CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208030Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	New NDA
Application Number	208030
Priority or Standard	Standard
Submit Date	November 17, 2014
Received Date	November 17, 2014
PDUFA Goal Date	September 17, 2015
Division	Division of Hematology Products
Reviewer Name	Andrew Dmytrijuk M.D.
Review Completion Date	August 7, 2015
Established Name	Deferiprone
Trade Name	Ferriprox
Therapeutic Class	Iron Chelator
Applicant	ApoPharma 200 Barmac Dr. Toronto, Ontario M9L 2Z7 Canada
Formulation	100mg/mL Oral Solution
Dosing Regimen	25 mg/kg Orally Three Times Per Day
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

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 208030 supporting document 1 letter date November 17, 2014 for Ferriprox® (deferiprone 100mg/mL oral solution formulation) is for a new formulation of deferiprone. From a clinical perspective NDA 208030 should be granted accelerated approval for the following indication which is the same indication as the currently approved product Ferriprox® (NDA 21825; deferiprone tablets for oral use, i.e., deferiprone tablets) which was granted accelerated approval on October 14, 2011. NDA 208030 is a 505b(2) application that cross-references the safety and efficacy data in NDA 21825.

- 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

The deferiprone product label along with my labeling 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 oral solution formulation from a clinical perspective is based on the safety and efficacy of the marketed deferiprone tablet (Ferriprox®) product (NDA 21825) and the available deferiprone supportive safety information from the bioavailability/bioequivalence study LA21-BE. Support for the approval of this application for deferiprone comes from one comparative bioavailability and bioequivalence study, i.e., LA21-BE titled, “Randomized, Open Label, Comparative, Two-Way Crossover Bioavailability Study Of Deferiprone Oral Solution And Ferriprox® (Deferiprone) Tablets Under Fasting Conditions” which were conducted in a total of 42 normal healthy adult volunteers. In study LA21-BE the rate (Cmax) and the extent (AUC) of drug absorption of the deferiprone oral solution formulation and deferiprone tablet formulation were within 80-125% of the acceptance range for the bioavailability and bioequivalence. From a clinical perspective the results of these studies demonstrated that the deferiprone oral solution and deferiprone tablets had similar bioavailability and bioequivalence. The Clinical Pharmacology reviewer should also comment on the acceptability of the results of study LA21-BE to support approval of the drug. A summary of the key clinical pharmacology results from the clinical perspective is shown in section 4.4 Clinical Pharmacology in this review.

No new or additional safety concerns were identified in this Clinical Review of NDA 208030 for the deferiprone oral solution formulation or in the review of the deferiprone tablet NDA 21825 Annual Report supporting document 236 letter date November 3, 2014 (covering the reporting period from September 1, 2013 to August 31, 2014) or NDA 21825 Periodic Adverse Drug Experience Report (PADER) supporting document 231 letter date September 29, 2014 (covering the reporting period from June 1, 2014 to August 31, 2014) completed by Dr. Andrew Dmytrijuk final signature date August 7, 2015. Overall, the risk benefit assessment favors the approval of the deferiprone oral solution formulation for the same indications as that of the deferiprone tablet formulation. Deferiprone oral solution offers patients with iron overload a potentially more palatable treatment option compared to the approved deferiprone tablet formulation.

The sponsor is claiming exemption from the Pediatric Research Equity Act (PREA) requirements for deferiprone 100 mg/mL oral solution (NDA 208030). The basis for the sponsor's PREA exemption claim is an 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. Deferiprone oral solution may provide an alternative treatment formulation for pediatric patients who can't swallow tablets or can't tolerate other formulations of iron chelators, e.g., deferoxamine dispersible tablets.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No post-marketing risk evaluation and mitigation strategy (REMS) is recommended for the deferiprone oral solution formulation.

1.4 Recommendations for Postmarket Requirements and Commitments

There is no clinical data available in patients who were treated with deferiprone oral solution formulation. Bioavailability studies and pharmacokinetics (PK) studies supporting the approval of deferiprone oral solution formulation were conducted in normal healthy subjects. Post-Marketing Commitments (PMCs) and Post-Marketing Requirements (PMRs) which were issued during the accelerated approval of deferiprone tablets on October 14, 2011 should also apply to deferiprone oral solution. However, those PMCs and PMRs that have been fulfilled for deferiprone tablets can also be considered fulfilled for deferiprone oral solution. The sponsor should complete PMR 1828-1 and PMR 1828-2 issued on October 14, 2011. These remaining PMRs for deferiprone tablets in NDA 21825 are described in section 8 Post-Market Experience in this review.

2 Introduction and Regulatory Background

2.1 Product Information

Deferiprone oral solution is an orally bioavailable iron chelator formulation. The sponsor cross-references NDA 21825 for deferiprone tablets to support the safety and efficacy of the deferiprone oral solution formulation. Deferiprone 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.

In NDA 208030 supporting document 1 letter date November 17, 2014 the sponsor proposes that deferiprone oral solution is indicated for the same indication as deferiprone tablets.

2.2 Tables of Currently Available Treatments for Proposed Indications

The reviewer's table below shows the currently available treatments and their indications.

Table 1. Currently Available Treatments for Proposed Indications

Generic Name	**Deferasirox**	**Deferasirox**	**Deferiprone**	**Deferoxamine**
Trade Name	Exjade	Jadenu	Ferriprox	Desferal
NDA Number	21882	206910	21825	16267
Sponsor	Novartis Pharmaceuticals Corp.	Novartis Pharmaceuticals Corp.	ApoPharma Inc.	Novartis Pharmaceuticals Corp.
Dosage Form	Tablets	Film Coated Tablet	Film Coated Tablet	Powder For Injection Solution
Original Approval Date	November 2, 2005	March 30, 2015	October 14, 2011	April 1, 1968
Indication(s)	Exjade is indicated for the treatment of chronic iron overload due to	Same as for Exjade	Ferriprox is indicated for the treatment of patients with	Desferal is indicated for the treatment of acute iron intoxication and

	blood transfusions in patients 2 years of age and older. This indication is based on reduction in serum ferritin and liver iron concentration (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		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.	of chronic iron overload due to transfusion-dependent anemias.

	5 mg Fe/g dw. An improvement in survival or disease-related symptoms has not been established.			

Reviewer's table

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient for deferiprone oral solution is the same as that for deferiprone 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 deferiprone oral solution are the same as for deferiprone tablets. 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 the ANC weekly on therapy. (5.1)**
- **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 tablet label Boxed Warning (see website http://www.ferriprox.com/us/pdf/ferriprox_full_pi.pdf last accessed August 7, 2015)

In addition, the deferiprone tablet product label has the following Limitation of Use. The sponsor proposes the same Boxed Warning and Limitation of Use for deferiprone oral solution as that of deferiprone tablets.

- 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

A Pre-NDA Meeting was held with the sponsor for deferiprone oral solution on July 11, 2014. The Filing Meeting for NDA 208030 was held on January 13, 2015.

Reviewer comment for section 2. The sponsor proposes the same indications and labeling information for deferiprone oral solution as for deferiprone tablets.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

On January 23, 2015 a Request for Biopharmaceutical Inspections was sent to the Office of Study Integrity and Surveillance (OSIS). The inspection request was for the (b) (4) Study LA21-BE. Dr. John Kadavil (Pharmacologist from the Office of Study Integrity and Surveillance) states in his review final signature date (b) (4) The review by Dr. Kadavil states that the Division of New Drug Bioequivalence Evaluation (DNDBE) recommends accepting the (b) (4) data for NDA 208030, Study LA21-BE without an on-site inspection of the (b) (4) The review by Dr. Kadavil provides the rationale for this recommendation and explains why DNDBE declined to inspect the (b) (4) site which is summarized as follows.

- (b)(4)
- Study LA21-BE was submitted to NDA 021825 in March 2007, for the evaluation of the tablet formulation. Dr. Joseph Grillo, Office of Clinical Pharmacology, reviewed study LA21-BE in September 20, 2011, to support pediatric labeling. The review by Dr. Grillo found study LA21-BE acceptable. A re-inspection of the same study at this time would not be useful.
- (b) (4) ithout finding significant objectionable conditions or repeats of the objectionable conditions documented during previous inspections.
- OSIS suspects that electronic records for Study LA21-BE are in a format unique to specialized chromatographic software. However, because (b) (4) an on-site inspection of source electronic records is not possible. Although, the

Division of Hematology Products provided a revised inspection request indicating that study records are stored at [redacted] (b) (4) (based on applicant information), audit of these records would provide limited information in the absence of full access to electronic source records.

3.2 Compliance with Good Clinical Practices

All studies were conducted in compliance with the current revision of the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practices and local regulatory requirements. The protocol was approved by an Institutional Review Board prior to initiation and implementation of the studies and changes. Written informed consent provided by the subject was required in order to enroll into the studies supporting NDA 208030. The informed consent, protocol violations and site-specific issues were reviewed and found to be within accepted standards.

3.3 Financial Disclosures

No investigators participating in the trials supporting NDA 208030 reported a financial interest. The sponsor states that no clinical investigators are full or part-time employees of ApoPharma.

Reviewer comment for section 3: The recommendation by the DNDBE that NDA 208030 Study LA21-BE [redacted] (b)(4) data is acceptable without an on-site inspection of the [redacted] (b)(4) site is reasonable. I agree with Dr. Kadavil's rationale for this recommendation. All studies were conducted in compliance with the current revision of the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practices and local regulatory requirements. No investigators in the studies supporting NDA 208030 reported an equity interest.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The following Chemistry, Manufacturing and Controls (CMC) comment was sent to the sponsor in the Filing Communication – Filing Review Issues Identified letter which was sent to the sponsor on January 30, 2015. The CMC review of NDA 208030 supporting document 1 is ongoing.

- The method suitability testing supporting the final product for microbial limits testing per USP <61> and <62> could not be located in the submission. Provide either the location in the submission or provide the reports.

4.2 Clinical Microbiology

The following Clinical Microbiology comment was sent to the sponsor in the Filing Communication – Filing Review Issues Identified letter which was sent to the sponsor on January 30, 2015. The Clinical Microbiology review of NDA 208030 supporting document 1 is ongoing.

- Provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganism *Burkholderia cepacia*. We recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria. Your test method should be validated and a discussion of those methods should be provided.

4.3 Preclinical Pharmacology/Toxicology

In her review of NDA 208030 supporting document 1 Dr. Brenda Gehrke (Division of Hematology Oncology Toxicology Reviewer, final signature date June 2, 2015) states that the nonclinical studies supporting the approval of deferiprone were reviewed under NDA 21825 by Dr. David Bailey (Reviews dated: June 27, 2007, August 4, 2008, and September 22, 2009). Prior to the approval of deferiprone in October 2011, a review by Dr. Haleh Saber (Dated October 8, 2011) contained a summary of the nonclinical studies and the recommended labeling. At the time of approval there were no nonclinical issues to preclude approval of Ferriprox (deferiprone) for the proposed indication considering the life-threatening nature of the disease and lack of adequate chelation therapy. Dr. Gehrke states that nonclinical studies reviewed under NDA 21825 to support the initial approval of Ferriprox (deferiprone) provide sufficient information to support the use of deferiprone 100 mg/mL oral solution for the proposed indication.

4.4 Clinical Pharmacology

Clinical Pharmacology review of NDA 208030 supporting document 1 is ongoing. Support for the approval of this application for deferiprone comes from one comparative bioavailability and bioequivalence study LA21-BE titled, “Randomized, Open Label, Comparative, Two-Way Crossover Bioavailability Study Of Deferiprone Oral Solution And Ferriprox® (Deferiprone) Tablets Under Fasting Conditions” which were conducted in a total of 42 normal healthy adult volunteers. Additional details regarding these studies can be found in section 5.1 Table of Studies in this review. A summary of Study

LA21-BE can be found below in section 5.3 Discussion of Individual Studies. Key efficacy results (from a clinical perspective) and safety results from study LA21-BE are summarized in section 6 Review of Clinical Efficacy and section 7 Review of Safety, respectively, in this review.

Reviewer comment for Section 4. CMC, Clinical Microbiology and Clinical Pharmacology reviews of NDA 208030 are ongoing. These reviewers should comment on the approvability of NDA 208030. No CMC, Clinical Microbiology or Clinical Pharmacology concerns for NDA 208030 have been identified from a Clinical perspective.

5 Sources of Clinical Data

5.1 Table of Studies

The table below shows the study included to support NDA application 208030 for deferiprone oral solution.

Table 2. Table of Studies

Type of study	Study identifier/ Study Title	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s), Dosage regimen; Route of administration	No. of subjects	Health subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
Comparative BA and BE	LA21-BE: Randomized, open label, comparative, two-way crossover bioavailability study of deferiprone oral solution and Ferriprox® (deferiprone) tablets under fasting conditions.	Module 5.3.1.2	To determine the relative bioavailability of deferiprone oral solution and deferiprone tablets in healthy subjects under fasting conditions	Randomized, open label, comparative, two-way crossover	Test Product: Ferriprox® (deferiprone) 500 mg film-coated tablets; 1500 mg of deferiprone, single dose, oral OR deferiprone solution 100 mg/mL; 1500 mg of deferiprone solution, single dose; Oral	42 dosed 41 completed both periods	Healthy subjects	Single dose	Completed; Full

Sponsor's table NDA 208030 section 5.2 Tabular list of Clinical Studies

5.2 Review Strategy

NDA 208030 is a 505b(2) application that cross-references the safety and efficacy data of the marketed deferiprone product in NDA 21825. Clinical review of the study shown in section 5.1 Tables of Studies is in this review. This Clinical Review for deferiprone oral solution (NDA 208030) focuses on the available safety information from study LA21-BE. Note that the sponsor cross references the safety and efficacy of deferiprone tablets in NDA 21825 to support the current application for deferiprone oral solution

NDA 208030. The Cross Discipline Team Leader Review by Dr. Kathy Robie-Suh (Clinical Team Leader Division of Hematology Products final signature date September 29, 2011) summarizes the relevant reviews of deferiprone tablets for the indications listed in section 1.1 Recommendation on Regulatory Action. Deferiprone tablets (ND A21825) were granted accelerated approval on October 14, 2011.

5.3 Discussion of Individual Studies

Studies supporting the deferiprone oral solution application NDA 208030 are described in section 5.1 Table of Studies in this review, i.e., study LA21-BE. Briefly, study LA21-BE was an open label, single-dose, randomized, two-way crossover comparative bioavailability study. A total of 42 subjects (29 male and 13 female) adult (age 18-55 years) were enrolled in the study. A single oral dose of 1500 mg of deferiprone was administered in the form of 15 mL of deferiprone oral solution 100 mg/mL or 1500 mg of deferiprone administered in the form of 3 deferiprone 500 mg film-coated tablets under fasting conditions. The two periods were separated by a seven-day washout period. All samples were taken at the nominal time with deviation windows shown in the sponsor's table below.

Table 3. Sample Times

Nominal Time	Reporting Standard
0.0-0.5 h	± 30 seconds
>0.5-2.0 h	± 60 seconds
>2.0-8.0 h	± 2 minutes
>8.0-10 h	± 5 minutes

Sponsor's table Study Report LA21-BE page 40

The 90% confidence intervals of the ratio of least-squares means for AUC0-t, AUC0-∞ and Cmax of the test formulation to reference formulation were to be within the 80% to 125% range. Safety was assessed by monitoring adverse events throughout the study. Key efficacy results (from a clinical perspective) and safety results from study LA21-BE are summarized in section 6 Review of Clinical Efficacy and section 7 Review of Safety, respectively, in this review.

Reviewer comment for section 5. From a clinical perspective the study supporting the Jadenu application NDA 206910, i.e., LA21-BE, appears to be reasonably well designed to support a bioavailability and bioequivalence comparison of deferiprone oral solution to the reference product deferiprone tablets. The Clinical Pharmacology review of NDA 208030 is ongoing. The safety assessment considerations for these studies are acceptable. Routine physical examinations, evaluations for laboratory adverse reactions and clinical adverse reactions such as electrocardiographic (ECG) changes were performed.

6 Review of Clinical Efficacy

In NDA 208030 supporting document 1 letter date November 17, 2014 the sponsor proposes that deferiprone oral solution is indicated for the same indications as deferiprone tablets, i.e.,

- 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.

The approval of this indication for deferiprone oral solution is supported by the efficacy results from study LA21-BE which is described in section 5.3 Discussion of Individual Studies in this review. The sponsor's table below summarizes the key pharmacology results of study LA21-BE from a clinical perspective. The sponsor's table shows that pharmacokinetic parameters are similar between the deferiprone oral solution and the deferiprone tablets.

Table 4. Pharmacokinetic Results Study LA21-BE

Parameter	Solution (A)	Tablet (B)
AUC_{0-t} * (µg·h/mL)	48.2 (22.6) n = 41	48.0 (23.3) n = 41
AUC_{inf} * (µg·h/mL)	49.3 (22.9) n = 41	49.2 (23.4) n = 41
C_{max} (µg/mL)*	18.9 (30.8) n = 41	19.2 (36.2) n = 41
t_{max} (h)	0.805 (66.6)	0.911 (50.5)
kel (1/h)	0.412 (13.8)	0.410 (14.3)
Half-life (h)	1.71 (13.4)	1.72 (13.3)

n: number of observations

*Geometric means are presented for these parameters.

Sponsor's table Study Report LA21-BE page 43

The pharmacokinetic statistical results for deferiprone oral solution compared to deferiprone tablets are shown in the sponsor's table below. The results demonstrate that deferiprone oral solution compared to deferiprone tablets was within 80-125% of the acceptance range for bioavailability and bioequivalence.

Table 5. Pharmacokinetic Statistical Results Study LA21-BE

Ratios of LSM % (90% Confidence Intervals)

Parameter	Deferiprone Solution (A) vs Tablet (B)
AUC_{0-t}	100.6% (98.0% – 103.4%)
AUC_{inf}	100.4% (97.7% – 103.1%)
C_{max}	98.3% (88.9% – 108.7%)

Sponsor's table Study Report LA21-BE page 43

Reviewer comment for section 6. The sponsor cross references the efficacy and safety of deferiprone tablets in NDA 21825 to support the current application for deferiprone oral solution NDA 208030. From a clinical perspective the bioavailability and bioequivalence appears to be similar for deferiprone oral solution compared to deferiprone tablets as demonstrated in the comparative bioavailability/bioequivalence study LA21-BE submitted in NDA 208030 supporting document 1 letter date November 17, 2014. The Clinical Pharmacology review of NDA 208030 is ongoing. The Clinical Pharmacology reviewer should comment on the acceptability of the results of study LA21-BE to support approval of the deferiprone oral solution formulation.

7 Review of Safety

7.1.1 Methods

Study LA21-BE discussed in section 5 Sources of Clinical Data was reviewed to evaluate the safety of deferiprone oral solution in the application NDA 208030.

7.1.2 Categorization of Adverse Events

Adverse events (AEs) were characterized according to Medical Dictionary for Regulatory Activities (MedDRA) v. 8.0 terminology.

7.2 Adequacy of Safety Assessments

Overall 42 adult healthy male (n=29) and female (n=13) subjects ranging in age from 18-55 years were enrolled in study LA21-BE. One male subject (#42) age 29 years received 3 x 500 mg deferiprone tablets in Period 1 and experienced no adverse events (AEs). In Period 2 this subject complained of dizziness 3 minutes after taking the 1500mg deferiprone oral solution. At 4 minutes postdose the subject vomited nearly all the medication. The subject was then withdrawn from the study. All other subjects completed the study.

7.3 Major Safety Results

7.3.1 Deaths

No subjects died in study LA21-BE.

7.3.2 Nonfatal Serious Adverse Events

No serious adverse events (SAEs) were reported in study LA21-BE. One subject (#42 described in section 7.2 Adequacy of Safety Assessments) was withdrawn from the study due to vomiting.

7.3.3 Dropouts and/or Discontinuations

There was one subject (#42 described in section 7.2 Adequacy of Safety Assessments) who was withdrawn from the study due to vomiting.

7.3.4 Significant Adverse Events

The deferiprone tablet product label contains a Boxed Warning that states deferiprone may increase the risk for agranulocytosis. No AE of this type was reported in study LA21-BE.

7.4.1 Supportive Safety Results

The most common adverse events reported in ≥ 4 (10%) of subjects in study LA21-BE overall are shown in the sponsor's table below. The table shows that fatigue, feeling cold and headache were the most common AEs reported for deferiprone oral solution or tablets. All AEs in study LA21-BE were reported to of mild to moderate severity.

Table 6. Most Common Adverse Events (AEs) in Study LA21-BE

	Number of subjects (%) with adverse event		
Adverse Event	Deferiprone solution	Deferiprone tablet	Total
Fatigue	6 (14%)	3 (7%)	8 (19%)
Feeling cold	2 (5%)	3 (7%)	5 (12%)
Headache	2 (5%)	4 (10%)	5 (12%)

Note: A subject may have had reported the same adverse event after dosing with deferiprone solution and deferiprone tablets, the subject is counted only once in the Total category.

Sponsor's table Study Report LA21-BE page 45

7.4.2 Laboratory Findings

Clinical laboratories that were evaluated with each period included hematologic, hepatic and renal function tests. No significant laboratory changes were reported for subjects enrolled in study LA21-BE.

7.4.3 Vital Signs and Electrocardiograms (ECGs)

No significant changes in vital signs or ECGs were reported during any treatment period in study LA21-BE.

7.4.4 Immunogenicity

No immunogenicity concerns are expected with the small molecule deferiprone. No immunogenicity assays were performed for deferiprone oral solution.

7.5 Additional Safety Evaluations

No additional safety evaluations were reported by the sponsor for deferiprone oral solution.

The sponsor is claiming exemption from the requirements governed by the Pediatric Research Equity Act (PREA) for deferiprone 100 mg/mL oral solution (NDA 208030). The proposed therapeutic indication for deferiprone oral solution is identical to the approved indication for the currently marketed deferiprone tablets (NDA 21825). The basis for the sponsor's PREA exemption claim is an 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.

Reviewer comment for Section 7. Review of safety in study LA21-BE supporting the deferiprone oral solution application NDA 208030 does not raise new or additional safety concerns for deferiprone oral solution formulation compared to the marketed deferiprone tablet product formulation. This study was conducted in normal healthy male and female subjects. The safety labeling described in the deferiprone tablet product label is the same the safety labeling for the proposed deferiprone oral solution product label. It should be noted that the existing Postmarketing Requirements (PMRs) and Postmarketing commitments (PMCs) for pediatric studies of deferiprone tablets under NDA 21825 should be completed and studies may be modified to allow use of the deferiprone oral solution formulation.

The sponsor is claiming exemption from the Pediatric Research Equity Act (PREA) requirements for deferiprone 100 mg/mL oral solution (NDA 208030). The proposed therapeutic indication for deferiprone oral solution is identical to the approved indication for the currently marketed deferiprone tablets (NDA 21825). The basis for the sponsor's PREA exemption claim is an existing Orphan Designation granted on December 12, 2001 to the active ingredient deferiprone for treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. Deferiprone oral solution may provide an alternative treatment formulation for pediatric patients who can't swallow tablets or can't tolerate other formulations of iron chelators, e.g., deferoxamine dispersible tablets.

8 Postmarket Experience

There are no clinical data in patients treated with deferiprone oral solution. Clinical review of the deferiprone tablets NDA 21825 Annual Report supporting document 236 letter date November 3, 2014 (covering the reporting period from September 1, 2013 to August 31, 2014) or NDA 21825 Periodic Adverse Drug Experience Report (PADER) supporting document 231 letter date September 29, 2014 (covering the reporting period from June 1, 2014 to August 31, 2014) completed by Dr. Andrew Dmytrijuk final signature date August 7, 2015 did not identify any new or significant safety concerns. The Annual Report letter date November 3, 2014 states that 892,077 dosage units of deferiprone tablets for oral suspension were distributed In the US.

Post Marketing Requirements (PMRs) were issued during the accelerated approval of deferiprone tablets for oral suspension for the indication treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate on October 14, 2011. 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 deferiprone oral solution. The clinical review of the deferiprone tablets NDA 21825 Annual Report supporting document 236 letter date November 3, 2014 and NDA 21825 Periodic Adverse Drug Experience Report (PADER) supporting document 231 letter date September 29, 2014 completed by Dr. Andrew Dmytrijuk final signature date August 7, 2015 concludes that no new safety issues were identified during the review of these reports.

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 deferiprone tablets for oral suspension on October 14, 2011 should also apply to deferiprone oral solution. However, those PMCs and PMRs that have been fulfilled for deferiprone tablets for oral suspension can also be considered fulfilled for deferiprone oral solution. The sponsor should complete PMRs 1828-1 and 1828-2. Use of the deferiprone oral solution formulation should be allowed in the deferiprone PMR studies.

9 Appendices

9.1 Literature Review/References

No new or additional safety concerns were identified in the review of the deferiprone tablet NDA 21825 Annual Report supporting document 236 letter date November 3, 2014 (covering the reporting period from September 1, 2013 to August 31, 2014) or NDA 21825 Periodic Adverse Drug Experience Report (PADER) supporting document 231 letter date September 29, 2014 (covering the reporting period from June 1, 2014 to August 31, 2014) completed by Dr. Andrew Dmytrijuk final signature date August 7, 2015.

9.2 Advisory Committee Meeting

No Advisory Committee Meeting is planned.

9.3 Labeling Recommendations

The deferiprone oral solution label attached below incorporates the labeling recommendations from FDA review divisions. Key clinical labeling recommendations for the (b) (4) product label are as follows (proposed wording additions in underline and highlighted format and my proposed wording deletions in strikethrough and highlighted format).

- Section 8 Use in Specific Populations § 8.7 Hepatic Impairment: (b) (4)

Reviewer comment: The wording above, i.e (b) (4) *should be deleted because no specific instructions for patients with severe hepatic impairment is included in the product label.*

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

---

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

/s/

ANDREW DMYTRIJUK
08/26/2015

KATHY M ROBIE SUH
08/26/2015
Final wording of labeling is being developed through discussions with the entire review team and negotiation with the sponsor.