CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212269Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 212269
Review #1

Drug Name/Dosage Form	Ferriprox [redacted] (b) (4) tablets
Strength	1000 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	ApoPharma, a Division of Apotex Inc.
US agent, if applicable	Kiran Krishnan

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	19-Jul-2019	All
Amendment	04-Sept-2019	Process/Facilities
Amendment	12-Nov-2019	Process/Facilities
Amendment	29 nov-2019	DP
Amendment	16-Mar-2020	Biopharm

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Soumya Mitra	Ali Al Hakim
Drug Product	Amit Mitra	Anamitro Banerjee
Process/Facility	Zhijin Chen	Bogdan Kurtyka
Microbiology	n/a	n/a
Biopharmaceutics	Zhuojun Zhao	Banu Zolnik
Regulatory Business Process Manager	Rabiya Laiq	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	Amit Mitra	Anamitro Banerjee

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
010867	Type II	Apotex Pharmachem	Deferiprone Drug Substance	n/a	4/13/2020	Reviewed in conjunction with NDA
(b) (4)	Type III		(b) (4)	n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	021825	Ferriprox (deferiprone) 500 mg tablets
NDA	208030	Ferriprox (deferiprone) 100 mg/mL oral solution
IND	45,724	Deferiprone drug substance

2. CONSULTS

N/A

Executive Summary

1. Recommendations and Conclusion on Approvability

OPQ recommends APPROVAL of NDA 212269 for Ferriprox [redacted] tablets, 1000 mg. As part of this action, OPQ recommends an 18-month expiration period for the drug product when stored at "20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). There are no outstanding issues and no post-approval quality agreements to be conveyed to the applicant.

2. Summary of Quality Assessments

1. Product Overview

ApoPharma submitted NDA 212269 for Ferriprox [redacted] Tablets, 1000 mg in accordance with section 505(b)(1) of the Food, Drug and Cosmetic Act. FERRIPROX [redacted] is indicated for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. Deferiprone is a bidentate iron chelator that preferentially binds trivalent iron cations (Fe^{3+}) in a 3:1 (deferiprone: iron) complex. Currently, there are three approved deferiprone formulations all of which are owned by the applicant:

1. Ferriprox (deferiprone) 500 mg tablets approved under NDA 021825 in October 2011
2. Ferriprox (deferiprone) 100 mg/mL oral solution approved under NDA 208030 in September 2015
3. Ferriprox (deferiprone) 80 mg/mL oral solution approved as a supplement to NDA 208030 in April 2018.

The drug substance is manufactured by [redacted] The drug substance used in the manufacture of the proposed drug product is the same as the drug substance used in the manufacture of Ferriprox 500 mg tablets and Ferriprox 100 mg/mL and 80 mg/mL oral solutions. The applicant references DMF 10867 for the manufacture and control of the drug substance. The drug product is [redacted] tablet are white to off-white, capsule shaped, biconvex coated tablets, with "FPX" score "DR" engraved on one side and "APO" score "1000" on the other side. The current formulation offers an alternative to the immediate release formulations.

The recommended initial dosing regimen of the currently marketed formulations of Ferriprox (deferiprone) is 25 mg/kg body weight, orally, three times a day for a total daily dose of 75 mg/kg body weight.

Based on the information provided in this application (original submission and in responses to information requests), OPQ considers all review issues adequately addressed and potential risks to patient safety, product efficacy, and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 212269 and an **18-**

month expiration period for the drug product when stored at controlled room temperature (20° to 25°C [68° to 77°F]); excursions permitted to 15°-30°C (59° to 86°F).

Proposed Indication(s) including Intended Patient Population	FERRIPROX [redacted] (b) (4) is an iron chelator indicated for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate
Duration of Treatment	
Maximum Daily Dose	75 mg/kg body weight
Alternative Methods of Administration	None

2. Quality Assessment Overview

Drug Substance

Deferiprone drug substance is a synthetic, orally active, iron chelating agent that has a molecular formula of $C_7H_9NO_2$ and a relative molecular weight of approximately 139.15. Deferiprone is a white to pinkish-white, non-hygroscopic powder that is sparingly soluble in water. The drug substance is manufactured by Apotex Pharmachem Inc. The applicant references DMF 10867 for the manufacture and control of the drug substance. DMF 10867 was reviewed by Dr. Soumya Mitra on April 13, 2020 in conjunction with this NDA. This DMF is adequate to support this NDA with no outstanding product quality issues. A separate drug substance review was not performed for this NDA.

NDA 212269 is recommended for approval from a drug substance perspective.

Drug Product and Drug Process

The drug product, Ferriprox [redacted] (b) (4) tablets is presented as a white to off-white, capsule shaped, beveled edge, biconvex coated tablets, engraved "FPX" score "DR" on one side and "APO" score "1000" on the other side. The drug product formulation includes hypromellose acetate succinate, magnesium oxide, colloidal silicon dioxide and magnesium stearate. The coating formulation ([redacted] (b) (4) includes triethyl citrate, [redacted] (b) (4) talc, methacrylic acid copolymer [redacted] (b) (4) All excipients used in the manufacture of the drug product are compendial, commonly used in [redacted] (b) (4) solid oral dosage forms and demonstrate good compatibility with the drug substance.

The drug product is manufactured by Apotex of Ontario Canada at a commercial batch size of [redacted] (b) (4) kg which translates to approximately [redacted] (b) (4) tablets. Ferriprox [redacted] (b) (4) [redacted] (b) (4) tablets are manufactured by [redacted] (b) (4)

[redacted] The proposed process parameters and in-process controls were justified and described in sufficient detail. The applicant demonstrated the suitability of the manufacturing process for the drug product. The description of the manufacturing process includes appropriate in-process controls and operating parameters.

Ferriprox [redacted] tablets will be packaged in the following three packaging configurations: (1) 50 count 75 cc, white, white HDPE container with a [redacted] cap and a [redacted] seal; (2) 500 count 750 cc, white, white HDPE container with a [redacted] cap and a [redacted] seal and (3) 50 count [redacted] blister packs. All packaging components comply with USP <661>.

The drug product specifications included appearance, average weight, identification, dissolution, assay, content uniformity, sub-division of tablets content uniformity, sub-division of tablets dissolution, individual and total degradants, [redacted], loss on drying, and microbial limits. The drug product specification was devoid of testing for polymorphic form of the drug substance in the drug product and for elemental impurities. The drug substance crystal form was not tested as a part of the drug product stability program stability. This is acceptable as the applicant indicates no known reports of deferiprone polymorphism except [redacted] which is unlikely to occur for this product. The applicant included a risk assessment for elemental impurities as per ICH Q3D/USP <232>. The results demonstrated that the Class I, II and III elements were below the 30% PDE limits for individual elements for a parenteral drug product. Accordingly, based on the applicant's justification and batch results the risk assessment is acceptable and a test for elemental impurities is not required in the drug product release specifications (see drug product review for details).

The drug product specifications are consistent with ICH Q6A and are based on batch analyses and stability data. The drug product specifications provide adequate controls to ensure the quality of the drug product throughout the product expiry. The proposed specification and acceptance criteria for the drug product, together with controls for impurities in the drug substance are adequate to ensure that the critical quality attributes of this product are well controlled.

Up to 18-months of stability data were provided for three registration batches of the drug product packaged in each of the aforementioned commercial container closure systems (50 count in 75 cc HDPE bottles; 500 count in 750 cc HDPE bottles and 50 count in blister pack). All batches were manufactured at [redacted] kg. The drug product was stored under long term (30°C/65 %RH) and accelerated conditions (40°C/NMT 75%RH). In addition to the primary stability data, the applicant included data from photostability studies and forced degradation studies.

The description section of the PI indicates that the tablets can be broken in half along the score line. The applicant included a tablet scoring study to demonstrate that the split tablet portions met the same quality criteria as the whole tablets and can be stored for up to 90 days. The drug product reviewer indicated that the applicant provided sufficient information to support a 90 in-use period for the split tablets.

The applicant requested an 18-month expiry for the drug product when stored under controlled room temperature 20 to 25°C (68° to 77°F) with excursions permitted to 15 to 30°C (59° to 86°F). The stability data shows consistency over time and supports the proposed expiry. Therefore, based on the available stability data provided, the applicant proposed, and the FDA accepts the expiration dating period of **18-months** for the drug product when stored at stored under controlled room temperature.

NDA 212269 is recommended for approval from a drug product and drug process perspective with an assigned drug product expiry of 18-months.

Biopharmaceutics

The biopharmaceutics review focused on (1) the acceptability of the proposed in vitro dissolution method and acceptance criterion for the routine QC testing of the proposed drug product at batch release and on stability (2) the proposed tablet scoring/ alcohol dose dumping study and (3) bridging of the between the clinical and commercial formulations the evaluation of the need for bridging.

Dissolution Specification and Method: The dissolution method includes a USP Apparatus I (Basket) at 100 rpm in 900 mL of 0.1N HCl (Acid Stage) and 0.05 M Phosphate Buffer, pH 6.8 (Buffer Stage) at 37°C. The proposed dissolution acceptance criteria are included in below:

Stage	Time	Acceptance Criteria	
		Whole	Half Tablets
Acid Stage:	120 mins (2 hrs)	(b) (4)	
Buffer Stage:	150 mins (2.5 hrs)		
	180 mins (3 hrs)		
	240 mins (4 hrs)		

The proposed dissolution method and acceptance criteria were deemed acceptable for batch release and stability testing for the drug product based on the data provided.

Tablet Scoring: The proposed tablet scoring did not result in dose dumping and was found acceptable based on the results from the BE study results. A slightly faster release dissolution profiles for the split tablets was expected and observed. These results support the proposed separate dissolution acceptance criteria for the half tablets.

Alcohol-Induced Dose-Dumping Potential: The study was conducted to evaluate the dose-dumping potential of the proposed drug product with alcohol consumption of. An in vitro study showed significant increases of deferiprone release at 2 hours to

approximately (b) (4)% and of the label claim in the presence of 40% and approximately (b) (4)% of the label claim in the presence of 20% alcohol. The effect of 10% alcohol on drug release was negligible at 2 hours. This information was communicated to the appropriate review disciplines for labeling recommendations.

Bridging of the Clinical Formulations: With the exception of the (b) (4) coating top coat (b) (4) the Phase III tablets are identical to the proposed commercial product. (b) (4) The applicant provided adequate dissolution data to support the bridging between the commercial composition and the composition used for the clinical batch. The data fully supports the bridging between the Phase III and proposed commercial product

Based on the information provided (i.e. dissolution profile data for pivotal clinical batches and stability data), the proposed dissolution method and acceptance criterion were considered acceptable for batch release and stability testing for the drug products. Based on the dissolution profile comparison, the Biopharmaceutics review team concluded that bridging between of the Phase III product to the proposed commercial product is established. Accordingly, this application is recommended for approval from a biopharmaceutics perspective.

Facilities: NDA 212269 included 5 sites:

- **Apotex Pharmachem Inc.**– Drug substance manufacturing, testing and release site
- (b) (4) Drug substance manufacturing, testing and release
- **Apotex Inc.**- Manufacturing, packaging (both primary and secondary), labelling, release and stability testing of the drug product. Testing of drug substance and excipients.
- **Apotex Inc.**- Alternate site for drug product packaging (both primary and secondary). Storage and distribution site of the drug product
- **Apotex Inc.**- Alternative site for testing drug substance, excipients and drug product
- **Apotex Inc**.- Microbial testing of excipients and drug product

All facilities listed in NDA 212269 were deemed acceptable for the responsibilities listed in the application. Accordingly, NDA 212269 is recommended for approval from a compliance perspective.

Environmental Assessment

The applicant provided a claim for categorical exclusion and a statement of no extraordinary circumstances under 21 Code of Federal Regulations (CFR) Sections 25.31(b). The categorical exclusion cited is appropriate based on the estimated amount of drug to be produced for direct use (b) (4) The claim of categorical exclusion is therefore acceptable and granted.

3. **Special Product Quality Labeling Recommendations (NDA only)**

n/a

4. **Final Risk Assessment (see Attachment)**

Included in Drug Product review.

Sherita McLamore

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{For NDA only}

R Regional Information (NDA 212269)

1.14 Labeling

1. Package Insert: Is being conducted with the labeling review. ***

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

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: FERRIPROX (b) (4) Established Name: deferiprone (b) (4) tablets	Satisfactory
Dosage form, route of administration	tablets, oral	Satisfactory
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Tablets: 1000 mg with (b) (4) with functional scoring	Satisfactory

Reviewer's Assessment: The highlight is satisfactory with respect to proprietary and established name, dosage form and strengths. The PI is yet to be finalized.

(b) "Full Prescribing Information" Section

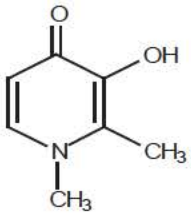
 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	(b) (4) tablets	Satisfactory
Strengths: in metric system	1000 mg	Satisfactory
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	1000 mg (b) (4) tablets with functional scoring	Not satisfactory. Imprinting, color etc. not included. Revise the statement from: "1000 mg (b) (4) tablets with functional scoring" to "FERRIPROX (b) (4) tablets are white to off-white capsule-shaped, beveled edge, biconvex coated tablets, and have a functional score engraved "FPX" bisect "DR" on one side, "APO" bisect "1000" on the other".

Reviewer's Assessment: This section may be modified to be consistent with "HOW SUPPLIED" Section. The PI was revised with reviewer's assessment for identifying characteristics provided above. The PI is yet to be finalized.

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

FERRIPROX [redacted] tablets [redacted] contain 1,000 mg 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 powder. It is sparingly soluble [redacted] in deionized water and has a melting point range of 272°C-278°C.

FERRIPROX [redacted] tablets are white to off-white, capsule-shaped tablets, and imprinted with "FPX" score "DR" on one sid [redacted] nd "APO" score "1000" on the other. The tablets can be broken in half along the score line. Each tablet contains 1,000 mg deferiprone and the following inactive ingredients: Tablet core: Hypromellose acetate succinate, magnesium oxide, colloidal silicon dioxide and magnesium stearate. Coating: triethyl citrate, talc, titanium dioxide, and methacrylic acid and ethyl acrylate copolymer.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Proprietary name: Ferriprox (b) (4) Established name: deferiprone (b) (4) tablets	Satisfactory
Dosage form and route of administration	(b) (4) tablets, Oral	Satisfactory
Active moiety expression of strength with equivalence statement for salt (if applicable)	FERRIPROX (b) (4) tablets are white to off-white, capsule-shaped tablets, and imprinted with "FPX" score "DR" on one side, and "APO" score "1000" on the other. The tablets can be broken in half along the score line. Each tablet contains 1,000 mg deferiprone and the following inactive ingredients: Tablet core: hypromellose acetate succinate, magnesium oxide, colloidal silicon dioxide and magnesium stearate. Coating: triethyl citrate, talc, titanium dioxide, and methacrylic acid and ethyl acrylate copolymer.	Not a salt. Satisfactory
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	See the text above under "Description" section	Revise the (b) (4) to "methacrylic acid and ethyl acrylate copolymer"
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	Iron-chelating agent	Satisfactory

Chemical name, structural formula, molecular weight	Yes	Satisfactory
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Deferiprone is a white to pinkish-white powder. It is sparingly soluble (b) (4) in deionized water and has a melting point range of 272°C-278°C.	Solubility is included.

Reviewer's Assessment: Edits (highlighted in yellow) of the "Description Section" was included in the PI. The PI is yet to be finalized.

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

FERRIPROX (b) (4)			
Package Configuration	**Capsule/Tablet Strength (mg)**	**NDC**	**Print (description)**
50 count bottles	(b) (4) tablets/1000 mg	(b) (4)	Functional score engraved "FPX" bisect "DR" on one side, "APO" bisect "1000" on the other
500 count bottles	(b) (4) tablets/1000 mg		Functional score engraved "FPX" bisect "DR" on one side, "APO" bisect "1000" on the other
Blister pack of 50 tablets	(b) (4) tablets/1000 mg		Functional score engraved "FPX" bisect "DR" on one side, "APO" bisect "1000" on the other

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	1000 mg (b) (4) tablets	Satisfactory
Available units (e.g., bottles of 100 tablets)	Bottle of 50, bottle of 500 and child resistant blisters of 50	Satisfactory
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	off-white capsule-shaped, beveled edge, biconvex coated tablets, and have a functional score engraved "FPX" bisect "DR" on one side, "APO" bisect "1000" on the other	Satisfactory
Special handling (e.g., protect from light, do not freeze)	None	Satisfactory
Storage conditions	Store at 20 °C to 25 °C (68 °F to 77 °F); excursions permitted to 15 °C to 30 °C (59 °F to 86 °F) [see USP Controlled Room Temperature].	Satisfactory

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., Weston, FL, United States of America, 33326. Manufactured by Apotex Inc., Toronto, Ontario, Canada, M9L 1T9.	Satisfactory

Reviewer's comment: The "How Supplied" section is satisfactory.

Immediate Container Label

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

1000 mg tablets (50 counts in bottles)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Proprietary name: Ferriprox (b) (4) Established name: deferiprone (b) (4) tablets	Satisfactory
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Correct strength (1000 mg) included	Satisfactory
Net contents (21 CFR 201.51(a))	bottles of 50 and 500; blisters of 50	Satisfactory
Lot number per 21 CFR 201.18	None	Satisfactory
Expiration date per 21 CFR 201.17	None	Satisfactory
"Rx only" statement per 21 CFR 201.100(b)(1)	None	Satisfactory
Storage (not required)	None	Satisfactory
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Included in bottle labels but not in blisters	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	None	Satisfactory
Name of manufacturer/distributor	None	Satisfactory
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.

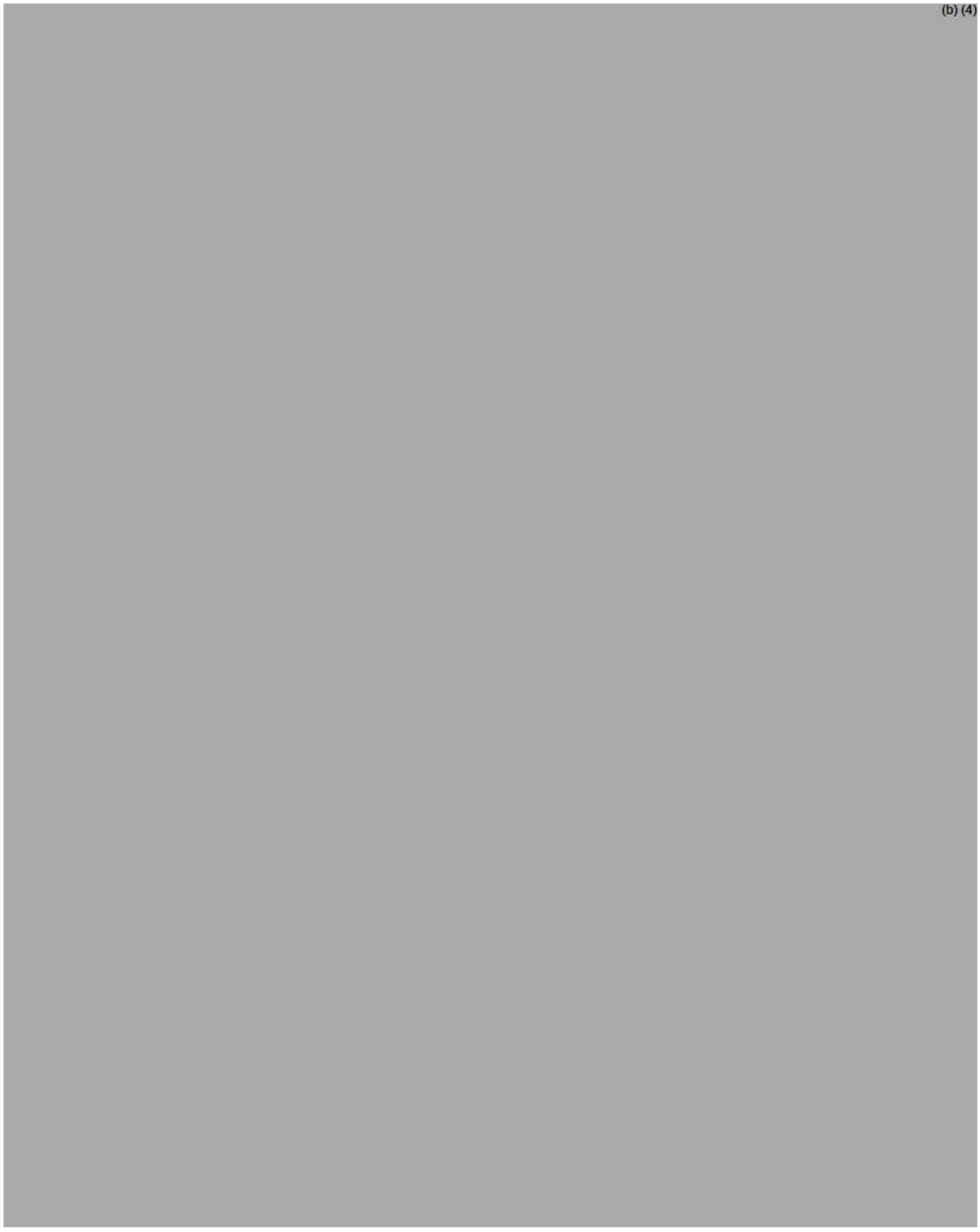
Carton for 50 tablets:

Item	Comments on the Information Provided in NDA	Conclusions
"Keep out of reach of children" (optional for Rx, required for OTC)	None	Satisfactory
"Rx only" statement per 21 CFR 201.100(b)(1)	None	Satisfactory
"See package insert for dosage information" (21 CFR 201.55)	Referenced	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	None	Satisfactory
Expiration date per 21 CFR 201.17	None	Satisfactory
Lot number per 21 CFR 201.18	None	Satisfactory
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	None	Satisfactory
Name of manufacturer/distributor	None	Satisfactory
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	None	Satisfactory
Net contents (21 CFR 201.51(a))	None	Satisfactory
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))	None	Satisfactory

Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	None	Satisfactory
Sterility Information (if applicable)	Not necessary for an oral dosage form	Satisfactory
Storage Conditions	None	Satisfactory
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	None	Satisfactory

Carton Labeling: Cartons for 5 blister packs each containing 10 tablets is included (see below)

(b) (4)



Reviewer's Assessment: The labels are satisfactory.

List of Deficiencies: **None**

Primary Labeling Reviewer Name and Date: Amit K. Mitra, Ph.D/3-16-2020

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Anamitro Banerjee, Ph.D

Amit Mitra

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Anamitro Banerjee

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CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	212269
Assessment Cycle Number	# 1
Drug Product Name/ Strength	FERRIPROX (b) (4) tablets, 1000 mg
Route of Administration	Oral
Applicant Name	ApoPharma, Inc.
Therapeutic Classification/OND Division	Metal Chelators-Hematology/DHP
RLD/INDNumber	NDA 021825 (FERRIPROX IR Tablets, 500 mg), NDA 208030 (FERRIPROX oral solution 100 mg/mL) and IND 45724
Proposed Indication	Treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate
Primary Assessors	*Zhuojun Joan Zhao, Ph.D.*
Secondary Assessors	*Banu Zolnik, Ph.D.*
Assessment	**Adequate**
Recommendation	Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 212269 for Deferiprone (b) (4) tablets, 1000 mg, is recommended for **APPROVAL**.

Assessment Summary:

ApoPharma submitted a 505(b) (1) application for the proposed FERRIPROX (b) (4) tablets, 1000 mg for the treatment of patients with transfusion iron overload due to thalassemia syndromes when current chelation therapy is inadequate.

The clinical basis for this NDA is the demonstration of bioequivalence of the Applicant's proposed FERRIPROX (b) (4) tablets to FERRIPROX (deferiprone) IR tablets in two bioavailability studies.

The Biopharmaceutics review is focused on the evaluation and acceptability of the proposed dissolution method and acceptance criteria, the proposed tablet scoring, alcohol dose dumping study and the evaluation of the need for bridging.

Dissolution method and Acceptance Criteria:

Based on the provided dissolution data, the proposed dissolution method and acceptance criteria are found acceptable:

Parameters	Acid Stage	Buffer Stage
Medium	0.1 N HCl	0.05 M Phosphate Buffer, pH 6.8
Apparatus	USP I (Basket)	
Volume	900 mL	
Rotation Speed	100 RPM	
Temperature	37°C	

Stage	Time	Acceptance Criteria	
		Whole	Half Tablets
Acid Stage:	120 mins (2 hrs)	(b) (4)	
Buffer Stage:	150 mins (2.5 hrs)		
	180 mins (3 hrs)		
	240 mins (4 hrs)		

Tablet Scoring:
The proposed tablet scoring is found acceptable based on the BE study results, i.e. no dose dumping in vivo from the half tablets. The slightly faster release dissolution profiles of the split tablets (mechanically and manually) support the proposed separate dissolution acceptance criteria for the half tablets.

Alcohol-Induced Dose-Dumping Potential:
Results of in vitro study suggest a dose-dumping potential of the proposed FERRIPROX (b) (4) with consumption of alcohol. An in vitro study showed significant increases of deferiprone release from the FERRIPROX (b) (4) Tablets at 2 hours to approximately (b) (4) % and (b) (4) % of the label claim in the presence of 40% and 20% alcohol, respectively. Effect of 10% alcohol on drug release was not observed at 2 hours. Pertinent labeling recommendation has been communicated to the Clinical and the Clinical Pharmacology review teams.

Bridging Formulations:
The (b) (4) coating formulation for the proposed commercial product contains titanium dioxide (**Table 2**), which replaced (b) (4) in the clinical batch FD245-37 (**Table 8**). The Applicant provided adequate dissolution data to support the bridging between the commercial composition and the composition used for the clinical batch (FD245-37).

List Submissions being assessed:

Document(s) Assessed	Date Received
0001 (1) Original Submission	**July 19, 2019**
0011 (11) (IR Response)	**March 16, 2020**

Highlight Key Issues from Last Cycle and Their Resolution: NA

Concise Description of Outstanding Issues): None

B.1 BCS DESIGNATION

Solubility:

Solubility of the drug substances are provided as shown below:

Table 1 Solubility Profiles of Deferiprone at Ambient Temperature

Solvent	Solubility (mg/mL)	Dose(1000 mg)/solubility volume (mL)
0.1N HCl, pH 1.2	32.7	30.6
0.05M phosphate buffer (pH 4.5)	14.6	68.5
0.05M phosphate buffer (pH 6.8)	13.4	74.6
0.05M phosphate buffer (pH 7.5)	13.3	75.2

Permeability:

Permeability data are not provided, nor required.

Assessment:

The Applicant did not request an official BCS designation. Based on the proposed strength of 1000 mg, the drug substance, Deferiprone, is considered as a high solubility drug substance.

B.2 FORMULATION

The proposed FERRIPROX [redacted] (b) (4) tablets are white to off-white, capsule shaped, beveled edge, biconvex coated tablets, engraved "FPX" score "DR" on one side and "APO" score "1000" on the other side. The proposed FERRIPROX [redacted] (b) (4) Tablet is formulated with a [redacted] (b) (4) coating. The qualitative and quantitative composition of the proposed Deferiprone 1000 mg [redacted] (b) (4) tablets for commercialization is provided in **Table 2**.

Table 2: Quantitative and Qualitative Composition of the Proposed FERRIPROX [redacted] Tablets

Non-proprietary or Common Name of Drug Product	Deferiprone 1000 mg [redacted] tablet		
Component and Quality Standard (and Grade, if applicable)	Function	Strength (label claim)	
		1000 mg	
		Quantity per unit (mg/tablet)	%w/w
[redacted]			
Deferiprone	Active ingredient	1000	[redacted]
Hypromellose acetate succinate NF	[redacted]		
Magnesium oxide USP			
Colloidal silicon dioxide NF			
[redacted]			
[redacted]			
Magnesium stearate NF	[redacted]		
Colloidal silicon dioxide NF			
[redacted]			
COATING:			
Triethyl citrate NF	[redacted]		
Talc USP [redacted]			
Titanium dioxide USP			
Methacrylic acid and ethyl acrylate copolymer [redacted] NF**			
[redacted]			
Total Solution:			[redacted]
Total Coating Solids:			
Total coated tablet			
[redacted]			

B.3 DISSOLUTION METHOD

The Applicant proposed the following dissolution method for the proposed FERRIPROX [redacted] Tablets.

Parameters	Acid Stage	Buffer Stage
Medium	0.1 N HCl	0.05 M Phosphate Buffer, pH 6.8
Apparatus	USP I (Basket)	
Volume	900 mL	
Rotation Speed	100 RPM	
Temperature	37°C	

The Applicant provided results of experiments for the choice of dissolution conditions of the above proposed dissolution method in the Dissolution Method Development Report (Module 3.2.P.2).

(b) (4)

[redacted]

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(b) (4)

Assessment: ***{Adequate}***

The proposed dissolution method is found acceptable for the QC of the proposed drug product. (b) (4)

B.4 DISSOLUTION ACCEPTANCE CRITERIA

Based on the dissolution study result of whole and half tablets of the BE study batch FD245-37, the Applicant proposed the following acceptance criteria (**Table 5**).

Table 5: Dissolution Results of Clinical Batch (L) FD245-37 and the proposed Acceptance criteria

Stage	Time (accumulated)	Whole Tablets		Half Tablets	
		Mean (range)	Specification (b) (4)	Mean (range)	Specification (b) (4)
Acid Stage:	**120 mins (2 hrs)**	**7 (5-9)**		**15 (12-17)**	
Buffer Stage:	**150 mins (2.5 hrs)**	**43 (39-46)**		**53 (47-59)**	
	180 mins (3 hrs)	**62 (56-66)**		71 (64-76)	
	210 mins (3.5 hrs)	79 (72-84)		87 (79-94)	
	240 mins (4 hrs)	92 (85-97)		97 (90-104)	
	270 mins (4.5 hrs)	97 (93-100)		100 (94-107)	
	300 mins (5 hrs)	97 (95-100)		100 (94-107)	

Assessment: ***{Adequate}***

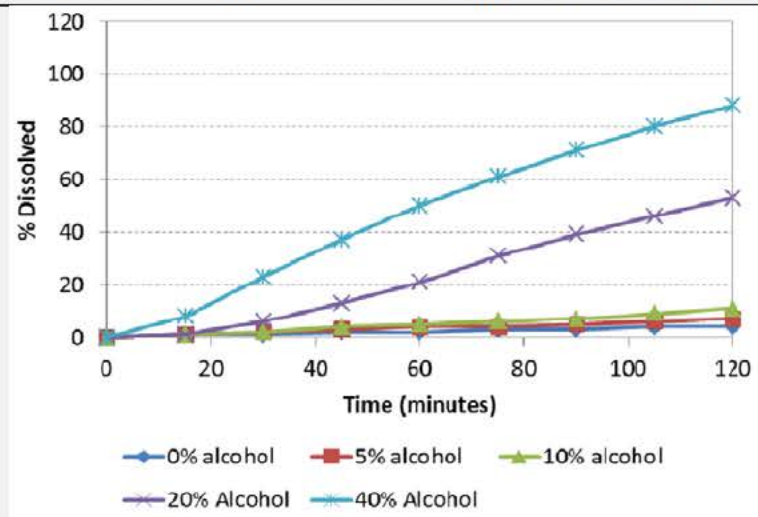
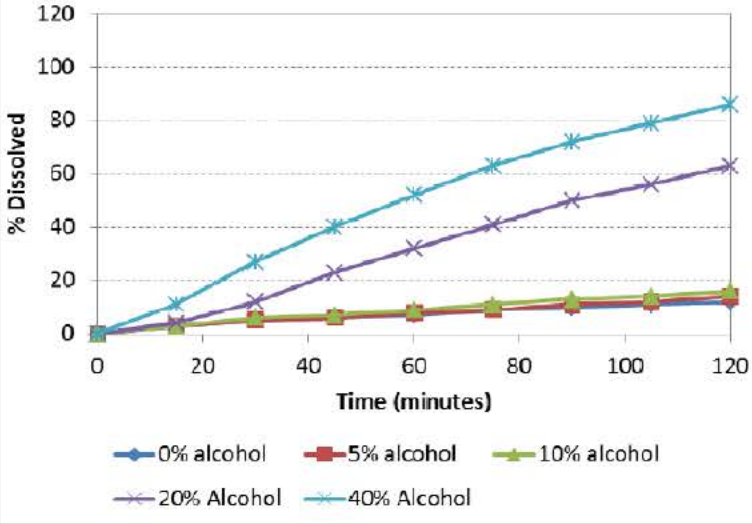
Even the proposed Deferiprone (b) (4) *Tablet is an* (b) (4) *coated tablet, the Applicant not only proposed a two-stage dissolution method but also proposed three time points of the buffer stage covering the early, middle and late stages of the release profiles. In addition,*

separate acceptance criteria are proposed for the half tablets. Based on the submitted dissolution data in Table 5, Table 7 and Table 9, the proposed dissolution acceptance criteria are found acceptable.

B.5 ALCOHOL DOSE DUMPING

The applicant conducted in vitro alcohol dose dumping study to evaluate the effect of alcohol on the proposed deferiprone (b) (4) tablets using the submission batch FD245-130 for both whole and half tablets[1]. The test conditions are Apparatus 1 @ 75 rpm with 900 mL 0.1 N HCl containing up to 40% of alcohol (USP ethanol): 0%, 5%, 10%, 20% and 40%. The profiles with different levels of alcohol are shown in Table 6.

Table 6: Dissolution profiles of Deferiprone 1000 mg (b) (4) Tablets (L) FD245-130 in 0.1 N HCl Containing Different Levels of Alcohol (Apparatus 2 @ 75 rpm)

Whole Tablets	
Half Tablets	

[1] \\cdsesub1\evsprod\nda212269\0001\m3\32-body-data\32p-drug-prod\deferiprone-1000-mg- (b) (4) tablets-apotex-inc\32p2-pharm-dev\pharmaceutical-development-4.pdf

Assessment: {Adequate}

The drug release data in the presence of increasing amount of ethanol at 40% and 20% (i.e., [redacted]% of drug release with 40% and 20% alcohol, respectively) indicate a dose dumping potential of the proposed [redacted] drug product (Table 6).

Results of in-vitro study for alcohol-induced dosing dumping potential was communicated to the Clinical and the Clinical Pharmacology review teams for the proper labeling recommendation. Per the Clinical Pharmacology reviewer, Dr. Oluseyi Adeniyi, the potential for alcohol to increase the rate of deferiprone release from deferiprone [redacted] will be indicated in the labelling.

B.6 TABLET SCORING

The Applicant conducted a scoring study for the proposed FERRIPROX [redacted] tablets[2].

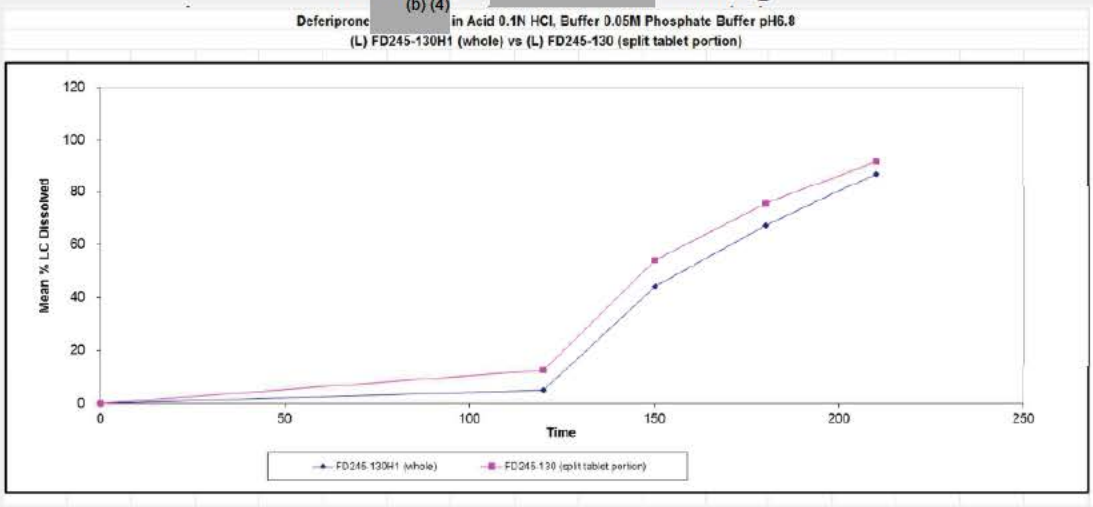
The dissolution results on whole and split tablets (mechanically) of the submission batch FD245-130 using the proposed dissolution method are shown in **Table 7** and **Figure 2**.

Table 7: Dissolution Results for Deferiprone [redacted] Tablets Mechanically Split Tablet Portions (equivalent to 500mg) Lot FD245-130

Lot/Strength	Split Mechanically by Splitter (worst-case scenario)				
	Time	Mean	% RSD	Min.	Max.
FD245-130H1 (split tablet 500mg)	Acid stage: 120 minutes	13	14	11	16
	Buffer stage: 2.5 hrs	54	5	50	59
	Buffer stage: 3 hrs	76	4	70	81
	Buffer stage: 4 hrs	100	4	92	105
FD245-130 (whole tablet 1000mg)	Acid stage: 120 minutes	5	22	3	7
	Buffer stage: 2.5 hrs	44	7	40	50
	Buffer stage: 3 hrs	67	5	64	74
	Buffer stage: 4 hrs	101	2	98	106

[2] \\cdsesub1\evsprod\nda212269\0001\m3\32-body-data\32p-drug-prod\deferiprone-1000-mg[redacted]tablets-apotex-inc\32p2-pharm-dev\pharmaceutical-development-5.pdf

Figure 2: Similarity Factor (*f*2=54) between Half Tablets and Whole Tablets for Deferiprone (b) (4) 1000mg



Assessment: ***{Adequate}***

The Applicant initially only provided dissolution data of mechanically split half tablet. The Applicant was requested to provide dissolution data of the manually split half tablet in IR letter dated February 20, 2020. The dissolution data of both mechanically and manually split (Appendix 1) half tablet showed slightly faster release than the whole tablet. Nevertheless, the scored tablets splitting was investigated in BE study LA53-0116 and was found there was no dose dumping from the half tablets by the Clinical Pharmacology reviewer, Dr. Olusevi Adeniyi. Therefore, tablet scoring of the proposed FERRIPROX (b) (4) tablets is acceptable. Furthermore, the Applicant's proposed separate dissolution acceptance criteria for the half tablets were supported by the submitted data.

B.7 BRIDGING OF FORMULATIONS

The formulation for the proposed commercial FERRIPROX (b) (4) tablets is listed in **Table 2**, while the qualitative and quantitative composition of the clinical batch FD245-37 used in the bioavailability studies, LA53-0116 and LA45-0116 is presented in **Table 8**.

Table 8: Quantitative and qualitative composition of deferiprone 1000 mg tablets used in bioavailability studies, LA53-0116 and LA45-0116

Non-proprietary or Common Name of Drug Product	Deferiprone 1000 mg [redacted] tablet		
Component and Quality Standard (and Grade, if applicable)	Function	Strength (label claim) 1000 mg	
		Qty per unit (mg/tablet)	% (w/w)
[redacted]			
Deferiprone	Active	1000	[redacted]
Hypromellose acetate succinate (NF) [redacted]	[redacted]		
Magnesium Oxide USP [redacted]			
Colloidal silicon dioxide NF [redacted]			
[redacted]			
Magnesium stearate NF	[redacted]		
Colloidal silicon dioxide NF [redacted]			
COATING:			
Triethyl citrate NF [redacted]	[redacted]		
Talc USP [redacted]			
Methacrylic acid and ethyl acrylate copolymer [redacted] NF** [redacted]			
Total Solution:			[redacted]
Total Coating Solids:			
TOTAL COATED TABLET:			
[redacted]			

The Applicant replaced the [redacted] coating formulation used in batch FD245-37 [redacted] To support proposed change in coating composition, the Applicant conducted comparative dissolution testing in multi-pH conditions as well as the proposed QC method (**Table 3**). The profiles of the submission batch are similar to the profiles of the clinical batch. Therefore, the Applicant concluded that the change in the coating composition between the clinical and submission bath has no impact on the drug performance.

Assessment: {Adequate}

The comparative dissolution data (f2>61) using the proposed QC dissolution method (Table 3) support the bridge between the proposed commercial composition (Table 2) [redacted] *and the clinical batch composition (Table 8).*

B.8 BIOWAIVER REQUEST

Assessment: ***N/A***

The Applicant is seeking approval for only one dosage strength (1000 mg) and thus biowaiver request is not applicable for the application.

R. REGIONAL INFORMATION

Comparability Protocols: N/A

Post-Approval Commitments: N/A

Lifecycle Management Considerations: N/A

APPENDIX 1: Biopharmaceutics Information Request dated February 20, 2020 and the Applicant's response on March 16, 2020

Biopharmaceutics Request Comment:

Provide dissolution data using one half tablet per vessel (individual, mean, standard deviation, N=12) to support the manual break of the proposed Deferiprone (b) (4)

Applicant's Response to Biopharmaceutics Comment:

The manufacturer has conducted a dissolution test on Ferriprox (b) (4) tablets, Batch No. FD245-130H1, using the proposed method (b) (4) The study was performed on 12 units using half tablets that were split non-mechanically by hand. The dissolution results are presented in Table 1. Results complied with the acceptance criteria as per release specification for subdivision of tablets dissolution.

Acceptance criteria for Subdivision of Tablets Dissolution:

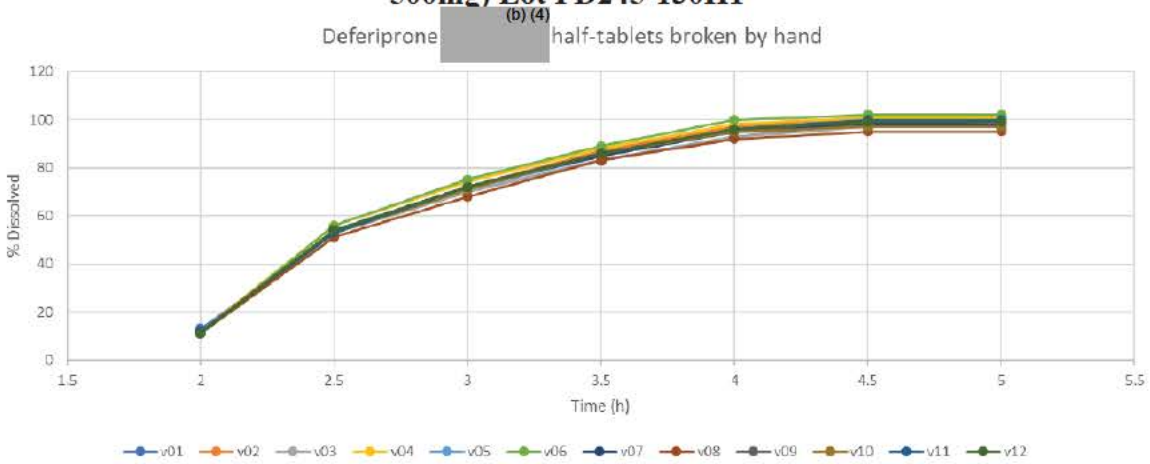
Acid Stage:
NMT (b) (4)% dissolved in 120 minutes

Buffer Stage:
2.5 hrs (b) (4)%
3 hrs: (b) (4)%
4 hrs: (b) (4)%

Table 9: Dissolution Results for Deferiprone (b) (4) Manually Split Tablet Portions (equivalent to 500mg) Lot FD245-130H1

Time (hrs)	Vessel #												Mean	SD	% RSD	Min.	Max.
	1	2	3	4	5	6	7	8	9	10	11	12					
Acid stage:																	
2 (120 mins)	(b) (4)													1	6		(b) (4)
Buffer stage:																	
2.5														1.4	2.6		
3														1.8	2.6		
3.5														1.9	2.3		
4.0														2.2	2.3		
4.5														2.0	2.0		
5.0														2.0	2.0		

Figure 3: Dissolution Profiles of Manually Split Tablets Portions (equivalent to 500mg) Lot FD245-130H1



Reviewer Note:

The Applicant's response is satisfactory.

Zhuojun Zhao

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Banu Zolnik

Digitally signed by Banu Zolnik
Date: 4/08/2020 07:47:11AM
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Sherita McLamore

Digitally signed by Sherita McLamore
Date: 4/15/2020 07:14:25PM
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/s/

SHERITA D MCLAMORE
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