CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212269Orig1s000

<u>OTHER REVIEW(S)</u>

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 18, 2020
Requesting Office or Division:	Division of Nonmalignant Hematology (DNH)
Application Type and Number:	NDA 212269
Product Name, Dosage Form, and Strength:	Ferriprox (deferiprone) tablet 1,000 mg
Applicant/Sponsor Name:	ApoPharma
FDA Received Date:	May 15, 2020
OSE RCM #:	2019-1539-3
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

ApoPharma submitted revised container labels and carton labeling for Ferriprox (deferiprone) on May 15, 2020 (Appendix A). The revisions are in response to recommendations that we made during a previous label and labeling review memo.[a]

2 DISCUSSION

In the response to our label and labeling recommendations, ApoPharma agreed to all recommended changes for the container labels and carton labeling for NDA 212269.[b] Additionally, ApoPharma noted the following regarding their plan to transition patients to the new formulation of Ferriprox, (b) (4)

[a] DeGraw, S. Label and Labeling Review for Ferriprox (deferiprone) Twice A Day NDA 212269. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 15. RCM No.: 2019-1539-2.
[b] Response to Label and Labeling Recommendations. 2020 MAY 15. Available at: \\cdsesub1\evsprod\nda212269\0019\m1\us\12-cover-letters\response-to-labeling-recommendations.pdf

Further, ApoPharma agreed to the recommendation to include a frequency of administration statement on the 1,000 mg tablet container label for NDA 021825 noting, *"A statement regarding the frequency of administration (i.e. THREE TIMES A DAY) of Ferriprox 1,000 mg immediate release tablets will be included in the next labelling update. A tag bearing the frequency of administration of Ferriprox 1,000 mg immediate release tablets (THREE TIMES A DAY) will be added to the inventory on hand to distinguish it from Ferriprox 1,000 mg tablets for twice-a-day dosing."* We will recommend ApoPharma submit a prior approval supplement to revise the container label for the Ferriprox 1,000 mg immediate release tablets for Agency review.

3 CONCLUSION

DMEPA concludes the revised container labels and carton labeling are acceptable from a medication error perspective. We have no additional recommendations for the labels and labeling for NDA 212269 at this time.

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/s/

STEPHANIE L DEGRAW
05/18/2020 03:28:45 PM

HINA S MEHTA
05/18/2020 03:35:38 PM

Division of Hematology Products Associate Director for Labeling Review of the Prescribing Information

Product Title	FERRIPROX ™ (deferiprone) tablets, for oral use
Applicant	Apopharma Inc. c/o Apotex Corp
Application/Supplement Number	212269
Is Proposed Labeling in Old Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Proposed Indication(s)	FERRIPROX (deferiprone) is an iron chelator indicated for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate
Date FDA Received Application	07/19/2019
Review Classification (Priority/Standard)	Standard
Action Goal Date	05/19/2020
Review Date	05/14/2020—review update
Reviewer	Virginia Kwitkowski, MS, ACNP-BC

This Associate Director for Labeling (ADL) review provides recommendations on the content and format of the Warnings and Precautions section of the prescribing information (PI) to help ensure that PI:

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements[1]
- Is consistent with labeling guidance recommendations[3] and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

Background:
This document amends my prior review, archived on 04/01/20. Since that review, the Clinical Pharmacology team has determined that the new 1000 mg tablet [redacted] (b) (4) mandated several new considerations and labeling changes.

Ferriprox is marketed in the US under two NDA numbers: 21825 (tablets) and 208030 (oral solutions). There are two USPIs under 21825 for a 500 mg tablet and a 1000 mg tablet. There are also two USPIs

[1] See *January 2006 Physician Labeling Rule*; 21 CFR 201.56 and 201.57; and *December 2014 Pregnancy and Lactation Labeling Rule* (the PLLR amended the PLR regulations). For applications with labeling in non-PLR "old" format, see 21 CFR 201.56(e) and 201.80.
[3] See *PLR Requirements for PI* website for PLR labeling guidances.

under NDA 208030 for the 100 mg/mL and the 80 mg/mL oral solution. The Applicant proposes to add a 5th USPI for the new 1000 mg tablet (which is dosed twice daily, instead of the thrice daily like all other Ferriprox products).

Reviewer Comments: With the recent determination that the new 1000 mg tablet [redacted] (b) (4) that they already market. There was concern that having two 1000 mg tablets (same dosage form) would lead to medication errors (inadvertent substitutions for one another). The tablets are similar in shape, size, and color, and only differ in their embossing. The carton packaging for the new tablet does have the words [redacted] (b) (4) printed above the proprietary name, which will assist in reducing accidental substitutions. There are plans by DMEPA to ask the Applicant to add "Three Times Daily" to the currently approved Ferriprox cartons.

We sought acceptable methods for naming the new product in labeling, to minimize confusion of the two products, and decided that it would be less confusing to have both 1000 mg tablets in one USPI, to prevent a prescriber from looking at the incorrect labeling. We had previously asked the Applicant if they intended to withdraw the existing 1000 mg tablets if the new one were approved, and they indicated that they did not intend to do so. Some of the reasons provided were that some patients may not tolerate going down to twice daily dosing. They did not expect all patients who take Ferriprox TID to transition to the BID schedule.

I consulted with DMEPA (Hina Mehta), Labeling Policy Team (Ann Marie Trentacosti and Eric Brodsky), Office of Clinical Pharmacology Labeling Specialists (Joseph Grillo and Mongthuong Tran). I consulted with the OPPQ Labeling Policy Team (Jibril Abdus-Samad) on 05/12/2020 and he recommended when using the "twice daily" terminology before the non-proprietary name that we use lower case letters to inadvertently appear as part of the established name. DMEPA preferred that the schedules be referred to as "twice a day" and "three times a day" for clarity.

The Applicant submitted a document that describes "marketing plans to prevent medication errors" to the NDA. [redacted] (b) (4)

Also, the Clinical Pharmacology team has communicated that there does not appear to be an impact on safety or efficacy if the products were accidentally substituted for one another, due to a very similar PK profile; though the tablets are not considered substitutable.

Reviewer Comment: The Applicant's plans for prescriber and patient education appear comprehensive and distribution is controlled. The risk of substitution of the products for one another is limited, if these plans are followed. Also, the risks of accidental substitution do not appear to be significant.

On 05/12/20, DNH asked the Applicant to add the information about the new 1000 mg tablet to the current 1000 mg Ferriprox labeling and submit by 5/15/20 10am EST. They responded by asking about naming convention preference and offered two options for DNH to select from [proposed options in grey highlight below].

(b) (4)

Reviewer Comment: Dr. Grillo, Dr. Tran, and I had some concerns about (b) (4) We will need to include information on the tablet embossing in the Dosage and Administration section to clearly communicate which tablet is being discussed. This is not a usual practice, but will be necessary for clarity.

On 05/13/20, DNH responded to the Applicant's request for an option choice for naming conventions by stating that Option 2 would be our preference.

We also advised them (on 5/12/20) that if they intended to use the proprietary name Ferriprox for the new tablet to submit a request for proposed proprietary name to NDA 212269 by 05/13/20. This was submitted on 05/13/20 and DMEPA archived a review that indicated it was acceptable.

Revised labeling was received on 05/15/20 and the Applicant agreed with all of our revisions. The only outstanding issue is in Section 11 with the proposed engraving on the tablet, which currently uses "DR" as one of the engravings. (b) (4) We consulted DMEPA on this issue, and they did not have a concern.

Regulatory Recommendation: This NDA is recommended for approval with the labeling submitted on 05/15/2020 constituting final labeling after a left margin line is added to Section 2.1 (for RMCs).

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/s/

VIRGINIA E KWITKOWSKI
05/18/2020 03:57:57 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 15, 2020
Requesting Office or Division:	Division of Nonmalignant Hematology (DNH)
Application Type and Number:	NDA 212269
Product Name, Dosage Form, and Strength:	Ferriprox (deferiprone) tablet 1,000 mg
Applicant/Sponsor Name:	ApoPharma
FDA Received Date:	May 11, 2020
OSE RCM #:	2019-1539-2
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

ApoPharma submitted revised container labels and carton labeling for Ferriprox (deferiprone) on May 11, 2020 (Appendix A). [redacted] (b) (4) This memo supersedes our previous reviews of the labels and labeling.[a,b]

2 DISCUSSION

Ferriprox (deferiprone) is currently available as 500 mg and 1,000 mg immediate-release tablets (NDA 021825) and 100 mg/mL and 80 mg/mL oral solution (NDA 208030). The currently available formulations of deferiprone are administered three times per day. ApoPharma submitted NDA 212269 proposing a [redacted] (b) (4) tablet formulation of deferiprone which is intended to be administered twice daily.

However, on May 1, 2020, the Agency sent a communication to ApoPharma which stated the following:

[a] DeGraw, S. Label and Labeling Review Memo for Ferriprox [redacted] (b) (4) NDA 212269. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 03. RCM No.: 2019-1539-1.
[b] DeGraw, S. Label and Labeling Review for Ferriprox [redacted] (b) (4) NDA 212269. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 FEB 06. RCM No.: 2019-1539.

(b) (4)

Therefore, per Clinical Pharmacology, the twice-daily frequency of administration is appropriate for the proposed formulation, (b) (4)

We note that the previously proposed proprietary name (b) (4) was replaced with the newly proposed proprietary name "Ferriprox"[d] (b) (4) was replaced with "tablets". As such, the proposed twice-daily 1,000 mg tablet formulation has the same proprietary name, established name, dosage form, and strength as the currently available three-times-daily 1,000 mg tablet formulation. We note that ApoPharma added a statement indicating the (b) (4) frequency of administration on the principal display panel of the carton labeling and container labels to help differentiate the two formulations from a dispensing perspective.

We note that the currently available immediate-release 1,000 mg tablet and the proposed new 1,000 mg tablet formulation of deferiprone may introduce medication error concerns. Specifically, there is the risk that the although both tablets are the same strength, the immediate-release tablets are administered three times a day while the proposed tablets are administered twice a day. In a teleconference with ApoPharma on May 6, 2020 to discuss the clinical pharmacology issue on the tablet designation, we asked ApoPharma to submit their plans to prevent medication errors between the two 1,000 mg tablet formulations. On May 11, 2020, ApoPharma responded with the following marketing plan:[e]

(b) (4)

[c] Kacuba, A. Email: FDA Communication for NDA 212269. 2020 MAY 1. Available at: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8055e351&_afrRedirect=782569860516300

[d] DeGraw, S. Proprietary Name Review Memo for Ferriprox (deferiprone) NDA 212269. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 15. RCM No.: 2020-39890272.

[e] Connelly, J. Cover Letter: Submission of Updated Marketing Plans to Minimize Errors. 2020 MAY 11. Available at: \\cdsesub1\evsprod\nda212269\0016\m1\us\12-cover-letters\cover-letter-sn0016.pdf

(b) (4)

In addition, we note, based on email conversations with the clinical review team that if the products were to be confused for one another (i.e., if the patient was intended to receive the currently marketed Ferriprox formulation at a dose of 1,000 mg three times daily, but was inadvertently dispensed the proposed ("twice daily") formulation of 1,000 mg three times daily), the serious adverse reaction is agranulocytosis/neutropenia which is NOT dose dependent. Additionally, an overdose would potentially decrease the body store of iron levels, but the patient's serum ferritin concentration is monitored every two to three months which limits the degree of over/under chelation with these products. Therefore, from a clinical perspective, there is minimal concern if these products were to be confused for one another, especially in the short term.

Furthermore, Clinical Pharmacology noted in the May 1, 2020 communication to ApoPharma that "*given the similarity of these PK parameters, it is reasonable to expect that at doses equivalent to deferiprone delayed release, deferiprone immediate release will produce similar deferiprone exposure when dosed twice daily. We note that when 1500 mg deferiprone delayed release administered twice daily is compared to 1000 mg deferiprone immediate release administered three times a day in Study LA45-0116, the geometric mean ratio (90% confidence*

interval) for dose-normalized AUC $_{(0-8)}$, was 99.4% (90-96.6)."[f] Clinical Pharmacology went on to note in a separate email that "*the same total daily dose of either formulation will produce similar exposure, thus expecting similar clinical outcome. However, at the same single dose (i.e. 1,000 mg of the approved formulation and 1000 mg of the new formulation) the approved formulation will produce similar AUC but ~30% increase in Cmax as compared to the new formulation. There is no safety data to show the higher Cmax has any meaningful clinical implication.*" Therefore, it stands to reason that if either 1,000 mg tablet formulation is given two times or three times a day, there is minimal concern with regards to efficacy and safety.

Our review of the proposed container labels and carton labeling identified additional improvements that can be made to prevent medication errors between these two formulations. We provide our recommendations below for the container labels and carton labeling.

3 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective. We recommend revising the labels and labeling to further differentiate this product from the currently approved Ferriprox (deferiprone) 1,000 mg tablet. We provide our recommendations below for the Sponsor.

3.1 RECOMMENDATIONS FOR APOPHARMA

A. General Comments
   1. We note as part of your marketing plans that you [redacted] (b) (4)

B. Comments for the 50-Count Bottle, 500-Count Bottle, and Carton Labeling
   1. To clearly communicate that this product is a new twice-daily formulation to users and to differentiate the new formulation from the currently approved three-times-daily 1,000 mg tablet formulation, we recommend the following:
      i. Revise the frequency of administration statement to "TWICE-A-DAY" and increase the prominence by enlarging the font size as space will allow and use boxing techniques. For example:

[f] Kacuba, A. Email: FDA Communication for NDA 212269. 2020 MAY 1. Available at: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8055e351&_afrRedirect=782569860516300

(b) (4)

ii. Add the statement “NEW FORMULATION” on the principal display panel. The statement should be in bolded, red font and placed in a box to draw attention to this important information. For example:

(b) (4)

This statement can be added directly to the principal display panel label or can be achieved through a sticker. We recommend including this statement for approximately six months as patients are transitioned.

C. Comments for the Blister Pack

1. Revise the frequency of administration statement to “TWICE-A-DAY” in alignment with the recommendation for the 50-Count Bottle, 500-Count Bottle, and Carton Labeling.

D. Comments for the Currently Approved 1,000 mg Tablet Container Labels (NDA 021825)

To further differentiate the new twice-daily 1,000 mg tablet formulation from the currently approved three-times-daily 1,000 mg tablet formulation, we recommend adding a frequency of administration statement (i.e., THREE TIMES A DAY) to the principal display panel of the currently approved 1,000 mg tablet container label.

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/s/

STEPHANIE L DEGRAW
05/15/2020 02:33:40 PM

HINA S MEHTA
05/15/2020 02:45:37 PM

Division of Hematology Products Associate Director for Labeling Review of the Prescribing Information

Product Title	FERRIPROX [redacted] (b) (4) tablets, for oral use
Applicant	Apopharma Inc. c/o Apotex Corp
Application/Supplement Number	212269
Is Proposed Labeling in Old Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Proposed Indication(s)	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
Date FDA Received Application	07/19/2019
Review Classification (Priority/Standard)	Standard
Action Goal Date	05/19/2020
Review Date	04/01/2020
Reviewer	Virginia Kwitkowski, MS, ACNP-BC

This Associate Director for Labeling (ADL) review provides recommendations on the content and format of the Warnings and Precautions section of the prescribing information (PI) to help ensure that PI:

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements[1]
- Is consistent with labeling guidance recommendations[3] and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

Background:

ApoPharma, through their U.S. Agent, Apotex Corp., has submitted a new drug application for Ferriprox [redacted] (b) (4) tablets. The proposed indication is the same as Ferriprox 500 mg immediate release film-coated tablets and oral solution, which is the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. The new formulation [redacted] (b) (4)

[1] See *January 2006 Physician Labeling Rule*; 21 CFR 201.56 and 201.57; and *December 2014 Pregnancy and Lactation Labeling Rule* (the PLLR amended the PLR regulations). For applications with labeling in non-PLR "old" format, see 21 CFR 201.56(e) and 201.80.

[3] See *PLR Requirements for PI* website for PLR labeling guidances.

(b) (4) allowing twice daily dosing instead of three times daily dosing necessary for the immediate release tablets and oral solution. The proposed (b) (4) tablets will reduce the treatment burden by requiring less doses per day and less tablets per day.

Reviewer Comments: The USPI and Medication guide were reviewed with the intention of maintaining consistency with the approved Ferriprox labelings (NDA 21825 [tablets] and NDA 208030 [oral solution]). The differences between the approved labelings and the new labeling were mostly limited to product-specific differences. The labeling was reviewed by the multi-disciplinary and two formal multi-disciplinary labeling meetings were held. The labeling was considered SCPI (substantially complete prescribing information) and sent to the labeling consult teams on 02/27/20. Upon completion of the labeling consult reviews and incorporation of their suggested edits/comments, the USPI and Medication Guide were sent to the Applicant on 03/13/20. The labeling documents were received back from the Applicant on 03/23/20. The multidisciplinary team has reviewed the returned labeling, and further edits will be communicated to the Applicant in the coming few days. Labeling negotiations will likely be finalized within the next week.

Regulatory Recommendation: This NDA is recommended for approval upon completion of labeling negotiations.

Attachments: Revised labeling with track changes edits and bubble comments explaining the revisions (version sent to the Applicant on 03/13/20).

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VIRGINIA E KWITKOWSKI
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 10, 2020

To: Linda Akunne, MPH, Senior Regulatory Project Manager, (on behalf of DHP)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling, DHM1

From: Rebecca Falter, PharmD, BCACP, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for FERRIPROX (b) (4) tabelts, for oral use

NDA: 212269

In response to DHP's consult request dated September 10, 2019, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for Ferriprox DR.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DHP (Linda Akunne) on February 27, 2020 and is provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on March 9, 2020.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on February 27, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

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/s/

REBECCA A FALTER
03/10/2020 11:12:24 AM

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

PATIENT LABELING REVIEW

Date:	March 6, 2020
To:	Linda C. Akunne (Onaga), MPH Senior Regulatory Project Manager **Division of Hematologic Malignancies (DHM1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	(b) (6)
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Rebecca Falter, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	FERRIPROX (b) (4)
Dosage Form and Route:	(b) (4) tablets, for oral use
Application Type/Number:	NDA 212269
Applicant:	ApoPharma, a Divison of Apotex Inc

1 INTRODUCTION

On July 19, 2019, ApoPharma, a Division of Apotex Inc., submitted for the Agency's review a New Drug Application (NDA) 212269 for FERRIPROX (b) (4) [redacted] tablets. The proposed therapeutic indication is the same as that approved for FERRIPROX (deferiprone) 500 mg immediate release film-coated tablets (NDA 021825) and FERRIPROX (deferiprone) 100 mg/ml oral solution (NDA 208030), which is for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematologic Malignancies I (DHM1) on September 10, 2019, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for FERRIPROX [redacted] (b) (4) tablets.

2 MATERIAL REVIEWED

- Draft FERRIPROX [redacted] (b) (4) tablets MG received on July 19, 2019, revised by the Review Division throughout the review cycle and received by DMPP and OPDP on February 27, 2020.
- Draft FERRIPROX [redacted] (b) (4) tablets Prescribing Information (PI) received on July 19, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 27, 2020.
- Approved FERRIPROX (deferiprone) tablets labeling dated February 20, 2020.
- Approved FERRIPROX (deferiprone) oral solution labeling dated February 20, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG,we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
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REBECCA A FALTER
03/09/2020 09:30:24 AM

(b) (6)

LASHAWN M GRIFFITHS
03/09/2020 11:11:51 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 3, 2020
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 212269
Product Name, Dosage Form, and Strength:	Ferriprox [redacted] (b) (4) 1,000 mg
Applicant/Sponsor Name:	ApoPharma
FDA Received Date:	February 27, 2020
OSE RCM #:	2019-1539-1
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

ApoPharma submitted revised carton and container labels for Ferriprox [redacted] (b) (4) on February 27, 2020 (Appendix A). The revisions are in response to recommendations that we made during a previous label and labeling review[a].

2 DISCUSSION

We note that the recommendation to use a different color for the trademark (i.e., consider printing [redacted] (b) (4)) was not implemented. ApoPharma noted that they are proposing to [redacted] (b) (4) Additionally, ApoPharma cited other examples of approved products that use a similar approach. We concur with their justification.

ApoPharma also noted that Chiesi USA Inc. was appointed as the distributor for Ferriprox [redacted] (b) (4) As such "the proposed container labels have been updated to reflect the Chiesi name, logo and labeler codes".

[a] DeGraw, S. Label and Labeling Review for Ferriprox [redacted] (b) (4) NDA 212269. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 FEB 06. RCM No.: 2019-1539.

3 CONCLUSION

DMEPA concludes the revised container label and carton labeling is acceptable from a medication error perspective. We have no additional recommendations at this time.

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/s/

STEPHANIE L DEGRAW
03/03/2020 10:21:43 AM

HINA S MEHTA
03/05/2020 03:42:56 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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Date of This Review:	February 6, 2020
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 212269
Product Name and Strength:	Ferriprox [redacted] (b) (4) 1,000 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	ApoPharma
FDA Received Date:	July 19, 2019, December 10, 2019, and January 16, 2020
OSE RCM #:	2019-1539
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1. REASON FOR REVIEW

ApoPharma submitted NDA 212269 Ferriprox [redacted] (b) (4) tablets on July 19, 2019. Ferriprox [redacted] (b) (4) an iron chelator proposed for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. We evaluated the proposed container labels, carton labeling, Prescribing Information (PI), and Medication Guide (MG) for areas of vulnerability that could lead to medication errors.

2. BACKGROUND & REGULATORY HISTORY

Ferriprox (deferiprone) tablets were approved under NDA 021825 on October 14, 2011, for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. Ferriprox (deferiprone) oral solution was approved under NDA 208030 on September 9, 2105 for the same indication. The dose for the tablets and oral solution is 25 mg/kg to 33 mg/kg body weight three times per day, for a total daily dose of 75 mg/kg to 99 mg/kg body weight.

ApoPharma is proposing Ferriprox [redacted] (b) (4) [redacted] is to be administered as 75 mg/kg/day to 99 mg/kg/day divided into two doses taken approximately 12 hours apart.

3. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Information Request	F
Currently Marketed Ferriprox Container Label	G
Proposed Labels and Labeling	H

N/A=not applicable for this review
*We do not typically search ISMP Newsletters or FAERS for our label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

4. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container labels, carton labeling, PI, and MG for Ferriprox (b) (4) to identify deficiencies that may lead to medication errors and other areas of improvement.

We note that the proposed (b) (4) tablet is being introduced to reduce patients' tablet burden. However, from a medication error perspective, we are concerned about the potential similarity in appearance between the currently marketed 1,000 mg immediate-release tablets and the proposed (b) (4) tablets (both tablets are white to off-white, capsule-shaped, and have a functional score), which may lead to dispensing errors. Therefore, through an Information Request (IR) dated December 2, 2019, we requested ApoPharma submit their marketing plans for the currently approved immediately-release tablets and the proposed (b) (4) tablets and their plans to mitigate the risk of confusion between the formulations (see Appendix F).

On December 10, 2019, ApoPharma responded to the IR, stating that the current marketing plan is (b) (4)

(b) (4)

(b) (4)

ApoPharma also noted (b) (4) (i.e., "APO" and "1000" on the one side, "FPX" and "DR" on the other side) will be different from the immediate-release tablets (i.e., "APO" and "1000" on the one side, plain on the other side).

As part of our evaluation of the proprietary name, Ferriprox (b) (4) we discussed with the clinical review team the clinical significance of wrong drug errors if the products were to be confused for one another (i.e., if a patient intended to receive Ferriprox (b) (4) 1,000 mg three times daily, but receives Ferriprox (b) (4) 1,000 mg three times daily; or alternatively if a patient intended to receive Ferriprox (b) (4) 1,000 mg twice daily, but receives Ferriprox (b) (4) 1,000 mg twice daily).[a]

According to the medical officer via email communication on August 20, 2019, a serious and fatal adverse reaction with deferiprone (b) (4) is agranulocytosis/neutropenia; however, "there is no dose-dependence for this adverse reaction and the mechanism of action for this adverse reaction is unknown". Furthermore, the medical officer stated that "no cases of acute overdose have been reported and neurological disorders such as cerebellar symptoms, diplopia, lateral nystagmus, psychomotor slowdown, hand movements and axial hypotonia have been observed in children treated with 2.5 to 3 times the recommended dose for more than one year; [however], the neurological disorders progressively regressed after deferiprone discontinuation." With respect to efficacy, an overdose would potentially decrease the body store of iron levels and an underdose would potentially increase the body store of iron levels. However, per the medical officer and in the products' labeling, the patient's serum ferritin concentration is monitored every two to three months which limits the degree of over or under chelation with these products.

On January 10, 2020, we sent an additional IR as a follow-up to the Sponsor's December 10, 2019 response seeking clarificatio (b) (4)

On January 16, 2020, ApoPharma responded to the IR, stating the following:

- Similar to the current marketing practice of Ferriprox 500 mg and 1,000 mg film-coated tablets, ApoPharma proposes (b) (4)

[a] Mena-Grillasca, C. Proprietary Name Review for Ferriprox DR (NDA 212860). FDA, CDER, OSE, DMEPA (US); 2019 OCT 11. Panorama No. 2019-33248849.

- The timeline for the marketing of the 50-count and 500-count bottles will be based on the market need/preference.

[redacted] (b) (4)

Our review of the proposed PI identified areas in the PI and on the container labels and carton labeling that can be modified to improve the clarity of the information presented and address any residual risk of confusion between the currently marketed Ferriprox and the proposed [redacted] (b) (4) formulation.

5. CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI and labels can be improved to increase clarity of important information to promote the safe use of the product. We provide recommendations for the Division in Section 4.1 and recommendations for ApoPharma in Section 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights of Prescribing Information
   1. We recommend revising the dosage and administration statement to specify ideal or actual body weight and to describe individual doses before the total daily dose to improve clarity. [redacted] (b) (4)

B. Dosage and Administration [2]
   1. Dosing [2.1]
      a. Starting Dose
         i. We recommend revising the initial dose statement to specify ideal or actual body weight and to describe the individual dose rather than the total daily dose to improve clarity. For example, revise to read, [redacted] (b) (4)
      b. Dose Adjustments
         i. We recommend revising the maximum dose statement to specify ideal or actual body weight and to describe the individual dose rather than the total daily dose to improve clarity. For example, revise to read, [redacted] (b) (4)

C. Dosage Forms [3]

1. We recommend revising this statement to include a description of the tablet. For example, [redacted] (b) (4) 1,000 mg capsule-shaped, white to off-white, tablets with functional scoring, engraved with "FPX" bisect "DR" on one side and "APO" bisect "1000" on the other.

D. How Supplied / Storage and Handling [16]

1. We recommend revising the blister pack statement to more accurately reflect the contents of the cartons containing blister packs. For example, revise to read:

   1,000 mg [redacted] (b) (4) tablets, carton of 5 x 10-count blister packs [redacted] (b) (4)

E. Patient Counseling Information [17]

1. We recommend presenting the storage information with the Fahrenheit temperature statement before Celsius as this is more familiar to lay persons.

4.2 Recommendations for ApoPharma

A. Container Label – Bottles

1. We recommend including the frequency of administration (i.e., Twice-A-Day) on the principal display panel above the tradename to highlight the difference in frequencies of administration between Ferriprox [redacted] (b) (4) two divided doses taken approximately 12 hours apart) and Ferriprox (ee times daily).

2. To further differentiate Ferriprox [redacted] (b) (4)

3. We recommend revising the graphic element [redacted] (b) (4)

4. Net Quantity Statement

   a. We recommend reducing the font size and de-bolding "50" and "500" in the net quantity statements as post-marketing experience has shown that the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is of similar prominence to strength statement.

   b. To improve readability, we recommend revising the net quantity statements so that the number of tablets (i.e., 50 and 500) and the word "tablets" appear on the same line.

5. To ensure consistency with the Prescribing Information, revise [redacted] (b) (4) to read "Dosage: see prescribing information".

B. Blister Carton Labeling

1. We recommend including the frequency of administration (i.e., Twice-A-Day) on the principal display panel above the tradename to highlight the difference in frequencies of administration between Ferriprox [redacted] (b) (4) two divided doses taken approximately 12 hours apart) and Ferriprox (i.e., three times daily).

2. To further differentiate Ferriprox [redacted] (b) (4)

3. We recommend revising the graphic element utilized [redacted] (b) (4)

4. We recommend revising the strength statement "1,000 mg" to state "1,000 mg per tablet" to make it clear that the designated strength is per unit (tablet).

5. Net Quantity Statement
   a. We recommend revising the net quantity statement to read:
      Contains 50 tablets
      5 blister packs each containing 10 tablets

   b. We recommend reducing the font size and de-bolding "50" in the net quantity statement as post-marketing experience has shown that the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is of similar prominence to strength statement.

6. To ensure consistency with the Prescribing Information, revise [redacted] (b) (4) to read "Dosage: see prescribing information".

APPENDICES: METHODS & RESULTS FOR MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ferriprox [redacted] (b) (4) on July 19, 2019, from ApoPharma and Ferriprox (NDA 021825 and NDA 208030) excerpted from Drugs@FDA[b,c].

Table 2. Product Characteristics of Ferriprox [redacted] (b) (4)		
	Ferriprox [redacted] (b) (4)	**Ferriprox**
Active Ingredient	deferiprone	deferiprone
Indication	treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate.	treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate.
Route of Administration	oral	oral
Dosage Form	Tablet [redacted] (b) (4)	Tablet Oral solution
Strength	1,000 mg	1,000 mg 40 g/500 mL (80 mg/mL) 20 g/250 mL (80 mg/mL)
Dose and Frequency	75 mg/kg/day divided into two doses taken approximately 12 hours apart, with a meal. Doses should be round to the nearest 500 mg (half-tablet).	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. Doses for the tablet formulation should be round to the nearest 500 mg (half-tablet).
How Supplied	The [redacted] (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. They are supplied in child-resistant blister packs or HDPE bottles. 1,000 mg [redacted] (b) (4) tablets, blister pack of 50 tablets NDC [redacted] (b) (4) 1,000 mg [redacted] (b) (4) tablets, bottle of 50 tablets NDC [redacted] (b) (4)	The tablets are white to off-white capsule-shaped tablets, film-coated, and have a functional score imprinted with "APO" score "1000" on one side and are plain on the other. They are provided in HDPE bottles. 1,000 mg film-coated tablets, 50 tablets NDC [redacted] (b) (4) The oral solution is provided in amber polyethylene terephthalate (PET) bottles with child resistant closures

[b] https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021825s004lbl.pdf

[c] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208030s002lbl.pdf

	1,000 mg (b) (4) tablets, bottle of 500 tablets NDC (b) (4)	(polypropylene). Each pack contains one bottle of 500 mL (b) (4) (b) (4)
Storage	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].	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]. (b) (4) (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 21, 2019, we searched for previous DMEPA reviews relevant to this current review using the term 'Ferriprox' and 'deferiprone'. Our search identified eight previous label and labeling reviews and we considered our previous recommendations to see if they are applicable for this current review.

Reviewer	Title of Review	Application No.	Date	RCM No.
DeGraw, S.	Label and Labeling Review for Ferriprox (deferiprone) Tablets	NDA 021825/S-004	2019 MAY 31	2019-574
Rahimi, L.	Label and Labeling Review Memo for Ferriprox (deferiprone) Tablets	NDA 021825/S-004	2018 APR 06	207-1913-1
Rahimi, L.	Label and Labeling Review for Ferriprox (deferiprone) Tablets	NDA 021825/S-004	2018 FEB 15	207-1913
Rahimi, L.	Label and Labeling Review for Ferriprox (deferiprone) Oral Solution	NDA 208030/S-002	2018 JAN 30	2017-1629
Rutledge, M.	Label and Labeling Review for Ferriprox (deferiprone) Oral Solution	NDA 208030	2015 JUN 15	2014-2427
Holmes, L.	Label and Labeling Review Memo for Ferriprox (deferiprone) Tablets	NDA 021825	2011 OCT 14	2009-355
Holmes, L.	Label and Labeling Review Memo for Ferriprox (deferiprone) Tablets	NDA 021825	2011 JUL 11	2009-355
Abdus-Samad, J.	Label and Labeling Review for Ferriprox (deferiprone) Tablets	NDA 021825	2009 OCT 23	2009-355

APPENDIX F. INFORMATION REQUESTS

On December 2, 2019, DMEPA submitted an information request (IR)[d] to ask the Applicant to submit the following for our review:

1. Your marketing plans for the currently approved 1,000 mg immediate-release tablets. Will both formulations [redacted] (b) (4) be concurrently marketed?
2. Your plan(s) to mitigate the risk of confusion between the formulations.

Additionally, we request you send five (5) intent-to-market samples of the blister pack and carton to assist in completion of our review.

On December 10, 2019, ApoPharma responded to our IR and stated the following:[e]

(b) (4)

[redacted]

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[d] https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8052bcc2&_afrRedirect=1108629790293190

[e] \\cdsesub1\evsprod\nda212269\0008\m1\us\12-cover-letters\response-to-ir-dt-02dec2019.pdf

On January 16, 2020, ApoPharma responded to our IR and stated the following:[g]

(b) (4)

[redacted]

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/s/

STEPHANIE L DEGRAW
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HINA S MEHTA
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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 20, 2019

TO: Bing Li, Ph.D.
Acting Director
Office of Bioequivalence (OB)
Office of Generic Drugs (OGD)

John Leighton, M.D.
Director
Division of Hematology, Oncology, Toxicology (DHOT)
Office of New Drugs (OND)

FROM: Sripal Reddy Mada, Ph.D.
Pharmacologist
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

Melkamu Getie-Kebtie, Ph.D., R.Ph.
Pharmacologist
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: John A. Kadavil, Ph.D.
Deputy Director
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Surveillance inspection (b) (4)

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) inspected the analytical portions of studies (b) (4)

We did not observe objectionable conditions and did not issue a Form FDA 483 at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

1.1. Recommendation

Based on our review of the inspectional findings, we conclude the data from the audited studies are reliable to support a regulatory decision.

2. Inspected Studies

(b) (4)

[redacted]

3. Scope of Inspection

OSIS scientists Sripal Reddy Mada, Ph.D. and Melkamu Getie-Kebtie, Ph.D., R.Ph. audited the analytical portion of the above studies at [redacted] (b) (4)

The inspection included a thorough examination of study records, facility, laboratory equipment, method validation, and sample analysis, and interviews with the firm's management and staff.

4. Inspectional Findings

At the conclusion of the inspection, we did not observe objectionable conditions. We did not issue a Form FDA 483 to [redacted] (b) (4) However, we discussed the following item with management during the inspection and at the close-out meeting.

4.1. Discussion item

During the inspection, we noted that the firm employed a [redacted] (b) (4)

Firm's Response: The firm explained that a correction factor for extraction efficiency should be applied to QCs and study samples to compensate for the loss of TBI during extraction. The firm calculated the correction factor by comparing samples that were passed through extraction cartridges with samples that were not passed through the cartridges. By applying this extraction correction factor, [redacted] (b) (4)

 (b) (4)

OSIS Evaluation: (b) (4) (b) (4)

5. Conclusion

After review of the inspectional findings, we conclude that data from the audited studies are reliable. (b) (4) (b) (4)

Studies using similar methods conducted between the previous inspection (b) (4) and the end of the current surveillance interval should be considered reliable without an inspection.

Final Classification:

NAI - (b) (4)

cc: OTS/OSIS/Kassim/Mitchell/Fenty-Stewart/Taylor/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas

OTS/OSIS/DGDSI/Cho/Kadavil/Choi/Skelly/Au/Getie-Kebtie/Mada
ORA/OMPTO/OBIMO/FDAInternational BIMO@fda.hhs.gov

Draft: SRM 10/30/2019, 11/19/2019
Edit: MGK 11/05/2019, 11/12/2019; YMC 11/07/2019, 11/19/2019; JAK 11/19/2019, 11/20/2019

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ [redacted] (b) (4)

OSIS File: [redacted] (b) (4)

BE 8700 (NDA 212269)
[redacted] (b) (4)

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Sripal Mada, Ph.D.

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Melkamu Getie-Kebtie, R.Ph., Ph.D.

[redacted] (b) (6)

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John A. Kadavil, Ph.D.

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/s/

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(b) (6)

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11/20/2019 09:58:04 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 10/1/2019

TO: Division of Hematology Products
Office of Hematology and Oncology Products

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 212269

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) inspected the sites in June 2019, which falls within the surveillance interval. The inspection was conducted under the following submission: (b) (4)

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	(b) (4)	

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/s/

FOLAREMI ADEYEMO
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