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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:	September 21, 2022
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Product Name:	Livalo (pitavastatin)
Pediatric Labeling Approval Date:	May 16, 2019
Application Type/Number:	NDA 022363
Applicant:	Kowa Pharmaceuticals America, Inc.
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for pitavastatin in pediatric patients less than 17 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 serious unlabeled adverse events associated with pitavastatin in pediatric patients.

Pitavastatin approved by the FDA on August 3, 2009, is indicated as an adjunctive therapy to diet in adult patients with primary hyperlipidemia or mixed dyslipidemia to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C). It is also indicated as an adjunctive therapy to diet in pediatric patients aged 8 years and older with heterozygous familial hypercholesterolemia (HeFH) to reduce elevated TC, LDL-C, and Apo B. This pediatric postmarketing pharmacovigilance review was prompted by the May 16, 2019, pediatric labeling change following the approval of pitavastatin use in pediatric patients. A pediatric safety review for pitavastatin has not previously been presented to the Pediatric Advisory Committee (PAC).

DPV-I reviewed all serious FAERS reports with pitavastatin in the pediatric population (ages 0 - < 17 years) and identified one case for our series. A single case reporting Guillain-Barre syndrome with the use of pitavastatin contained limited information to permit a meaningful causality assessment.

DPV-I did not identify any new pediatric safety concerns for pitavastatin at this time.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Livalo (pitavastatin) in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA). This review focuses on serious unlabeled adverse events associated with pitavastatin in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY[1,2]

Livalo® (pitavastatin) is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, approved by the FDA on August 3, 2009. It is currently indicated as an adjunctive therapy to diet in:

- Adult patients with primary hyperlipidemia or mixed dyslipidemia to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C).
- Pediatric patients aged 8 years and older with heterozygous familial hypercholesterolemia (HeFH) to reduce elevated TC, LDL-C, and Apo B.

Livalo was approved by the FDA for use in pediatric patients on May 16, 2019. The recommended dosage of Livalo in pediatric patients aged 8 years and older is 2 mg once daily and the maximum recommended dosage is 4 mg once daily. Livalo is supplied as a film coated tablet in 1 mg, 2 mg, and 4 mg strengths.

The safety and effectiveness of Livalo has been established in pediatric patients with HeFH aged 8 years and older in two clinical studies:

- A 12-week, double-blind, placebo-controlled trial in 82 pediatric patients 8 to 16 years of age with HeFH.
- A 52-week open-label trial in 85 pediatric patients aged 8 to 16 years of age with HeFH

In the randomized controlled trial, pharmacokinetic (PK) data showed a dose-dependent increase in plasma concentrations of pitavastatin and its major metabolite, pitavastatin lactone, at trough and 1-hour post-dose at steady state. Treatment with pitavastatin resulted in a statistically significant, clinically meaningful effect on the primary endpoint, demonstrating dose-dependent decreases in LDL-C versus placebo.[2] For the placebo-controlled trial and the single-arm open-label extension study, the safety population consisted of all randomized patients who received at least one dose of study drug. The safety data submitted in support of the supplemental application were consistent with the known safety profile of pitavastatin and the statin class in general.

The results of the placebo-controlled trial are summarized in the USE IN SPECIFIC POPULATIONS, Pediatric Use, section of the product labeling and provided in Section 1.2 of this review.

This pediatric postmarketing pharmacovigilance review was prompted by the May 16, 2019, pediatric labeling change following the approval of pitavastatin use in pediatric patients. A pediatric safety review for pitavastatin has not previously been presented to the Pediatric Advisory Committee (PAC).

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

The following provides a summary of safety information and information on use in pediatrics excerpted from the pertinent sections of the pitavastatin labeling.

4 CONTRAINDICATIONS

LIVALO is contraindicated in the following conditions:

- Known hypersensitivity to pitavastatin or any inactive ingredient in LIVALO. Hypersensitivity reactions including rash, pruritus, and urticaria have been reported with LIVALO *[see Adverse Reactions (6.1)]*.
- Concomitant use of cyclosporine *[see Drug Interactions (7)]*.
- Active liver disease including unexplained persistent elevations of hepatic transaminase levels *[see Warnings and Precautions (5.3)]*.
- Pregnancy *[see Use in Specific Populations (8.1, 8.3)]*.
- Lactation. It is not known if pitavastatin is present in human milk; however, another drug in this class passes into breast milk. Since HMG-CoA reductase inhibitors have the potential for serious adverse reactions in breastfed infants, females who require pitavastatin treatment should not breastfeed their infants *[see Use in Specific Populations (8.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 Myopathy and Rhabdomyolysis

- LIVALO may cause myopathy (muscle pain, tenderness, or weakness with creatine kinase (CK) above ten times the upper limit of normal) and rhabdomyolysis (with or without acute renal failure secondary to myoglobinuria). Rare fatalities have occurred as a result of rhabdomyolysis with statin use, including LIVALO.

  Risk Factors for Myopathy

- Risk factors for myopathy include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, concomitant use of certain drugs, and higher LIVALO dosage. Dosages of LIVALO greater than 4 mg once daily were associated with an increased risk for severe myopathy in premarketing clinical studies. The maximum recommended dose of LIVALO is 4 mg once daily *[see Dosage and Administration (2.2)]*.

  Steps to Prevent or Reduce the Risk of Myopathy and Rhabdomyolysis

- LIVALO is contraindicated in patients taking cyclosporine and not recommended in patients taking gemfibrozil *[see Contraindications (4) and Drug Interactions (7)]*. There are LIVALO dosage restrictions for patients taking erythromycin or rifampin *[see Dosage and Administration (2.4)]*. The following drugs when used concomitantly with LIVALO may also increase the risk of myopathy and rhabdomyolysis: lipid-modifying dosages of niacin (>1grams/day), fibrates, and colchicine *[see Drug Interactions (7)]*.

- Discontinue LIVALO if markedly elevated CK levels occur or myopathy is diagnosed or suspected. Muscle symptoms and CK increases may resolve if LIVALO is discontinued. Temporarily discontinue LIVALO in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to rhabdomyolysis, e.g., sepsis; shock; severe

hypovolemia; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.

- Inform patients of the risk of myopathy and rhabdomyolysis when starting or increasing the LIVALO dosage. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness particularly if accompanied by malaise or fever.

5.2 Immune-Mediated Necrotizing Myopathy

- There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; and improvement with immunosuppressive agents. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required.

5.3 Hepatic Dysfunction

- Increases in serum transaminases have been reported with LIVALO *[see Adverse Reactions (6)]*. In most cases, the elevations were transient and either resolved or improved on continued therapy or after a brief interruption in therapy. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including LIVALO.
- Patients who consume substantial quantities of alcohol and/or have a history of liver disease may be at increased risk for hepatic injury.
- Consider liver enzyme testing before the initiation of LIVALO and thereafter, when clinically indicated. LIVALO is contraindicated in patients with active liver disease including unexplained persistent elevations in hepatic transaminase levels *[see Contraindications (4)]*. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue LIVALO.

5.4 Increases in HbA1c and Fasting Serum Glucose Levels

- Increases in HbA1c and fasting serum glucose levels have been reported with statins, including LIVALO. Optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices.

6 ADVERSE REACTIONS

Adverse Reactions in Pediatric Patients Aged 8 Years and Older with HeFH

In a 12-week, double-blind, placebo-controlled trial of LIVALO 1 mg, 2 mg, and 4 mg once daily in 82 pediatric patients 8 years to 16 years of age with HeFH and a 52-week open-label trial in 85 pediatric patients with HeFH, the safety profile was similar to that observed in the adult population.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of LIVALO as an adjunctive therapy to diet to reduce elevated TC, LDL-C, and Apo B in pediatric patients aged 8 years and older with HeFH have been established. Use of LIVALO

for this indication is supported by a 12-week, double-blind, placebo-controlled trial in 82 pediatric patients 8 to 16 years of age with HeFH *[see Clinical Studies (14.2)]* and a 52-week open-label trial in 85 pediatric patients with HeFH.

The safety and effectiveness of LIVALO have not been established in pediatric patients younger than 8 years of age with HeFH or in pediatric patients with other types of hyperlipidemia (other than HeFH).

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	June 17, 2022
Time period of search	August 3, 2009† - June 16, 2022
Search type	RXLogix PV Reports Quick Query
Product terms	Product Active Ingredient: Pitavastatin, pitavastatin calcium
MedDRA search terms (Version 24.1)	All PTs

* See Appendix A for a description of the FAERS database.
† US approval date for Livalo (pitavastatin)
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term

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 August 3, 2009, to June 16, 2022 with pitavastatin.

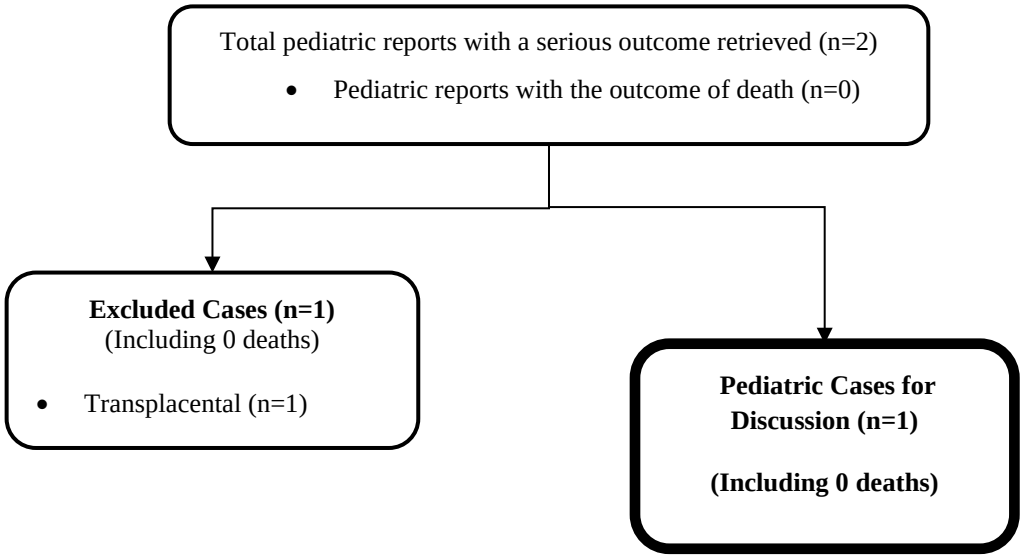
Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From August 3, 2009 to June 16, 2022 With Pitavastatin			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	1270 (544)	935 (223)	62 (5)
Pediatrics (0 - <17 years)	2 (0)	2 (0)	0 (0)

* 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, or other serious important medical events.

3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved two pediatric reports from August 3, 2009, through June 16, 2022, with the use of pitavastatin. One report of transplacental exposure was excluded from our case series. We summarize the remaining case in the sections below. Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious Pediatric Cases with pitavastatin



Appendix B contains a line listing of the pediatric case included in our discussion.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event cases.

3.1.4 Summary of Pediatric Cases (N=1)

We identified one pediatric adverse event case coded with the MedDRA PTs Guillain-Barre syndrome and Product administered to patient of inappropriate age.

FAERS 12903017 (Japan, 2016): A physician reported that a 9-year-old female developed Guillain-Barre syndrome an unknown time after starting therapy with pitavastatin to treat Type IIa hyperlipidemia. Forty-seven days after pitavastatin initiation, the patient experienced myalgia but "did not worry" because she played volleyball. Clinical tests showed no abnormality. Ten days later, the family told the reporting physician the patient experienced feelings of weakness. The following day pitavastatin was discontinued. Two days later, the weakness spread from the lower to the upper limbs. The trunk and neck moved normally but it was difficult to move the fingers. The creatinine kinase (CK) value was 250 IU/L and the myoglobin blood value was normal. Walking like "muscular dystrophy" was observed as an objective finding. It was recommended the patient visit pediatric neurology because new onset Guillain-Barre syndrome was suspected. On unknown date, the patient was diagnosed with Guillain-Barre syndrome by the pediatric neurologist. The outcome of the event was unknown.

<u>Reviewer comment</u>: This patient was diagnosed with Guillain-Barre syndrome an unknown time after receiving pitavastatin to treat Type IIa hyperlipidemia. Antecedent infections are the most commonly identified precipitant of Guillain-Barre syndrome (e.g. cytomegalovirus, Epstein-Barr virus, mycoplasma pneumoniae, influenza-like illnesses).[3] *Other triggering events include immunization, surgery, trauma, or bone-marrow transplantation.*[3] *It is unclear if the patient had a prior febrile respiratory or gastrointestinal infection or what her immunization status was prior to administration of pitavastatin in this case. It is challenging to establish a causal association between Guillain-Barre syndrome and pitavastatin given the limited information contained in this case (e.g., medical history, concomitant drugs,*

outcome of the event). A search of the FAERS database through July 25, 2022, for pitavastatin or pitavastatin calcium and the PT Guillain-Barre syndrome retrieved one additional case describing an adult patient. This case had similar limitations in clinical information. There is insufficient evidence to support a signal of Guillain-Barre with pitavastatin at this time. Of note none of the other statin drugs are labeled for Guillain-Barre syndrome.

4 DISCUSSION

DPV-I reviewed all serious FAERS reports with pitavastatin in the pediatric population (ages 0 - < 17 years) during the period August 3, 2009, to June 16, 2022, and identified one case for our case series. A single case reporting Guillain-Barre syndrome with the use of pitavastatin contained limited information to permit a meaningful causality assessment.

5 CONCLUSION

DPV-I did not identify any new pediatric safety concerns for pitavastatin at this time.

6 RECOMMENDATION

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

7 REFERENCES

1. Livalo (pitavastatin) [package insert]. Montgomery, AL: Kowa Pharmaceuticals America, Inc. Revised May 2019.
2. Sharretts J. NDA 022363/ S-015, Pitavastatin Cross-Discipline Team Leader Review, May 16, 2019
3. Ryan M (2022) Guillain-Barre syndrome in children: Epidemiology, clinical features, and diagnosis. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com/contents/guillain-barre-syndrome-in-children-epidemiology-clinical-features-and-diagnosis?search=guillain%20barre%20syndrome%20children&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

8 APPENDICES

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

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 (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=1)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	2016-11-02	12903017	1	JP-KOWA-16JP001776	Expedited	9.00000	F	Japan	OT

*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, a congenital anomaly/birth defect, or 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. Abbreviation: OT=other medically significant

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