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APPLICATION NUMBER:

203565Orig1s000

MEDICAL REVIEW(S)

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: July 21, 2013

From: Kathy M. Robie-Suh, M.D., Ph.D.
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Subject: Medical Team Leader Secondary Clinical Review
NDA 203565, submitted 1/30/2013 (received 1/30/2013); updated clinical safety information, submitted 3/13/2013 and 3/20/2013 (received 3/13/2013 and 3/20/2013)
Injectafer (VIT-45, ferric carboxymaltose injection; FCM) for the treatment of iron deficiency anemia
Sponsor: Luitpold Pharmaceuticals, Inc.

To: NDA 203565

This application seeks approval of Injectafer (ferric carboxymaltose) for the broad indication of the treatment of iron deficiency anemia. The proposed dosing is 15 mg/kg up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron delivered by intravenous infusion or injection.

Background:
This is a resubmission for this application which was initially submitted on September 30, 2011. Clinical review of the original submission found the application acceptable for approval from a clinical viewpoint (M. Lu, 6/8/2012; K. Robie Suh, 7/20/2012). However, the application was not able to be approved due to Chemistry, Manufacturing and Controls (CMC) deficiency for the drug product manufacture leading to an overall withhold recommendation for the inspections of the manufacturing and testing facilities (see CDTL review, 7/21/2012). A Complete Response (CR) letter for the application was issued on July 23, 2012.

The current resubmission is intended to address all the CMC concerns in the July 23, 2012 CR letter. In addition on March 13, 2013 and March 20, 2013 the sponsor provided updated safety information for the drug (Periodic Safety Update Report (PSUR) from Luitpold covering June 18, 2011-June 17, 2012 and PSUR Addendum from Vifor Pharma covering June 18, 2012-January 31, 2013). The initial clinical review (M. Lu, 6/8/12) included safety data up to June 17, 2011. The primary clinical review of this resubmission and Safety Updates has been conducted by M. Lu, (signed 7/9/2013).

Ferric carboxymaltose (brand name Ferinject^{R}) is currently approved in the European Union and a number of other countries (first approval 7/6/2007 in The Netherlands), mainly for the

indication stated as "for treatment of iron deficiency when oral iron preparations are ineffective or cannot be used. The diagnosis must be based on laboratory tests." Generally the product is labeled that use is contraindicated in cases of known hypersensitivity to Ferinject or to any of its excipients, in anemia not attributed to iron deficiency, and where there is evidence of iron overload or disturbances in utilization of iron. In some countries it is also contraindicated in pregnant women in the first trimester.

Safety Update:
June 18, 2011 through June 17, 2012 PSUR (3/13/2013 submission): From June 18, 2011 through June 17, 2012 the sponsor reports 1,004 patients randomized to Ferinject and 485 patients exposed to Ferinject in clinical trials. Postmarketing exposure was estimated to be 197,291 patient years during this time with estimated total of 482,868 patient years of exposure. The sponsor reports in total 700 new cases of adverse events. Of these cases 149 patients experienced serious events of which 53 were unlisted.
There were 9 deaths reported during this time all due to serious unlisted adverse events. Two cases (both postmarketing) were considered related to Ferinject. These were:

- A 56 year old woman with "asiderotic anaemia"who received 100 mg of Ferinject over 15 minutes and began to experience dyspnea, agitation, bronchospasm and cardiorespiratory arrest beginning 5 minutes after start of the infusion. The infusion was stopped and patient received adrenaline, ketamine and other interventions but suffered neurological damage due to severe ischemia and she expired several days later. Event was considered related to Ferinject. The patient had also received pneumococcal vaccination 15 minutes prior to start of event which sponsor states as alternative explanation for the event.
- An 80 year old woman with multiple medical problems including global heart failure, chronic heart disease, hypertension and hyperthyroidism received 500 mg of Ferinject diluted in 250 mL administered over 30 minutes for iron deficiency anemia. She presented 6 hrs later with left hemiparesis and was confirmed as having a partial middle cerebral artery stroke. She died approximately (b) (6) later. Event was considered possibly related to Ferinject.

The other fatal events (not considered drug-related) were: myocardial infarction (3 patients); increasing respiratory insufficiency in 1 patient with lung neoplasm; severe respiratory tract infection and cardiorespiratory arrest in 1 patient; 1 patient due to cardiac failure (b) (6) after receiving Ferinject; 1 patient due to cardiac failure, pulmonary edema, and renal failure (b) (6) (b) (6) after receiving Ferinject.

The sponsor indicates that cumulatively through December 31, 2011 there have been 236 hypersensitivity associated cases of which 178 were serious (sponsor calculated rate of 0.045% for serious hypersensitivity cases). The events were reported as occurring within 30 minutes post dose in 56.4% (133/236) of cases; however, in 21.6% of cases timing of the hypersensitivity reaction was not reported. The sponsor states no patients died due to hypersensitivity reactions. Hypersensitivity events occurred at single doses ranging from 50-1,500 mg iron in most cases (155/236). From June 18, 2011 through June 17, 2012 there were 13 new reports of hypersensitivity reactions, 8 serious. The sponsor indicates there were no reported deaths due to hypersensitivity. Outcome was not reported for 3 cases.

June 18, 2012 through January 31, 2013 PSUR Bridging Report (3/20/2013 submission):
From June 18, 2012 through January 31, 2013 the sponsor reports an additional 194,300 patient years of exposure to give an estimated total cumulative postmarketing exposure through January 31, 2013 of 677,168 patient years. During this time also an additional 326 patients were enrolled in clinical trials (163 receiving Ferinject [53 pregnant women, 17 patients with chronic heart failure and an additional estimated 93 (blinded) patients with chronic heart failure]). The sponsor reports a total 544 new cases of adverse events (108 serious)(excludes 17 cases [4 serious] from consumers). There were 47 serious unlisted cases. There were 7 fatal cases, including 2 fetal deaths. Only one fatal case was deemed related to Ferinject: a 58 year old woman with pulmonary non-Hodgkin's lymphoma, post-actinic cardiomyopathy, and other illnesses who experienced Grade IV hypersensitivity reaction and anaphylactic shock with dyspnea, hypotension, and bradycardia beginning 3 minutes after start of Ferinject infusion (received about 36 mg iron in 30 mL saline) and died.

Pregnancy-related cases of serious unlisted events including fetal deaths are described in Dr. Min Lu's Medical Officer Review (July 9, 2013). There were 7 pregnancy-related serious unlisted event cases and 6 fetal deaths. One patient died as described above and one recovered with unspecified sequelae. There were 18 cases of hypersensitivity that had some unlisted event term among the listed events. These are shown in the table below.

Table 3 Unlisted Events per Case Deemed as a Hypersensitivity Case

Case Number	Unlisted HSR Event
VIT-2012-02347[1]	Circulatory problems and cyanosis
VIT-2012-02507[1]	Cardiac arrhythmia
VIT-2012-02992	Allergic rhinitis and conjunctivitis
VIT-2012-03006	Papules
VIT-2012-03179[1]	Collapse vascular
VIT-2012-03565	Fatal outcome (see Section 6.5)
VIT-2012-03680[1]	Polyuria
VIT-2012-03681	Oxygen saturation decreased
VIT-2012-03693[1]	Throat tingling and throat discomfort
VIT-2012-03702[1]	Collapse
VIT-2012-03709[1]	Circulatory collapse
VIT-2012-03718[1]	Respiratory depression
VIT-2012-03820	Anaphylactic shock[2] and respiratory distress
VIT-2012-03980	Foetal bradycardia (see Section 6.6)
VIT-2012-04014[1]	Cyanosis
VIT-2012-04072	Increased blood pressure, cyanosis and face-oedema
VIT-2012-04331	Red plaques on thighs and little petechial area on left groin and right knee
VIT-2013-00023	Asthma attack

1 HSR was not a reported diagnosis, these cases were assessed as HSR by the MAH.
2 As no antibodies specific to Ferinject have been detected, the MAH codes the anaphylactic reaction as anaphylactoid reaction, which is a listed event.
Notes: HSR = Hypersensitivity; MAH = Marketing authorisation Holder.

No increases in frequency of certain identified events, including hypersensitivity, hemosiderosis, cardiotoxicity, hyperphosphatemia, overdose or hypertension were identified.

The data in the safety updates did not raise new safety concerns or change the overall benefit-risk assessment. Post-marketing data should be reflected in the labeling.

Sponsor's proposal to address Pediatric Research Equity Act (PREA):
No pediatric patients were studied for the current NDA. To address PREA (Pediatric Research Equity Act) the sponsor requests a waiver for patients less than (b)(4) years of age and requests a deferral for studies in pediatric patients (b)(4) to 17 years of age.

Waiver Request (ages birth to less than (b)(4) years):
The sponsor has requested a waiver for pediatric patients birth to (b)(4) years. Regarding this age group the sponsor states:

> "Based on our previous pediatric experience with our other approved IV iron (Venofer), recruiting patients from birth to (b)(4) years of age into our Phase III trials (Post marketing study) was waived by the Division.
>
> Luitpold Pharmaceuticals, Inc., respectfully requests a waiver from conducting a pediatric study in the 0-(b)(4) years of age group due to logistical challenges associated with subjects of this age range. This request for a waiver is to meet the requirements of Pediatric Research Equity Act (PREA)."

It should be noted that pediatric studies of Venofer for iron deficiency anemia in patients age <2 years with non-dialysis dependent chronic kidney disease (CKD) receiving or not receiving an erythropoietin were waived (NDA 21-135 letter dated June 17, 2005) (too few children with disease to study). With the original approval of Venofer for iron deficiency anemia in patients with hemodialysis-dependent chronic kidney disease, pediatric studies of Venofer in neonates and infants were not required, however, a post-marketing commitment (PMC) #1 requested additional information for possible need for and risks involved with Venofer® use in very young pediatric patients (approval letter dated November 6, 2000). A letter was sent to the sponsor on December 6, 2001 that PMC #1 for Venofer had been fulfilled.

Deferral Request (ages (b)(4) years to 17 years):
For pediatric patients age (b)(4) to 17 years the sponsor proposes to conduct two trials of Injectafer: (1)a pharmacokinetic/pharmacodynamic (PK/PD) study to characterize the PK of serum iron and determine appropriate dosing of FCM for the pediatric population with iron deficiency anemia and (2)a safety and efficacy trial of FCM versus iron sucrose.

I concur with Dr. Lu's recommendation in the previous Clincal Review (signed 6/8/2012) that pediatric studies in this age range may be deferred.

Following is suggested wording for the post-marketing requirements (PMR) to address PREA:

1. Identify an optimal dose of Injectafer for the pediatric patient population. Conduct one or more pharmacokinetic (PK) and pharmacodynamic (PD) trials in pediatric patients aged (b)(4) to < 17 years with iron deficiency anemia sufficient to justify and to

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