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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:	November 3, 2022
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Product Name:	Katerzia (amlodipine benzoate)
Pediatric Labeling Approval Date:	July 8, 2019
Application Type/Number:	NDA 211340
Applicant:	Silvergate Pharmaceuticals, Inc.
TTT Record ID:	2022-2156

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Katerzia (amlodipine) oral suspension in pediatric patients through age 16 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 serious unlabeled adverse events associated with Katerzia in pediatric patients.

FDA first approved Katerzia on July 8, 2019. Katerzia is available as an oral suspension containing 1 mg/mL of amlodipine. It is a calcium channel blocker that may be used alone or in combination with other antihypertensive and antianginal agents for the treatment of:

- Hypertension
    - Katerzia is indicated for the treatment of hypertension in adults and children 6 years and older, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.
- Coronary Artery Disease
    - Chronic stable angina
    - Vasospastic angina (Prinzmetal's or variant angina)
    - Angiographically documented coronary artery disease in patients without heart failure or an ejection fraction <40%

This review was stimulated by the original approval for Katerzia, which included approval of use in pediatric patients 6 years and older. DPV has not previously presented Katerzia to the Pediatric Advisory Committee.

DPV reviewed all serious FAERS reports for Katerzia in the pediatric population (ages 0 to 16 years) from July 8, 2019, through September 29, 2022. All reports described adverse events that are already well described in the Katerzia product labeling. There were no new pediatric safety signals identified.

DPV did not identify any new pediatric safety concerns for Katerzia at this time. DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of Katerzia.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Katerzia (amlodipine) oral suspension in pediatric patients through age 16 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 serious unlabeled adverse events associated with Katerzia in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY[1,2]

FDA first approved Katerzia on July 8, 2019. Katerzia is available as an oral suspension containing 1 mg/mL of amlodipine. It is a calcium channel blocker that may be used alone or in combination with other antihypertensive and antianginal agents for the treatment of:

- Hypertension
    - Katerzia is indicated for the treatment of hypertension in adults and children 6 years and older, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.
- Coronary Artery Disease
    - Chronic stable angina
    - Vasospastic angina (Prinzmetal's or variant angina)
    - Angiographically documented coronary artery disease in patients without heart failure or an ejection fraction <40%

Evidence of safety and efficacy for Katerzia in pediatric patients 6 years and older relied on a randomized, three-way cross over study (Study SG05-02) characterizing pharmacokinetics of amlodipine following administration of Katerzia compared with the reference listed drug, Norvasc (amlopdipine) tablet, under fasted conditions. Study results demonstrated that both peak concentration (C_{max}) and area under the curve (AUC) for amlodipine is bioequivalent between Katerzia and Norvasc, thus establishing a bridge to borrow FDA's previous finding of safety and effectiveness for Norvasc.[2,3]

DPV has not previously presented Katerzia before the Pediatric Advisory Committee (PAC). This review was stimulated by the approval of Katerzia on July 8, 2019, that included approval for treatment in pediatric patients 6 years and older. Katerzia is not approved for use in patients <6 years old.

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

The Katerzia labeling contains the following safety information excerpted from the Highlights section of the product labeling and the Pediatric Use subsection. For further labeling information, please refer to the full prescribing information.

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

- Known sensitivity to amlodipine. (4)

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

- Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. However, acute hypotension is unlikely. (5.1)
- Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine, particularly in patients with severe obstructive coronary artery disease. (5.2)
- Titrate slowly in patients with severe hepatic impairment. (5.3)

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

Most common adverse reaction to amlodipine is edema which occurred in a dose related manner. Other adverse experiences not dose related but reported with an incidence >1.0% are fatigue, nausea, abdominal pain, and somnolence. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Silvergate Pharmaceuticals, Inc., at 1-855-379-0383 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- Do not exceed doses greater than 20 mg daily of simvastatin. (7.2)

8.4 Pediatric Use

Amlodipine (2.5 to 5 mg daily) is effective in lowering blood pressure in patients 6 to 17 years *[see Clinical Studies (14.1)]*. Effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

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	September 30, 2022
Time period of search	July 8, 2019† - September 29, 2022
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Query
Product terms	Product name: Katerzia NDA: 211340
MedDRA search terms (Version 25.0)	All PT terms

* See Appendix A for a description of the FAERS database.

† U.S. Approval date for Katerzia.

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, NDA=New drug application, 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 July 8, 2019, through September 29, 2022, with Katerzia.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From July 8, 2019 through September 29, 2022, with Katerzia

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	45 (19)	42 (16)	2 (1)
Pediatrics (0 - <17 years)	8 (7)	7 (6)	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 seven serious pediatric reports from July 8, 2019, through September 29, 2022, with Katerzia.

We reviewed all FAERS pediatric reports with a serious outcome. After hands on review, we excluded all reports from the case series as they all described labeled adverse events with Katerzia.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for further discussion.

3.1.4 Summary of Non-Fatal Pediatric Serious Cases (N=0)

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

4 DISCUSSION

DPV reviewed all serious FAERS reports for Katerzia in the pediatric population (ages 0 to 16 years) from July 8, 2019, through September 29, 2022. All reports described adverse events that are already well described in the Katerzia product labeling. There were no new pediatric safety signals identified at this time.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for Katerzia.

6 RECOMMENDATION

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

7 REFERENCES

1. Katerzia (amlodipine) oral suspension [Prescribing Information]. Greenwood Village, CO: Silvergate Pharmaceuticals, Inc.; July 2019.
2. Hariharan S. Cross-Discipline Team Leader Review for Katerzia (amlodipine besylate). July 2019. Available at: https://www.fda.gov/media/131625/download
3. Norvasc (amlodipine besylate) tablets for oral administration [Prescribing Information]. New York, NY: Pfizer, Inc.; October 2017.

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.

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