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Office of Surveillance and Epidemiology**

Pediatric Postmarketing Pharmacovigilance

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Product Name: Ofirmev (acetaminophen) injection

**Pediatric Labeling
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Application Type/Number: 022450

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OSE RCM #: 2018-1656

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Ofirmev (acetaminophen) injection in pediatric patients through age <17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on adverse events associated with Ofirmev in U.S. pediatric patients reporting a serious outcome.

The FDA approved Ofirmev on November 2, 2010 for the management of mild-to-moderate pain, moderate-to-severe pain with adjunctive opioid analgesics, and reduction of fever. The approved pediatric labeling is for mild-to-moderate pain and moderate-to-severe pain in ages 2 years or older and reduction of fever.

We reviewed all serious FAERS reports with Ofirmev in the pediatric population through age <17 years during the period March 31, 2012 to July 31, 2018 and identified one fatal case and three serious non-fatal cases. In the fatal case, Ofirmev was used for a labeled indication of fever for a 7-year-old patient with relapsed stage 4 high-risk neuroblastoma. The patient developed fulminant hepatic failure that progressed to a fatal multiorgan failure. The autopsy was consistent with a drug-related hepatotoxicity as a primary cause of death. This case was confounded with concomitant drugs, including fenretinide, ceftriaxone, and ibuprofen, all of which may have contributed to the fatal event of fulminant hepatic failure. There were three serious non-fatal cases, including two cases of hepatotoxicity and one case of toxic epidermal necrolysis (TEN). One of the cases that described hepatotoxicity is from medication dosing errors with Ofirmev at doses that exceeded the labeled recommendation. The other report described a 1-month old patient who developed cytolytic hepatitis after receiving Ofirmev, but the case was confounded by co-administration of cefotaxime, and intravenous amoxicillin which are both labeled for hepatic dysfunction. The TEN case described an 11-year-old patient who received Ofirmev at an unspecified time and developed TEN symptoms. This case lacked information to assess temporal association between Ofirmev and TEN and the causality assessment was complicated by concomitant medications including ibuprofen, piperacillin-tazobactam, that are also labeled for severe cutaneous adverse reactions, including TEN.

The pediatric safety profile described in the FAERS cases is consistent with the known safety profile and the current Ofirmev label. DPV did not identify any new pediatric safety concerns for Ofirmev and recommends no regulatory action at this time. We will continue to monitor all adverse events associated with the use of Ofirmev injection.

1 INTRODUCTION

This review evaluates Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) reports for Ofirmev (acetaminophen) injection in pediatric patients through <17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on adverse events associated with Ofirmev in U.S. pediatric patients reporting a serious outcome.

1.1 PEDIATRIC REGULATORY HISTORY

Ofirmev is an intravenous (IV) acetaminophen formulation for the management of acute pain and fever. Ofirmev was approved by the FDA on November 2, 2010, for use in both adults and children age 2 years and older for:

- Management of mild-to-moderate pain
- Management of moderate-to-severe pain with adjunctive opioid analgesics, and
- Reduction of fever

At the time of initial new drug application (NDA) approval, the Sponsor was granted a deferral for the PREA postmarketing requirement that included a randomized, double-blind, adequately controlled study of efficacy, safety, pharmacokinetics, and pharmacodynamics of IV acetaminophen for the treatment of acute pain in pediatric patients from 0 to 2 years of age. Several Pediatric Written Requests (PWRs) were also issued, which specified that a superiority trial (opioid with add-on acetaminophen superior to opioid with add-on placebo) be performed in infants younger than 24 months old.¹

The Sponsor submitted an efficacy supplement that included one study (Study NCT01635101),² a Randomized, Placebo-Controlled, Multicenter Study of the Efficacy, Pharmacokinetics and Pharmacodynamics of Intravenous Acetaminophen For the Treatment of Acute Pain in Pediatric Patients on April 29, 2016 intended to fulfill both PWR and PREA requirements.¹ Pediatric patients less than 2 years of age, including neonates from 28 to 40 weeks gestational age at birth, who had undergone surgery or traumatic injury where an IV analgesic would be needed to manage pain for at least 24 hours were included in the study. Study patients were randomized to receive opioid plus IV acetaminophen or opioid plus placebo. The study consisted of 198 pediatric patients (128 in the opioid plus IV acetaminophen group and 70 in the opioid plus placebo group). The study results failed to demonstrate the efficacy of Ofirmev injection in pediatric patients less than 2 years of age. The study demonstrated no statistical significance differences between Ofirmev and placebo for both primary endpoint (total rescue opioid consumption during 24 hours after Ofirmev) and secondary endpoints (number of rescue doses and time to first rescue medication). The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) determined that the data were not adequate to establish labeling changes for the treatment of pain in children younger than 2 years old.

The Sponsor also submitted data from Study MNK14501041, a Single-Dose, Open-Label Study Comparing the Plasma Acetaminophen Concentrations with Blood Samples Collected at the Same Time with Different Blood Drawing Routes and Collection Methods in Health Subjects, to

cross-validate bioanalytical methods used for the analysis of acetaminophen in plasma, venous dried blood samples, and capillary dried blood samples. The data submitted showed that acetaminophen concentrations in neonates and infants following the proposed doses (12.5 mg/kg in neonates and 15 mg/kg in infants) are generally consistent with concentrations observed in adults following the approved dosing regimen.³ Based on the pharmacokinetic and safety data available, Ofirmev was approved for fever reduction in pediatric patients younger than two years old on January 1, 2017.

DPV previously evaluated postmarketing adverse event reports with a serious outcome for Ofirmev in pediatric patients. DPV's evaluation, dated June 11, 2012, was prompted by the initial approval of Ofirmev on November 2, 2010.⁴ FDA presented DPV's evaluation to the Pediatric Advisory Committee (PAC) on September 11, 2012. DPV did not identify any new safety concerns, and recommended return to routine monitoring for adverse events with Ofirmev.

1.2 RELEVANT LABELED SAFETY INFORMATION⁵

Warning: risk of medication errors and hepatotoxicity

Take care when prescribing, preparing, and administering Ofirmev Injection to avoid dosing errors which could result in accidental overdose and death.

Ofirmev contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed the recommended maximum daily limits, and often involve more than one acetaminophen-containing product (5.1).

-----CONTRAINDICATIONS-----

Acetaminophen is contraindicated:

- In patients with known hypersensitivity to acetaminophen or to any of the excipients in the IV formulation. (4)
- In patients with severe hepatic impairment or severe active liver disease. (4)

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

- Administration of acetaminophen in doses higher than recommended (by all routes of administration and from all acetaminophen-containing products including combination products) may result in hepatic injury, including the risk of liver failure and death. (5.1)
- Use caution when administering acetaminophen in patients with the following conditions: hepatic impairment or active hepatic disease, in cases of alcoholism, chronic malnutrition, severe hypovolemia, or severe renal impairment (creatinine clearance \leq 30 mL/min). (5.1)
- Discontinue Ofirmev immediately at the first appearance of skin rash and if symptoms associated with allergy or hypersensitivity occur. Do not use in patients with acetaminophen allergy. (5.2, 5.4)
- Take care when prescribing, preparing, and administering Ofirmev injection to avoid dosing errors which could result in accidental overdose and death. (5.3)

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

The most common adverse reactions in patients treated with Ofirmev were nausea, vomiting, headache, and insomnia in adult patients; nausea, vomiting, constipation, and pruritus in pediatric patients. (6.1)

Section 8 USE IN SPECIFIC POPULATIONS, the Pediatric Use subsection includes the following information:

8.4 Pediatric Use

Treatment of Acute Pain

The safety and effectiveness of Ofirmev for the treatment of acute pain in pediatric patients ages 2 years and older is supported by evidence from adequate and well-controlled studies of Ofirmev in adults and safety and pharmacokinetic data from adult and 483 pediatric patients across all age groups [see *Dosage and Administration (2.3) and Pharmacokinetics (12.3)*].

The effectiveness of Ofirmev for the treatment of acute pain in pediatric patients younger than 2 years of age has not been established.

In patients younger than 2 years, efficacy was not demonstrated in a double-blind, placebo-controlled study of 198 pediatric patients younger than 2 years. Pediatric patients less than 2 years of age, including neonates from 28 to 40 weeks gestational age at birth, were randomized to receive opioid plus acetaminophen or opioid plus placebo. No difference in analgesic effect of intravenous acetaminophen, measured by assessment of reduced need for additional opioid treatment for pain control, was observed.

Treatment of Fever

The safety and effectiveness of Ofirmev for the treatment of fever in pediatric patients, including premature neonates born at ≥ 32 weeks gestational age is supported by adequate and well-controlled studies of Ofirmev in adults, clinical studies in 244 pediatric patients 2 years and older, and safety and pharmacokinetic data from 239 patients younger than 2 years including neonates ≥ 32 weeks gestational age.

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FAERS Search Strategy

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

	Search #1	Search #2 [†]
Date of search	October 15, 2018	October 15, 2018
Time period of search	March 31, 2012 [‡] - July 31, 2018	March 31, 2012 [‡] - July 31, 2018
Search type	Quick Query	Quick Query
Product terms	Product Name: Ofirmev, NDA: 022450	Product Active Ingredient: Acetaminophen
Search parameters	All ages, all outcomes, worldwide	All ages, all outcomes, worldwide Administration routes: intravenous (not otherwise specified), intravenous bolus, intravenous drip; parenteral
<p>* See Appendix A for a description of the FAERS database.</p> <p>[†] We included search strategy #2 to ensure we captured reports of Ofirmev that may have been miscoded as intravenous acetaminophen only. Any cases found in this search strategy would refer to Ofirmev product even though two generic acetaminophen (injection) products were approved by the FDA on March 22, 2016 (Sandoz, ANDA 204052) and June 13, 2016 (Custopharm, ANDA 202605), but both products were never manufactured as of March 18, 2018 (Sandoz) and July 17, 2018 (Custopharm).</p> <p>[‡] Previous review of pediatric postmarket adverse events with Ofirmev completed on June 11, 2012 reviewed the FAERS database through March 31, 2012.⁴ Therefore, this date was used to inform the start date of the search for this review.</p>		

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

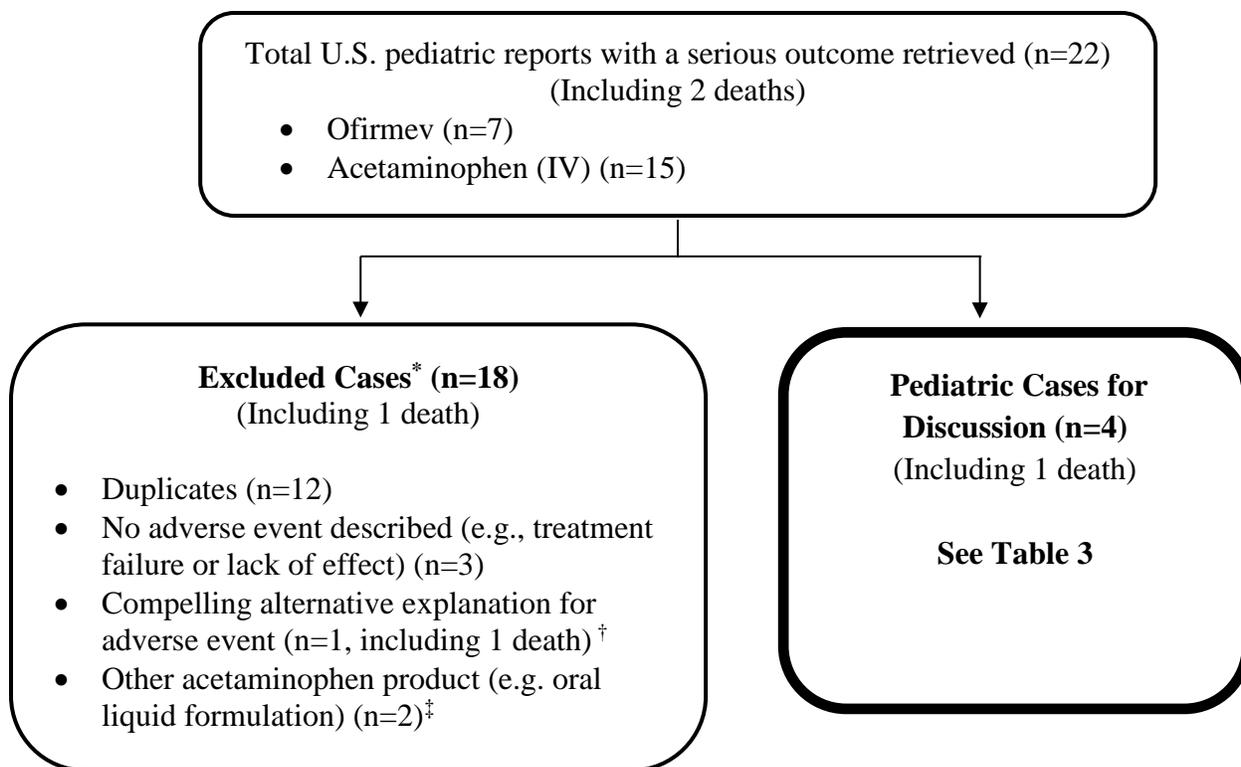
Table 2 presents the number of adult and pediatric FAERS reports from March 31, 2012 to July 31, 2018 with Ofirmev and with IV acetaminophen, respectively.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA from March 31, 2012 to July 31, 2018 with Both Ofirmev, NDA 022450 and Acetaminophen (Injection) FAERS Search Strategies (see Table 1)			
	All Reports (U.S.)	Serious[†] (U.S.)	Death (U.S.)
Adults (≥ 17 years)	1482 (309)	1379 (209)	241 (64)
Pediatrics (0 - <17 years)	174 (38)	157 (22)	14 [‡] (2)
* May include duplicates and transplacental exposures, and have not been assessed for causality			
[†] For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.			
[‡] See Figure 1. Two additional report of pediatric death was identified among reports not reporting an age.			

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

Our FAERS searches retrieved 22 U.S. pediatric reports with a serious outcome from March 31, 2012 to July 31, 2018. Although we reviewed all U.S. pediatric reports in FAERS with a serious outcome, we excluded reports from the case series for further discussion for various reasons, such as if the adverse event had compelling alternative explanations (e.g., the report was confounded by co-morbid diseases or concomitant medications), the report pertained to lack of efficacy, or the report described other acetaminophen products. We summarize the remaining cases in the sections below.

Figure 1. Selection of Serious U.S. Pediatric Cases with Ofirmev (acetaminophen) injection.



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above

† The report described a premature infant born at 24 weeks gestation with birth weight of 555 grams who received Ofirmev on day of life 11 to 12. The patient had severe lung disease with pulmonary interstitial emphysema; respiratory culture was positive for *Candida albicans* on day of life 11. The patient developed a significant episode of bradycardia and life-sustaining measures were withdrawn when the patient was 15 days old. Overwhelming infections are common complications for micro preemie patients. The clinical context suggests that complications from the patient’s underlying prematurity are plausible and compelling alternative etiologies for this fatal event.

‡ Two cases of patients who inadvertently received oral acetaminophen suspension by IV route. In one case, a 4-year-old patient received oral formulation of acetaminophen intravenously and developed emesis and cyanosis requiring intubation. The other case involved an 11-year-old who received a combination of oral acetaminophen and midazolam 15 mg via IV route preoperatively and remained unconscious for 50 minutes and was treated with antibiotics for unspecified indications.

3.1.3 Characteristics of Pediatric Cases

Appendix B contains a line listing of the 4 pediatric cases.

Table 3 summarizes the four U.S. pediatric cases in FAERS with Ofirmev reporting a serious outcome received by FDA from March 31, 2012 to July 31, 2018.

Age	1 month	1
	8 months	1
	4 years	1

Table 3. Characteristics of the FAERS U.S. Serious Pediatric Cases with Ofirmev by FDA from (N=4)		
	7 years	1
Sex	Male	2
	Female	1
	Unknown	1
Reported reason for use	Fever	2
	Unknown	2
Serious outcome*	Death	1
	Hospitalization	2
	Other Serious	1
* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. A case may have more than one serious outcome.		

3.1.4 Summary of Fatal Pediatric Cases (N=1)

FAERS Case #10784989, USA, Expedited, FDA Received Date February 9, 2015

A literature case reported a 7-year-old male with relapsed stage 4 high-risk neuroblastoma received a 5-day infusion of IV fenretinide emulsion as part of a phase I study (NCT00646230).^{6,7} The patient developed fever (38.2° C) on day 4 of IV fenretinide infusion. He received treatment with Ofirmev (10 mg/kg that was increased to 15 mg/kg on the second dose) every 4 hours and two doses of ibuprofen for fever management and ceftriaxone for possible bacteremia. Fenretinide levels doubled from 56 µM on day 4 to 100 µM on day 5 and dropped to 80 µM within two hours of fenretinide discontinuation. The patient's condition deteriorated rapidly over the next three days despite negative blood cultures. On day 7, he developed acute liver failure that progressed to fulminant hepatic failure and multisystem organ failure. The patient expired on day 20. Autopsy showed extensive hepatocellular damage and diffuse abdominal bleeding without evidence of tumor, infection, or allergic reaction. Liver findings included complete destruction of liver architecture with extensive hemorrhagic necrosis of liver parenchyma, marked bile duct proliferation, and abundant hemosiderin, consistent with cholestasis. The autopsy was consistent with drug-related hepatotoxicity as the primary fatality-inducing event.

Reviewer's comments: There is a temporal relationship between administration of Ofirmev and the other concomitant medications, ibuprofen and ceftriaxone, and the development of liver function test (LFT) abnormalities. The authors report significant elevation in fenretinide serum concentration that correlate with the rise in LFT values.⁷ The authors postulate that fenretinide was potentially causally associated with the death through a potential mechanism of a drug-drug interaction between fenretinide, ceftriaxone, and Ofirmev; however, pharmacokinetic samples within the study were not informative. The case did not contain additional details and our search of the medical literature did not yield information to contribute to the causality assessment.

3.1.5 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=3)

We identified three FAERS cases with Ofirmev in the U.S. pediatric population reporting a non-fatal serious outcome. The narrative summary is described below.

3.1.5.1 Hepatotoxicity (n=2)

FAERS Case #8878101, France, Expedited, FDA Received Date October 26, 2012

A 1-month old female developed a fever and received Ofirmev, cefotaxime and amoxicillin for three days. Baseline serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were 37 and 27 IU/L, respectively. On day 3, AST level was 936 IU/L and ALT level was 256 IU/L. The patient was diagnosed with drug induced hepatitis and viral hepatitis. All medications were discontinued and two days later, transaminase levels improved; AST level was 114 IU/L and ALT level was 104 IU/L. The patient had complete recovery with no sequelae. No further clinical details were provided.

FAERS Case #9244830, USA, Non-Expedited, FDA Received Date November 30, 2012

A literature case reported an 8-month-old patient developed liver injury and required hospitalization in the pediatric intensive care unit for 24 hours following an overdose administration of Ofirmev 113 mg/kg.^{a,8} Although serum acetaminophen concentrations never exceeded the Rumack-Matthew nomogram^b treatment line to indicate the need for N-acetylcysteine, the patient experienced unspecified liver injury and received N-acetylcysteine as a hepatoprotectant. The patient's liver injury resolved, and no additional complications occurred.

Reviewer's comments: Case #9244830 contained insufficient information to determine factors contributing to the medication error leading to the overdose of Ofirmev. In case #8878101, the patient was diagnosed with drug induced hepatitis after Ofirmev therapy. Acute acetaminophen toxicity typically results in elevations of hepatic aminotransferases starting 24 to 48 hours after acute ingestion with peak elevations seen from 72 to 120 hours after ingestion.⁹ The patient has substantial elevation of hepatic aminotransferases on day 3 that follows the patterns of acetaminophen hepatotoxicity, which is well characterized in Ofirmev labeling. However, no other hepatic aminotransferases were reported; therefore, a laboratory trend could not be identified with a single time point of hepatic aminotransferases. Other possible causes of cytolytic hepatitis are amoxicillin and cefotaxime, both of which are labeled for hepatic dysfunction that can result in elevations in hepatic aminotransferases and acute cytolytic hepatitis.^{10,11} The report states the patient had viral hepatitis but no further information is available regarding the diagnostic evaluation or outcome of the viral hepatitis. This report describes a temporal association between Ofirmev and hepatitis and the reported aminotransferase level improvement following drug discontinuation represents a positive dechallenge. However, interpretation of these data is difficult in the setting of concomitant medication and limited clinical history.

^a Approved dosage is 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day.

^b Heard KJ. Acetylcysteine for acetaminophen poisoning. *N Engl J Med.* 2008;359(3):285-292.

3.1.5.2 Toxic Epidermal Necrolysis (TEN) (n=1)

FAERS Case #14319310, USA, Expedited, FDA Received Date December 22, 2017

An 11-year-old African-American male with a history of gastroschisis, splenectomy, and multivisceral transplant consisting of liver, stomach, pancreas, small and large intestines, developed Toxic Epidermal Necrolysis (TEN) after Ofirmev treatment. Concomitant medications included ibuprofen and piperacillin-tazobactam; information about additional immunosuppressive therapy following transplant was not reported. The patient showed signs of moderate to severe rejection following transplantation and remained hospitalized for a prolonged period with multiple bacterial and viral infections. Approximately four months after his transplant, he developed bullae with positive Nikolsky's sign on his face and mouth which gradually progressed over the next two months to cover an estimated 40% of his body including his scalp, face, chest, limbs, and abdomen. He underwent an infectious workup that was negative. Biopsy of the lesions showed apoptotic keratinocytes with epithelial necrosis consistent with TEN. The reaction was thought to be secondary to ibuprofen, IV acetaminophen or piperacillin-tazobactam. Initial conservative management with frequent wound care failed. The patient then underwent treatment with therapeutic plasma exchange and IV immune globulin and had almost immediate improvement in the appearance of his lesions. The patient displayed a severe leukemoid reaction after completing plasma exchange. The patient's skin was completely healed with only patches of hypopigmentation by the time of discharge two months later.

Reviewer's comments: Ofirmev is labeled for TEN in Section 5.2 of the Warnings and Precautions section of the product label.⁵ Ibuprofen and piperacillin-tazobactam are also labeled for the TEN in Sections 5.9 and 5.2 of the Warnings and Precautions section of their respective product labels.^{12,13} In clinical practice, patients with this clinical course typically require varied pharmaceutical interventions, however, the report lacks information regarding other concomitant products that may have contributed to this adverse event. Of note, the medical literature contains reports of TEN and TEN-like reactions following hematopoietic stem cell transplantation and liver transplantation as a severe cutaneous manifestation of acute graft versus host disease (GVHD).¹⁴ It is not possible to determine if TEN developed secondary to any of the labeled drugs or the patient's underlying transplant rejection.

4 DISCUSSION

We reviewed all serious FAERS reports with Ofirmev in the pediatric population ages 0 through <17 years from March 31, 2012 to July 31, 2018. Of the reports reviewed, there was one fatal case and three non-fatal pediatric U.S. cases. In the fatal case, Ofirmev was used for a labeled indication of fever for a 7-year-old patient and resulted in hepatic failure that led to multisystem organ failure and death; the events occurred in the context of multiple concomitant medications that may have also contributed to fulminant hepatic failure. In the non-fatal reports, one case of medication dosing errors that resulted in the use of Ofirmev at doses exceeding the labeled recommendation. Medication errors are currently labeled in the Boxed Warning and the Warnings and Precautions (5.3) sections of the Ofirmev label. Other non-fatal reports included a case of cytolytic hepatitis and TEN, which are labeled in the Warnings and Precautions (5.1 and 5.2, respectively). Both of these cases were confounded with concomitant medications and had limited information which precluded a meaningful causality assessment. The pediatric safety

profile described in the FAERS cases is consistent with the known safety profile and the current Ofirmev label. There were no new safety signals identified in this case series.

5 CONCLUSION

The pediatric safety profile described in the FAERS cases is consistent with the known safety profile and the current Ofirmev label. DPV did not identify any new pediatric safety concerns for Ofirmev at this time.

6 RECOMMENDATION

DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of Ofirmev.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

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 the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

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 or not 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.

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=4)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	10/26/2012	8878101	1	2012CP000140	Expedited	0.083	Female	USA	OT
2	11/30/2012	9244830	1	2012CP000098	Non-Expedited	0.667	Not reported	USA	HO
3	02/09/2015	10784989	1	2733296	Expedited	7	Male	USA	DE
4	12/22/2017	14319310 (13956873, 11844681, 11863387, 11866534, 11867098, 13107250)†	1	US-MALLINCKRODT- T201506107	Expedited	4	Male	USA	HO

* As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case may have more than one serious outcome.

Abbreviations: DE=Death, HO=Hospitalization, OT=Other medically significant

† Duplicate cases

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUPRAT N SAELY
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