CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208030Orig1s000

CHEMISTRY REVIEW(S)

Overall Manufacturing Inspection Recommendation

Edit Custom Form

Custom Form
Facility Inspection - Overall Application Recommendation

Facility Inspection - Overall Application Recommendation

Facility Inspection - Overall Application Recommendation
Approve

Facility Inspection - Overall Application Re-evaluation Date
9/17/15

Navigation Links

Form Link
http://panorama.fda.gov/task/view?ID=546c248300002e72f6ddbf15a6f2689d&activeTab=content-dashboard__5418eab10003b6cd5f0c5f929c4fa823

Assigned To

OPF Reviewer

Zhong Li

IM - OPF Reviewer

Edit Assignment

This was done on
Aug 4, 2015
(15 days ago)

Status
Complete

Requested by
DARRTS Migration

This task is waiting on
2 Tasks

Last Update
Aug 4, 2015

Submitted On
Nov 19, 2014

Reference Number
(b) (4)

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/s/

MARY GRACE LUBAO
09/16/2015

Recommendation: Approval

NDA 208030
Review # 1

Drug Name/Dosage Form	Ferriprox (deferiprone) oral solution
Strength	100 mg/ml
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	ApoPharma Inc.
US agent, if applicable	Lynda Sutton

SUBMISSION(S) REVIEWED eCTD no. (SDN #), SD category	DOCUMENT DATE
0000 (1), Original Submission	11/14/2014
0003 (4), Quality response to IR	1/15/2015
0005 (6), Quality Amendment	5/6/2015
0006 (7), Draft Labeling	4/30/2015
0007 (8), Quality response to IR	5/1/2015
0008 (9), Quality response to IR	5/5/2015
0010 (11), Package Insert Draft	5/7/2015
0011 (12), Quality response to IR	5/22/2015
0012 (13), Quality response to IR	6/10/2015
0013 (14), Labeling, container carton	6/24/2015
0014 (15), Quality response to IR	7/9/2015
0015 (16), Labeling	7/15/2015
0016 (17) Quality response to IR	7/31/2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Katherine Windsor	Branch 1, New Drug API
Drug Product	Donghao Lu	Branch 2, DNDP1
Process	Lin Qi	Branch 7, DPA3
Microbiology	Denise Miller	Branch 2, DMA
Facility	Zhong Li	Branch 1, DIA
Biopharmaceutics	Banu Zolnik	Branch 1, Biopharmaceutics
Project/Business Process Manager	Rabiya Laiq	Branch 1, OPQ
Application Technical Lead	Janice Brown	Branch 2, DNDP1
Laboratory (OTR)	None Assigned	None
ORA Lead	Sharon Thoma	
Environmental Assessment (EA)	Donghao Lu	Branch 2, DNDP1

Table of Contents

Quality Review Data Sheet

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

2. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II	(b) (4)	(b) (4)	Adequate	03-APR-2015	Review #5
	Type IV			Adequate	08-APR-2009	(In addition, ANDA-203330, Approved, 11/18/2014)
	Type IV			Adequate	16-APR-2013	(In addition, ANDA (b) (4) Approved, 12/02/2013)
	Type III			Adequate		Based on information provided in the NDA
	Type III			Adequate		Based on information provided in the NDA
	Type III			Adequate		Based on information provided in the NDA

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Cross-referenced NDA	21825	Ferriprox 500 mg tablet

3. **CONSULTS:** None

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 208030 is recommended for APPROVAL from a product quality standpoint. Include the following statement in the action letter:

An expiration dating period of 18 months is granted for Ferriprox (deferiprone) oral solution, when stored at 25°C (77°F) excursions permitted between 15°C to 30°C (59°F to 86°F), protected from light.

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

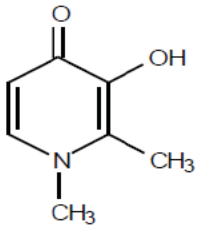
None

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

Deferiprone (3-hydroxy-1,2-dimethylpyridin-4(1H)-one) is a bidentate iron chelator that preferentially binds trivalent iron cations (Fe3+) in a 3:1 (deferiprone:iron) complex. The applicant cross-referenced the CMC information for deferiprone to DMF (b) (4). DMF (b) (4) was reviewed and found adequate to support NDA 208030.

Properties, CQAs Relevant to Drug Product Quality: Deferiprone is a white to pinkish white crystalline powder with a very bitter taste. Deferiprone exists in diketo and enol crystalline forms, in a weight percentage ratio of (b) (4) Deferiprone has the following structural formula:



Deferiprone is not hygroscopic since the drug substance stability data does not show an increase in moisture content over time. The solubility of deferiprone is (b) (4) in (b) (4) Therefore, the drug substance is sufficiently soluble throughout the (b) (4). Forced degradation studies demonstrate deferiprone in solution can degrade (b) (4)

Deferiprone in a solid state is thermally [redacted] and photo-stable under [redacted] in an [redacted] container for up to [redacted] weeks. In contrast, deferiprone in solution will degrade in the presence of [redacted]t. Open container studies of deferiprone in solution with high intensity [redacted] for [redacted] results in a [redacted] loss of potency after exposure to [redacted]) for [redacted] days results and a [redacted] loss of potency. To mitigate the risk of photo-induced degradation, the deferiprone oral solution drug product is filled in amber bottle and stored in the carton.

In addition to binding to [redacted] but with a lower binding affinity (see nonclinical review of NDA 21825 by Dr. Haleh Saber dated October 11, 2011). The deferiprone drug substance specification includes a test for heavy metals to limit the presence of [redacted]

Synthesis – Deferiprone is synthesized [redacted]

Impurities: The maximum daily dose (MDD) of deferiprone is > 2 g, thus requiring qualification of impurities exceeding the ICH Q3A threshold of 0.05%. [redacted] which is higher than the 0.05% qualification threshold for a drug with a maximum daily dose of > 2 g/day. The limit of [redacted]% was previously found acceptable and has not changed since the 2011 approval of Ferriprox tablets in the US. Other impurities, if present, are controlled at NMT [redacted]%, which is below the qualification threshold. A [redacted] in some lots of deferiprone is caused by the presence [redacted]. This potential impurity is controlled [redacted] with a limit of NMT [redacted]% in the drug substance specification.

There are no genotoxic impurities; however, the drug substance, deferiprone, is considered [redacted]

The only organic solvent used in the synthesis of deferiprone is [redacted], which is controlled to a limit of NMT [redacted] [redacted] is a [redacted] solvent with a permitted daily exposure (PDE) of 30 mg, according to the ICH Q3C guideline. At the specified limit of [redacted] and a maximum daily clinical dose of deferiprone of 100 mg/kg, the daily intake of [redacted]l from Ferriprox does not exceed [redacted] or [redacted] for a 60 kg person. Therefore, no risk to patients from impurities present in deferiprone is predicted.

Container Closure: [redacted]

Retest Period, Storage Conditions, and Container/Closure – Stability data supports a retest period of (b) (4) months for deferiprone drug substance manufactured (b) (4) (b) (4)

B. Drug Product [Established Name] Quality Summary

Description - Ferriprox oral solution is a clear, reddish orange solution. Each mL contains 100 mg deferiprone, hydroxyethyl cellulose, glycerin, purified water, hydrochloric acid, artificial cherry flavor, peppermint oil, FD&C Yellow No. 6, and sucralose. Each bottle contains 500 mL of Ferriprox oral solution.

Product Design - Deferiprone oral solution was initially developed based on the applicant's previous experience with similar oral solutions, not prospectively using a quality target product profile (QTPP). Although not prospectively defined, the elements of a QTPP were adequately addressed in the submission including dosage form, strength, drug product quality criteria, dosing cup, container closure system, and bioequivalence of the Ferriprox oral solution with the Ferriprox tablet.

Optimization of the formulation was based on physical testing and feedback obtained from subjects. Hydrochloric acid is added (b) (4) hydroxyethyl cellulose (b) (4) (b) (4) the addition of sucralose (b) (4) artificial cherry flavor (b) (4) and peppermint oil to (b) (4) The color of the drug product was modified by adding FD&C Yellow No. 6, to improve the appearance for patient acceptability. Glycerol is incorporated in Ferriprox oral solution at (b) (4) and acts as a (b) (4) (b) (4) According to the applicant however, antimicrobial effectiveness testing (AET) performed on stability samples at 24 months failed to meet the USP AET acceptance criterion. This is further discussed under the heading titled, Expiration Date & Storage Conditions below.

Excipients meet the USP/NF/EP/BP compendial standards except peppermint oil, artificial cherry flavor, and FD&C Yellow No. 6. The specifications for the non-compendial excipients were satisfactorily provided in the application. The level of excipients were either within the FDA inactive ingredient database (hydroxyethyl cellulose, artificial cherry flavor, peppermint oil, and FD&C Yellow No. 6) or were found acceptable by the nonclinical reviewer (glycerol and sucralose).

Manufacturing Process – The commercial production batch size is (b) (4). Ferriprox oral solution is (b) (4)

[redacted]

The filling operation must be completed within [redacted] Filled bottles are labeled, security sealed, placed in a carton, and packaged. Each carton contains one filled, neck-banded and labelled bottle, one physicians insert, and one dosing cup. [redacted].

Drug Product Specification - The finished product specification includes tests for appearance, identity (UV/HPLC), pH (USP), net content, deferiprone assay (HPLC), [redacted] total aerobic count (USP), total yeast and mold count, USP, *Enterobacteria, E. coli, Salmonella, and P. aeruginosa* (USP). Batch analysis data provided comply with the specifications and indicate consistent and reproducible manufacture.

Impurities/Degradants - The levels of individual unidentified impurities are controlled at NMT [redacted]%, which is below the ICH Q3B (R2) identification threshold. No new impurities or degradants are present in Ferriprox 100 mg/mL oral solution.

Container Closure - The drug product is filled into a 500 mL amber polyethylene terephthalate (PET) round bottle and closed with a white polypropylene child-resistant (CR) cap with foam liner. The amber color of the PET bottles provides protection from light induced degradation.

Leachables were identified as a moderate risk in the risk assessment 1. According to the drug product review, the extractable/leachable analysis in the primary container closure is adequate.

Shelf life & Storage Conditions - A shelf life of 18 months is granted for Ferriprox (deferiprone) oral solution, when stored at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F), protected from light.

The applicant proposed a [redacted] month shelf-life for Ferriprox oral solution based on 24-months of long-term stability data. At the 24-month test station, batches GT9874, GT9986, and GT9880 failed the USP AET acceptance criteria for the organism *Aspergillus niger*. Based on these failures, ApoPharma agreed to reduce the proposed shelf life to 18 months.

Based on the photostability study of deferiprone solution (described in the drug substance section of the executive summary), there is significant degradation in the presence of UV

and fluorescent light. Since it is known that deferiprone degrades in solution, the drug product photostability study was conducted with the product in the secondary packaging material (carton) and exposed in its primary container (amber bottle). Product appearance, pH, assay, and degradation products conformed to the drug product specification at the end of the study for both test conditions (product exposed to light when stored in the carton and directly in the amber bottle without the carton). To minimize the risk of photo-induced degradation, the labeling states that the drug product should be stored in the carton.

Ferriprox oral solution is a multi-dose product and is microbiologically and chemically stable for 35 days after the container is opened for the first time. (b)(4)

Patients do not need to take special precautions with regard to light exposure during dosing.

List of co-packaged components – A 30 mL clear polypropylene dosing cup with graduation marks is also supplied with the drug product.

The risk assessment identified dosing accuracy as a moderate risk. For the dosing cup, uniformity of mass delivered per dose (accuracy and precision of the delivered dose) was performed. Dosing accuracy test results did not exceed 10%. The clinical reviewer did not find an issue with a 10% dosing variation since dosing is based on the patient serum ferritin levels. In addition, the dose is rounded to the nearest 2.5 mL by the prescriber.

Facility Review – The Office of Process and Facilities found no significant, outstanding manufacturing risks that prevent approval of this application. Based on firm inspectional history and district file review, the manufacturing facilities for NDA 208030 are acceptable.

Biopharmaceutics Review - The proposed product is an oral solution, therefore there is no dissolution information in the submission. The BE/BA studies LA 21-BE and LA-20-BA are reviewed by the Office of Clinical Pharmacology. No biopharmaceutics information was included in this NDA.

Final Discipline Recommendations - No product quality issues that preclude approval were found and the product quality reviewers recommended approval of the NDA. Table 2 includes the individual review disciple recommendations for NDA 208030.

Table 2: Final Discipline Recommendations

DISCIPLINE	REVIEWER	BRANCH/DIVISION	Final Recommendation
DMF Reviewer DMF (b) (4)	Katherine Windsor	Branch 1, New Drug API	Adequate
Drug Substance	Katherine Windsor	Branch 1, New Drug API	Approval
Drug Product	Donghao Lu	Branch 2, DNDP1	Approval
Process	Lin Qi	Branch 7, DPA3	Approval
Microbiology	Denise Miller	Branch 2, DMA	Approval
Facility	Zhong Li	Branch 1, DIA	Approval
Biopharmaceutics	Banu Zolnik	Branch 1, Biopharmaceutics	No biopharmaceutics information submitted. Defer to the other disciplines for the approvability decision
Application Technical Lead	Janice Brown	Branch 2, DNDP1	Approval

Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Ferriprox
Non Proprietary Name of the Drug Product	deferiprone oral solution
Non Proprietary Name of the Drug Substance	deferiprone
Proposed Indication(s) including Intended Patient Population	Treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate.
Duration of Treatment	Lifetime
Maximum Daily Dose	25 mg/kg to 33 mg/kg body weight, orally, three times per day, for a total daily dose of 75 mg/kg to 99 mg/kg body weight.
Alternative Methods of Administration	None

C. Biopharmaceutics Considerations

1. BCS Classification:

Deferiprone is a BCS class 1 compound (high solubility and permeability). Since the proposed drug product is an oral solution, there is no BCS-1 designation issue associated with this NDA.

2. Biostudies

The Applicant conducted LA 21-BE (Randomized, open label, comparative, two-way crossover bioavailability study of Ferriprox oral solution and Ferriprox tablets under fasting conditions in 42 healthy subjects) as the clinical basis to support the approval of the proposed drug product.

D. Novel Approaches - None

E. Any Special Product Quality Labeling Recommendations -

F. Process/Facility Quality Summary (see Attachment A)

G. Life Cycle Knowledge Information (see Attachment B)

51 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

ASSESSMENT OF THE BIOPHARMACEUTICS

33. Are the in-vitro dissolution test and acceptance criteria adequate for assuring consistent bioavailability of the drug product?

The proposed product is an oral solution, therefore there is no dissolution testing conducted.

34. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

The Applicant conducted LA 21-BE (Randomized, open label, comparative, two-way crossover bioavailability study of Ferriprox oral solution and Ferriprox tablets under fasting conditions in 42 healthy subjects) as the clinical basis to support the approval of the proposed drug product. The Applicant also conducted LA-20-BA (single dose-three way crossover relative BA study of Ferriprox tablets and oral solution of deferiprone under fasting and fed condition in 15 healthy subjects). It should be noted that the formulation (referred as F2) used in LA20-BA study is not the to-be-marketed formulation. This issue was communicated to the Office of Clinical Pharmacology (OCP) reviewer since these studies are reviewed by OCP.

Reviewer's Assessment:

The proposed product is an oral solution, therefore there is no dissolution information in the submission. The BE/BA studies LA 21-BE and LA-20-BA are reviewed by the Office of Clinical Pharmacology therefore from the biopharmaceutics perspective there is no biopharmaceutics information to be reviewed in this NDA.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:

The Division of Biopharmaceutics defers to the other disciplines for the approvability decision since there is no biopharmaceutics information to be reviewed in this NDA.

Banu Zolnik, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
ONDP/OPQ

Supervisor Comments and Concurrence:

I concur.

Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
ONDP/OPQ

Note: additional reviewers can be added, as appropriate

ASSESSMENT OF MICROBIOLOGY

35. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response:

Antimicrobial Effectiveness Testing (AET) – The sponsor states that the glycerin, which is present in the product at (b) (4) (b) (4) The sponsor also noted that products containing (b) (4) glycerin are usually (b) (4). Data supporting this statement was not provided. They conducted AET testing per USP <51> on two lots in the in-use stability study and on six stability lots using the acceptance criteria for a Category 3 product.

AET testing – In use stability Study (35 days)
Two lots were tested per USP <51> at the Initial time point and at the end of the in-use testing. Both lots meet USP <51> acceptance criteria at all time-points tested.
AET testing – stability
Six lots were tested per USP <51> at 18 and 24 months on stability. All lots meet the acceptance criteria at the 18 month time point. The 24 month time point, failures (b) (4) was reported at the Day 14 testing for three lots with two of these lots continuing to fail at the 28 day time point. All other organisms meet the acceptance criteria. As the AET testing reported failures for the (b) (4) of the test at the 24 month time point, an information request was sent to limit the shelf life to 18 months. The sponsor responded on 22 May 2015 agreeing to reduce the shelf life to 18 months.

Microbial Limits – Microbial limits are tested per internal SOP M-3 and the absence of specified organisms is tested per internal SOP M-19. Method suitability testing was not provided. A request for this information was included in the 74 day letter.

- Specification
  - Total Aerobic Microbial Count: NMT (b) (4)
  - Total Yeast and Mold Count: NMT (b) (4)
  - Absence of *E.coli*, *Enterobacteriaceae*, *P. aeruginosa* and *Salmonella*

Note: The absence of *Burkholderia cepacia* was not listed. As this an aqueous product, this organism is considered objectionable. A request for testing for the absence of *B. cepacia* and the validation of the test method was requested in the 74 day letter.

In response to the 74 letter requests, the method suitability testing was provided along with a justification for not testing for *B. cepacia*. The suitability testing

was performed per USP <61> and supports the routine testing for TAMC and TYMC for the product. The spiking studies with *B. cepacia* determined that the organism could not be recovered from the product due to bactericidal nature of the product. Other organisms were recoverable with the exception of *P. aeruginosa*. Routine testing of the facility water systems and manufacturing environment has not recovered *B. cepacia*, therefore the sponsor does not feel that the product is at risk for *B. cepacia* contamination and does not need to be tested for.

Review of Response:

Reviewer's Assessment: The microbial limits testing and specifications are appropriate for a nonsterile oral drug product. The tests are supported by the method suitability testing as per USP <61> and <62>. The absence of *B. cepacia* in the historical trending of the environmental testing and the bactericidal nature of the product results in a low risk of *B. cepacia* contamination for this oral drug product and testing is not necessary. The proposed 18 month expiration date is supported by the antimicrobial effectiveness testing.

2.3.P.6 Reference Standards or Materials

36. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response: NA

Reviewer's Assessment: The information is not required for a non-sterile oral drug product.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

37. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: NA

Reviewer's Assessment: There are no components of biological origin.

38. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: NA

Reviewer's Assessment: There are no components of biological origin.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: I recommend approval based on the drug product information presented in this application.

Denise A. Miller 16-June-2015

Supervisor Comments and Concurrence: I concur.

Neal J. Sweeney, Ph.D. July 22, 2015
Acting Microbiology Quality Assessment Lead
OPQ/OPF/Division of Microbiology Assessment

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

-----**DOSAGE FORMS AND STRENGTHS**-----
Oral solution: 100 mg/mL

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Established Name: **Deferiprone**	Adequate
Dosage form, route of administration	Dosage: **Oral solution** Route: **Oral**	Adequate
Controlled drug substance symbol (if applicable)	N/A	
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	**Oral solution: 100 mg/mL**	Adequate

Conclusion: Adequate

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

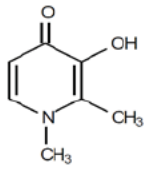
Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Oral solution	Adequate
Strengths: in metric system	100 mg/mL	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	A clear, reddish orange solution with a peppermint and cherry-flavored aroma.	Adequate

Conclusion: Adequate

#11: Description (21CFR 201.57(c)(12))

11 DESCRIPTION

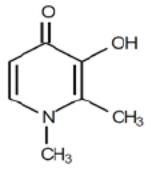
Ferriprox (deferiprone) oral solution contains 100 mg/mL deferiprone (3-hydroxy-1,2-dimethylpyridin-4-one), a synthetic, orally active, iron-chelating agent. The molecular formula for deferiprone is $C_7H_9NO_2$ and its molecular weight is 139.15 g/mol. Deferiprone has the following structural formula:



Deferiprone is a white to pinkish-white crystalline powder. It is sparingly soluble in deionized water and has a melting point range of 272°C - 278°C.

Ferriprox oral solution is a clear, reddish orange colored (b) (4) solution. Each mL of oral solution contains 100 mg deferiprone and the following inactive ingredients: purified water; hydroxyethylcellulose; glycerin; hydrochloric acid (b) (4); artificial cherry flavor; peppermint oil; FD&C Yellow No. 6; and sucralose.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Deferiprone Deferiprone	Adequate
Dosage form and route of administration	The drug product is deferiprone solution. It is intended to be used for oral administration.	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	N/A	
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	The inactive ingredients of [TRADENAME] are: purified water; hydroxyethylcellulose; glycerin; hydrochloric acid, (b) (4); artificial cherry flavor; peppermint oil; FD&C Yellow No. 6; sucralose.	Adequate
Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	Deferiprone is a bidentate iron chelator.	Adequate
Chemical name, structural formula, molecular weight	Chemical name: 3-hydroxy-1,2-dimethylpyridin-4-one. It has a molecular formula C7H9NO2 with a molecular mass of 139.15 g/mol. Deferiprone has the following chemical structure:	Adequate (statement added to the labeling regarding the molecular formula and molecular weight)

		
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa, solubility, or pH)	Deferiprone is a white to pinkish white crystalline powder. Deferiprone is sparingly soluble in de-ionized water (b) (4)	Adequate

Conclusion: Adequate

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16 HOW SUPPLIED/STORAGE AND HANDLING

FERRIPROX® (deferiprone) oral solution is provided in amber polyethylene terephthalate (PET) bottles with child resistant closures (polypropylene). Each pack contains one bottle of 500 mL oral solution and a graduated measuring cup (polypropylene).

Oral solution, 500 mL (100 mg deferiprone per mL), NDC 52609-4502-7

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Store in the original package in order to protect from light. After first opening, use within 35 days.

Keep Ferriprox out of the reach and sight of children.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	FERRIPROX® (deferiprone) is supplied as 100 mg/mL oral solution.	Adequate
Available units (e.g., bottles of 100 tablets)	Each bottle contains 500 mL of deferiprone oral solution.	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	A clear, reddish orange solution with a peppermint and cherry-flavored (b) (4). NDC 52609-4502-7	Adequate
Special handling (e.g., protect from light, do not freeze)	Store in the original package in order to protect from light. After first opening, use within 35 days.	Adequate. However, a statement "After 35 days, discard the contents of the bottle." Should be added.
Storage conditions	Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].	Adequate

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Distributed by ApoPharma USA, Inc., Rockville, MD, United States of America, 20850. Manufactured by Apotex Inc., Toronto, Ontario, Canada, M9L 1T9.	Adequate

Conclusion: Adequate. However, a statement "After 35 days, discard the contents of the bottle." Should be added.

2. Labels

1) Immediate Container Label

Reviewer's Assessment: A statement "After 35 days, discard the contents of the bottle." should be added.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))		Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		Adequate
Net contents (21 CFR 201.51(a))		Adequate
Lot number per 21 CFR 201.18		Adequate
Expiration date per 21 CFR 201.17		Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)		Adequate
Storage (not required)		Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		Adequate
Bar Code per 21 CFR 201.25(c)(2)**		Adequate
Name of manufacturer/distributor		Adequate
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Adequate.

2) Cartons

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))		Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		Adequate
Net contents (21 CFR 201.51(a))		Adequate
Lot number per 21 CFR 201.18		Adequate
Expiration date per 21 CFR 201.17		Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]		Adequate
Sterility Information (if applicable)		**N/A**
"Rx only" statement per 21 CFR 201.100(b)(1)		Adequate
Storage Conditions		Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		Adequate
Bar Code per 21 CFR 201.25(c)(2)**		Adequate
Name of manufacturer/distributor		Adequate
"See package insert for dosage information" (21 CFR 201.55)		Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)		**N/A**
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))		**N/A**

Conclusion: Adequate.

II. List of Deficiencies To Be Communicated

A. Drug Substance: None

B. Drug Product: None

C. Process/Facility: None

D. Biopharmaceutics: None

E. Microbiology**:** None

F. Label/Labeling: Labeling negotiations are ongoing.

III. Attachments

A. Facility

OVERALL RECOMMENDATION:				
DRUG SUBSTANCE				
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**INITIAL RISK IDENTIFICATION**	**FINAL RECOMMENDATION**
CSN – Primary Drug substance manufacturing, testing and release site	(b) (4)	(b) (4)	Profile not recently updated	Acceptable Based on District Recommendation
CSN – Alternative Drug substance manufacturing, testing and release site			Pending regulatory action	Acceptable Based on District Recommendation
CTL – Alternative testing site for drug substance			Low	Acceptable Based on Profile
CTL – Alternative testing site for drug substance			Low	Acceptable Based on Profile
DRUG PRODUCT				
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**INITIAL RISK IDENTIFICATION**	**FINAL RECOMMENDATION**
LIQ – Fabrication, packaging, labelling, testing of drug substance, excipients and drug product. Stability testing and microbiological testing of drug product.	(b) (4)	(b) (4)	(b) (4)	Acceptable Based on District Recommendation

B. Lifecycle Knowledge Management

a) Drug Substance

There were no moderate- to high-risk CQAs associated with the drug substance identified in the initial risk assessment.

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Initial Risk Ranking***	**Justification**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations / Comments****
Metal binding affinity	N/A	(b) (4)	(b) (4)	Acceptable	N/A
Solution stability under basic conditions	N/A	(b) (4)	(b) (4)	Acceptable	N/A
Solution stability upon light exposure	N/A	(b) (4)	Stored in a light resistant container.	Acceptable	N/A

b) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	2 (Release) 6 (Stability)	Specification tests, validation of the testing methods and stability studies	Low	Post approval commitment on stability
Physical stability (phase separation)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2 (Release) 6 (Stability)	Pharmaceutical development studies were adequately conducted	Low	
Dosing accuracy	• Dosing device • Formulation	30	Justification based clinical	Low	

	• Process Parameters • Scale/equipment • Site		relevance was evaluated; formulation studies were adequately conducted		
Palatability	• Formulation • Excipient change • Process parameters • Scale/equipment • Site	45	Formulation studies were adequately conducted	Low	
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	4 (Release) 12 (Stability)	Pharmaceutical development studies were adequately conducted	Low	
Leachables	• Formulation • Container closure • Process parameters • Scale/equipment • Site	30	Pharmaceutical development studies were adequately conducted	Low	

*Risk ranking applies to product attribute/CQA

**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

IV. Administrative

A. Reviewer's Signature: See discipline specific review sections for the primary and secondary signatures.

B. Endorsement Block

Reviewer Name/Date: Refer to comments in IV., A.
Secondary Reviewer Name/Date: Refer to comments in IV., A.
Project Manager Name/Date: Rabiya Laiq, 06-Aug-2015

Digitally signed by Janice T. Brown -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, 0.9.2342.19200300.100.1.1=1300101685,
cn=Janice T. Brown -A
Date: 2015.08.06 13:20:04 -04'00'