Exjade®/Jadenu® (deferasirox) briefing document

Pediatric Advisory Committee Meeting

September 20, 2018

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1 INTRODUCTION

A pediatric-focused safety review for Exjade (deferasirox) was presented to the Pediatric Advisory Committee (PAC) on September 16, 2015. [ref. 1] Two public presentations at this meeting raised questions among PAC members about the safety of Exjade in young children, and specifically its safety among young children who have fever. A mother described the unexpected death of her 35-month-old daughter who was transfusion dependent due to β-thalassemia, and who had received Exjade therapy at an approved pediatric dosage for approximately 11 months. In another presentation, the National Executive Director for the Cooley's Anemia Foundation (CAF) shared concerns from family members of other thalassemia patients about when Exjade use should be interrupted, based on this index case. The Foundation representative asked the PAC to opine on the use of Exjade during febrile-related illness, and to consider amending the label to recommend interruption of Exjade use when a fever is present. The PAC recommended continued routine surveillance of Exjade, but the PAC solicited FDA to acquire any data regarding the safety of continued Exjade treatment among children who have fever and to report to the PAC at a future meeting. The CAF representative made an additional statement at the April 2016 PAC meeting expressing continued concern for the issues presented at the previous PAC meeting.

The Division of Pharmacovigilance (DPV) made a preliminary assessment of pediatric acute illnesses and known toxicities of deferasirox. DPV advocated for an expansion of the investigation to include acute illnesses with dehydration or volume depletion, based on the common occurrence of volume loss with acute illnesses in children, with or without fever, and the known risk of renal toxicity with deferasirox (DFS). A Tracked Safety Issue (TSI) was created on April 13, 2016 to engage multiple disciplines within the Center for Drug Evaluation and Research in conducting comprehensive analyses of whether children receiving Exjade, and who develop acute illnesses with fever and or dehydration, have increased susceptibility to deferasirox-related nephrotoxicity, hepatotoxicity, or both. At the March 2017 PAC meeting the FDA gave a presentation to the PAC of preliminary findings and an evaluation plan. The FDA completed the evaluation of this pediatric safety concern in April 2018, and the product labels with the active ingredient, deferasirox, were updated based on these findings in May 2018. These evaluations include reviews by the Division of Pharmacovigilance, the Division of Epidemiology, the Office of Clinical Pharmacology, and the Division of Pediatric and Maternal Health. Those reviews are summarized in section 2, Significant Review Findings.

1.1 BACKGROUND

1.1.1 Transfusional iron overload

Iron overload is a serious complication of frequent red blood cell transfusion. With continued transfusion and iron loading, iron overload causes end organ toxicity including liver injury leading to cirrhosis, cardiac injury with arrhythmias and decreased ventricular function, and endocrine disorders including diabetes mellitus, hypothyroidism, and hypogonadism. Individually, or through interactions, these organ system dysfunctions can be life threatening. Chelation is necessary to prevent these complications for those who have a long-term dependency on red blood cell transfusions.

Transfusion dependent thalassemia is the most common indication for deferasirox use in the pediatric age group. Thalassemia is a disorder of production of the globin portion of the hemoglobin (Hb) molecule, which transports oxygen from the lungs to the rest of the body. The red blood cells' principal function is to contain Hb. With severe, chronic anemia, the body undergoes extreme adaptations to the liver, spleen bones and other organs to improve tissue oxygen delivery. There is a range of severity of thalassemia, from a form which causes no symptoms and requires genetic testing to detect the abnormality, to the forms of thalassemia that are included within the term transfusion dependent thalassemia. Children with the severe forms of thalassemia require RBC transfusions about once a month to have normal growth and development. Regular monthly transfusion inevitably results in body iron overload with associated risks of injury. Persons with other forms of thalassemia, which are collectively called non-transfusion-dependent thalassemia syndromes, can also develop iron overload primarily due to excess iron absorption from the diet. Iron overload most often manifests as disorders of liver, heart and endocrine organ function. Chelation therapy increases iron loss from the body, and it can prevent the complications of iron overload.

1.2 REGULATORY HISTORY

Exjade (deferasirox, DFS) is the first FDA approved oral iron chelator. Accelerated approval was granted in November, 2005 for ages 2 years and older for the indication, chronic iron overload due to blood transfusions. In 2013 it was approved for patients 10 years of age and older for the indication, chronic iron overload in non-transfusion-dependent thalassemia syndromes. Prior to Exjade's approval, the chelator deferoxamine, which is delivered subcutaneously typically over 10 to 12 hours, or infrequently intravenously over a similar duration, was the only iron chelator available. Failure to adhere to the required minimum deferoxamine administration of five nights per week was a frequent cause of treatment failure. Exjade was approved for an expanded indication in January 2013 to include chronic iron overload in patients 10 years of age and older with non-transfusion dependent thalassemia syndromes and with a liver iron (Fe) concentration (LIC) of at least 5 mg Fe per gram of dry weight and serum ferritin greater than 300 mcg/L. The labeling notes that an improvement in survival or disease-related symptoms has not been established for either indication.

In March 2015, Jadenu, a film coated tablet formulation of DFS was approved with New Drug Application (NDA) 206910. Due to increased absorption, the dosage and administration section is different from the Exjade label, but all safety labeling is identical to Exjade. In May 2017, a granule form of Jadenu (NDA 207968) was approved with the same dosage recommendation and the same safety information as the Jadenu coated tablet. DFS products carry a Boxed Warning for renal toxicity, including failure; hepatic toxicity, including failure, and gastrointestinal hemorrhage. Following completion of the pediatric safety evaluation, the deferasirox labels underwent extensive revisions. These changes are described in section four.

2 SIGNIFICANT REVIEW FINDINGS

2.1 DIVISION OF PHARMACOVIGILANCE

The Division of Pharmacovigilance (DPV) did an initial review of the hospital records of the index case, the product information, and the investigators' brochure. DPV concluded that acute pediatric

illness should be defined by events and synonyms for the terms “fever” and “dehydration or hypovolemia”, and we sought to identify subsequent adverse events in the kidney and liver system organ class (SOC). DPV also determined that the salient features of the index case, liver failure and hyperammonemia, should be evaluated using the same methods.

DPV searched FAERS and the literature for pediatric age (ages 2-15 years for this review) patients who were receiving DFS for an interaction between episodes of fever and/ or dehydration and the outcomes of serious adverse events of renal or hepatic preferred terms (PTs) among children who were receiving DFS. A renal or hepatic adverse event was recorded if it occurred in the period 7 days prior to the fever or dehydration event, or within 28 days after it.

The 7-day period prior to fever or dehydration was chosen to allow for some expected minor temporal discrepancies in spontaneous reports. Broad criteria were used to capture any renal or hepatic event based on diagnoses noted by reporters or laboratory value derangement without specific threshold requirements.

The fever and dehydration cases were representative of the general pediatric deferasirox population in age and sex ratio. An important finding is described in table 2.1. Fever increases insensible water loss from the body, and can cause decreased intake due to malaise and lethargy. Fever may also be an indicator of more severe acute illnesses with associated emesis or diarrhea. This table shows an association between risk factors for volume depletion and the incidence of serious events of renal impairment. However, FAERS data cannot differentiate the contributions to this observation of a pre-renal effect, from a drug exposure effect, on the reports of renal impairment.

Table 2.1 FAERS Cases Of Subsequent Renal Impairment After 149 Episodes Of Fever And/or Dehydration

	% No renal impairment	% Renal impairment	N total
Fever only	95	5	58
Dehydration only	75	25	68
Fever and dehydration	52	48	23

The DPV review found no association of fever and/or dehydration with liver impairment. The FAERS data were not able to determine an effect of DFS discontinuation in association with fever and/or dehydration on liver or kidney impairment. DPV did not identify literature cases supporting an increased risk of adverse events with uncomplicated fever or dehydration.

In the same review, which was in response to the TSI, DPV evaluated the safety event hyperammonemia/acute liver failure. A search of FAERS identified 13 cases that met the case definition of liver failure (report of liver failure with supporting findings of encephalopathy or severe coagulopathy), and two cases from the literature.[1,2] A third literature case was published in 2017, and was added to this case series.[3] The cases are summarized below (Table 3.1.2). The median age of this group was 5 years and the range was 2 to 15 years; one case did not report an age. Coagulopathy was defined as an INR > 2.0, a prothrombin time > 30 sec, or administration of plasma for coagulopathy. A patient was identified as developing acute kidney injury (AKI) when the serum creatinine was at least two times the reported baseline value, the reporter stated the patient had renal failure, or there was a report of the patient requiring renal dialysis. A patient was considered to have hypovolemia when the narrative included a report of vomiting, diarrhea, or at least one day of anorexia. Patients were considered at risk for overchelation when the narrative reported a dose > 25 mg/kg/day when SF < 1000 mcg/L, or a dose > 20 mg/kg/day when SF < 500 mcg/L. Causality was based on the WHO criteria.

Table 2.2 Summary of FAERS and literature cases of acute liver failure in pediatric age group during deferasirox use

	Encephal-opathy (E); Coagulopathy (C)	AKI	Hypo-volemia	Over-chelation	Causality	Outcome
FAERS N=13	E: 13 C:4, NR:7	Yes:10 NR:3	Yes: 11 NR:2	Yes:7 NR:6	Probable: 8 Possible: 5	Recovery: 10 Death: 3
Literature N=3	E: 2 C: 3	Yes: 2 NR: 1	Yes: 3	Yes:3	Probable: 3	Recovery: 3

NR: the report did not contain any information about this criterion

These findings were interpreted to support the concepts: acute liver failure does occur among the pediatric age group exposed to DFS; hypovolemia is associated with AKI; AKI is associated with acute liver failure; overchelation is associated with AKI and ALF, and children age 6 and under are represented at a high proportion in this case series. The DPV review recommended requesting information from the sponsor to evaluate a possible role for overchelation in acute liver and kidney injury in the pediatric age group.

[1] Ling G, Pinsk V, Golan-Tripto I, et al. Acute liver failure in a pediatric patient with congenital dyserythropoietic anemia type I treated with deferasirox. Hematology Reports 2015; 7:5987.
[2] Wei H-Y, Yang C-P, Cheng C-H, et al. Fanconi syndrome in a patient with b-thalassemia major after using deferasirox for 27 months. Transfusion 2011;51: 949-954.
[3] Menaker N, Halligan K, Shur N, et al. Acute Liver Failure During Deferasirox Chelation: A Toxicity Worth Considering. J Pediatr Hematol Oncol 2017; 39:217-222.

2.2 DIVISION OF EPIDEMIOLOGY

The Division of Epidemiology (DEPI) review incorporates four components as below. A more detailed description of study analyses is included in Appendix 1.

- An analysis, of a subset of pediatric patients from the pivotal clinical trial data set who experienced fever or dehydration
- A nested case control study to investigate the effect of deferasirox dose and serum ferritin on acute kidney injury (AKI), and the possible interactions between the two risk factors
- An analysis of exposure adjusted incidence rates of adverse events from clinical trials
- An analysis of eGFR values during Study CICL670A2411 - 5-year Pediatric Registry.

An analysis, of a subset of pediatric patients from the pivotal clinical trial data set who experienced fever (n=237) or dehydration (n=126; total n=273), found that among patients with a normal baseline serum creatinine, 20% of subjects with a dehydration AE developed a serum creatinine increase of at least 33% OR an increase in Urine protein/creatinine ratio (UPCR) of > or = 0.4, whereas 14% of 232 patients who developed a fever AE had the same renal parameter changes.

The nested case control study used clinical trial data sets provided by the sponsor and were derived from ten Exjade studies of transfusion-dependent thalassemia patients and provided adequate serum ferritin data among patients ages 2 to 15 at enrollment. A total of 162 AKI cases from seven studies were identified in our primary analysis. Matching produced 621 control visits with normal renal function. See Figure 2.1.

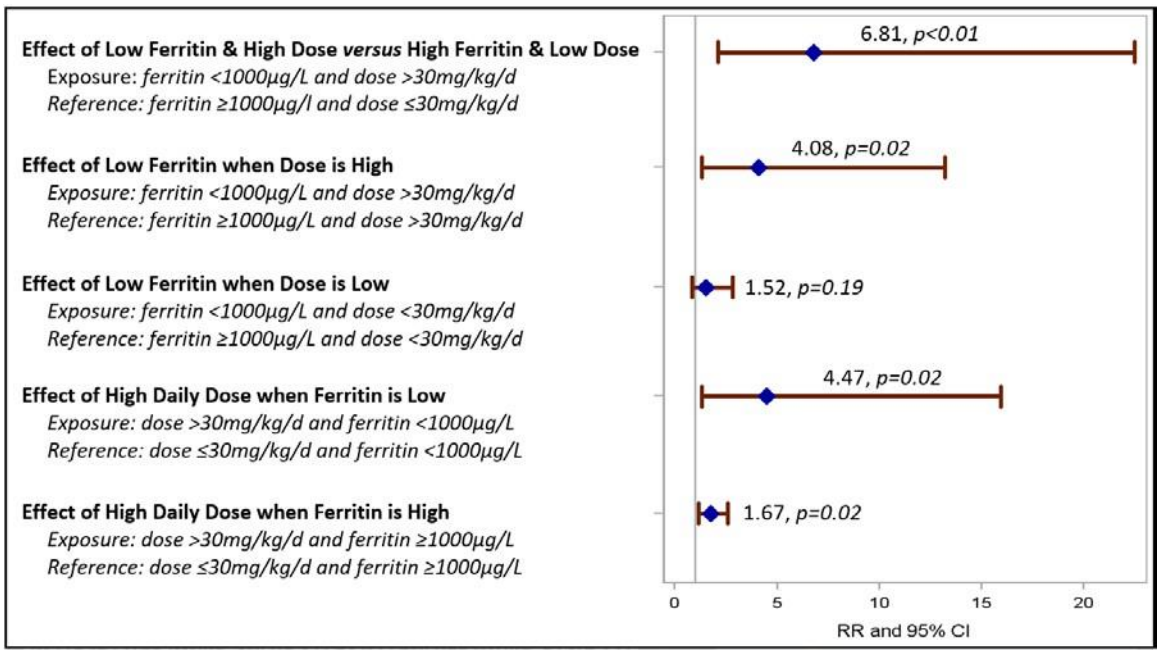

Figure 2.1 Forest Plot summarizes the analysis of the interactions between deferasirox dosage >30mg/kg/d and serum ferritin <1000 g/L on risk for AKI.

DEPI concluded that the use of high-dose deferasirox with lower serum ferritin levels was associated with a higher risk of AKI than either high dosage or low ferritin alone, consistent with overchelation as a causative factor.

The analysis of exposure-adjusted incidence rates of adverse events from pooled clinical trials used datasets constructed by the sponsor of patients with transfusion-dependent thalassemia who received deferasirox doses > 25 mg/kg/day when their serum ferritin was < 1000 mcg/L. These data were developed over a series of information requests. Clinical and laboratory adverse events (AEs) with onset during the first periods when patient dose was >25 mg/kg/day and serum ferritin was <1000 mcg/L, concurrently (referred to in this review as "simultaneous criteria" or "SC") were identified by the sponsor. Exposure-adjusted incidence rates (EAIRs) were calculated (as events per 100 subject treatment years).

The principal findings were a statistically significant increase in incidence rate ratios (IRR) for preferred terms in the renal and urinary disorders SOC among patients during the SC met periods, compared to the SC never met cohort (IRR = 3.750; 95% CI: 1.615 – 8.709; p=0.001), and also when comparing to the SC met periods to the time period prior to meeting the SC (IRR = 6.000; 95% CI: 1.75 – 21.36; p=0.005). An additional finding was that the time periods when SC were met had a 2.056-fold increased IRR (95% CI: 1.333 – 3.17; p=0.0008) for dose interruptions when compared to the time period before SC was met. The exposure-adjusted incidence rate for hearing loss, one of the adverse events of special interest (AESI grouped term as defined by the sponsor), had an IRR = 5.500 (95% CI: 1.297 – 16.99) for the comparison between patients during the SC met periods, and the SC never met cohort.

The 5-year pediatric registry (Study CICL670A2411) was conducted by the sponsor in fulfillment of Subpart H Postmarketing Study Commitment (PMC) 750-1. The PMC was issued at the time of approval to obtain additional safety information on deferasirox in pediatric patients, age < 6 years at enrollment. The Final Study Report was submitted by the sponsor on January 29, 2016 and was reviewed by the Division of Hematology Products. The DEPI identified a problem with the values applied for determination of whether a subject's serum creatinine was within the normal range. Since the oldest children in Study 2411 would have been less than 12 years old while participating in the registry, the upper limit of normal (ULN) for serum creatinine should have been $\leq$ 62 µmol/L (0.7 mg/dL) based on standard published reference ranges. However, DEPI found that 44 of the 53 study centers (83%) had ULN values > 62 µmol/L. Due to this inconsistency in determination of serum creatinine relative to normal values for age, DEPI undertook an analysis of the clinical laboratory dataset from Study 2411 to assess patterns of kidney injury measured as decreases in estimated glomerular filtration rate (eGFR). The 5-year Registry included 242 patients who had pre- and post-baseline eGFR measurements. Of these, 116 (48%) patients had a decrease in eGFR of ≥33% observed at least once. Twenty-one (18%) of these 116 patients with decreased eGFR had a dose interruption, and 15 (13%) of these 116 patients had a dose decrease within 30 days.

Summary

- Analyses of fever and dehydration events in pediatric patients support role of hypovolemia as a risk factor for kidney injury

- Results of the pooled analyses of clinical data support overchelation as a causative factor for AKI among pediatric patients receiving deferasirox

- Longitudinal analysis of eGFR values during 5-year pediatric registry shows that clinically important kidney injury occurs commonly in pediatric patients receiving deferasirox

2.3 OFFICE OF CLINICAL PHARMACOLOGY

DPV consulted the Office of Clinical Pharmacology (OCP) with questions regarding interactions between renal function and drug exposure, and drug exposure and hepatotoxicity. OCP used data obtained in pediatric patients from three studies measuring deferasirox plasma concentrations - Study CICL670A2409, Study CICL670A0107, and Study CICL670A2201- to evaluate the relationship between renal function (eGFR) and dose-normalized drug exposure (Cmin). The change in Cmin in relation to the eGFR was estimated using a linear mixed effect model. The model was fitted to the data using a dose-normalized log-transformed observed Cmin as the dependent variable and eGFR calculated using the modified Schwartz equation as the independent variable. Figure 2.1 shows the predicted dose-normalized Cmin and eGFR for the average Caucasian patient with thalassemia for a BSA of 0.729 m^2, 0.991 m^2, and 1.31 m^2. OCP found that a decrease in eGFR was significantly associated with a moderate increase in dose normalized Cmin. Based on the model, a 33% decrease in eGFR, from 120 ml/min/1.73 m^2 to 80 ml/min/1.73 m^2, was predicted to result in a 29% increase in Cmin. This suggests that, despite an eGFR within normal limits (> 90 mL/min per FDA criteria), small changes in eGFR could lead to significant increases in drug exposure. A notable finding is that BSA was correlated with exposure. As such, patients with a small BSA have higher Cmin (exposure) at all values of eGFR compared to patients with larger BSA. An implication of this finding is that there may be an increased risk for excess exposure with acute changes to eGFR in the youngest group compared to those with higher BSA's, since BSA is a surrogate for age. Using the 50th percentile for boys' and girls' height and weight, the BSA for a 6-year-old is < 0.85 m^2, but the BSA for 7 year olds is > 0.85 m^2.

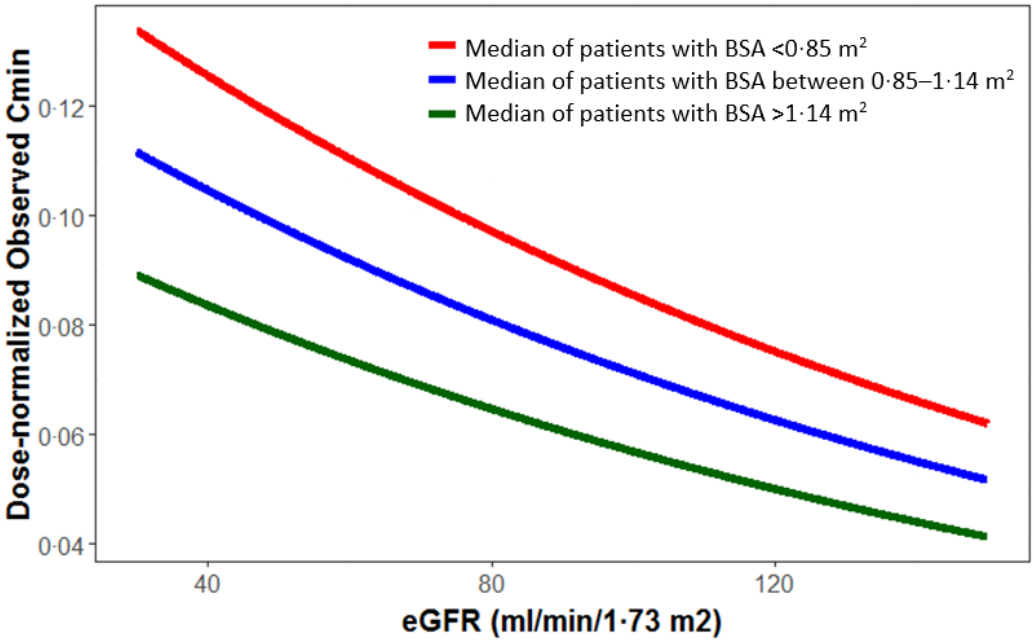

Figure 2.2 Relationship between eGFR and Cmin in pediatric patients

In addition, a study performed by the sponsor and reviewed by the Office of Clinical Pharmacology found a statistically significant relationship between exposure and the probability of renal toxicity (increase in serum creatinine and urinary protein) based on data in pediatric patients in 3 clinical studies. The sponsor found no relationship between exposure and the probability of liver test elevation in pediatric patients in the 3 clinical studies. However, this review used the term 'vicious cycle' to describe the possible sequence of high dose DFS producing decreased eGFR, which may be exacerbated by volume depletion of an acute illness. This decrease in eGFR would be predicted by the model to cause an increased in exposure (Cmin) and further deterioration in eGFR, with subsequent increases in Cmin that may affect the liver.

2.4 DIVISION OF PEDIATRIC AND MATERNAL HEALTH

The Division of Pediatric and Maternal Health (DPMH) was initially consulted to address whether dehydration during an acute illness could compromise renal function enough to require dosage adjustment as recommended in the contemporary DFS label (33% increase in serum creatinine above the average baseline measurement and greater than the age appropriate upper limit of normal), especially in children age 6 and younger. DPMH made the following conclusions:

- The labeled direction for dose adjustment could potentially be applied to any condition (not limited to dehydration) which results in a fluid deficit and reduced effective circulating volume (ECV) in pediatric patients of any age, but that young pediatric patients, such as those less than 6 years of age, are theoretically more susceptible to developing fluid deficits because they rely on their caregivers for adequate provision of fluids since they may not be able to physically access fluids to satisfy their thirst or articulate that they are thirsty.

- Not all pediatric patients with dehydration or other conditions resulting in reduced ECV will need to hold Exjade therapy, but they will require increased vigilance and monitoring for signs of volume depletion to make a careful assessment. Furthermore, the magnitude of change in renal function will vary depending on the extent and duration of reduction in the ECV, which in turn, will depend on the size and age of the patient, the extent of the fluid deficit, and the severity of the predisposing condition.
- Among children with volume depletion, prompt correction of the underlying condition, or the associated fluid deficit, will normalize renal perfusion but, if continued uncorrected, can lead to intrinsic renal damage (a.k.a. acute kidney injury [AKI]). Therefore, fluid resuscitation followed by repletion of the fluid deficit is essential during early stages of decreased renal perfusion, and can be life-saving since development of AKI is an independent risk factor for mortality.
- Given the known renal toxicity of DFS, dose interruption would be particularly important if concomitant use of other nephrotoxins (e.g., NSAIDs such as ibuprofen) is initiated to provide symptomatic relief (fever reduction, pain relief) of the acute interval illness predisposing to extra-cellular volume depletion.

DPMH was later consulted to review renal findings from pre- and post-marketing multi-disciplinary reviews for Exjade as well as from the literature to provide recommendations to strengthen existing labeling language to enhance the safety of deferasirox use in patients 2 years to less than 6 years of age. The DPMH review noted that deferasirox-related renal tubular toxicity was first noted in the non-clinical development program for Exjade and consisted of a spectrum of changes primarily affecting renal tubular cells in all animal species tested. The precise mechanism for deferasirox-induced renal proximal tubule (PT) toxicity is debated in the literature and not fully elucidated, but multiple investigators speculate that the lipophilicity of deferasirox increases its movement across cell membranes compared to other iron chelators such as deferoxamine. Intracellular accumulation at high levels may lead to scavenging of iron in intracellular sites, resulting in ATP depletion and consequent PT dysfunction.

Given the non-clinical signal for renal tubular toxicity with deferasirox exposure, only patients with normal baseline serum creatinine levels, no pre-existing renal disease, and no known risk factors for renal disease were allowed to enroll in the clinical development program for Exjade. Therefore, at the time of initial U.S. approval, the effects of Exjade in adults and pediatric patients with baseline acute or chronic kidney injury were unknown. Following Exjade's November 2005 initial accelerated approval in adults and pediatric patients down to 2 years of age, FDA approved a series of safety labeling changes to strengthen language about renal toxicity which became evident with Exjade's more widespread use in the postmarketing setting. These safety labeling changes were implemented predominantly on the basis of serious, including fatal, adverse reactions in elderly adults with low renal reserve. Many had transfusional hemosiderosis from causes other than thalassemia. As a result, the revised safety labeling language is targeted to adults and not all the specified renal parameters are applicable to pediatric patients. Similarly, the renal dosing adjustment parameters added to subsection 8.6 appear to apply to both the approved adult and pediatric populations but were derived from an adult study in older patients with myelodysplastic syndrome (MDS) and baseline renal dysfunction.

DPMH provided the following recommendations:

- Current labeling language should be strengthened to convey the importance of regularly monitoring pediatric patients for evidence of both glomerular and tubular injury.

- Rely on estimated glomerular filtration rate (eGFR) rather than on serum creatinine or creatinine clearance to establish baseline renal function before initiating therapy and to guide subsequent pediatric drug dosing decisions. The review gave extensive background and discussion on the inherent problem of relying on creatinine clearance rather than eGFR to estimate renal function in pediatric patients, and the importance of using a creatinine-based prediction equation validated for use in the pediatric population.

- In pediatric patients with an abnormal baseline eGFR or with deferasirox-induced renal tubular and/or glomerular injury, careful consideration is warranted of deferasirox's benefits in reducing total body iron burden compared with the risks of continued or progressive renal injury. If the risk benefit profile is considered favorable, then the minimum effective dose of deferasirox should be administered with frequent monitoring of renal tubular and glomerular function. Dose titration in these cases should be individualized and guided by improvement in the renal injury. If the risk benefit profile is considered unfavorable, then temporary discontinuation of Exjade treatment and changing to alternative therapies, which appear to be less nephrotoxic, should be considered until the renal dysfunction returns to baseline.

- Development of either renal tubular and/or glomerular injury in the presence of other risk factors such as dehydration should prompt immediate, temporary discontinuation of Exjade before the renal damage becomes severe and irreversible.

- Pediatric patients with renal impairment will need dosing modification of Exjade, but DPMH is unable to provide specific recommendations for pediatric renal dosing modifications based on the available PK data which were derived from elderly adults with MDS. While the clinical pharmacology of Exjade in renally impaired adults and pediatric patients should be the same, the renal toxicity resulting from the increased Exjade exposure in this setting may be different between adults and pediatric patients.

3 CONCLUSIONS

Through an extensive analysis of clinical trial, postmarketing and literature information, this pediatric focused safety review of deferasirox identified cardinal features of pediatric safety, which are congruent with principal features of the index case. These include:

- There is a risk of acute liver failure in children receiving deferasirox

- There is a risk of renal impairment associated with acute illnesses that have some component of volume depletion

- Decreased renal function by any mechanism results in increased exposure, and increased exposure results in decreased renal function, with the potential for an exacerbating cycle and hepatic toxicity

- The risks of high deferasirox dose and low serum ferritin (as a measure of body iron) are additive for the development of diminished renal function

- There is a risk of life-threatening adverse events when full dose (20-40 mg/kg/day) Exjade is continued while the body iron burden is approaching or within the normal range

4 SUMMARY OF CHANGES TO EXJADE AND JADENU PRODUCT INFORMATION

Each of the disciplines made recommendations to modify the product information to improve the safe use of deferasirox products in the pediatric age group. The Sponsor agreed to these recommendations, and they were incorporated into the deferasirox product information with a May 2018 label update. The labeling changes are summarized below; the sections to which the specific change was added are in parentheses.

- Interrupt dose with hypovolemia and monitor more frequently. Resume when volume is replaced, and normal oral intake resumes, with dose based on renal function (Boxed Warning (BW), sections 2.1, 2.2, 2.5, 5.1, 5.5, 17)

- DFS exposure increases when eGFR decreases (sections 2.5, 8.4, 12.2)

- Use estimated glomerular filtration rate (eGFR, ml/min/1.73m^2), as the method for monitoring and adjusting drug dose, rather than the current method of creatinine clearance (ml/min) (sections 2.1, 2.4, 2.5, 4, 5.1, 8.4, 8.6)

- There is a risk of kidney and liver failure with continued use of DFS doses 20-40 mg/kg/day, when the body iron burden is approaching or within the normal range (sections 5.2, 5.5, 5.6)

- Adjust dose or increase monitoring when SF < 1,000 mcg/L (sections 2.1, 5.6, 8.4)

- Renal impairment risk increases when DFS > 25 mg/kg/day, while SF < 1,000 mcg/L (BW, sections 5.6, 6.1, 8.4)

- An increased risk of auditory adverse events among pediatric patients was associated with use of Exjade doses greater than 25mg/kg/day, when serum ferritin was less than 1,000 mcg/L (section 5.10)

5 APPENDICES

5.1 APPENDIX 1. POOLED ANALYSES OF PEDIATRIC CLINICAL STUDIES

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