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Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date: December 16, 2024

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Product Names	**Pediatric Labeling Approval Dates**	**Application Type/Number**	**Applicant**
Exjade (deferasirox) tablet for oral suspension	December 12, 2018	NDA 021882	Novartis Pharmaceuticals Corp
Jadenu (deferasirox) tablet	December 12, 2018	NDA 206910	Novartis Pharmaceuticals Corp
Jadenu Sprinkle (deferasirox) tablet	December 12, 2018	NDA 207968	Novartis Pharmaceuticals Corp

TTT Record ID: 2024-9599

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Exjade (deferasirox) tablet for oral suspension, Jadenu (deferasirox) tablet, and Jadenu Sprinkle (deferasirox) granule in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with deferasirox in pediatric patients less than 18 years of age.

Exjade (deferasirox) tablet for oral suspension was approved on November 2, 2005, Jadenu (deferasirox) tablet for oral use on March 30, 2015, and Jadenu Sprinkle (deferasirox) granule for oral use on May 18, 2017.

Deferasirox is an iron chelator indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. It is also indicated for the treatment of chronic iron overload in patients 10 years of age and older with non-transfusion-dependent thalassemia (NTDT) syndromes, and with a liver iron (Fe) concentration (LIC) of at least 5 mg Fe per gram of dry weight and a serum ferritin greater than 300 mcg/L.

This pediatric postmarketing safety review was stimulated by the pediatric labeling change for Exjade, Jadenu, and Jadenu Sprinkle on December 12, 2018, which reported that a trial conducted in treatment naïve pediatric patients, ages 2 years to less than 18 years with transfusional iron overload (NCT02435212) did not provide additional relevant information about the safety or effectiveness of the deferasirox granules dosage form (Jadenu Sprinkle) compared to the deferasirox oral tablets for suspension dosage form (Exjade).

DPV reviewed all U.S. serious FAERS reports with deferasirox in pediatric patients less than 18 years of age from March 1, 2015, through August 14, 2024, and identified 208 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths of unlabeled events directly associated with deferasirox in pediatric patients less than 18 years of age.

DPV did not identify any new pediatric safety concerns for deferasirox at this time and will continue routine pharmacovigilance monitoring for deferasirox.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Exjade (deferasirox) tablet for oral suspension, Jadenu (deferasirox) tablet, and Jadenu Sprinkle (deferasirox) granule in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with deferasirox in pediatric patients less than 18 years of age.

1.1 PEDIATRIC REGULATORY HISTORY

Exjade (deferasirox) tablet for oral suspension was approved on November 2, 2005, Jadenu (deferasirox) tablet for oral use on March 30, 2015, and Jadenu Sprinkle (deferasirox) granule for oral use on May 18, 2017.

Deferasirox is an iron chelator indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. It is also indicated for the treatment of chronic iron overload in patients 10 years of age and older with non-transfusion-dependent thalassemia (NTDT) syndromes, and with a liver iron (Fe) concentration (LIC) of at least 5 mg Fe per gram of dry weight and a serum ferritin greater than 300 mcg/L.[1,2,3]

This pediatric postmarketing safety review was stimulated by the pediatric labeling change for Exjade, Jadenu, and Jadenu Sprinkle on December 12, 2018, which reported that a trial conducted in treatment naïve pediatric patients, ages 2 years to less than 18 years with transfusional iron overload (NCT02435212) did not provide additional relevant information about the safety or effectiveness of the deferasirox granules dosage form (Jadenu Sprinkle) compared to the deferasirox oral tablets for suspension dosage form (Exjade).

On July 13, 2015, the Office of Surveillance and Epidemiology (OSE) completed a review of postmarketing adverse event reports with a serious outcome for Exjade in pediatric patients. OSE's evaluation did not identify any new safety concerns and recommended a return to routine monitoring for adverse events with deferasirox.[4] On September 16, 2015, OSE's evaluation was presented to the Pediatric Advisory Committee (PAC). Two public presentations at this meeting raised questions among PAC members about the safety of deferasirox in young children who have fever.[5] In response to these questions DPV, Division of Epidemiology (DEPI), Division of Pediatric and Maternal Health (DPMH), Office of Clinical Pharmacology (OCP), and Office of Hematology and Oncology Products (OHOP) began an evaluation to determine if pediatric patients, who develop fever and/or dehydration in the context of an acute illness, are more susceptible to deferasirox related nephrotoxicity, hepatotoxicity, or both.

OSE completed their evaluation in April 2018 and found:

1) There is a risk of acute liver failure in children receiving deferasirox.
2) There is a risk of renal impairment associated with acute illnesses that cause volume depletion.

3) Decreased renal function results in increased levels of deferasirox which results in further decreasing renal function, with the potential for an exacerbating cycle and hepatic toxicity.
4) The risks of a high deferasirox dose and low serum ferritin are additive for the development of decreased renal function.
5) There is a risk of life-threatening adverse events when full dose deferasirox is continued when body iron burden is approaching or within the normal range.
6) An increased risk of auditory adverse events among pediatric patients was associated with use of deferasirox >25mg/kg/day and a serum ferritin < 1,000 mcg/L.[6]

The product labeling for deferasirox were updated based on these findings in May 2018.[7,8] OSE's evaluation was presented to the PAC on September 20, 2018.[9]

1.2 RELEVANT LABELED SAFETY INFORMATION FOR EXJADE

The Exjade labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Exjade labeling information, please refer to the full prescribing information.[1]

WARNING: RENAL FAILURE, HEPATIC FAILURE, and GASTROINTESTINAL HEMORRHAGE

See full prescribing information for complete boxed warning.

Exjade may cause:

- **acute kidney injury, including acute renal failure requiring dialysis and renal tubular toxicity including Fanconi syndrome (5.1)**
- **hepatic toxicity, including failure (5.2)**
- **gastrointestinal hemorrhage (5.3)**

Exjade therapy requires close patient monitoring, including laboratory tests of renal and hepatic function. (5)

----------CONTRAINDICATIONS----------

- Estimated GFR less than 40 mL/min/1.73 m^2.
- Patients with poor performance status.
- Patients with high-risk myelodysplastic syndrome (MDS).
- Patients with advanced malignancies.
- Patients with platelet counts less than 50 x 10^9/L.
- Known hypersensitivity to deferasirox or any component of Exjade.

----------WARNINGS AND PRECAUTIONS----------

- Acute Kidney Injury: Measure serum creatinine in duplicate before starting therapy. Monitor renal function during Exjade therapy and reduce dose or interrupt therapy for toxicity.
- Hepatic Toxicity: Monitor hepatic function. Reduce dose or interrupt therapy for toxicity.
- Fatal and Nonfatal Gastrointestinal Bleeding, Ulceration, and Irritation: Risk may be greater in patients who are taking Exjade in combination with drugs that have known ulcerogenic or hemorrhagic potential.
- Bone Marrow Suppression: Neutropenia, agranulocytosis, worsening anemia, and thrombocytopenia, including fatal events; monitor blood counts during Exjade therapy. Interrupt therapy for toxicity.

- Age-related Risk of Toxicity: Monitor elderly and pediatric patients closely for toxicity.
- Hypersensitivity Reactions: Discontinue Exjade for severe reactions and institute medical intervention.
- Severe Skin Reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Discontinue Exjade.

----------ADVERSE REACTIONS----------

In patients with transfusional iron overload, the most frequently occurring (greater than 5%) adverse reactions are diarrhea, vomiting, nausea, abdominal pain, skin rashes, and increases in serum creatinine. In Exjade-treated patients with NTDT syndromes, the most frequently occurring (greater than 5%) adverse reactions are diarrhea, rash, and nausea.

----------USE IN SPECIFIC POPULATIONS----------

8.4 Pediatric Use

Transfusional Iron Overload

The safety and effectiveness of Exjade have been established in pediatric patients 2 years of age and older for the treatment of transfusional iron overload.

Safety and effectiveness have not been established in pediatric patients less than 2 years of age for the treatment of transfusional iron overload.

Pediatric approval for treatment of transfusional iron overload was based on clinical studies of 292 pediatric patients 2 years to less than 16 years of age with various congenital and acquired anemias. Seventy percent of these patients had beta-thalassemia. In those clinical studies, 173 children (ages 2 to < 12 years) and 119 adolescents (ages 12 to < 17 years) were exposed to deferasirox.

A trial conducted in treatment-naïve pediatric patients, 2 to < 18 years of age with transfusional iron overload (NCT02435212) did not provide additional relevant information about the safety or effectiveness of the deferasirox granules dosage form (Jadenu Sprinkle) compared to the deferasirox oral tablets for suspension dosage form (Exjade).

Iron Overload in Non-Transfusion-Dependent Thalassemia Syndromes

The safety and effectiveness of Exjade have been established in patients 10 years of age and older for the treatment of chronic iron overload with non-transfusion-dependent thalassemia (NTDT) syndromes.

Safety and effectiveness have not been established in patients less than 10 years of age with chronic iron overload in NTDT syndromes.

Pediatric approval for treatment of NTDT syndromes with liver iron (Fe) concentration (LIC) of at least 5 mg Fe per gram of dry weight and a serum ferritin greater than 300 mcg/L was based on 16 pediatric patients treated with Exjade therapy (10 years to less than 16 years of age) with chronic iron overload and NTDT. Use of Exjade in these age groups is supported by evidence from adequate and well-controlled studies of Exjade in adult and pediatric patients.

In general, risk factors for deferasirox-associated kidney injury include preexisting renal disease, volume depletion, overchelation, and concomitant use of other nephrotoxic drugs. Acute kidney injury, and acute liver injury and failure has occurred in pediatric patients. In a pooled safety analysis, pediatric patients with higher Exjade exposures had a greater probability of renal toxicity and decreased renal function, resulting in increased deferasirox exposure and progressive renal toxicity/kidney injury. Higher rates of renal

adverse reactions have been identified among pediatric patients receiving Exjade doses greater than 25 mg/kg/day when their serum ferritin values were less than 1,000 mcg/L.

Monitoring Recommendations for pediatric patients with Transfusional Iron Overload and NTDT

It is recommended that serum ferritin be monitored every month to assess the patient's response to therapy and to minimize the risk of overchelation.

Monitor renal function by estimating GFR using an eGFR prediction equation appropriate for pediatric patients and evaluate renal tubular function. Monitor renal function more frequently in pediatric patients in the presence of renal toxicity risk factors, including episodes of dehydration, fever and acute illness that may result in volume depletion or decreased renal perfusion. Use the minimum effective dose.

Interrupt Exjade in pediatric patients with transfusional iron overload and consider dose interruption in pediatric patients with non-transfusion-dependent iron overload, for acute illnesses, which can cause volume depletion, such as vomiting, diarrhea, or prolonged decreased oral intake, and monitor more frequently. Resume therapy as appropriate, based on assessments of renal function, when oral intake and volume status are normal. Evaluate the risk benefit profile of continued Exjade use in the setting of decreased renal function. Avoid use of other nephrotoxic drugs.

Juvenile Animal Toxicity Data

Renal toxicity was observed in adult mice, rats, and marmoset monkeys administered deferasirox at therapeutic doses. In a neonatal and juvenile toxicity study in rats, deferasirox was administered orally from postpartum Day 7 through 70, which equates to a human age range of term neonate through adolescence. Increased renal toxicity was identified in juvenile rats compared to adult rats at a dose based on mg/m2 approximately 0.4 times the recommended dose of 20 mg/kg/day. A higher frequency of renal abnormalities was noted when deferasirox was administered to non-iron overloaded animals compared to iron overloaded animals.

1.3 RELEVANT LABELED SAFETY INFORMATION FOR JADENU AND JADENU SPRINKLE

The Jadenu and Jadenu Sprinkle labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For Jadenu and Jadenu Sprinkle labeling information, please refer to the full prescribing information.[2,3]

WARNING: RENAL FAILURE, HEPATIC FAILURE, and GASTROINTESTINAL HEMORRHAGE

See full prescribing information for complete boxed warning.

Exjade may cause:

- **acute kidney injury, including acute renal failure requiring dialysis and renal tubular toxicity including Fanconi syndrome (5.1)**
- **hepatic toxicity, including failure (5.2)**
- **gastrointestinal hemorrhage (5.3)**

Exjade therapy requires close patient monitoring, including laboratory tests of renal and hepatic function. (5)

----------CONTRAINDICATIONS----------

- Estimated GFR less than 40 mL/min/1.73 m^2.
- Patients with poor performance status.
- Patients with high-risk myelodysplastic syndrome (MDS).

- Patients with advanced malignancies.
- Patients with platelet counts less than 50 x 10^9/L.
- Known hypersensitivity to deferasirox or any component of Jadenu.

----------WARNINGS AND PRECAUTIONS----------

- Acute Kidney Injury: Measure serum creatinine in duplicate before starting therapy. Monitor renal function during Jadenu therapy and reduce dose or interrupt therapy for toxicity.
- Hepatic Toxicity: Monitor hepatic function. Reduce dose or interrupt therapy for toxicity.
- Fatal and Nonfatal Gastrointestinal (GI) Bleeding, Ulceration, and Irritation: Risk may be greater in patients who are taking Jadenu in combination with drugs that have known ulcerogenic or hemorrhagic potential.
- Bone Marrow Suppression: Neutropenia, agranulocytosis, worsening anemia, and thrombocytopenia, including fatal events; monitor blood counts during Jadenu therapy. Interrupt therapy for toxicity.
- Age-related Risk of Toxicity: Monitor elderly and pediatric patients closely for toxicity.
- Hypersensitivity Reactions: Discontinue Jadenu for severe reactions and institute medical intervention.
- Severe Skin Reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Discontinue Jadenu.

----------ADVERSE REACTIONS----------

In patients with transfusional iron overload, the most frequently occurring (greater than 5%) adverse reactions are diarrhea, vomiting, nausea, abdominal pain, skin rashes, and increases in serum creatinine. In deferasirox-treated patients with NTDT syndromes, the most frequently occurring (greater than 5%) adverse reactions are diarrhea, rash, and nausea.

----------USE IN SPECIFIC POPULATIONS----------

8.4 Pediatric Use

Transfusional Iron Overload

The safety and effectiveness of Jadenu have been established in pediatric patients 2 years of age and older for the treatment of transfusional iron overload.

Safety and effectiveness have not been established in pediatric patients less than 2 years of age for the treatment of transfusional iron overload.

Pediatric approval for treatment of transfusional iron overload was based on clinical studies of 292 pediatric patients 2 years to less than 16 years of age with various congenital and acquired anemias. Seventy percent of these patients had beta-thalassemia. In those clinical studies, 173 children (ages 2 to < 12 years) and 119 adolescents (ages 12 to < 17 years) were exposed to deferasirox.

A trial conducted in treatment-naïve pediatric patients, 2 to < 18 years of age with transfusional iron overload (NCT02435212) did not provide additional relevant information about the safety or effectiveness of the deferasirox granules dosage form (Jadenu Sprinkle) compared to the deferasirox oral tablets for suspension dosage form (Exjade).

Iron Overload in Non-Transfusion-Dependent Thalassemia Syndromes

The safety and effectiveness of Jadenu have been established in patients 10 years of age and older for the treatment of chronic iron overload with non-transfusion-dependent thalassemia (NTDT) syndromes.

Safety and effectiveness have not been established in patients less than 10 years of age with chronic iron overload in NTDT syndromes.

Pediatric approval for treatment of NTDT syndromes with liver iron (Fe) concentration (LIC) of at least 5 mg Fe per gram of dry weight and a serum ferritin greater than 300 mcg/L was based on 16 pediatric patients treated with deferasirox therapy (10 years to less than 16 years of age) with chronic iron overload and NTDT. Use of Jadenu in these age groups is supported by evidence from adequate and well-controlled studies of deferasirox in adult and pediatric patients.

In general, risk factors for deferasirox-associated kidney injury include preexisting renal disease, volume depletion, overchelation, and concomitant use of other nephrotoxic drugs. Acute kidney injury, and acute liver injury and failure has occurred in pediatric patients. In a pooled safety analysis, pediatric patients with higher deferasirox exposures had a greater probability of renal toxicity and decreased renal function, resulting in increased deferasirox exposure and progressive renal toxicity/kidney injury. Higher rates of renal AEs have been identified among pediatric patients receiving Exjade doses greater than 25 mg/kg/day equivalent to 17.5 mg/kg/day JADENU when their serum ferritin values were less than 1,000 mcg/L.

Monitoring Recommendations for all pediatric patients with Transfusional Iron Overload and NTDT

It is recommended that serum ferritin be monitored every month to assess the patient's response to therapy and to minimize the risk of overchelation.

Monitor renal function by estimating GFR using an eGFR prediction equation appropriate for pediatric patients and evaluate renal tubular function. Monitor renal function more frequently in pediatric patients in the presence of renal toxicity risk factors, including episodes of dehydration, fever and acute illness that may result in volume depletion or decreased renal perfusion. Use the minimum effective dose.

Interrupt Jadenu in pediatric patients with transfusional iron overload, and consider dose interruption in pediatric patients with non-transfusion-dependent iron overload, for acute illnesses, which can cause volume depletion, such as vomiting, diarrhea, or prolonged decreased oral intake, and monitor more frequently. Resume therapy as appropriate, based on assessments of renal function, when oral intake and volume status are normal. Evaluate the risk benefit profile of continued Jadenu use in the setting of decreased renal function. Avoid use of other nephrotoxic drugs.

Juvenile Animal Toxicity Data

Renal toxicity was observed in adult mice, rats, and marmoset monkeys administered deferasirox at therapeutic doses. In a neonatal and juvenile toxicity study in rats, deferasirox was administered orally from postpartum Day 7 through 70, which equates to a human age range of term neonate through adolescence. Increased renal toxicity was identified in juvenile rats compared to adult rats at a dose based on mg/m2 approximately 0.4 times the recommended dose of 20 mg/kg/day. A higher frequency of renal abnormalities was noted when deferasirox was administered to non-iron overloaded animals compared to iron overloaded animals.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy[*]	
Date of search	August 15, 2024
Time period of search	March 1, 2015[†] - August 14, 2024
Search type	RxLogix Pediatric Focused Review Alert - DPV

Table 1. FAERS Search Strategy*	
Product terms	Product Active Ingredient: Deferasirox Product Name: Deferasirox, Deferasirox oral, Deferasirox oral granules
MedDRA search terms (Version 27.0)	All Preferred Terms
Other search terms‡	Case Seriousness: Serious

* See Appendix A for a description of the FAERS database.
† The FAERS search period for the most recently completed DPV pediatric postmarketing pharmacovigilance review for deferasirox ended on February 28, 2015.
‡ For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.
Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities

3 RESULTS

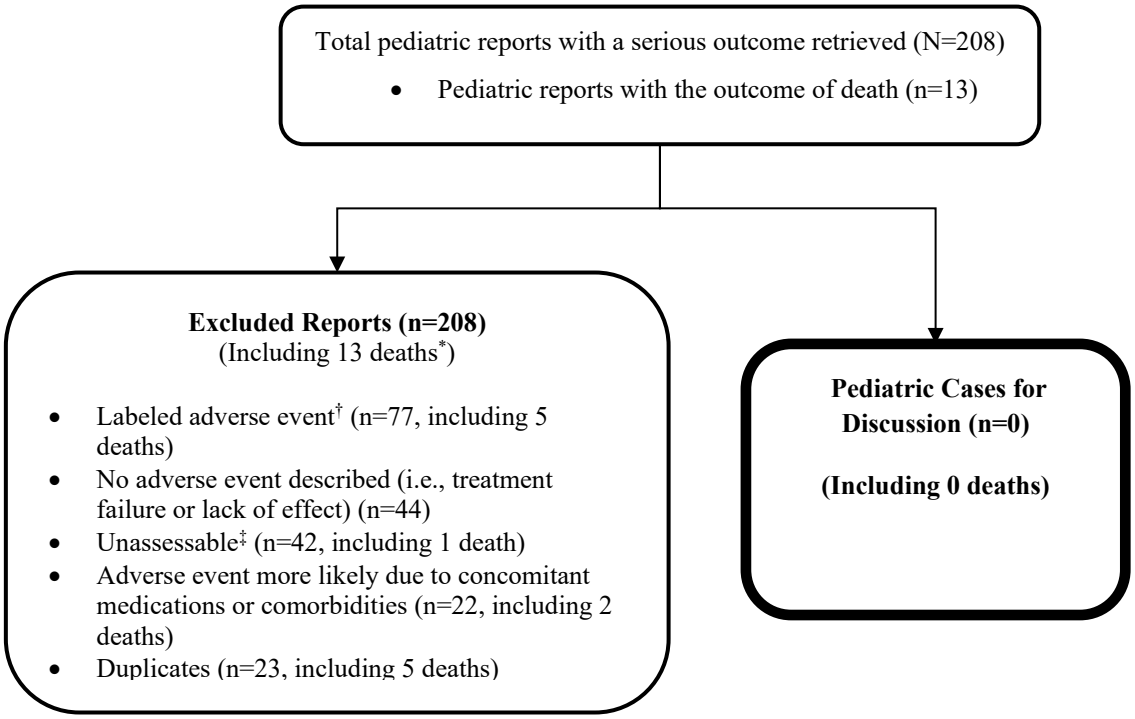
3.1 FAERS

3.1.1 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 208 U.S. serious pediatric reports for patients less than 18 years old from March 1, 2015, through August 14, 2024.[a] We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all 208 reports from the case series for the reasons listed in Figure 1. Figure 1 presents the selection of cases for the pediatric case series.

[a] Includes two pediatric reports that were identified among reports not coded with an age.

Figure 1. Selection of U.S. Serious Pediatric Cases with Deferasirox



* Thirteen excluded U.S. FAERS reports described fatal outcomes. After accounting for duplicate reports (n=5), we identified eight unique cases describing fatal outcomes. Five cases described death following hepatic failure, which is described in the BOXED WARNING and WARNINGS AND PRECAUTIONS sections of the product labeling. There were no features suggestive of new or worsening features of hepatic failure that would represent a new safety signal. Two cases described fatalities related to complications of underlying disease (acute chest syndrome n=1, acute myeloid leukemia n=1). One case lacked sufficient clinical information to understand the fatal event or determine causality with deferasirox.

† Labeled adverse event does not represent increased severity.

‡ Unassessable: The report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), the information is contradictory, or information provided in the report cannot be supplemented or verified.

3.1.2 Summary of U.S. Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.3 Summary of U.S. Serious Non-Fatal Pediatric Cases (N=0)

There are no non-fatal pediatric adverse event cases for discussion.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with deferasirox in pediatric patients less than 18 years of age from March 1, 2015, through August 14, 2024, and identified 208 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths of unlabeled events directly associated with deferasirox in pediatric patients less than 18 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for deferasirox at this time and will continue routine pharmacovigilance monitoring for deferasirox.

6 REFERENCES

1. Exjade (deferasirox) [package insert]. East Hanover, NJ. Novartis Pharmaceuticals Corporation. Revised July 2020.

2. Jadenu (deferasirox) [package insert]. East Hanover, NJ. Novartis Pharmaceuticals Corporation. Revised July 2020.

3. Jadenu (deferasirox) [package insert]. East Hanover, NJ. Novartis Pharmaceuticals Corporation. Revised July 2020.

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7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.