Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	May 2, 2024
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Product Name:	Kapspargo Sprinkle (metoprolol succinate) extended-release capsule
Pediatric Labeling Approval Date:	January 26, 2018
Application Type/Number:	NDA 210428
Applicant:	Sun Pharma Industries, Ltd.
TTT Record ID:	2024-8464

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Kapspargo Sprinkle (metoprolol succinate) capsules extended-release in pediatric patients less than 17 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 metoprolol in pediatric patients.

Kapspargo Sprinkle (metoprolol succinate) extended-release capsule is a $beta_1$-adrenergic blocker initially approved in the U.S. on January 26, 2018. It is currently indicated for the treatment of hypertension, to lower blood pressure; angina pectoris; and heart failure, to reduce the risk of cardiovascular mortality and heart-failure hospitalization.

Because Kapspargo Sprinkle extended-release capsules represented a new formulation, Pediatric Research Equity Act (PREA) requirements applied. The Applicant requested and received waivers for pediatric studies for angina and heart failure in all pediatric age groups on the basis that such studies would be impossible or highly impractical. Additionally, the Applicant requested deferral for pediatric studies for hypertension in patients < 6 years old with birth weight > 7 kg on the basis that an age-appropriate formulation is not yet available and juvenile animal studies were still outstanding at time of approval. FDA agreed to the proposed deferral and waivers.

This pediatric postmarketing safety review was stimulated by the pediatric labeling at initial approval on January 26, 2018, that included an indication for pediatric hypertension in pediatric patients aged 6 years and older. The safety and effectiveness of metoprolol succinate have not been established in patients <6 years. FDA has not previously performed a pediatric postmarketing pharmacovigilance review for metoprolol for the Pediatric Advisory Committee.

DPV reviewed all U.S. serious FAERS reports with metoprolol in pediatric patients less than 17 years of age through February 22, 2024, and identified 205 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity any labeled adverse events, and no deaths directly associated with metoprolol in pediatric patients less than 17 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Kapspargo Sprinkle (metoprolol succinate) capsules extended-release in pediatric patients less than 17 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 metoprolol in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Kapspargo Sprinkle (metoprolol succinate) extended-release capsule is a $beta_1$-adrenergic blocker initially approved in the U.S. on January 26, 2018. It is currently indicated for the treatment of hypertension, to lower blood pressure; angina pectoris; and heart failure, to reduce the risk of cardiovascular mortality and heart-failure hospitalization.[1]

Because Kapspargo Sprinkle extended-release capsules represented a new formulation, Pediatric Research Equity Act (PREA) requirements applied. The Applicant requested and received waivers for pediatric studies for angina and heart failure in all pediatric age groups on the basis that such studies would be impossible or highly impractical. Additionally, the Applicant requested deferral for pediatric studies for hypertension in patients < 6 years old with birth weight > 7 kg on the basis that an age-appropriate formulation is not yet available and juvenile animal studies were still outstanding at time of approval. FDA agreed to the proposed deferral and waivers.[2]

This pediatric postmarketing safety review was stimulated by the pediatric labeling at initial approval on January 26, 2018, that included an indication for pediatric hypertension in pediatric patients aged 6 years and older. The safety and effectiveness of metoprolol succinate have not been established in patients <6 years. FDA has not previously performed a pediatric postmarketing pharmacovigilance review for metoprolol for the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

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

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

- Known hypersensitivity to product components. (4)
- Severe bradycardia: Greater than first degree heart block, or sick sinus syndrome without a pacemaker. (4)
- Cardiogenic shock or decompensated heart failure. (4)

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

- Abrupt cessation may exacerbate myocardial ischemia. (5.1)
- Heart Failure: Worsening cardiac failure may occur. (5.2)
- Bronchospastic Disease: Avoid beta blockers. (5.3)
- Concomitant use of glycosides, clonidine, diltiazem and verapamil with betablockers can increase the risk of bradycardia. (5.4)
- Pheochromocytoma: Initiate therapy with an alpha blocker. (5.5)

- Major Surgery: Avoid initiation of high-dose extended-release metoprolol in patients undergoing non-cardiac surgery. Do not routinely withdraw chronic beta-blocker therapy prior to surgery. (5.6, 6.1)
- Hypoglycemia: May increase risk for hypoglycemia and mask early warning signs. (5.7)
- Thyrotoxicosis: Abrupt withdrawal in patients with thyrotoxicosis might precipitate a thyroid storm. (5.8)
- Peripheral Vascular Disease: Can aggravate symptoms of arterial insufficiency. (5.9)
- Patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction. (5.10)

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

- Most common adverse reactions: tiredness, dizziness, depression, shortness of breath, bradycardia, hypotension, diarrhea, pruritus, rash. (6.1)

8.4 Pediatric Use

One hundred forty-four hypertensive pediatric patients aged 6 to 16 years were randomized to placebo or to one of three dose levels of metoprolol succinate (0.2, 1 or 2 mg/kg once daily) and followed for 4 weeks. The study did not meet its primary endpoint (dose response for reduction in SBP). Some pre-specified secondary endpoints demonstrated effectiveness including:

- Dose-response for reduction in DBP
- 1 mg/kg vs. placebo for change in SBP, and
- 2 mg/kg vs. placebo for change in SBP and DBP.

The mean placebo corrected reductions in SBP ranged from 3 to 6 mmHg, and DBP from 1 to 5 mmHg. Mean reduction in heart rate ranged from 5 to 7 bpm but considerably greater reductions were seen in some individuals [see Dosage and Administration (2.1)].

No clinically relevant differences in the adverse event profile were observed for pediatric patients aged 6 to 16 years as compared with adult patients.

Safety and effectiveness of metoprolol succinate have not been established in patients < 6 years of age.

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 23, 2024
Time period of search	All dates through February 22, 2024
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product active ingredient: Metoprolol, metoprolol succinate, metoprolol fumarate, metoprolol tartrate
MedDRA search terms (Version 26.1)	All Preferred Terms
* See Appendix A for a description of the FAERS database. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

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 through February 22, 2024, with metoprolol.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA Through February 22, 2024, With Metoprolol

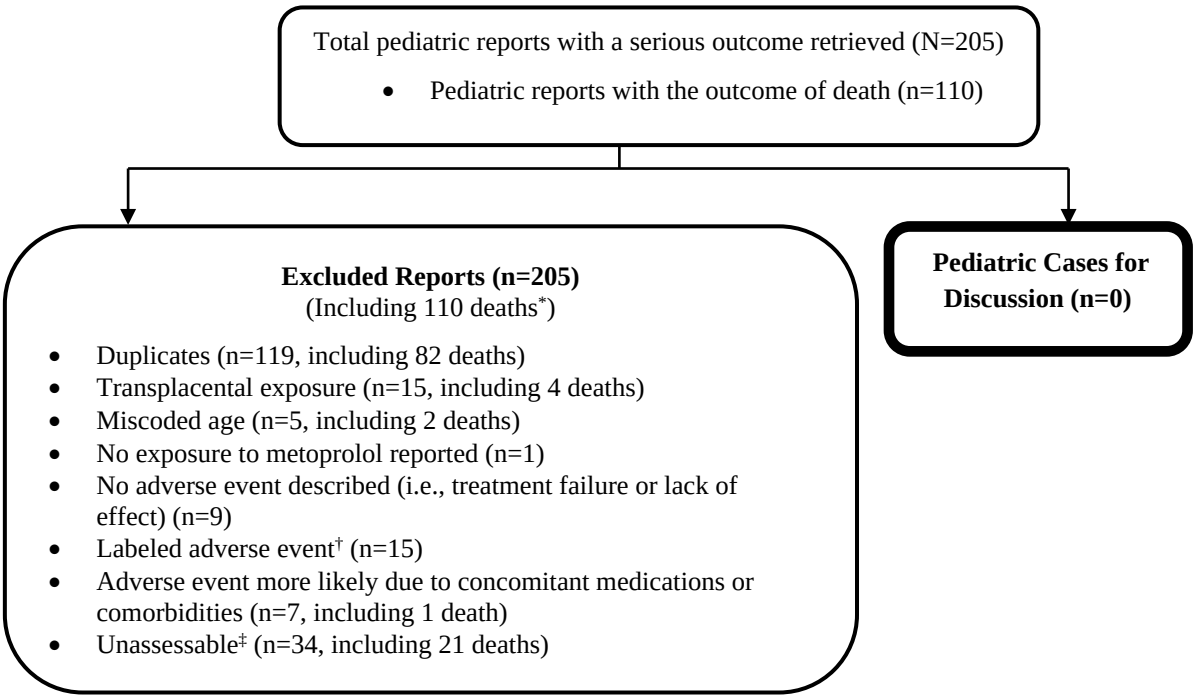
	All Reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	42,332 (27,319)	34,682 (19,813)	7,809 (6,584)
Pediatrics (0 - < 17 years)	844‡ (217)	831‡ (205)	174‡ (110)

* 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.
‡ Thirteen additional reports of U.S. pediatric deaths were identified among reports not reporting an age. These reports are reflected in the counts of pediatric reports.

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

Our FAERS search retrieved 205 U.S. serious pediatric reports through February 22, 2024. DPV reviewed all U.S. FAERS pediatric reports with a serious outcome and excluded all 205 reports from the case series for the reasons listed in **Figure 1**.

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



* Of the excluded U.S. FAERS reports, 110 reports described fatal outcomes. None of the deaths were determined to be attributed to metoprolol. After accounting for duplicate reports (n=82), we identified 28 unique cases with a fatal outcome. Of these, four excluded death reports described patients who had transplacental exposure to metoprolol during medically complex pregnancies including multiple medications; two reports involved premature neonates who died from complications of congenital disorders and the remaining two reports did not provide sufficient clinical information to determine cause of death. Two death reports described adult patients miscoded as pediatric age. One report described a pediatric death related to underlying cardiovascular disease. Twenty-one death reports did not have sufficient clinical information for a causality assessment with metoprolol.
† Labeled adverse event does not represent increased severity or frequency.

‡ 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.

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

There are no fatal pediatric adverse event cases for discussion.

3.1.4 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 metoprolol in pediatric patients less than 17 years of age through February 22, 2024, and identified 205 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity any labeled adverse events, and no deaths directly associated with metoprolol in pediatric patients less than 17 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Kapspargo Sprinkle (metoprolol succinate) capsules extended-release. [Prescribing information]. Cranbury, NJ; Sun Pharmaceutical Industries, Inc.: April, 2023.
2. Approval letter. NDA 210428. January 26, 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/210428Orig1s000Replacementltr.pdf

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.

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