4)	
Related Compounds	RM3078-04	
Assay (HPLC)	RM3078-03	
Particle size	(b) (4)	
(b) (4)	(b) (4)	
Bulk/tapped Density	USP <616> Method I	
Determination of	(b) (4)	
(b) (4)	(b) (4)	

*These attributes will be tested on every 5th batch of deferiprone or on one batch per year whichever is greater

Table 2.3.S.4.1-3 Testing specifications for deferiprone at Apotex Inc. - Richmond Hill site

Test	Method	Specification
Description	GM-87	(b) (4)
Identification	GM-57 (USP/BP/EP)	
Identification	GM-59 (USP)	
Melting range	GM-86 (USP)	
Residue on ignition/ Sulphated ash	GM-18 (USP/BP/EP)	
Heavy metals	GM-7 (USP)	
(b) (4)	(b) (4); (b) (4) (USP/BP/EP)	
(b) (4)	(b) (4); (b) (4) (House)	
(b) (4)	(b) (4) (House)	
Related compounds	RM-3078-04 HPLC (House)	
Assay	RM-3078-03 HPLC (House)	

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Drug product (tablets)

Ferriprox tablet is available as a 500 mg immediate release, white to off-white, capsule-shaped film-coated tablet with “APO” bisects “500” imprinted on one side, plain on the other. Ferriprox is packaged in 120 mL, round, white high-density polyethylene (HDPE) bottles with blue 38-400 plastic child resistant (CR) caps. Each bottle contains 100 tablets. Composition and components for tablets are provided in the following table

Table 2.3.P.1-2 Qualitative and quantitative composition of Ferriprox 500 mg film-coated tablets

Component name	Weight (mg/tablet)	Component function	Monograph standard
Core tablet			
Deferiprone	500.0	Active ingredient	In-house
Microcrystalline cellulose	[REDACTED]	[REDACTED]	(b) (4) NF
Magnesium stearate			NF
Colloidal silicon dioxide			NF
Weight of core tablet			
Coating*†			
Hydroxypropyl methylcellulose (b) (4)			USP
Polyethylene glycol (b) (4)			NF
Titanium dioxide (b) (4)			USP
			USP
Weight of tablet coating			
Weight of coated tablet			
		(b) (4)	

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Critical attributes of the drug product (tablets)

It is essential that all excipients be evaluated, particularly, [REDACTED] (b) (4). The reviewer needs to make sure that all certification and related documentations with respect to [REDACTED] (b) (4) complying with FDA policy and guidelines were provided in the application. Reviewing and subsequent evaluation of the excipients used in the tablet core and the tablet coating including [REDACTED] (b) (4), etc, should performed with main emphasis on the quality, process control and analytical testing.

Synopsis of the manufacturing process and its critical parameters

The manufacturing process is a capsule-shaped, immediate release, film coated tablet manufactured using a [REDACTED] (b) (4)

[REDACTED]

Justifications for the proposed specifications and analytical testing including critical attributes such as impurities, dissolution, hardness, etc, should be evaluated.

The NDA contains a pharmaceutical development report which described the various development stages of the drug development and the significant changes between the clinical and the commercial batches. Therefore, the reviewer needs to assess the report with respect to the manufacturing process and formulation development.

Microbiological tests should be evaluated regarding the adequacy of these tests their suitability to the solid oral dosage form.

Early clinical trial batch formula, comparative dissolution profile between the clinical development batches and the proposed commercial presentation should be assessed regarding any significant differences.

Evaluation of the development of the proposed formulation as described in the pharmaceutical development/formulation report with respect to choice of excipients compatibility with API, dissolution, stability, etc, which resulted in the final optimized formulation needs to be conducted.

Development and subsequent implementation of the dissolution method with respect to (b) (4) and method development should be reviewed.

Scoring issue for the tablet to facilities breakage in half. Divisibility testing regarding average content should be examined and evaluated accordingly. See formulation and analytical report on divisibility and related process validation.

With respect to the container/closure system (HDPE bottle and blue (b) (4) CR screw caps foam liner), the NDA does not contain a DMF for these materials. However, the applicant provided CMC information including name of manufacturer, description, figures, certificate of analysis and analytical methods and specifications in the NDA.

Therefore, the reviewer may need to review and evaluate the information regarding the completeness and adequacy of the container closure system.

Drug Product manufacturing flow chart and release specifications for the tablet are provided in the following two tables.

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/s/

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