FDA Briefing Document

Pediatric Advisory Committee Meeting

March 6, 2017

Update on safety issues associated with Exjade (deferasirox) use in young children who have fever

Disclaimer Statement

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Pediatric Advisory Committee (PAC). The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We brought the update on safety issues associated with Exjade (deferasirox) use in young children who have fever to this PAC in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation, and instead is intended to focus on issues identified by the Agency for discussion by the PAC.   The FDA will not issue a final determination on the issues at hand until input from the PAC process has been considered and all reviews are finalized. The final determination may be affected by issues not discussed at this meeting.

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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.[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 been receiving Exjade therapy at an approved pediatric dosage for approximately 11 months. In another presentation the National Executive Director for the Cooley's Anemia Foundation 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 agreed with continued routine surveillance of Exjade, but 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.[1]

2   BACKGROUND

2.1   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.[2]

Exjade (deferasirox) was the first oral iron chelator when approved by FDA in November 2005. The initial indication was for ages 2 years and older. Prior to the approval of Exjade, Desferal (deferoxamine) was the only approved chelator. Deferoxamine is delivered subcutaneously typically over 10 to 12 hours, or infrequently by the intravenous route over a similar duration. Failure to adhere to the required minimum deferoxamine administration of five nights per week was a frequent cause of treatment failure. The alternative of an oral chelator was considered an important component of controlling iron overload in the transfusion dependent community.[3]

2.2   REGULATORY HISTORY

Exjade is an orally active iron chelator indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older. 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 2015 FDA approved Jadenu (deferasirox) tablets, a new formulation of deferasirox (DFS), for the same indications as Exjade. However, Jadenu dosing is distinct from Exjade due to differences in absorption. A Boxed Warning was added in 2010 which warns of renal impairment, hepatic impairment, and gastrointestinal hemorrhage with the use of Exjade.[4,5]

2.3 PRODUCT LABELING[4]

2.3.1 Boxed Warning

The following excerpt from the Boxed Warning in the current Exjade USPI describes the risk of potentially fatal renal failure and liver failure, and the necessity of baseline and monthly monitoring of serum creatinine, serum transaminases, and bilirubin:

Renal Failure

- Exjade can cause acute renal failure and death, particularly in patients with comorbidities and those who are in the advanced stages of their hematologic disorders.
  Measure serum creatinine and determine creatinine clearance in duplicate prior to initiation of therapy and monitor renal function at least monthly thereafter. For patients with baseline renal impairment or increased risk of acute renal failure, monitor creatinine weekly for the first month, then at least monthly. Consider dose reduction, interruption, or discontinuation based on increases in serum creatinine.

Hepatic Failure

- Exjade can cause hepatic injury including hepatic failure and death.
- Measure serum transaminases and bilirubin in all patients prior to initiating treatment, every 2 weeks during the first month, and at least monthly thereafter.

2.3.2 Dosage and Administration

Section 2 (DOSAGE AND ADMINISTRATION) of the current Exjade USPI states the following regarding need for baseline and periodic clinical laboratory monitoring and dose adjustment:

Prior to starting therapy, obtain:
• serum ferritin level
• baseline serum creatinine in duplicate (due to variations in measurements) and determine the creatinine clearance (Cockcroft-Gault method)
• serum transaminases and bilirubin

The recommended initial dose of Exjade for patients 2 years of age and older is 20 mg per kg body weight orally, once daily. Calculate doses (mg per kg per day) to the nearest whole tablet.

After commencing therapy, monitor serum ferritin monthly and adjust the dose of Exjade, if necessary, every 3-6 months based on serum ferritin trends. Make dose adjustments in steps of 5 or 10 mg per kg and tailor adjustments to the individual patient's response and therapeutic goals. In patients not adequately controlled with doses of 30 mg per kg (e.g., serum ferritin levels persistently above 2500 mcg/L and not showing a decreasing trend over time), doses of up to 40 mg per kg may be considered. Doses above 40 mg per kg are not recommended.

If the serum ferritin falls consistently below 500 mcg/L, consider temporarily interrupting therapy with Exjade.

2.3.3   Recommendation for Dose Adjustment Due to Increases in Serum Creatinine

Section 2.5 (Dose Modifications for Increases in Serum Creatinine on Exjade) of the current Exjade USPI recommends that the dose should be adjusted as follows in pediatric patients:

Pediatric Patients (ages 2–15 years):
Reduce the dose by 10 mg per kg if serum creatinine increases to greater than 33% above the average baseline measurement and greater than the age appropriate upper limit of normal.

2.3.4   Summary of Recommendations for Monthly Monitoring and Dose Adjustment

The Boxed Warning describes the need for ongoing monthly monitoring of serum creatinine, serum transaminases, and bilirubin. In Sections 2.1 (Dosage and Administration) and 5.10 (Overchelation), there are recommendations for monthly monitoring of serum ferritin with the caveat that "If the serum ferritin falls below 500 mcg/L, consider interrupting therapy with Exjade, since overchelation may increase Exjade toxicity."

In addition, Section 5.1 (Warnings and Precautions, Renal Toxicity, Renal Failure, and Proteinuria) recommends monthly monitoring for proteinuria and notes the following rationale: Renal tubular damage, including Fanconi's Syndrome, has been reported in patients treated with Exjade, most commonly in children and adolescents with beta-thalassemia and serum ferritin levels <1500 mcg/L.

Intermittent proteinuria (urine protein/creatinine ratio >0.6 mg/mg) occurred in 18.6% of Exjade-treated patients compared to 7.2% of deferoxamine treated patients in Study 1. In clinical trials in patients with transfusional iron overload, Exjade was temporarily withheld until the urine protein/creatinine ratio fell below 0.6 mg/mg.

3   DEVELOPMENT OF A REVIEW STRATEGY

The committee posed a challenging question in their request to evaluate fever as a possible indicator to interrupt therapy. The reference standard for answering this clinical question, a randomized clinical trial designed to evaluate this specific question regarding fever, was not

available. The reviewers first considered the nature of acute pediatric illnesses, the descriptions of the index case, and the safety profile of DFS. We noted that fever is a very common event in the pediatric age group, and it was a common event among DFS clinical trial subjects, but none of the clinical trials attributed any specific adverse events (AEs) to fever. We also noted that the first report of fever for the index case was late in the course of illness at the time of evaluation in the Emergency Department, and that the medical record described diarrhea in the twenty-four hours prior to presentation. Therefore, it seemed reasonable that a broader evaluation would address the committee's concerns more effectively. Accordingly, we extended the scope of the evaluation to include hypovolemia/dehydration events. The rationales include: DFS has nephrotoxic potential as indicated in multiple sections of the DFS labels; hypovolemia can increase the risk of nephrotoxicity; dehydration often accompanies fever, but it is not easily quantified; acute pediatric illness events can involve dehydration events without fever.

A Tracked Safety Issue (TSI) was subsequently created to engage multiple disciplines within the FDA's Center for Drug Evaluation and Research (CDER) in the evaluation of whether pediatric patients, who develop fever and/or dehydration in the context of an acute illness, are more susceptible to DFS-related nephrotoxicity, hepatotoxicity, or both. Divisions of Pharmacovigilance (DPV), Epidemiology (DEPI), Pediatric and Maternal Health (DPMH), and the Offices of Clinical Pharmacology (OCP), and of Hematology and Oncology Products (OHOP) are contributors to the TSI. The OCP issued an information request to the sponsor, which addressed multiple aspects of drug metabolism and pharmacokinetics in children. Following the expected receipt of a response to this request in early March, the OCP will analyze the information and make recommendations. The Division of Hematology of OHOP is analyzing the data submitted from the registry study, "A 5 year observational study (registry) of children aged 2 to <6 years at enrollment with transfusional hemosiderosis treated with DFS".

4 FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) SEARCH METHODS AND RESULTS – FEVER AND/OR DEHYDRATION

4.1 METHODS

Case Selection Criteria

FAERS reports were reviewed and included if:
- Patient was on DFS therapy and experienced fever, dehydration, or both
    - FAERS reports were identified using the fever and dehydration related preferred terms (PT) (see Appendix A).

- FAERS reports were excluded if:
    - Duplicate
    - Sickle cell disease (due to high frequency of disease related renal and hepatic adverse events)
    - Narrative does not support fever or dehydration

       o   Insufficient information for further assessment (e.g., no narrative provided, conflicting temporal sequence, unclear exposure to DFS therapy at the time of fever or dehydration, etc.)

When a fever or dehydration event was identified, the disposition (i.e., continue, discontinue, unknown) of DFS was noted. We evaluated the disposition of DFS therapy as a possible risk factor for subsequent renal or hepatic AEs. For the purpose of this analysis, a patient was considered to "continue" therapy if they received at least one dose of DFS during the post-fever/dehydration event. Thus, even if a patient attempted to take DFS and missed a dose due to vomiting, they were still categorized as "continue" so long as they received at least one dose. A patient was considered to "discontinue" therapy if they stopped DFS on the first day of the fever or dehydration event, whether this decision was due to a caregiver's discretion or under healthcare provider direction. If the DFS disposition was unclear, the status was considered to be "unknown".

After noting the drug disposition status, the report was examined for renal and hepatic AEs. A renal or hepatic AE was recorded if a patient experienced it within 7 days prior to or 28 days after fever or dehydration. The 7 day period prior to fever or dehydration was chosen to allow for some expected minor temporal discrepancies in spontaneous reports. With regard to classification of renal and hepatic AEs, 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. For example, if the narrative mentioned an event such as "acute liver failure" or "increased serum creatinine", these events were noted even if corroborating laboratory data was not reported. Laboratory values were recorded if reported (e.g., serum creatinine, liver biochemical tests, coagulation labs).
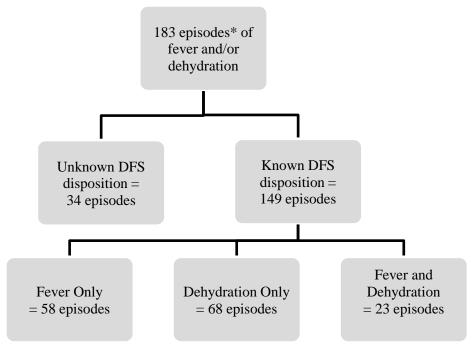
Some reports described multiple episodes of fever or dehydration over time for the patient. Data was collected for each individual episode. Subgroup analyses were conducted to evaluate fever only, dehydration only, and concurrent fever and dehydration episodes.

4.2 RESULTS

As of November 17, 2016, there were a total of 259,603 FAERS reports of AEs for all drugs among persons age 2-15 years; 1,198 of these FAERS reports were associated with DFS therapy. The current FAERS search, based on methods described in section 4.1, retrieved 422 reports. After applying the case selection criteria, DPV identified 162 FAERS cases for inclusion in our analysis. Seventeen of the 162 cases had multiple episodes of fever and/or dehydration. Analysis of the total episodes of fever and/or dehydration among the FAERS cases would be most informative in order to address the patients who had multiple episodes of fever and/or dehydration. Therefore, among the 162 cases, there were a total of 183 episodes of fever and/or dehydration.

When a fever or dehydration event was identified, the disposition (i.e., continue, discontinue, unknown) of DFS was noted. FAERS data reported disposition of DFS therapy for 149 of the 183 episodes of fever and/or dehydration. The 149 episodes included 58 fever only episodes, 68 dehydration only episodes, and 23 fever and dehydration episodes. (see Figure 1).

Figure 1. Fever and/or Dehydration Episodes


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                    ┌─────────────────┐
                    │ 183 episodes* of│
                    │   fever and/or  │
                    │   dehydration   │
                    └────────┬────────┘
              ┌──────────────┴──────────────┐
    ┌─────────────────┐          ┌─────────────────┐
    │  Unknown DFS    │          │   Known DFS     │
    │  disposition =  │          │  disposition =  │
    │   34 episodes   │          │   149 episodes  │
    └─────────────────┘          └────────┬────────┘
                      ┌───────────────────┼───────────────────┐
            ┌─────────────────┐ ┌─────────────────┐ ┌─────────────────┐
            │   Fever Only    │ │ Dehydration Only│ │    Fever and    │
            │  = 58 episodes  │ │  = 68 episodes  │ │   Dehydration   │
            │                 │ │                 │ │  = 23 episodes  │
            └─────────────────┘ └─────────────────┘ └─────────────────┘
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* Out of 162 cases

4.2.1 Key Findings for Individual Episodes of Fever and/or Dehydration (Known Drug Disposition)

In total, there were 82 episodes where patients continued DFS therapy during fever and/or dehydration and 67 episodes where patients discontinued DFS therapy during fever and/or dehydration.

Continued DFS (n=82 episodes)
- 19 episodes (23.2%) developed renal and/or hepatic impairment
  - Renal impairment (n=5)
  - Hepatic impairment (n = 12)
  - Concurrent renal and hepatic impairment (n=2)

Discontinued DFS (n=67 episodes)
- 34 episodes (50.7%) developed renal and/or hepatic impairment
  - Renal impairment (n=13)
  - Hepatic impairment (n = 10)
  - Concurrent renal and hepatic impairment (n=11)

Table 4.2.1.1 shows the renal and hepatic AEs among the three subgroups.

Table 4.2.1.1 Subsequent Renal Or Hepatic Impairment After Episode Of Fever And/Or Dehydration

Fever Only – Total Episodes of Fever (n=58 episodes)

Serious AEs	Continue DFS (n=34)	Discontinue DFS (n=24)
Yes Event	4 (11.8%)	8 (33.3%)
Renal impairment	1	2
Hepatic impairment	3	6
Renal and Hepatic impairment	0	0
No Event	30 (88.2%)	16 (66.7%)

Dehydration Only – Total Episodes of Dehydration (n=68 episodes)

Serious AEs	Continue DFS (n=37)	Discontinue DFS (n=31)
Yes Event	12 (32.4%)	16 (51.6%)
Renal impairment	4	7
Hepatic impairment	7	4
Renal and Hepatic impairment	1	5
No Event	25 (67.6%)	15 (48.4%)

Fever and Dehydration – Total Episodes of Fever and Dehydration (n=23 episodes)

Serious AEs	Continue DFS (n=11)	Discontinue DFS (n=12)
Yes Event	3 (27.3%)	10 (83.3%)
Renal impairment	0	4
Hepatic impairment	2	0
Renal and Hepatic impairment	1	6
No Event	8 (72.7%)	2 (16.7%)
DFS = Deferasirox		

4.2.2 Analysis of Cases with Multiple Episodes of Fever and/or Dehydration

We evaluated the 17 cases with multiple episodes of fever and/or dehydration to determine if any of these patients were experiencing a "progressive worsening" of renal and/or hepatic impairment over time. See Appendix B.

- Analysis for changing outcomes as patients' number of fever and dehydration experiences increased over time
  - 9 patients had no renal or hepatic impairment events following any episode of fever or dehydration
  - 2 patients had a renal or hepatic event after the 1st fever or dehydration, then did not have any renal or hepatic event after a subsequent fever or dehydration
  - 3 patients had no renal or hepatic event after the 1st episode of fever or dehydration, and a renal or hepatic AE after 2nd episode of fever or dehydration
  - 3 patients had renal or hepatic events following all episodes of fever or dehydration

Reviewers' comment: We did not find a pattern of progression of renal or hepatic impairment in this limited data set.

5 LITERATURE OVERVIEW

The goal of the literature search was to identify published material which could inform our understanding of factors that increase the risk for liver or kidney injury among patients in the pediatric age group exposed to DFS.

The literature review did not find support for respiratory syncytial virus infection (as occurred in the index case), fever, or dehydration/hypovolemia as risk factors for liver or kidney injury among patients in the pediatric age group exposed to DFS. The identified dehydration/hypovolemia cases were confounded by prior or concomitant exposures to drugs labeled for nephrotoxicity. There are multiple sources that indicate a relationship between risk of renal and hepatic AEs, DFS dose, and indicators of iron burden. These are three sources:

Serum creatinine increase: "At any given dose of deferasirox, serum creatinine increases occurred more frequently in patients receiving infrequent blood transfusions and in those with lower liver iron concentration and serum ferritin."[6]

Renal tubular damage: "Renal tubular damage, including Fanconi's Syndrome, has been reported in patients treated with Exjade, most commonly in children and adolescents with beta-thalassemia and serum ferritin levels <1500 mcg/L".[4]

Transaminase elevation: Subjects (N=71) with liver iron content < 7 mg Fe per gram of dry weight had 5.6% frequency of transaminase elevation compared to 1% among subjects (N=303) with liver iron content $\geq$ 7 mg Fe per gram of dry weight.[7]

5.1 PHARMACOLOGY

Literature reports described a lack of correlation between dose and measured exposure. Allegra et al. reported an evaluation of a linear correlation between DFS dose and plasma DFS area under the curve (AUC in μg/ml). They found an r value = 0.363 and a nonsignificant p-value (p=0.115), indicating a lack of correlation.[8] Similarly, Mattioli et al. studied dose and plasma drug levels in 80 subjects, of whom 15 were children or adolescents. They found "no linear correlation between dose and DFS concentration (p=0.3)".[9] An earlier study by Chirnomas et al. found two distinct groups based on dose exposure analysis. They reported pharmacokinetic results on transfusion dependent patients who were segregated based on their response to DFS. The 10 patients with an inadequate response, defined as a rising ferritin trend or rising liver iron on DFS doses > 30 mg/kg per day after > 6 months on therapy, had significantly ($P < 10^{-5}$) lower drug exposure (AUC = 479.59 +/-259.42 μM•h) compared to the five subjects with an adequate response (AUC = 1123.11 +/-63.4 μM•h). However, they concluded that the basis for the difference in exposure was variable bioavailability, since C_{max}, volume of distribution/bioavailability, and elimination half-life were not different between the groups.[10]

Reviewers' comment: The data of Chirnomas et al., Mattioli et al., and Allegra et al. raise the concern that the relationship between dose and exposure is not adequately predictable. This possible lack of a predictable exposure could increase the risk for adverse effects and for ineffective chelation. Plasma drug level monitoring is one approach that may improve predictability of exposure.

5.2 PHARMACOGENOMICS

Lee et al. observed 98 patients taking DFS for transfusion related iron overload. They identified 9 patients (9.2%) receiving DFS with serum creatinine > 50% above baseline at least one time and analyzed their UGT1A1 genotypes. Patients who were homozygous for UGT1A1*6 had 14.17-times higher risk of creatinine elevation than wild type patients on multivariate analysis (OR = 14.17, 95% CI = 1.34–150.35, P = 0.028). There were insufficient subjects with the UGT1A1*28 mutation, a mutation also associated with the disorder, Gilbert syndrome, to evaluate it as a risk for serum creatinine elevation. Homozygosity for UGT1A1*6 is associated with 70% reduction in enzyme activity, and UGT1A1*28 has a similar effect on enzyme activity. Hepatotoxicity, defined as ALT or AST > 5 x ULN, or total bilirubin > 3 x ULN, occurred among 15 patients. It was associated with absence of wild-type haplotypes of the MRP2 gene (multivariate odds ratio = 7.17, 95% CI = 1.79-28.67; p=0.005).[11] Cusato et al. identified UGT1A1, UGT1A3, and ABCG2 single-nucleotide polymorphisms as markers which influenced pharmacokinetics and efficacy. They did not evaluate safety parameters.[12]

6 CLINICAL TRIAL DATA

6.1 ANALYSIS OF LIVER OR KIDNEY INJURY AFTER FEVER OR DEHYDRATION ADVERSE EVENTS

An analysis of Study CICL670A0107 (Study 0107) was conducted to evaluate whether signs or symptoms of fever or dehydration may be useful indicators for treatment interruption to prevent severe nephrotoxicity or hepatotoxicity in children receiving therapy with deferasirox (DFS).

6.2 METHODS

6.2.1 Data and Information Sources

Study 0107, the pivotal study on which the original approval of Exjade was based, is a randomized, comparative open label phase 3 trial of the efficacy and safety of long-term treatment with DFS compared to deferoxamine in β-thalassemia patients with transfusional hemosiderosis, followed by an extension study. The current analysis included study subjects with fever or dehydration AEs who received DFS during the randomized or the extension phase of the study.

Datasets identifying fever and dehydration adverse events (AEs) in children (ages 2 to 15 years) participating in Exjade clinical trials were submitted by Novartis at the request of FDA. The sponsor's submission included demography, dose, and clinical and laboratory safety data. The analysis dataset for Study 0107 was extracted from the larger dataset, and comprised adequate laboratory data to evaluate 237 fever AEs and 126 dehydration AEs in 273 pediatric patients from Study 0107.

6.2.2 Criteria Used

The following clinical laboratory-based definitions of liver injury and kidney injury were developed for the purposes of this analysis:

6.2.2.1 Evidence of potential liver injury:

Laboratory values, including serum alanine aminotransferase (ALT) and total bilirubin (TBL) obtained after AEs of interest (fever or dehydration) were compared with lab values obtained before the event, using the following criteria for potential liver injury:

- Level 1 = ALT > upper limit of normal (ULN)
- Level 2 = ALT >2X ULN
- Level 3 = ALT >3X ULN
- Level 4 = ALT >3X ULN and TBL>2X ULN

No evidence of liver injury was defined as ALT < ULN.

6.2.2.2 Evidence of potential kidney injury:

Laboratory values, including serum creatinine (CREA) and urine protein to creatinine ratio ($U_{P/C}$) obtained after AEs of interest (fever or dehydration) were compared with lab values obtained before the event, using the following criteria for potential kidney injury:

- Level 1 = serum creatinine (CREA) increase $\geq$ 25% compared to most recent CREA value prior to fever/dehydration AE or $U_{P/C}$ > the most recent $U_{P/C}$ value prior to fever/dehydration AE
- Level 2 = CREA increase $\geq$ 33% compared to most recent CREA value prior to fever/dehydration AE or $U_{P/C} \geq 0.4$
- Level 3 = CREA value >ULN or $U_{P/C} \geq 0.6$

No evidence of kidney injury was defined as CREA increase < 25% compared to most recent CREA value prior to fever/dehydration AE and $U_{P/C} \leq$ the most recent $U_{P/C}$ value prior to fever/dehydration AE.

6.3 DATA ANALYSIS

AEs associated with fever or dehydration were identified by Novartis in response to a request from FDA. The following MedDRA search criteria were used:

- Fever searches included: High Level Terms (HLT) "Febrile disorders" and Preferred Terms (PT) "Body temperature increased"
- Dehydration searches included the following MedDRA PTs: "Hypophagia; decreased appetite; diet refusal; eating disorder; fluid replacement; diarrhoea; faecal volume increased; abdominal distension; weight decreased; abnormal loss of weight; dehydration; stress polycythaemia; hypovolaemia; hypoperfusion; hypotension; blood pressure decreased; peripheral circulatory failure; hypovolaemic shock; shock; shock symptom; circulatory collapse; hypernatraemia; hypokalaemia; electrolyte imbalance; metabolic acidosis; metabolic alkalosis; specific gravity urine abnormal; urine output decreased; oliguria; mucosal dryness; thirst; lethargy; tachycardia."

The proportion of fever AEs and the proportion of dehydration AEs with laboratory evidence of liver or kidney injury and the distribution of "action taken" (i.e. interruption/adjustment vs continuation of DFS therapy) were assessed across the pre-specified criteria levels for laboratory

parameters. We also examined the proportion of fever AEs and the proportion of dehydration AEs with evidence of liver injury or kidney injury after interruption vs continuation of DFS therapy among patients whose ALT or CREA values had been within normal limits (WNL) prior to the AE. All analyses included an independent quality assurance (QA)/quality control (QC) that was performed by a separate analyst. All analyses were conducted in SAS, version 9.4.

6.4 RESULTS

Tabular summaries of the results of the fever/dehydration analysis are presented in this section for the subset of events where laboratory values for ALT or CREA were within normal limits (WNL) prior to the fever or dehydration AE.

6.4.1 Liver Injury After Fever Or Dehydration Adverse Events

Some evidence of liver injury was observed commonly, after approximately one-third of fever AEs, regardless of whether DFS therapy dose was adjusted or withheld. When the analysis was limited to events where ALT values were WNL before the fever AE, 27 (17%) of 157 fever AEs were followed by ALT >ULN overall (Table 6.4.1.1).

Table 6.4.1.1 Proportion of **FEVER** adverse events (AEs) in Study 0107 with evidence of **LIVER** injury after interruption or dose adjustment of DFS therapy *where ALT was WNL prior to AE*

| DFS dose was adjusted or withheld due to fever AE (action taken = 1) | Number (percent) of **fever** AEs followed by evidence of **liver** injury | | | | |
	No evidence of liver injury	ALT >ULN	ALT >2X ULN	ALT >3X ULN	ALT >3X ULN *and* TBL >2X ULN
Yes (n=23 AEs)*	19 (83%)	3 (13%)	0	0	0
No (n=134 AEs)**	109 (81%)	24 (18%)	10 (7%)	3 (2%)	0
Total (n=157 AEs)	128 (82%)	27 (17%)	10 (6%)	3 (2%)	0

All percentages are row percentages. Categories of lab values are not mutually exclusive.
Numbers are events from 107 unique pediatric patients with fever AEs from Exjade Study 0107.
* missing lab data for 1 event
** missing lab data for 1 event

Overall, 42 (33%) of 126 dehydration AEs in 73 unique pediatric patients were followed by ALT >ULN. As shown in the table below, when the analysis was limited to events where ALT values were WNL before the dehydration AE, 14 (15%) of 91 dehydration AEs were followed by ALT >ULN (Table 6.4.1.2).

Table 6.4.1.2: Proportion of **DEHYDRATION** adverse events (AEs) in Study 0107 with evidence of **LIVER** injury after interruption or dose adjustment of DFS therapy *where ALT was WNL prior to AE*

DFS dose was adjusted or withheld due to dehydration AE (action taken = 1)	Number (percent) of **dehydration** AEs followed by evidence of **liver** injury				
	No evidence of liver injury	ALT >ULN	ALT >2X ULN	ALT >3X ULN	ALT >3X ULN and TBL >2X ULN
Yes (n=4 AEs)*	2 (50%)	1 (25%)	1 (25%)	1 (25%)	1 (25%)
No (n=87 AEs)**	70 (80%)	13 (15%)	3 (3%)	1 (1%)	0
Total (n=91 AEs)	72 (79%)	14 (15%)	4 (4%)	2 (2%)	1 (1%)

All percentages are row percentages. Categories of lab values are not mutually exclusive.
Numbers are events from 73 unique pediatric patients with dehydration AEs from Exjade Study 0107.
*   missing lab data for 1 event
** missing lab data for 4 events

6.4.2   KIDNEY INJURY AFTER FEVER OR DEHYDRATION ADVERSE EVENTS

Some evidence of kidney injury was observed very commonly, after approximately half of fever AEs, regardless of whether DFS therapy dose was adjusted or withheld. When the analysis was limited to events where CREA values were WNL before the fever AE, 122 (53%) of 232 fever AEs were followed by an increase in CREA $\geq$25% or an increase in $U_{P/C}$ (Table 6.4.2.1).

Table 6.4.2.1 Proportion of **FEVER** adverse events (AEs) in Study 0107 with evidence of **KIDNEY** injury after interruption or dose adjustment of DFS therapy *where CREA was WNL prior to AE*

DFS dose was adjusted or withheld due to fever AE (action taken = 1)	Number (percent) of **fever** AEs followed by evidence of **kidney** injury			
	No evidence of kidney injury	CREA $\geq$25% increase *or* $U_{P/C}$ increase	CREA $\geq$33% increase *or* $U_{P/C}$ $\geq$0.4	CREA > ULN *or* $U_{P/C}$ $\geq$0.6
Yes (n=40 AEs)*	19 (48%)	20 (50%)	7 (18%)	2 (5%)
No (n=192 AEs)**	84 (44%)	102 (53%)	25 (13%)	14 (7%)
Total (n=232 AEs)	103 (44%)	122 (53%)	32 (14%)	16 (7%)

All percentages are row percentages. Categories of lab values are not mutually exclusive.
Numbers are events from 107 unique pediatric patients with fever AEs from Exjade Study 0107.
*   missing lab data for 1 event
** missing lab data for 5 events

Overall, 60 (48%) of 126 dehydrations AEs in 73 unique pediatric patients were followed by some degree of kidney injury based on an increase in CREA or $U_{P/C}$ compared to lab values prior to the AE. When the analysis was limited to events where CREA values were WNL before the

dehydration AE, 58 (50%) of 116 dehydration AEs were followed by an increase in CREA $\geq 25\%$ or an increase in $U_{P/C}$. Of note, 9 (8%) of 116 dehydration AEs were followed by CREA >ULN or $U_{P/C} \geq 0.6$ when DFS therapy was continued (Table 6.4.2.2). These 9 dehydration AEs occurred in 8 unique subjects and were coded as diarrhea in each case. A similar injury pattern was not observed in the small number of dehydration AEs where DFS therapy was interrupted/adjusted.

Table 6.4.2.2 Proportion of **DEHYDRATION** adverse events (AEs) in Study 0107 with evidence of **KIDNEY** injury after interruption or dose adjustment of DFS therapy *where CREA was WNL prior to AE*

DFS dose was adjusted or withheld due to dehydration AE (action taken = 1)	Number (percent) of **dehydration** AEs followed by evidence of **kidney** injury			
	No evidence of kidney injury	CREA $\geq 25\%$ increase *or* $U_{P/C}$ increase	CREA $\geq 33\%$ increase *or* $U_{P/C} \geq 0.4$	CREA > ULN *or* $U_{P/C} \geq 0.6$
Yes (n=5 AEs)*	3 (60%)	1 (20%)	0	0
No (n=111 AEs)**	47 (42%)	57 (51%)	23 (21%)	9† (8%)
Total (n=116 AEs)	50 (43%)	58 (50%)	23 (20%)	9 (8%)

All percentages are row percentages. Categories of lab values are not mutually exclusive.
Numbers are events from 73 unique pediatric patients with dehydration AEs from Study 0107.
†Note: There were 9 events in 8 unique subjects where new onset kidney injury occurred after a dehydration AE (all were diarrhea) and continuation of DFS therapy. A similar injury pattern was not observed in the small number of subjects who had DFS dose interrupted or adjusted.
* missing lab data for 1 event
** missing lab data for 6 events

Overall, results of this analysis showed that evidence of liver or kidney injury was observed commonly in Study 0107 after pediatric fever or dehydration AEs, regardless of whether or not DFS dose was interrupted/adjusted. Following dehydration or fever AEs, children receiving DFS in this study frequently developed lab values for CREA or $U_{P/C}$ in the range for which dose reduction or interruption are recommended in the current DFS label. Of note, CREA >ULN or $U_{P/C} \geq 0.6$ were observed in eight subjects with previously normal serum creatinine when DFS therapy was continued during a dehydration adverse event (diarrhea). A similar injury pattern was not observed in the small number of dehydration AEs where DFS therapy was interrupted/adjusted.

7 DISCUSSION

FDA's review team took the request from the PAC, "any data regarding safety of continued medication (deferasirox) to children who have fever", and interpreted it broadly using the PAC transcript, the medical records of the index case, and the Exjade product information. Based on this review, we developed a plan to evaluate cases of fever or dehydration.

7.1 FEVER OR DEHYDRATION

Our review of fever or dehydration used clinical trial data, FAERS cases, and a literature review to evaluate these adverse events as possible indicators of increased risk of continued use of DFS.

Analysis of Study CICL670A0107 showed that increases in CREA or $U_{P/C}$, in the range for which the current DFS label recommends dose reduction or interruption, were often observed following fever or dehydration AEs in children receiving DFS. While this *post hoc* analysis of clinical trial safety data provides a useful perspective to assess the relationship of DFS interruption or continuation during fever or dehydration AEs with subsequent signs of liver or kidney injury, there are important limitations that preclude formal statistical inferences. The comparison groups (adjustment/interruption versus continuation) were defined post-baseline. In addition, fever or dehydration AEs were identified based on descriptions of clinical adverse events provided by study site investigators in the case report forms, which would not be expected to capture all signs and symptoms that may have occurred during an acute pediatric illness, and could contribute to misclassification or under ascertainment of fever or dehydration AEs. Nonetheless, while these findings should be considered exploratory and hypothesis-generating, the frequent occurrence of laboratory evidence of acute kidney injury, in the range where DFS dosage adjustment or interruption is recommended in current labeling, seems a robust observation and is clinically relevant. In light of these results, and the known dose-related nephrotoxicity of DFS, we consider the benefit risk ratio to be altered during a dehydration/hypovolemia AE in children, and until there is resolution. The data for an increased risk of hepatic injury with fever or dehydration AEs is less clear.

FAERS data alone are not a reliable tool for determining the effect of DFS continuation or interruption in the fever and dehydration groups on subsequent renal/hepatic outcomes. The FAERS data analysis of fever and dehydration cases found a higher proportion of hepatic and/or renal AEs with fever, dehydration, or both among episodes in which DFS was discontinued. However, due to limitations of FAERS data, we do not have confidence in the observation that continuing DFS with fever, dehydration, or both, has an association with a lesser risk for renal and/or hepatic AEs. One of the major limitations of FAERS data is the incomplete nature of spontaneously reported information, which potentially impacts the two patient populations who comprise the "continue DFS" and "discontinue DFS" groups, and undermines our ability to determine their historical and contemporary risks for AEs. Although the proportion of cases with reported renal and/or hepatic impairment is larger for those who discontinued DFS, these patients could have been selected for discontinuation based on poor clinical status (channeling bias) either prior to, or contemporaneous with this event. In addition, it is challenging to assess whether the renal and hepatic AEs occurred after the onset of fever and/or dehydration, or whether they preceded the fever and/or dehydration event, but were identified after the onset in association with other evaluations of the acute illness by a healthcare provider. Further, the definition of "continue DFS" exposure at the time of fever or dehydration was modeled after an intent-to-treat approach. In total, 24 of 69 (35%) patients who continued DFS reported missing doses at some point during the fever or dehydration event, so exposure among the "continue DFS" group may vary, but reflects genuine usage patterns among this pediatric population. On the same note, the half-life of DFS is approximately 8-16 hours.[5] A patient with normal hepatic and renal function will not completely eliminate a DFS dose for approximately 5 half-lives, or 40 to 80 hours. Patients who discontinued DFS still have systemic drug exposure due to the DFS half-life, which is prolonged in the setting of hepatic or renal impairment. Additional limitations

are listed in Appendix C. We conclude that our analysis of FAERS data, with regard to interruption or continuation of DFS during fever or dehydration AEs, did not provide actionable observations for this specific safety question.

Our review of the literature did not identify reports of fever as a risk factor for subsequent adverse events. This is an important distinction from the implication of fever with the iron chelators, deferiprone or deferoxamine. Deferiprone has a Warning to interrupt therapy if patients "experience any symptoms indicative of infection", due to the risk of severe neutropenia and associated overwhelming bacterial infections.[13] Deferoxamine has a Precaution for specific infections, for which susceptibility may be enhanced by deferoxamine, and for which fever can be a presenting sign.[14] We also did not identify literature reports in which dehydration was a probable causal factor in development of renal adverse events. The cases in which there was an association between dehydration and renal adverse events were confounded by exposure to additional medications with nephrotoxic risks.

7.2 ADDITIONAL ONGOING SAFETY EVALUATIONS

The PAC's request for review of pediatric safety data for DFS resulted in safety evaluations in addition to those associated with fever and dehydration.

- Hyperammonemia
  - We are evaluating 14 cases with hyperammonemia from FAERS. These cases included patients with hepatic injury and failure, renal injury and failure, and encephalopathy. The majority of children were ages 2 to 6. Three cases, including the initially presented case, had a fatal outcome.

- Use of higher doses in young children
  - We are reviewing the clinical trial safety data of the experience of children ages 2 to 6 who received DFS doses greater than 30 mg per kg per day, and the experience of children who received doses of DFS greater than 25 mg per kg per day when serum ferritin, as a measure of body iron burden, showed a trend of decreasing and was less than 1000 mcg/L.

- Dose modification with decreased renal function in the pediatric age group
  - The pediatric nephrology review found that it was appropriate to assume that the clinical pharmacology of Exjade in renally impaired adults and pediatric patients should be the same, but that the renal toxicity resulting from the increased Exjade exposure in this setting may be different between adults and pediatric patients.

- Predictability of exposure and pharmacogenomic effects
  - These are among the topics addressed in the information request to the sponsor, which addressed multiple aspects of drug metabolism and pharmacokinetics in children. (See sections 5.1 and 5.2)

In addition, data from a pediatric registry study, "A 5 year observational study (registry) of children aged 2 to <6 years at enrollment with transfusional hemosiderosis treated with DFS" is under review.

8 CONCLUSIONS

The analysis of clinical trial data showed that increases in CREA or $U_{P/C,}$ in the range for which the current DFS label recommends dose reduction or interruption, were often observed following fever or dehydration AEs in children receiving DFS. We judge this finding to alter the benefit risk ratio during signs or symptoms of dehydration/hypovolemia with or without fever in children, and until there is resolution. Limitations of FAERS data analyses of fever or dehydration cases did not provide actionable observations about the influence of drug interruption on renal or hepatic AEs from that source.

9   APPENDICES

9.1   APPENDIX A: FEVER AND DEHYDRATION-RELATED PREFERRED TERMS USED IN FAERS SEARCHES

MedDRA 19.1:

Fever-related PTs: *hyperpyrexia; hyperthermia; pyrexia; body temperature increased*

Dehydration-related PTs: *abdominal distension; abnormal loss of weight; blood pressure decreased; circulatory collapse; dehydration; diarrhoea; electrolyte imbalance; faecal volume increased; fluid replacement; hypernatraemia; hypokalaemia; hyponatraemia; hypoperfusion; hypophagia; hypotension; hypovolaemia; hypovolaemic shock; lethargy; metabolic acidosis; metabolic alkalosis; mucosal dryness; oliguria; peripheral circulatory failure; shock; shock symptom; specific gravity urine abnormal; stress polycythaemia; tachycardia; thirst; urine output decreased; weight decreased; confusional state; dry mouth; heart rate increased; mental status changes; respiratory rate increased; skin turgor decreased; tachypnoea; vomiting; gastroenteritis; capillary nail refill test abnormal; anuria; urine sodium increased; blood bicarbonate decreased; blood urea nitrogen/creatinine ratio increased; decreased appetite; diet refusal; eating disorder; eating disorder symptom; anorexia and bulimia syndrome; anorexia nervosa*

FAERS reports were first identified based on PTs related to fever or dehydration as noted in list above. For the event of fever, the narratives were reviewed, and the reports were included if they contained the term fever or a fever-related PT. For the reports with PTs related to dehydration, these reports were further evaluated to confirm that a patient experienced a clinical dehydration event, which could be confirmed by supporting factors indicating volume loss (i.e., diarrhea, vomiting, hemorrhage, etc.). However, reports with lab abnormalities (e.g., hypokalemia) or aberrant vital signs (e.g., tachycardia) were not automatically considered to be a dehydration event without additional support from the narrative (e.g., in the setting of decreased oral intake, diarrhea, vomiting, etc.). For example, a patient who experiences tachycardia following a blood transfusion would be identified in the FAERS search due to the PT of "tachycardia", but the report would not be included as a dehydration event due to the clinical setting in which the tachycardia occurred.

9.2 APPENDIX B: SEQUENCE OF RENAL AND/OR HEPATIC IMPAIRMENT OUTCOMES FOR PATIENTS WITH MULTIPLE EPISODES OF FEVER AND/OR DEHYDRATION (N=17 PATIENTS)

Case #	Episode 1			Episode 2			Episode 3			Episode 4		
	Fever or Dehydration	Deferasirox therapy disposition	Renal or Hepatic Impairment	Fever or Dehydration	Deferasirox therapy disposition	Renal or Hepatic Impairment	Fever or Dehydration	Deferasirox therapy disposition	Renal or Hepatic Impairment	Fever or Dehydration	Deferasirox therapy disposition	Renal or Hepatic Impairment
10470960	DH	C	None	DH	C	None	F	C	None	--	--	--
10477545	F	C	None	F	DC	None	--	--	--	--	--	--
10557999	DH	DC	HP	DH	DC	HP	--	--	--	--	--	--
10645307	DH	C	None	F	C	None	DH	C	None	--	--	--
10664115	DH	C	None	DH	DC	None	--	--	--	--	--	--
10746437	F	C	HP	F	C	None	--	--	--	--	--	--
11159931	F	DC	None	F, DH	C	None	--	--	--	--	--	--
11209261	F,DH	U	HP	DH	DC	R,HP	--	--	--	--	--	--
11664587	DH	C	None	F	C	None	F	C	None	F	C	None
11664632	F	C	None	F	C	None	--	--	--	--	--	--
12188850	DH	DC	None	F	DC	None	--	--	--	--	--	--
12576044	F,DH	C	HP	F	DC	HP	--	--	--	--	--	--
6105750	DH	C	None	DH	DC	R	--	--	--	--	--	--
6764487	F,DH	C	HP	F	DC	None	--	--	--	--	--	--
7251848	F	C	None	F,DH	C	R,HP	--	--	--	--	--	--
9695103	DH	C	None	DH	C	None	--	--	--	--	--	--
9880694	DH	U	None	DH	C	R	--	--	--	--	--	--

F=Fever, DH=Dehydration
C=Continue, DC=Discontinue, U=Unknown
R=Renal impairment, HP=Hepatic impairment

9.3 APPENDIX C: ADDITIONAL LIMITATIONS OF FAERS DATA

Additional limitations of the FAERS data include the following: many cases were not spontaneous reports, but were patients under active surveillance due to involvement in a clinical trial or a patient assistance program. It is not possible to determine what impact this may have on the data. Second, calculated proportions for AEs in this analysis should not be construed as incidence rates, or compared with data from clinical trials because the true denominator cannot be determined from spontaneously reported events. Third, FAERS reports have limited information and are often incomplete. Further, among the 162 cases of fever or dehydration, the overwhelming majority (n=151) were using Exjade as the DFS product; however seven patients were using an unspecified DFS brand. Among these seven patients using an unspecified DFS product, six were likely using Exjade, as the report dates were from 2009-2014, prior to the approval of Jadenu. One of the seven patients reported DFS use in 2016, so we do not know which product was taken. An additional two patients were using Jadenu and two patients were using Asunra™, a foreign DFS containing product. Jadenu has a different dosing regimen than Exjade and this is an important limitation to consider in the overall interpretation of the results, particularly with regard to dosing.

10 REFERENCES

[1] Meeting of the Pediatric Advisory Committee. US Department of Health and Human Services, Food and Drug Administration. September 16, 2015. Print. Transcript.

[2] Cunningham MJ, Macklin EA, Neufeld EJ, et al. Complications of β-thalassemia major in North America. Blood. 2004;104:34-39.

[3] Vichinsky E. Oral Iron Chelators and the Treatment of Iron Overload in Pediatric Patients With Chronic Anemia. Pediatrics 2008; 121:1253-1258.

[4] Exjade® (deferasirox) [package insert]. Hanover, NJ: Novartis Pharmaceuticals Corporation; 2016.

[5] Jadenu™ (deferasirox) [package insert]. Handover, NJ: Novartis Pharmaceuticals Corporation; 2016.

[6] Ponticelli C, Musallam KM, Cianciulli P, et al. Renal complications in transfusion-dependent beta thalassaemia. Blood Rev 2010; 24:239-244.

[7] Porter JB, Elalfy MS, Taher AT, et al. Efficacy and safety of deferasirox at low and high iron burdens: results from the EPIC magnetic resonance imaging substudy. Ann Hematol 2013; 92:211–219.

[8] Allegra S, Cusatoa J, De Francia S, et al. Deferasirox pharmacokinetic evaluation in β-thalassaemia paediatric patients. Journal of Pharmacy and Pharmacology 2016; 68:1417-1421.

[9] Mattioli F, Puntoni M, Marini V, et al. Determination of deferasirox plasma concentrations: do gender, physical and genetic differences affect chelation efficacy? Eur J Haematol. 2014; 94: 310–317.

[10] Chirnomas D, Smith AL, Braunstein J, et al. Deferasirox pharmacokinetics in patients with adequate versus inadequate response. Blood. 2009; 114:4009-4013.

[11] Lee JW, Kang HJ, Choi J-Y, et al. Pharmacogenetic Study of Deferasirox, an Iron Chelating Agent. PLoS ONE 8(5): e64114.

[12] Cusato J, Allegra S, De Francia S, et al. Role of pharmacogenetics on deferasirox AUC and efficacy. Pharmacogenomics (2016) 17(6), 571–582.

[13] FerriproxTM (deferiprone) [package insert]. Rockville, MD: ApoPharma USA, Inc.; 2015

[14] Desferal® (deferoxamine mesylate) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2011