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CLINICAL REVIEW(S)

CLINICAL REVIEW

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Division	Division of Nonmalignant Hematology
Reviewer Name	Andrew Dmytrijuk M.D.
Review Completion Date	May 11, 2020
Established Name	Deferiprone
Trade Name	[Proposed] Ferriprox (b) (4)
Therapeutic Class	Iron Chelator
Applicant	ApoPharma 200 Barmac Dr. Toronto, Ontario M9L 2Z7 Canada
Formulation	1000mg (b) (4) Tablet
Dosing Regimen	(b) (4) mg/kg Administered Orally Twice Daily
Indication	Treatment of Patients with Transfusional Iron Overload Due to Thalassemia Syndromes When Current Chelation Therapy is Inadequate
Intended Population	Patients with Transfusional Iron Overload Due to Thalassemia Syndromes

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 212269 supporting document 1 letter date July 19, 2019 (received July 19, 2019) for [proposed name] Ferriprox (b) (4) (deferiprone 1000mg administered orally twice daily) (b) (4) a 1000mg tablet administered orally twice daily (recommended dose of 37mg/kg). The intent of this new deferiprone (b) (4) formulation is to decrease the pill burden compared to the immediate release (IR) deferiprone 500mg tablet formulation that is orally administered three times daily (recommended dose 25mg/kg) that was granted accelerated approval October 14, 2011 under NDA 21825. An IR deferiprone 1000mg orally administered tablet formulation was granted accelerated approval for marketing under NDA 21825 Supplement-004 on July 25, 2019. A deferiprone 100mg/mL oral solution was granted accelerated approval for marketing under NDA 208030 on September 9, 2015 and a deferiprone 80mg/mL oral solution was granted an accelerated approval for marketing under NDA 208030 on April 20, 2018. The sponsor states that based on the recommended deferiprone 75-99 mg/kg/day dosing a 60 kg patient is required to take 9 to 12 deferiprone IR 500 mg tablets daily compared to approximately 5 to 6 deferiprone (b) (4) tablets daily. In NDA 212269 for the deferiprone (b) (4) the sponsor cross-references the safety and efficacy data for deferiprone IR formulation under NDA 21825. No new efficacy and safety studies were conducted for this application. A bioequivalence study and a food effect study are submitted to support the application. Otherwise, no new clinical data was submitted under NDA 212269 for the deferiprone (b) (4)

To support this marketing application for the deferiprone (b) (4) under NDA 212269 the sponsor submitted data from study LA45-0116 titled, "Comparison of the Pharmacokinetics and Safety of Multiple Doses of Deferiprone Extended Release Tablets in Healthy Volunteers", that enrolled 36 normal healthy adult volunteers (age ≥18 to ≤ 55 years) male (n=30) or female (n=6) volunteers). Study LA45-0116 is a single center, randomized (1:1), multiple dose, open-label, 2-period, 2-sequence, crossover, bioavailability and bioequivalence study. The study was designed to compare the pharmacokinetics (PK) and safety of deferiprone DR to the marketed deferiprone IR formulation tables. Subjects received deferiprone DR 1500mg administered orally every 12 hours for 6 days or deferiprone immediate release 1000 mg administered orally every 8 hours for 9 days. The sponsor states that the 90% confidence intervals of the ratios of the PK parameters AUC0-t, AUCinf and Cmax for deferiprone in serum were within the 0.80 to 1.25 acceptance range and that the deferiprone 1000mg DR formulation and the marketed deferiprone 500mg IR formulation are bioequivalent. Also, the sponsor conducted study LA53-0116 titled, "Single-Dose Pharmacokinetic Study of Deferiprone Extended Release Tablets

under Fasting and Fed Conditions versus Ferriprox Immediate Release Tablets under Fed Conditions in Healthy Volunteers", that enrolled 28 normal healthy adult volunteers (age ≥18 to ≤ 55 years) male (n=17) or female (n=11) volunteers). Study LA53-0116 is a single center, randomized (1:1:1:1), single dose, open-label, 4-period, 4-sequence, crossover study bioavailability and bioequivalence study. The study was designed to compare the pharmacokinetics (PK) and safety of a single dose of deferiprone DR to the marketed deferiprone IR formulation tables. Subjects received deferiprone DR 1000mg administered orally once or deferiprone immediate release two 500mg tablets (total 1000 mg) administered orally once. The sponsor states that the 90% confidence intervals of the ratios of the PK parameters AUC0-t, AUCinf and Cmax for deferiprone in serum were within the 0.80 to 1.25 acceptance range and that the deferiprone 1000mg DR formulation and the marketed deferiprone 500mg IR formulation are bioequivalent. In these studies, all adverse events were graded as mild to moderate and only headache (n=3 subjects each) was reported in ≥ 3 subjects who received the deferiprone DR formulation. Studies LA53-0116 and LA45-0116 are under review by the Clinical Pharmacology review team. See the Clinical Pharmacology Review (pending) for further discussion and details.

From a clinical perspective NDA 212269 should be granted accelerated approval for the same indication as the currently approved product Ferriprox® (NDA 21825; deferiprone 500mg tablets for oral use; 1000mg tablets) and (NDA 208030; deferiprone 100mg/mL oral solution) which were granted accelerated approval on October 14, 2011 and September 9, 2015, respectively. A new label for the deferiprone (b) (4) under NDA 212269 should reflect the PK parameters of the drug that were observed in study LA45-0116 and LA53-0116. The clinical pharmacology reviewer should also comment on the acceptability of the results of study LA45-0116 and LA53-0116 to support the marketing application under NDA 212269 for the deferiprone (b) (4) and the proposed labeling changes. This marketing application for deferiprone (b) (4) tablet formulation NDA 212269 supporting document cross-references the safety and efficacy data for the deferiprone IR formulation under NDA 21825. No new clinical information apart from Studies LA45-0116 and LA53-0116 for the deferiprone (b) (4) was submitted under NDA 212269.

The indication is stated as:

- 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. Approval is based on a reduction in serum ferritin levels. There are no controlled trials demonstrating a direct treatment benefit, such as improvement in disease-related symptoms, functioning, or increased survival.

This reviewer's labeling recommendations for the deferiprone product label are in section 9.3 Labeling Recommendations in this review and incorporate comments and

recommendations from FDA reviewers from other disciplines. The reviewer recommendations in section 9.3 Labeling Recommendations in this review should be forwarded to the sponsor.

1.2 Risk Benefit Assessment

The recommendation for the approval of deferiprone (b) (4) from a clinical perspective is based on the safety and efficacy of the marketed deferiprone tablet (Ferriprox®) product (NDA 21825). No new clinical efficacy and safety studies were submitted for this application. There were no significant safety findings in the bioequivalence study and food effect study that were submitted to support the application. Support for the approval of this application for deferiprone also comes from the Periodic Adverse Drug Experience Report (PADER) and the Annual Report submitted to NDA 208030 and NDA 21825. No new or additional safety concerns were identified in this Clinical Review of NDA 208030 Supplement 002 for the new 80mg/mL deferiprone oral solution formulation based on review of safety information submitted under NDA 208030 and NDA 21825 from recent Periodic Adverse Drug Experience Reports (PADERs) and Annual Reports.

Overall, the risk benefit assessment favors the approval of the deferiprone (b) (4) tablet formulation for the same indication as that of the approved Ferriprox (deferiprone) products.

The sponsor is claiming exemption from the Pediatric Research Equity Act (PREA) requirements for deferiprone (b) (4) tablet formulation (NDA 212269). I agree with the sponsor's claim that the PREA exemption for NDA 212269 for the deferiprone (b) (4) formulation is based on the existing Orphan Designation granted on December 12, 2001 to the active ingredient deferiprone for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. The deferiprone (b) (4) formulation may provide an alternative treatment formulation for patients that may reduce pill burden.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No post-marketing risk evaluation and mitigation strategy (REMS) is recommended for the deferiprone (b) (4)

1.4 Recommendations for Postmarket Requirements and Commitments

There is no clinical data available in patients who were treated with deferiprone (b) (4) orally administered tablet formulation. The sponsor cross-references the safety and efficacy information that supported the accelerated approval of the deferiprone IR 500mg and 1000mg tablets under NDA 21825. A Bioavailability and PK study

supporting the approval of the deferiprone (b) (4) tablet formulation was conducted in normal healthy subjects under NDA 212269. PMR 2944-1 and PMR 2944-2 issued on September 9, 2015 for the deferiprone 100mg/mL oral solution under NDA 208030 are the same PMRs issued with different PMR numbers for PMR 1828-1 and PMR 1828-2 issued on October 14, 2011 for the deferiprone 500mg tablet under NDA 21825. These same PMRs should be issued for the deferiprone (b) (4) tablet formulation. The sponsor should complete PMR 1828-1 and PMR 1828-2 issued on October 14, 2011 for the deferiprone 500mg tablet and PMR 2944-1 and PMR 2944-2 issued on September 9, 2015 for the deferiprone 100mg/mL oral solution. These remaining PMRs for deferiprone 500mg tablets in NDA 21825 and deferiprone 100mg/mL oral solution are described in section 8 Post-Market Experience in this review.

Reviewer comment: PMR 2944-1 and PMR 2944-2 issued on September 9, 2015 for the deferiprone 100mg/mL oral solution under NDA 208030 are the same PMRs issued (with different PMR numbers) as PMR 1828-1 and PMR 1828-2 issued on October 14, 2011 for the deferiprone 500mg tablet under NDA 21825. These same PMRs should be issued for the deferiprone (b) (4) formulation. PMRs or PMCs that were issued for the 100mg/mL and 80mg/mL deferiprone oral solution under NDA 208030 and the 500mg and 1000mg deferiprone IR tablet formulation under NDA 21825 that are considered fulfilled should also be considered fulfilled for the new deferiprone (b) (4) tablet formulation under NDA 212269.

2 Introduction and Regulatory Background

2.1 Product Information

Deferiprone (b) (4) an orally bioavailable iron chelator formulation. The sponsor cross-references NDA 21825 for the deferiprone IR 500mg tablet presentation to support the safety and efficacy of the deferiprone (b) (4) tablet formulation. Deferiprone 500mg tablets were granted accelerated approval on October 14, 2011 for the following indication.

- 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. Approval is based on a reduction in serum ferritin levels. There are no controlled trials demonstrating a direct treatment benefit, such as improvement in disease-related symptoms, functioning, or increased survival.

A deferiprone IR 500mg orally administered tablet formulation was granted accelerated approval October 14, 2011 under NDA 21825 and a deferiprone IR 1000mg orally administered tablet formulation was granted accelerated approval for marketing under NDA 21825 Supplement-004 on July 25, 2019. A deferiprone 100mg/mL oral solution

was granted accelerated approval for marketing under NDA 208030 on September 9, 2015 and a deferiprone 80mg/mL oral solution was granted an accelerated approval for marketing under NDA 208030 on April 20, 2018. All formulations of deferiprone have the same indication as the deferiprone IR 500mg tablet formulation.

2.2 Tables of Currently Available Treatments for Proposed Indications

The reviewer's table below shows the currently available iron chelator drugs and their indications.

Table 1. Currently Available Treatments for Proposed Indications

Generic Name	**Deferasirox**	**Deferasirox**	**Deferasirox**	**Deferiprone**	**Deferiprone**	**Deferoxamine**
Trade Name	Exjade	Jadenu	Jadenu Sprinkle	Ferriprox	Ferriprox	Desferal
NDA Number	21882	206910	207968	21825	208030	16267
Sponsor	Novartis Pharm. Corp.	Novartis Pharm. Corp.	Novartis Pharm. Corp.	Apopharma Inc.	Apopharma Inc.	Novartis Pharm. Corp.
Dosage Form	Tablet for Oral Suspension	Film Coated Tablet	Granules	500mg and 1000mg Tablet	100mg/mL and 80mg/mL Oral Solution	Powder for Injection Solution
Original Approval Date	November 2, 2005	March 30, 2015	May 18, 2017	October 14, 2011 (500mg tablet) and July 25, 2019 (1000mg tablet)	September 9, 2015 (100mg/mL solution) and April 20, 2018 (80mg/mL solution)	April 1, 1968
Indication (s)	Exjade is indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. This indication is based on reduction in serum ferritin and liver iron concentration	Same as Exjade (NDA 21882)	Same as Exjade (NDA 21882)	Ferriprox is indicated for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. Approval is	Same as Ferriprox (NDA 21825)	Desferal is indicated for the treatment of acute iron intoxication and of chronic iron overload due to transfusion-dependent anemias.

	(LIC). An improvement in survival or disease-related symptoms has not been established. Exjade is indicated for the treatment of chronic iron overload in patients 10 years of age and older with non-transfusion-dependent thalassemia (NTDT) syndromes and with a liver iron (Fe) concentration (LIC) of at least 5 mg Fe per gram of dry weight and a serum ferritin greater than 300 mcg/L. This indication is based on achievement of an LIC less than 5 mg Fe/g dw. An improvement in survival or disease-related symptoms has not been established.			based on a reduction in serum ferritin levels. There are no controlled trials demonstrating a direct treatment benefit, such as improvement in disease-related symptoms, functioning, or increased survival.		

Reviewer's table

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient for deferiprone (b) (4) tablet formulation is the same as that for deferiprone 500mg tablets, i.e., deferiprone. Deferiprone tablets were originally approved for marketing in the United States on October 14, 2011.

2.4 Important Safety Issues with Consideration to Related Drugs

The safety concerns for the deferiprone (b) (4) tablet formulation are the same as for deferiprone IR 500mg and 1000mg tablets and deferiprone 100mg/mL and 80mg/mL oral solution formulations. The deferiprone tablet product label contains a Boxed Warning that has the following wording.

Figure 1. Deferiprone Tablet Boxed Warning

WARNING: AGRANULOCYTOSIS/NEUTROPENIA

See full prescribing information for complete boxed warning.

- **Ferriprox can cause agranulocytosis that can lead to serious infections and death. Neutropenia may precede the development of agranulocytosis. (5.1)**
- **Measure the absolute neutrophil count (ANC) before starting Ferriprox and monitor (b) (4)**
- **Interrupt Ferriprox if infection develops and monitor the ANC more frequently. (5.1)**
- **Advise patients taking Ferriprox to report immediately any symptoms indicative of infection. (5.1)**

Deferiprone 500mg tablet label Boxed Warning (label approved February 20, 2020 under NDA 21825) (see website http://www.ferriprox.com/us/pdf/ferriprox_full_pi.pdf last accessed May 11, 2020)

In addition, the deferiprone IR 500mg and 1000mg tablet product label (label approved February 20, 2020 under NDA 21825) have the following Limitation of Use. The sponsor proposes the same Boxed Warning and Limitation of Use for deferiprone (b) (4) tablet as that of the deferiprone IR 500mg tablets. The same Boxed Warning and Limitation of Use is contained in the deferiprone 100mg/mL and 80mg/mL oral solution formulation approved February 20, 2020 under NDA 208030.

- Safety and effectiveness have not been established for the treatment of transfusional iron overload in patients with other chronic anemias.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

No new clinical efficacy and safety studies were submitted by the sponsor to support NDA 212269. This submission contains only chemistry, manufacturing and controls (CMC) and PK information for the deferiprone (b) (4) tablet formulation. The sponsor cross-references the safety and efficacy information for the immediate release deferiprone 500mg and 1000mg tablet formulations in NDA 21825.

Reviewer comment for section 2. The sponsor proposes the same indications and labeling information for deferiprone (b) (4) tablet formulation as for the immediate release deferiprone 500mg and 1000mg tablets and the deferiprone 100mg/mL and 80mg/mL oral solution formulations. A new dosing table is provided to calculate dose because of the different (b) (4) formulation.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No new clinical efficacy and safety studies were submitted by the sponsor to support NDA 212269. This submission contains only CMC information and PK studies for the deferiprone (b) (4) tablet formulation. The sponsor cross-references the safety and efficacy information for deferiprone in NDA 21825 and NDA 208030. No consult review was required from the Office of Scientific Investigations (OSI) from a clinical perspective.

3.2 Compliance with Good Clinical Practices

The sponsor cross-references the safety and efficacy information for deferiprone in NDA 21825. No new clinical efficacy and safety studies were submitted under NDA 212269.

3.3 Financial Disclosures

This submission contains only CMC and PK information for the deferiprone (b) (4) tablet formulation. No financial disclosures were submitted by the sponsor in NDA 212269 because no investigator received ≥ $25,000 payment.

Reviewer comment for section 3: No new clinical efficacy and safety studies were submitted by the sponsor to support NDA 212269. This submission contains only CMC and PK information for the deferiprone (b) (4) tablet formulation. The sponsor cross-references the safety and efficacy information for deferiprone in NDA 21825 and NDA 208030.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry, Manufacturing and Controls (CMC) review of NDA 212269 recommended the application for approval from a drug product and drug process

perspective with an assigned drug expiry of 18-months. See the overall Quality Assessment Review completed by Sherita McLemore (final signature date April 15, 2020) for more details.

4.3 Preclinical Pharmacology/Toxicology

Dr Pedro Delvalle (Preclinical Reviewer in the Division of Nonmalignant Hematology States in his filing review of NDA 21269 final signature date September 6, 2019 that the proposed nonclinical sections of the label are identical to the label for deferiprone 500 mg immediate release film-coated tables (NDA 021825) issued on July, 2019 and deferiprone 100 mg/mL oral solution (NDA 208030) issued on April 2018 and that no further review of nonclinical study reports is needed.

4.4 Clinical Pharmacology

The Clinical Pharmacology review of NDA 212269 is ongoing.

Briefly, to support this marketing application for the deferiprone (b) (4) under NDA 212269 the sponsor submitted data from study LA45-0116 titled, "Comparison of the Pharmacokinetics and Safety of Multiple Doses of Deferiprone Extended Release Tablets in Healthy Volunteers", that enrolled 36 normal healthy adult volunteers (age ≥18 to ≤ 55 years) male (n=30) or female (n=6) volunteers). The study was designed to compare the pharmacokinetics (PK) and safety of deferiprone DR to the marketed deferiprone immediate release tables. Subjects received deferiprone DR 1500mg administered orally every 12 hours for 6 days or deferiprone immediate release 1000 mg administered orally every 8 hours for 9 days. The sponsor states that the 90% confidence intervals of the ratios of the PK parameters AUC0-t, AUCinf and Cmax for deferiprone in serum were within the 0.80 to 1.25 acceptance range and that the deferiprone 1000mg DR formulation and the marketed deferiprone 500mg IR formulation are bioequivalent.

Also, the sponsor conducted study LA53-0116 titled, "Single-Dose Pharmacokinetic Study of Deferiprone Extended Release Tablets under Fasting and Fed Conditions versus Ferriprox Immediate Release Tablets under Fed Conditions in Healthy Volunteers", that enrolled 28 normal healthy adult volunteers (age ≥18 to ≤ 55 years) male (n=17) or female (n=11) volunteers). Study LA53-0116 is a single center, randomized (1:1:1:1), single dose, open-label, 4-period, 4-sequence, crossover study bioavailability and bioequivalence study. The study was designed to compare the pharmacokinetics (PK) and safety of a single dose of deferiprone DR to the marketed deferiprone IR formulation tables. Subjects received deferiprone DR 1000mg administered orally once or deferiprone immediate release two 500mg tablets (total 1000 mg) administered orally once. The sponsor states that the 90% confidence intervals of the ratios of the PK parameters AUC0-t, AUCinf and Cmax for deferiprone in

serum were within the 0.80 to 1.25 acceptance range and that the deferiprone 1000mg DR formulation and the marketed deferiprone 500mg IR formulation are bioequivalent.

Reviewer comment for Section 4. See Clinical Pharmacology Review (pending) for more detailed discussion and comment on the acceptability of the results of studies LA45-0116 and LA53-0116 to support the marketing application under NDA 212269 for the deferiprone (b) (4) and the proposed labeling changes. The key labeling changes in NDA 212269 from a clinical perspective for the deferiprone (b) (4) tablet formulation are described in more detail under section 9.3 Labeling Recommendations in this review.

5 Sources of Clinical Data

NDA 212269 cross-references the safety and efficacy data in NDA 21825 and NDA 208030. No new clinical efficacy and safety studies for deferiprone were submitted under NDA 212269. This reviewer also reviewed safety information in recent Periodic Adverse Drug Experience Reports (PADERs), and the Annual Reports submitted under NDA 208030 and NDA 21825. These are discussed in more detail under section 7 Review of Safety in this review.

6 Review of Clinical Efficacy

No new clinical information was submitted by the sponsor to support efficacy in NDA 212269 for the deferiprone (b) (4) tablet formulation. The sponsor cross-references the safety and efficacy information for deferiprone in NDA 21825 for the deferiprone IR 500mg tablet formulation.

7 Review of Safety

7.1.1 Methods

This reviewer reviewed safety information from study LA45-0116 and LA53-0116. Otherwise, no new clinical information was submitted by the sponsor to support NDA 212269. The sponsor cross-references the safety and efficacy information for deferiprone in NDA 21825 for the IR deferiprone 500mg tablet formulation. Also, safety information was reviewed from the following submissions submitted under NDA 21825 and NDA 208030.

- NDA 21825 Periodic Benefit-Risk Evaluation Report supporting document 339 letter date November 7, 2019 (received November 7, 2018) covering the reporting period from September 1, 2018

- NDA 21825 Annual Report supporting document 338 letter date October 30, 2019 (received October 30, 2019) covering the reporting period from September 1, 2018 to August 31, 2019.
- NDA 208030 Periodic Benefit-Risk Evaluation Report supporting document 120 letter date November 8, 2019 (received November 8, 2019) covering the reporting period from September 1, 2018 to August 31, 2019.
- NDA 208030 Annual Report supporting document 119 letter date October 30, 2019 (received October 30, 2019) covering the reporting period from September 1, 2018 to August 31, 2019.

7.1.2 Categorization of Adverse Events

- Study LA45-0116 submitted under NDA 212269.

In this study n=36 healthy subjects were enrolled. The mean age of subjects enrolled in the study was 37 years (standard deviation (SD) 10 years) and 30/36 (83%) were white. The mean body mass index (BMI was 26kg/m^2 (SD 3kg/m^2). Two subjects were discontinued from the study prematurely. The cases for the discontinued patients are summarized below.

- Subject (b) (6) (male age 46 years) received all 6 doses of Treatment A in Period 1 and 4 doses of Treatment B in Period 2, but withdrew consent (by the subject's own choice) from the study following the fourth dose of Treatment B. No adverse events (AEs) were reported for this subject.
- Subject (b) (6) (male age 49 years) received all 9 doses of Treatment B in Period 1 but was withdrawn from the study before dosing in Period 2 due to a high pre-dose creatinine value (165 µmol/L; reference range: 60–110 µmol/L) that was considered clinically significant and reported as an adverse event (AE), i.e., serum creatinine increased. The subjects baseline serum creatinine was reported to be within normal limits. At the scheduled post-study visit, the subject's serum creatinine value had returned to a normal level (97 µmol/L). No other concomitant medications or underlying disease conditions were reported for this subject.

The reviewer's table below summarizes the key safety data from study LA45-0116. There were no deaths, serious adverse events (SAEs) and all adverse events were reported to be mild or moderate severity. The most common AEs reported in ≥ 3 subjects was headache.

Table 2. Summary of Safety Results

	1000 DR mg tablet	**500mg tablet x 2 tablets**

Number of Subjects with SAEs	0	0
Deaths	0	0
Number of Subjects with Any AEs*	8	16
AEs reported ≥ 3 subjects: Headache (n=3 DR and n=3 500mg tab) **		

Reviewer's table derived from Completed Study Report (CSR) LA45-0116

- Study LA53-0116 submitted under NDA 212269

In this study n=28 healthy subjects were enrolled. The mean age of subjects enrolled in the study was 35 years (standard deviation (SD) 11 years) and 24/28 (86%) were white. The mean body mass index (BMI was 26kg/m^2 (SD 3kg/m^2). Six subjects were discontinued from the study prematurely. The cases for the discontinued patients are summarized below. The cases for the discontinued patients are summarized below.

- There were four subjects discontinued due to personal reasons (subjects (b) (6) (b) (6).
- Subject (b) (6) was discontinued due to cocaine use.
- Subject (b) (6) (male age 46 years) with no significant medical history received only one dose of study deferiprone DR study drug due to elevated serum lipase (110 U/L (reference range 13-60 U/L) after study drug administration.

There were no deaths, serious adverse events (SAEs) and all adverse events were reported to be mild or moderate severity. No AE was reported in ≥ 3 subjects.

- NDA 21825 Periodic Benefit-Risk Evaluation Report supporting document 339 letter date November 7, 2019 (received November 7, 2018) covering the reporting period from September 1, 2018 to August 31, 2019.

  The sponsor states that as of August 31, 2019 the IR deferiprone formulation 500 mg tablets, 1000 mg tablets (NDA 21825) and the deferiprone 100 mg/mL oral solution (NDA 208030) are authorized for marketing in 63, 37 and 52 countries, respectively. The deferiprone 80 mg/mL oral solution (NDA 208030) is approved for marketing only in the United States. The sponsor estimates there are 405.99 patient-years of exposure to all deferiprone products in the US during the reporting period. The deferiprone product labels under NDA 21825 and NDA 208030, both approved February 20, 2020 contain a Boxed Warning that states there is an increased risk of Agranulocytosis and neutropenia for patients that are treated with deferiprone (see section 2.4 Important Safety Issues with Consideration to Related Drugs for the Boxed Warning in this review above). During the reporting period there were two cases of agranulocytosis associated

with a report of death. These two cases are summarized below. The sponsor states that no labeling changes were made due to due to safety concerns during the reporting period. No new safety concerns were identified in this review.

- Case (b) (6) was a female age 71 years with a long history of pure red cell aplasia that required frequent red blood cell transfusions. The patient had a long history of hemochromatosis. Concomitant medications included acetylsalicylic acid, metoprolol, beclomethasone, tiotropium, sumatriptan. Prior iron chelation therapy was administered but the type of drug, dose and duration was not specified. The patient received deferiprone 100 mg/mL oral solution administered orally in divided in three daily doses (61 mg/kg/day, i.e., total 60 mL/day) but was reported to have a white blood cell (WBC) < 500/µL three months after starting deferiprone therapy. Deferiprone therapy was discontinued. Approximately one week later the patient developed neutropenic fever, admitted to the hospital and started on empiric antibiotic therapy. The patient died within one day of hospital admission. The patient's WBC at the time of death was reported to be 400/µL. No specific infections were identified.
- Case (b) (6) was a male (age not reported) who was prescribed iron chelation therapy, but the specific diagnosis was not reported. The dose and duration of deferiprone or any concomitant medications was not reported. The patient was reported to have a WBC < 500/µL.

- NDA 21825 Annual Report supporting document 338 letter date October 30, 2019 (received October 30, 2019) covering the reporting period from September 1, 2018 to August 31, 2019.

  The sponsor estimates there were 1,263,092 dose units and 900 dose units of the deferiprone IR 500mg tablet formulation and the deferiprone IR 1000mg tablet formulation distributed in the United States during the reporting period. The sponsor states that no labeling changes were made due to new or additional safety concerns for deferiprone during the reporting interval. No new or additional safety concerns for deferiprone were identified by this reviewer in this submission.

- NDA 208030 Periodic Benefit-Risk Evaluation Report supporting document 120 letter date November 8, 2019 (received November 8, 2019) covering the reporting period from September 1, 2018 to August 31, 2019 and NDA 208030 Annual Report supporting document 119 letter date October 30, 2019 (received October 30, 2019) covering the reporting period from September 1, 2018 to August 31, 2019.

NDA 208030 Periodic Benefit-Risk Evaluation Report supporting document 120 letter date November 8, 2019 (received November 8, 2019) covering the reporting period from September 1, 2018 to August 31, 2019 and NDA 208030 Annual Report supporting document 119 letter date October 30, 2019 (received October 30, 2019) covering the reporting period from September 1, 2018 to August 31, 2019 cross-reference the safety information submitted under NDA 21825 Periodic Benefit-Risk Evaluation Report supporting document 339 letter date November 7, 2019 (received November 7, 2018) and NDA 21825 Annual Report supporting document 338 letter date October 30, 2019 (received October 30, 2019). No new or additional safety concerns for deferiprone were identified by this reviewer.

Reviewer comment for Section 7. In study LA45-0116 there were no deaths, SAEs, and all adverse events were reported to be mild or moderate severity. The most common AEs reported in ≥ 3 subjects was headache. Also, no new safety concerns were identified by this reviewer in Periodic Benefit-Risk Evaluation Reports and Annual Reports covering the period from September 1, 2018 to August 31, 2019 submitted under NDA 21825 or NDA 208030. Review of safety information from these submissions does not raise new or additional safety concerns for the deferiprone (b) (4) tablet formulation compared to the marketed deferiprone IR tablet or oral solution formulations.

The safety labeling described in the deferiprone (b) (4) product label is the same as in the safety labeling for the proposed deferiprone IR tablet and oral solution product labels. It should be noted that the existing Postmarketing Requirements (PMRs) and Postmarketing commitments (PMCs) for studies of deferiprone tablets under NDA 21825 and NDA 208030 should be completed and studies may be modified to allow use of the deferiprone (b) (4) R or oral solution formulations.

8 Postmarket Experience

There are no clinical data in patients treated with deferiprone DR 1000mg tablet formulation. The sponsor cross-references the safety and efficacy information under NDA 21825 for the deferiprone IR 500mg and 1000mg tablet formulations to support the application for deferiprone (b) (4) tablet formulation under NDA 212269. Safety information was also reviewed from recent Annual Reports and Periodic Benefit-Risk Evaluation Reports submitted under NDA 21825 and NDA 208030 and these are discussed in more detail in section 7 Safety in this Review. This review did not identify any new or significant safety concerns for the deferiprone (b) (4) tablet formulation based on safety information for IR deferiprone 500mg tablets, 1000mg tablets or the 100mg/mL or 80mg/mL oral solution formulations, respectively.

Post Marketing Requirements (PMRs) were issued during the accelerated approval of deferiprone 500mg tablets under NDA 21825 on October 14, 2011 for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. The indication remains under Accelerated Approval status. The following list summarizes the ongoing PMRs for deferiprone tablets for oral suspension in the October 14, 2011 Accelerated Approval Letter. The reviewer comment below summarizes the current status of the PMRs issued in the October 14, 2011 Accelerated Approval Letter.

PMR 1828-1 Conduct a trial to determine the efficacy and safety of the use of deferiprone to treat iron overload in patients with sickle cell disease and transfusional hemosiderosis who have not been adequately treated with available chelating agents. Submit the protocol for review and concurrence prior to commencing. The trial will enroll a sufficient number of patients with sickle cell disease as described above, to provide sufficient evidence to assess the efficacy and safety in the sickle cell disease population described. The trial may enroll patients with other conditions who have developed transfusional iron overload. The trial will stratify for hematologic diagnosis for the randomization. The primary and secondary endpoints will measure changes in cardiac iron concentration and liver iron concentration.

Final Protocol Submission: February 2012
Trial Completion: January 2016
Final Report Submission: July 2016

PMR 1828-2 Establish a registry in order to perform an enhanced pharmacovigilance study of agranulocytosis. Submit a protocol to establish the registry and describe procedures for this enhanced pharmacovigilance prior to commencing the study. Procedures should include: Creation of marketing materials to inform and encourage clinicians to report agranulocytosis events to the sponsor; monitoring of all reported cases and active follow-up to characterize the demographics, recent prior blood counts, concomitant medications, co-existing conditions, duration of drug exposure prior to onset, outcomes of the event, and other factors that may help to characterize the agranulocytosis event. Sponsor also will institute procedures to obtain blood samples from patients with reported cases of agranulocytosis to store for later analysis of possible genetic underlying factors that may predict the risk of agranulocytosis. Submit interim reports annually describing the above results.

Final Protocol Submission: April 2012
Annual Interim Report #1: April 2013
Annual Interim Report #2: April 2014
Annual Interim Report #3: April 2015
Annual Interim Report #4: April 2016
Annual Interim Report #5: April 2017
Annual Interim Report #6: April 2018
Trial Completion: October 2018
Final Report Submission: April 2019

Reviewer comment for Section 8: There is no clinical data available in patients who were treated with the deferiprone DR 1000mg tablet formulation. No new safety concerns were identified by this reviewer upon review of recent Annual Reports and

Periodic Benefit-Risk Evaluation Reports covering the reporting period from September 1, 2018 to August 31, 2019 submitted under NDA 21825 and NDA 208030.

Briefly, the status of PMRs and PMCs issued in the Accelerated Approval Letter on October 14, 2011 is as follows: PMR1828-1 and PMR1828-2 are ongoing. The remaining PMRs/PMCs and their status are as follows (see Project Manager Review by Diane Leaman of NDA 21825 supporting document 236 final signature date November 26, 2014):

- *PMR1828-3 (completed and fulfilled June 3, 2014).*
- *PMR1828-4 (completed with final report submitted July 31, 2014).*
- *PMR1828-5 (completed with final report submitted April 15, 2014).*
- *PMC1828-6 (fulfilled April 20, 2012).*
- *PMC1828-7 (fulfilled April 5, 2013).*

PMCs and PMRs which were issued during the approval of the immediate release deferiprone 500mg tablets for oral suspension on October 14, 2011 under NDA 21825 should also apply to deferiprone (b) (4) tablet formulation under NDA 212269. However, those PMCs and PMRs that have been fulfilled for the immediate release formulations of deferiprone tablets for oral suspension under NDA 21825 and NDA 208030 can also be considered fulfilled for the deferiprone (b) (4) tablet formulation under NDA 212269 The sponsor should complete PMRs 1828-1 and 1828-2. Use of the deferiprone DR 1000mg tablet formulation should be allowed in the deferiprone PMR studies.

9 Appendices

9.1 Literature Review/References

A literature search did not reveal new or additional safety concerns for deferiprone IR tablets (500mg or 1000mg) or the oral solution (100mg/mL or 80mg/mL) formulations which supports the sponsor's application for the deferiprone (b) (4) tablet formulation under NDA 212269.

9.2 Advisory Committee Meeting

No Advisory Committee Meeting is planned.

9.3 Labeling Recommendations

The sponsor's proposed key labeling changes for deferiprone (b) (4) tablet formulation labeling changes under NDA 212269 are shown below (sponsor's proposed wording to be added is underlined, sponsor's wording to be deleted is in strikethrough format and FDA wording to be added is in double underlined format.)

- In NDA 212269 the sponsor proposes to incorporate a new name, i.e., Ferriprox (b) (4) new dosing information under the Highlights section and section 2 Dosage and Administration.
    - In the Highlights Section the sponsor proposes the following changes.
        - Tablets: 1,000 mg (b) (4) with functional scoring
        - Under section 2.1 Dosing subsection titled, "Starting Dose" the sponsor proposes to add the following table.

(b) (4)

- Under section 2.1 Dosing subsection titled, "Dose Adjustment" the sponsor proposes to add the following table.

(b) (4)

- Under section 6.1 Clinical Trial Experience the sponsor proposes to add the following wording to the second paragraph.

(b) (4)

Currently, there are no clinical data in patients with Ferriprox (b) (4) The following adverse reaction information represents the pooled data collected from 642 patients who participated in single arm or active-controlled clinical trials taking Ferriprox (deferiprone) tablets and oral solution.

- In section 12.3 Pharmacokinetics the sponsor proposes (b) (4)

(b) (4)

(b) (4)

Reviewer comment for section 9.3 Labeling Recommendations: I agree with the sponsor's key wording changes to incorporate new dosing information under the Highlights section and section 2 Dosage and Administration and incorporate new PK information for the deferiprone (b) (4) tablet formulation. (b) (4)

The Clinical Pharmacology reviewer should also comment on the acceptability of the sponsor's proposed wording changes for the deferiprone (b) (4) tablet formulation. The reviewer recommendations in section 9.3 Labeling Recommendations in this review should be forwarded to the sponsor.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANDREW DMYTRIJUK
05/15/2020 06:12:37 PM

KATHY M ROBIE SUH
05/15/2020 06:21:15 PM
Concur. Final wording of labeling will be developed in discussions with entire review team and negotiations with sponsor.