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:	November 2, 2023
Reviewer:	Ivone Kim, MD, Medical Officer Division of Pharmacovigilance I
Team Leader:	Carmen Cheng, PharmD Division of Pharmacovigilance I
Division Director:	Monica Muñoz, PharmD, PhD Division of Pharmacovigilance I
Product Name:	Conjupri (levamlodipine) tablets
Pediatric Labeling Approval Date:	December 19, 2019
Application Type/Number:	NDA 212895
Applicant:	CSPC Ouyi Pharmaceutical Co., Ltd.
TTT Record ID:	2023-5813

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Conjupri (levamlodipine) tablets 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 serious unlabeled adverse events associated with levamlodipine in pediatric patients.

Conjupri (levamlodipine) is a calcium channel blocker that was initially approved in the U.S. on December 19, 2019. Levamlodipine is currently indicated for use alone or in combination with other antihypertensive agents for the treatment of hypertension, to lower blood pressure.

This pediatric postmarketing safety review was prompted by pediatric labeling at FDA approval on December 19, 2019, that included the indication for use in pediatric patients aged 6 to 17 years. Safety and effectiveness in pediatric patients aged less than 6 years have not been established. A pediatric safety review for levamlodipine has not previously been presented to the Pediatric Advisory Committee.

DPV searched FAERS for all serious reports with levamlodipine in pediatric patients less than 18 years of age from December 19, 2019 – July 30, 2023, and did not identify any reports.

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

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Conjupri (levamlodipine) tablets 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 serious unlabeled adverse events associated with levamlodipine in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Conjupri (levamlodipine) is a calcium channel blocker that was initially approved in the U.S. on December 19, 2019. Levamlodipine is currently indicated for use alone or in combination with other antihypertensive agents for the treatment of hypertension, to lower blood pressure.[1]

This pediatric postmarketing safety review was prompted by pediatric labeling at FDA approval on December 19, 2019, that included the indication for use in pediatric patients aged 6 to 17 years.[1] Safety and effectiveness in patients aged 6 to 17 years were supported by a clinical trial involving 268 hypertensive patients aged 6 to 17 years old. Study subjects were randomized first to amlodipine 2.5 mg or 5 mg once daily for 4 weeks and then randomized again to the same dose or to placebo for another 4 weeks. Patients receiving 2.5 mg or 5 mg at the end of 8 weeks had significantly lower systolic blood pressure than those secondarily randomized to placebo. The magnitude of treatment effect was estimated to be less than 5 mmHg systolic on the 5 mg dose and 3.3 mmHg systolic on the 2.5 mg dose. Adverse events were similar to those seen in adults. Safety and effectiveness in pediatric patients aged less than 6 years have not been established.[1]

A pediatric safety review for levamlodipine has not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

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

----------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 reactions 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)

8.4 Pediatric Use
Levamlodipine (1.25 to 2.5 mg daily) is effective in lowering blood pressure in patients 6 to 17 years [see Clinical Studies (14.1)]. Effect of levamlodipine 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	July 31, 2023
Time period of search	December 19, 2019† - July 30, 2023
Search type	RxLogix Post-Market Cases
Product terms	Product Active Ingredient: levamlodipine, levamlodipine besylate, levamlodipine maleate
MedDRA search terms (Version 26.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database. † Conjupri U.S. approval date 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 from December 19, 2019 - July 30, 2023, with levamlodipine.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From December 19, 2019 - July 30, 2023, With Levamlodipine			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	11 (0)	11 (0)	0 (0)
Pediatrics (0 - < 18 years)	0 (0)	0 (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 zero serious pediatric reports from December 19, 2019 – July 30, 2023, with levamlodipine.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

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

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

4 DISCUSSION

DPV searched FAERS for all serious reports with levamlodipine in pediatric patients less than 18 years of age from December 19, 2019 - July 30, 2023, and did not identify any reports.

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

5 CONCLUSION

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

6 REFERENCES

1. Conjupri (levamlodipine) tablets, for oral use [Prescribing information]. Princeton, NJ; CSPC Ouyi Pharmaceutical Co., Ltd.: December, 2019.

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.

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/

IVONE E KIM
11/02/2023 12:03:35 PM

CARMEN CHENG
11/02/2023 12:22:56 PM

MONICA MUNOZ
11/02/2023 12:33:28 PM