Clinical Review for NDA 20-955/SE5-006

Executive Summary

I. Recommendations

A. Recommendation on Approvability

From a clinical perspective, Ferrlecit is approvable for the treatment of iron deficiency anemia in pediatric patients 6 to 15 years of age who are undergoing chronic hemodialysis and who are receiving supplemental epoetin therapy. The recommended dose regimen is 0.12 mL/kg (1.5 mg/kg of elemental iron) by intravenous infusion during eight consecutive hemodialysis sessions.

One multicenter, randomized, double-blind, dose response study was conducted in 67 pediatric patients 6 to 15 years of age undergoing chronic hemodialysis who were receiving epoetin supplemental therapy. The study showed a significant increase in hemoglobin from baseline with Ferrlecit 1.5 mg/kg dosing (0.8 g/dL) and with Ferrlecit 3.0 mg/kg dosing regimen (0.9 g/dL) at 2 weeks after treatment. The safety results showed that more patients in the 3.0 mg/kg dosing group experienced hypotension, tachycardia, fever, headache, abdominal pain, nausea, pharyngitis, and rhinitis than patients in the 1.5 mg/kg dosing group. Based on the benefit/risk analysis, a Ferrlecit dose of 1.5 mg/kg should be recommended for the pediatric patients 6 to 15 years of age.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

No new recommendations on Phase 4 study. Risk management includes that the sponsor should revise labeling as recommended (See appendix).

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Product name: Ferrlecit

Drug class: Intravenous iron products

In response to the Written Request, one pediatric study (FR01006) was conducted in 67 patients with iron deficiency anemia who were undergoing chronic hemodialysis and who were receiving supplemental epoetin therapy to support the indication for treatment of iron deficiency anemia in pediatric patients 6-15 years of age who were undergoing chronic hemodialysis and were receiving supplemental epoetin therapy. The proposed Ferrlecit dose regimen for pediatric patients 6 to 15 years of age is 0.12 mL/kg (1.5 mg/kg of elemental iron) by intravenous infusion at eight sequential dialysis sessions.

B. Efficacy

One pediatric study (FR01006) was submitted to support the indication of treatment of iron deficiency anemia in pediatric patients 6-15 years of age undergoing chronic hemodialysis who are receiving supplemental epoetin therapy.

Study FR01006 was a multicenter, randomized, double-blind, parallel groups, dose-response study of Ferrlecit in pediatric patients who underwent chronic hemodialysis and who were receiving supplemental epoetin therapy. Two doses of Ferrlecit (1.5 mg/kg and 3.0 mg/kg of elemental iron) IV infusion were studied and were administered during eight consecutive hemodialysis sessions over an approximately 22 day period. Patients 2 to 15 years of age were eligible for the study. Patients with TSAT<20% and/or serum ferritin <100 ng/mL at baseline and receiving a stable EPO dosing regimen were enrolled in the study. The mean hemoglobin at baseline was 9.4 g/dL in study patients. The primary efficacy endpoint was the change in hemoglobin from baseline to two weeks following the last Ferrlecit administration.

A total of 88 patients were screened, 67 were enrolled and randomized at 21 sites from 5 countries. A total of 66 patients received study drug (32 in the 1.5 mg/kg group and 34 in the 3.0 mg/kg group) and 57 (85%) patients (25 in the 1.5 mg/kg group and 32 in the 3.0 mg/kg group) were evaluated for primary efficacy endpoint. Among the 66 patients who were treated in the study, patients ranged in age from 6 to 15 years (mean age of 12 years) and no children were under 6 years of age due to scarcity of patients in this age range. There were 38 (58%) patients with age 6-12 years and 28 (42%) patients with age 12-15 years. There were similar numbers of male (34, 52%) and female (32, 48%) patients. Majority of patients were Caucasian (Caucasian 71%, Asian 18%, Hispanic 6%, Black 2% and others 3%).

The primary efficacy results showed that the mean increase from baseline in hemoglobin at 2 weeks after the last Ferrlecit administration was 0.8 g/dL in the 1.5 mg/kg group and 0.9g/dL in the 3.0 mg/kg group based on completer patient population (57 patients). The hemoglobin values at 2 weeks after the last Ferrlecit administration were significantly increased in both 1.5 mg/kg and 3.0 mg/kg dosing groups as compared to baseline ($p=0.0033$ and <0.0001, respectively). The mean increase in hemoglobin was maintained at 4 weeks after the treatment in both dosing groups (0.9 g/dL in the 1.5 mg/kg group and 1.0g/dL in the 3.0 mg/kg group). There was no significant difference in mean changes from baseline in hemoglobin at 2 weeks after treatment between the two dosing groups ($p=0.75$). There were similar results based on all treated patient population (66 patients).

Results of the secondary efficacy analyses were consistent with those of the primary efficacy analysis. The response rates (increase in hemoglobin ≥1 g/dL) at 2 weeks after treatment were similar between the two dosing groups (40% in the 1.5 mg/kg group and 50% in the 3.0 mg/kg group, $p=0.45$). Hematocrit increased 2.6% at 2 weeks after treatment from baseline in the 1.5 mg/kg group [$p=0.0031$] and 3.0% in the 3.0 mg/kg group [$p<0.0001$]. There were significant increases from baseline in TSAT (5.5% in the 1.5 mg/kg group [$p<0.01$] and 10.5% in the 3.0 mg/kg group [$p<0.0001$]), serum ferritin (192 ng/mL in the 1.5 mg/kg group [$p<0.0001$]and 314 ng/mL in the 3.0 mg/kg group [$p<0.0001$]) and CHr (1.3 pg in the 1.5 mg/kg group [$p<0.01$] and 1.2 pg in the 3.0 mg/kg group [$p<0.05$]) at 2 weeks after treatment in both dosing groups. HCRBC was not changed at 2 weeks after treatment from baseline in either dosing group. There was no statistically significant difference for any secondary endpoint between the two dosing groups ($p>0.05$). The results for the secondary efficacy endpoints based on all treated population were similar to those for the completer patient population.

In conclusion, Study FR01006 showed significant increases in hemoglobin at 2 weeks after treatment from baseline in both dosing groups and the effect was maintained at 4 weeks after treatment. There was no significant difference in efficacy between the 1.5 mg/kg and 3.0 mg/kg Ferrlecit dosing regimens.

C. Safety

One study (Study FR01006) was conducted in pediatric patients with iron deficiency anemia who were undergoing chronic hemodialysis and who were receiving supplemental epoetin therapy. A total of 67 patients 6 to 15 years of age were enrolled and 66 patients were treated in the study. Among the 66 patients, 60 (91%) patients received all eight infusions (28 in the 1.5 mg/kg group and 32 in the 3.0 mg/kg group), 3 (4.5%) patients received 7 infusions (2 in the 1.5 mg/kg group and 1 in the 3.0 mg/kg group), and 1 (1.5%) patient each received 5 (in the 3.0 mg/kg group) , 2 (in the 1.5 mg/kg group), and 1 (in the 1.5 mg/kg group) infusion, respectively.

In the study, 81.8% (54/66) of patients reported adverse events. The number of patients reporting adverse events (AEs) was similar between the 1.5 mg/kg treatment group (26 patients, 81.3%, 110 AEs) and the 3.0 mg/ kg treatment group (28 patients, 82.4%, 151

AEs). The overall most common AEs occurring in ≥5%, regardless of treatment group, were: hypotension (35%), headache (24%), hypertension (23%), tachycardia (17%), vomiting (11%), fever (9%), nausea (9%), abdominal pain (9%), pharyngitis (9%), diarrhea (8%), infection (8%), rhinitis (6%), and thrombosis (6%). The study showed that more patients in the higher dosing (3.0 mg/kg) group than in the lower dose group (1.5 mg/kg) experienced the following adverse events: hypotension (41% vs. 28%), tachycardia (21% vs. 13%), fever (15% vs. 3%), headache (29% vs. 19%), abdominal pain (15% vs. 3%), nausea (12% vs. 6%), vomiting (12% vs. 9%), pharyngitis (12% vs. 6%), and rhinitis (9% vs. 3%). Only 4 reported adverse events were considered to be related to study treatment by the investigator (nausea, vomiting, and diarrhea in one patient in the 1.5 mg/kg group, and anemia in one patient in the 3.0 mg/kg group).

There were 52 reported instances of hypotension occurring in 23 patients (34.8%); 14 events occurred in 9 patients (28.1%) in the 1.5 mg/kg treatment group and 38 events occurred in 14 patients (41.2%) in the 3.0 mg/kg treatment group. These instances of hypotension were not considered significant by the investigators for this patient population and were considered by the investigators to be related to the ultrafiltration procedure itself and not to Ferrlecit administration.
No deaths occurred during the study. A total of 12 serious adverse events (SAEs) were reported in 10 patients and the frequency of the reported SAEs was similar between the two dosing groups (5 patients reported 6 SAEs in each dosing groups). The SAEs included hemodialysis catheter related (infection [1], thrombosis [3] and leaking [1]), worsening of hypertension (2), infection (1), overhydration (1), worsening of anemia (1), progression of ESRD (1), and epilepsy (1). Only worsening of anemia was considered by the investigator to be related to the study treatment.

One patient in the 1.5 mg/kg group discontinued treatment due to progression of renal failure requiring kidney transplant. No patients were discontinued due to an adverse event related to study drug treatment in the study. No allergic reaction or anaphylactic reaction to Ferrlecit administration was reported in study.

In conclusion, Study FR01006 showed the frequency of adverse events (about 80%) and serious adverse events (about 15%) was similar between the two dosing groups. The most common adverse events were hypotension (35%), headache (24%), hypertension (23%), tachycardia (17%), vomiting (11%), fever (9%), nausea (9%), abdominal pain (9%), pharyngitis (9%), diarrhea (8%), infection (8%), rhinitis (6%), and thrombosis (6%). More patients in the higher dosing (3.0 mg/kg) group experienced hypotension, tachycardia, fever, headache, abdominal pain, nausea, pharyngitis, and rhinitis than patients in the lower dosing (1.5 mg/kg) group. These safety results were based on pediatric patients 6 to 15 years of age. No safety data were available in pediatric patients younger than 6 years of age.

D. Dosing

Two doses of Ferrlecit (1.5 mg/kg and 3.0 mg/kg) were studied in the trial. Both Ferrlecit dosing regimens showed significant increases from baseline in hemoglobin at 2 weeks after treatment (0.8 g/dL and 0.9 g/dL, respectively). No significant dose-response was seen for change in hemoglobin. The secondary efficacy analysis showed a statistically significant difference in the increase in serum ferritin from baseline to two weeks after the treatment between the two dosing groups (192 ng/mL in the 1.5 mg/kg group and 314 ng/mL in the 3.0 mg/kg group, p=0.0003). This suggests a dose-response relationship between the Ferrlecit dose and the increase in serum ferritin level. No dose-response relationship was observed for other secondary efficacy endpoints including Hct, CHr and HCRBC.

The safety results showed that more patients in the higher dosing (3.0 mg/kg) group experienced hypotension, tachycardia, fever, headache, abdominal pain, nausea, pharyngitis, and rhinitis than those in the lower dosing (1.5 mg/kg) group. This suggests these adverse events are dose-related.

To minimize the risk of adverse reactions with Ferrlecit, the 1.5 mg/kg dosing regimen should be recommended for pediatric patients 6 to 15 years of age in the labeling.

No patients younger than 6 years of age were included in the trial. Therefore, no dose recommendation can be made for patients younger than 6 years of age.

E. Special Populations

Gender

There were 34 males and 32 females who received Ferrlecit infusion in Study FR01006. No significant gender effect was observed in the trial.

Age

There were 38 patients with age of 6 to12 years and 28 patients with age of 13 to 15 years in the study. No patient younger than 6 years of age was enrolled. No significant age effect was observed in the trial.

Race

There were 47 Caucasian, 12 Hispanic, 4 Black, 1 Asians, and 2 others enrolled in the trial. No conclusion on race effect can be made because of the limited number of patients other than Caucasian race available in the study.

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