Department of Health and Human Services
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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	May 12, 2025
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Product Name:	SMOFlipid (lipid injectable emulsion) for intravenous use
Pediatric Labeling Approval Date:	March 22, 2022
Application Type/Number:	NDA 207648
Applicant:	Fresenius Kabi USA, LLC
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for SMOFlipid (lipid injectable emulsion) for intravenous use in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with SMOFlipid in pediatric patients.

SMOFlipid is a sterile, homogenous lipid injectable emulsion supplied as 20 g of lipid/100 mL in 100 mL single-dose Flexible Container, 50 g of lipid/250 mL in 250 mL single-dose Flexible Container, 100 g of lipid/500 mL in 500 mL single-dose Flexible Container, and 200 g of lipid/1000 mL in 1000 mL Pharmacy Bulk Package. SMOFlipid was initially approved in the U.S. on July 13, 2016, for use in adults as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. On March 22, 2022, FDA approved expanding the SMOFlipid indication to include use in adult and pediatric patients, including term and preterm neonates, as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.

This pediatric postmarketing safety review was prompted by pediatric labeling on March 22, 2022. DPV has not previously presented a pediatric postmarketing pharmacovigilance review for SMOFlipid for the Pediatric Advisory Committee.

DPV reviewed all U.S. serious FAERS reports with SMOFlipid in pediatric patients less than 18 years of age from July 13, 2016 – February 25, 2025, and identified 34 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 directly associated with SMOFlipid in pediatric patients less than 18 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for SMOFlipid (lipid injectable emulsion) for intravenous use in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with SMOFlipid in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

SMOFlipid is a sterile, homogenous lipid injectable emulsion supplied as 20 g of lipid/100 mL in 100 mL single-dose Flexible Container, 50 g of lipid/250 mL in 250 mL single-dose Flexible Container, 100 g of lipid/500 mL in 500 mL single-dose Flexible Container, and 200 g of lipid/1000 mL in 1000 mL Pharmacy Bulk Package. SMOFlipid was initially approved in the U.S. on July 13, 2016, for use in adults as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.[1] On March 22, 2022, FDA approved expanding the SMOFlipid indication to include use in adult and pediatric patients, including term and preterm neonates, as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.[2]

This pediatric postmarketing safety review was prompted by pediatric labeling on March 22, 2022. DPV has not previously presented a pediatric postmarketing pharmacovigilance review for SMOFlipid for the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

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

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

- Known hypersensitivity to fish, egg, soybean, peanut or any of the active or inactive ingredients. (4)
- Severe disorders of lipid metabolism characterized by hypertriglyceridemia (serum triglycerides >1,000 mg/dL). (4, 5.7)

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

- Clinical Decompensation with Rapid Infusion of Intravenous Lipid Emulsion in Neonates and Infants: Acute respiratory distress, metabolic acidosis, and death after rapid infusion of intravenous lipid emulsions have been reported. (5.1, 8.4)
- Parenteral Nutrition-Associated Liver Disease (PNALD): Increased risk in patients who receive parenteral nutrition for greater than 2 weeks, especially preterm neonates. Monitor liver tests; if abnormalities occur, consider discontinuation or dosage reduction. (5.2, 6.1, 8.4)
- Hypersensitivity Reactions: Monitor for signs or symptoms. Discontinue infusion if reactions occur. (5.3)
- Risk of Infections, Fat Overload Syndrome, Refeeding Syndrome, Hypertriglyceridemia, and Essential Fatty Acid Deficiency: Monitor for signs and symptoms; monitor laboratory parameters. (5.4, 5.5, 5.6, 5.7, 5.9)
- Aluminum Toxicity: Increased risk in patients with renal impairment, including preterm neonates. (5.8, 8.4)

----------ADVERSE REACTIONS----------
Most common adverse drug reactions (≥5%) from clinical trials in adults were nausea, vomiting, and hyperglycemia. Most common adverse drug reactions (≥5%) from clinical trials in pediatric patients were anemia, vomiting, increased gamma-glutamyltransferase, and nosocomial infection. (6.1)

8.4 Pediatric Use

The safety and effectiveness of SMOFlipid have been established as a source of calories and essential fatty acids for PN when oral or enteral nutrition is not possible, insufficient, or contraindicated in pediatric patients, including term and preterm neonates. Use of SMOFlipid in neonates is supported by evidence from short-term (i.e., 1-to 4-week) studies, and one study following neonates beyond 4 weeks [see Clinical Studies (14.2)]. Use of SMOFlipid in older pediatric patients is supported by evidence from a short-term (i.e., <28 days) study in pediatric patients 28 days to 12 years of age and additional evidence from studies in adults [see Clinical Studies (14)]. The most common adverse reactions in SMOFlipid-treated pediatric patients were anemia, vomiting, gamma-glutamyltransferase increased, and nosocomial infection [see Adverse Reactions (6.1)].

PNALD, also referred to as intestinal failure associated liver disease (IFALD), has been reported in pediatric patients who received SMOFlipid for more than 2 weeks. PNAC (a precursor to PNALD) was reported less frequently in SMOFlipid-treated patients compared to soybean oil lipid emulsion-treated patients in Pediatric Study 1 [see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]. Although clinically significant cases of EFAD were not observed during short-term use in pediatric clinical studies, cases of EFAD have been reported with the use of SMOFlipid in the postmarketing setting [see Warnings and Precautions (5.9), Adverse Reactions (6.1)]. Monitor pediatric patients for laboratory evidence of EFAD because they may be particularly vulnerable to neurologic complications if adequate amounts of essential fatty acids are not provided [see Warnings and Precautions (5.9)].

In the postmarketing setting, clinical decompensation with rapid infusion of intravenous lipid emulsion in neonates and infants, sometimes fatal, has been reported [see Warnings and Precautions (5.1)]. Because of immature renal function, preterm infants receiving prolonged treatment with SMOFlipid may be at risk for aluminum toxicity [see Warnings and Precautions (5.8)].

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	February 26, 2025
Time period of search	July 13, 2016† - February 25, 2025
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product term	Product active ingredient: Fish oil\medium-chain triglycerides\olive oil\soybean oil
MedDRA search terms (Version 27.1)	All Preferred Terms
Other criteria	Case Seriousness: Serious‡ Country Derived: USA
* See Appendix A for a description of the FAERS database. † SMOFlipid U.S. approval date. ‡ 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. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, USA=United States of America	

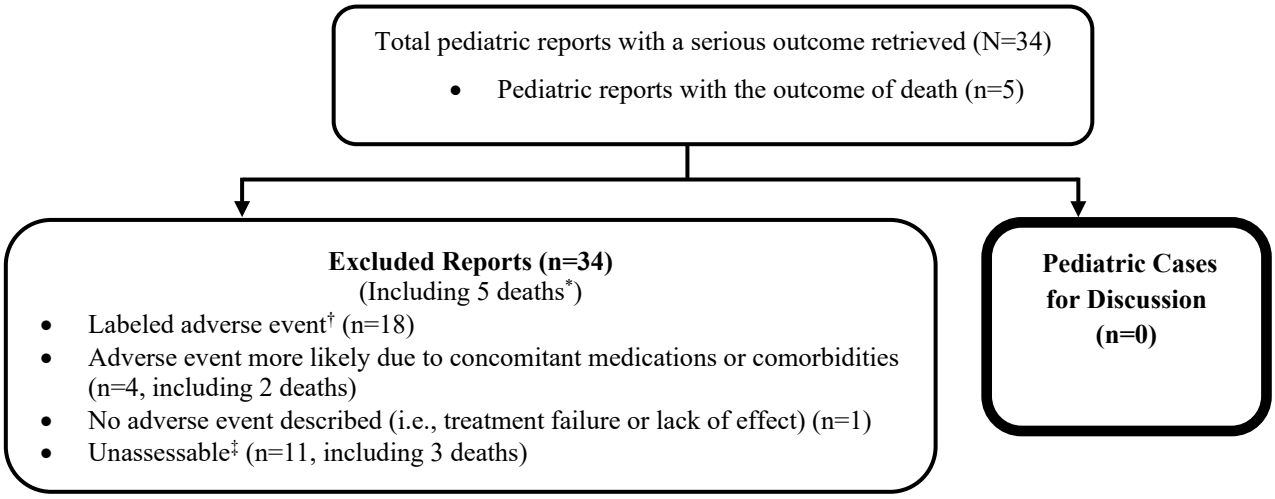
3 RESULTS

3.1 FAERS

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

Our FAERS search retrieved 34 U.S. serious pediatric reports for patients less than 18 years old from July 13, 2016 – February 25, 2025.[1] We excluded all 34 reports from the case series for the reasons listed in **Figure 1**. **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of U.S. Serious Pediatric Cases With SMOFlipid



* Five excluded U.S. FAERS reports described fatal outcomes. None of the deaths could be attributed to SMOFlipid. Three cases described patients with underlying critical conditions (extreme prematurity, gestational alloimmune liver disease with respiratory failure, and myelodysplastic syndrome post allogeneic bone marrow transplant) who received SMOFlipid for unreported indications and died at a later time; the cases did not provide sufficient clinical information to determine whether fatal events were related to SMOFlipid. Two cases described presumed neonates (ages not reported) who received SMOFlipid for parenteral nutrition and died from complications of sepsis and necrotizing enterocolitis.

† 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 SMOFlipid in pediatric patients less than 18 years of age from July 13, 2016 – February 25, 2025, and identified 34 reports; however, all reports were excluded from further discussion.

[1] Includes three pediatric reports that were identified among reports not coded with an age.

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

5 CONCLUSION

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

6 REFERENCES

1. SMOFlipid (lipid injectable emulsion) for intravenous use. [Prescribing information]. Uppsala, Sweden; Fresenius Kabi: May 2016.
2. SMOFlipid (lipid injectable emulsion) for intravenous use. [Prescribing information]. Uppsala, Sweden; Fresenius Kabi: March 2022.
3. SMOFlipid (lipid injectable emulsion) for intravenous use. [Prescribing information]. Uppsala, Sweden; Fresenius Kabi: May 2023.

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.