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

Pediatric Postmarketing Pharmacovigilance Review

Date:	July 21, 2021
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Product Name:	Tekturna (aliskiren hemifumarate)
Pediatric Labeling Approval Date:	November 14, 2017
Application Type/Number:	NDA 021985, NDA 210709
Applicant:	Noden Pharma
OSE RCM #:	2021-642

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports in pediatric patients less than 18 years of age reported with Tekturna (aliskiren hemifumarate) use. The Division of Pharmacovigilance-I (DPV-I) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA), the Pediatric Research Equity Act (PREA), and Best Pharmaceuticals for Children Act (BPCA). This review focuses on serious unlabeled adverse events associated with aliskiren in the pediatric population.

On March 5, 2007, FDA approved aliskiren oral tablets for the treatment of hypertension in adults. This review was triggered by FDA's approval on November 14, 2017 of aliskiren oral pellets in capsule for the treatment of hypertension in adults and children 6 years of age and older weighing at least 20 kg. Notably, aliskiren is contraindicated in patients less than 2 years of age.

As of April 15, 2021, the FDA has withdrawn the approval of aliskiren oral pellets at the request of the Applicant because the product was no longer marketed. As a result, the current labeling for aliskiren states that it is not approved in patients six years and older weighing 20 kg to less than 50 kg because of the lack of an appropriate pediatric dosage form. The current FDA-approved pediatric indication for aliskiren is for the treatment of hypertension in pediatric patients 6 years of age and older weighing 50 kg or more.

Our FAERS search did not identify any serious unlabeled pediatric adverse event reports associated with aliskiren from March 5, 2007 to March 15, 2021.

DPV-I did not identify any pediatric safety concerns for aliskiren 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 aliskiren.

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1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Tekturna (aliskiren hemifumarate) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance-I (DPV-I) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA), Pediatric Research Equity Act (PREA), and Best Pharmaceuticals for Children Act (BPCA). This review focuses on serious unlabeled adverse events associated with aliskiren use in pediatric patients less than 18 years of age.

1.1 REGULATORY HISTORY

Tekturna (aliskiren hemifumarate) is an orally active, nonpeptide, direct renin inhibitor used to treat hypertension. Aliskiren acts at the rate-limiting step of renin-angiotensin-aldosterone system (RAAS) thereby inhibiting the conversion of angiotensinogen to angiotensin I while causing a decrease in plasma renin activity, which plays an important role in the pathogenesis of hypertension.[1] On March 5, 2007, FDA approved aliskiren oral tablets (150 mg, 300 mg) for the treatment of hypertension in adults under NDA 021985. On November 14, 2017, FDA approved aliskiren oral pellets in capsule, a pediatric dosage form, for the treatment of hypertension in adults and children 6 years of age and older weighing at least 20 kg under NDA 210709. Aliskiren is contraindicated in patients less than 2 years of age because of the risk of high aliskiren exposures identified in juvenile animals due to immaturity of transporters and metabolic enzymes.[1] This review was triggered by pediatric studies completed under PREA and BPCA resulting in the approval of aliskiren in pediatric patients 6 years of age and older weighing at least 20 kg.

The safety and efficacy of aliskiren for the treatment of hypertension is supported by two randomized, double-blind clinical trials in pediatric patients with hypertension 6 years to 17 years of age weighing 20 kg or more. The first study was an 8-week trial, followed by a second 52-week extension trial. Across the studies in pediatric patients with hypertension, aliskiren has been evaluated for efficacy and safety in 267 pediatric hypertensive patients 6 to 17 years of age, including 208 patients who enrolled in the 52-week extension trial. Adverse reactions in pediatric patients 6 years of age and older are expected to be similar to those seen in adults. In addition, the pharmacokinetics of aliskiren were evaluated in an 8-day pharmacokinetic study in 39 pediatric patients with hypertension 6 years to 17 years of age.[1] The pharmacokinetic analysis provided support for doses in the pediatric population that provide similar exposures to efficacious doses in the adult population.[2]

As of April 15, 2021, the FDA has withdrawn approval of NDA 021985 (aliskiren oral pellets) at the request of the Applicant because the product was no longer marketed for business reasons.[3] The Agency will place aliskiren 37.5 mg oral pellets on the list of products for which a pediatric formulation was developed, studied and found to be safe and effective in pediatric patients but not marketed within one year of approval.[4] The current labeling for aliskiren states that it is not approved in patients six years and older weighing 20 kg to less than 50 kg because of the lack of an appropriate dosage form. The current FDA-approved indication for aliskiren is for the treatment of hypertension in pediatric patients 6 years of age and older weighing 50 kg or more.[1]

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The Office Surveillance and Epidemiology (OSE) has not previously completed a pediatric postmarketing pharmacovigilance review for aliskiren.

1.2 RELEVANT LABELED SAFETY INFORMATION

The aliskiren labeling contains the following safety information within the Highlights of Prescribing Information.[1]

CONTRAINDICATIONS

Do not use with angiotensin receptor blockers (ARBs) or angiotensin- converting enzyme inhibitors (ACEIs) in patients with diabetes. (4)
Hypersensitivity to any of the components. (4)
Tekturna is contraindicated in pediatric patients less than 2 years of age. (4)

WARNINGS AND PRECAUTIONS

- Avoid concomitant use with ARBs or ACEIs particularly in patients with renal impairment [creatinine clearance (CrCl) <60 mL/min]. (5.2, 5.4)
- Anaphylactic Reactions and Head and Neck Angioedema. (5.3)
- Hypotension: Correct imbalances in volume and/or salt depleted patients. (5.4)
- Impaired Renal Function: Monitor serum creatinine periodically. (5.5)
- Hyperkalemia: Monitor potassium levels periodically. (5.6)

ADVERSE REACTIONS

Most common adverse reaction: diarrhea (incidence 2.3%) (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Noden Pharma USA Inc. at 1-844-399-5701 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Cyclosporine or Itraconazole: Avoid concomitant use. (5.7, 7, 12.3)
- Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): Increased risk of renal impairment and loss of antihypertensive effect. (7)

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*

Date of search	March 16, 2021
Time period of search	March 5, 2007† - March 15, 2021
Search type	FBIS Quick Query
Product terms	Product active ingredient: aliskiren, aliskiren hemifumarate
MedDRA Search Terms (Version 23.1)	All Preferred Terms (PTs)

* See Appendix A for a description of the FAERS database.
† From U.S. approval date of aliskiren
Abbreviations: FBIS=FDA Business Intelligence System, MedDRA=Medical Dictionary for Regulatory Activities

3 RESULTS

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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 March 5, 2007 (U.S. approval date) to March 15, 2021.

Table 2. Total Adult and Pediatric Aliskiren FAERS Reports* Received by FDA From March 5, 2007 to March 15, 2021

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	3,998 (932)	3,677 (658)	483 (42)
Pediatrics (0 - <18 years)	16 (0)	14 (0)	0 (0)

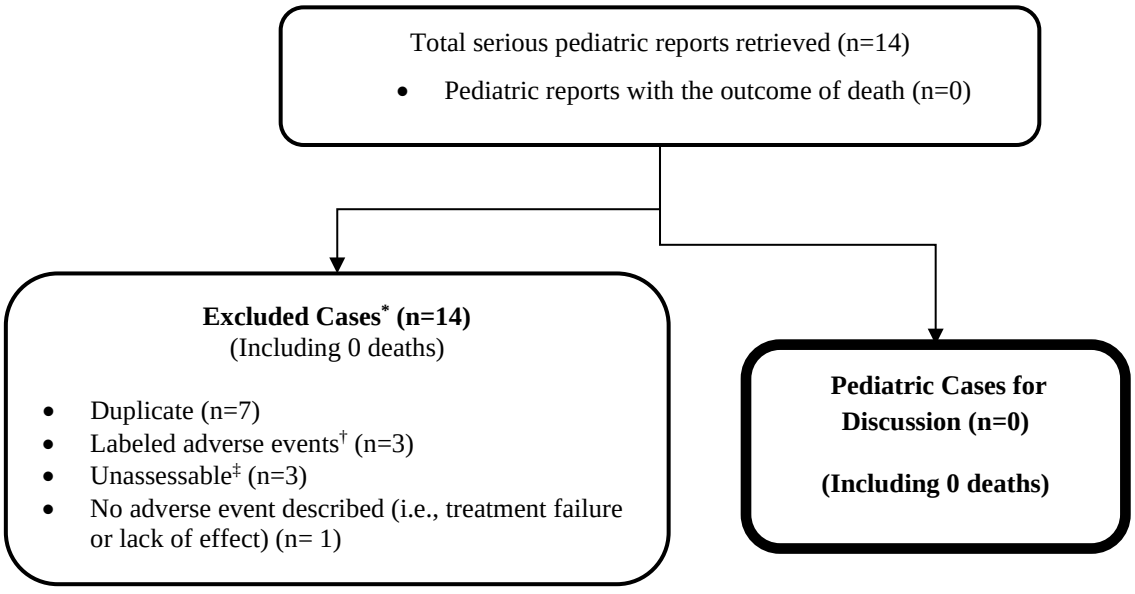
* May include duplicates and transplacental exposures, and have not been assessed for causality

† 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 Pediatric Cases in FAERS

Our FAERS search retrieved 14 serious pediatric reports from March 5, 2007 to March 15, 2021. DPV-I reviewed all 14 pediatric reports and excluded reports from further analysis if they described labeled adverse events that did not reflect an apparent increase in severity of the labeled events. We further excluded reports from the case series for various reasons, such as duplicate reports, no adverse event described (i.e., treatment failure or lack of effect), and unassessable cases (i.e., cases that cannot be clinically assessed for causality because information is insufficient or lacking). **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of Pediatric Cases Associated with Aliskiren Use



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above
† Includes the following aliskiren labeled adverse events: hyperkalemia, nausea, renal impairment
‡ Unassessable: Case cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, or clinical course and outcome).

3.1.3 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event reports associated with aliskiren.

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

We did not identify any serious unlabeled non-fatal adverse event reports associated with aliskiren in the pediatric population.

4 DISCUSSION

DPV-I reviewed all of the serious FAERS reports associated with aliskiren use in the pediatric population (ages 0 to < 18 years) from March 5, 2007 through March 15, 2021. During this time, the majority of the FAERS reports described serious adverse events that were consistent with known and labeled adverse events described in the aliskiren approved prescribing information. We did not identify an increase in severity in the labeled serious adverse events associated with aliskiren. There were no pediatric deaths reported with aliskiren use during the examined time period. Of the total pediatric serious FAERS reports evaluated, we did not identify any serious unlabeled non-fatal adverse events associated with aliskiren use in the pediatric population.

5 CONCLUSION

DPV-I did not identify any pediatric safety concerns associated with aliskiren use at this time.

6 RECOMMENDATION

DPV-I recommends no regulatory action specific to pediatric patients at this time, and will continue to monitor all adverse events associated with the use of aliskiren in the pediatric population.

7 REFERENCES

1. Tekturna (aliskiren hemifumarate) [Package Insert]. Noden Pharma USA Inc. Orlando, FL. Revised 6/2020.
2. Thompson, A. Tekturna (aliskiren) Cross-Discipline Team Leader Review Clinical (Medical) Review NDA 210709. November 13,2017. https://www.fda.gov/media/109484/download.
3. Noden Pharma Withdrawal of Approval of New Drug Applications. 86 FR 14447. https://www.federalregister.gov/documents/2021/03/16/2021-05368/bristol-meyers-squibb-company-et-al-withdrawal-of-approval-of-19-new-drug-applications. Accessed May 6. 2021.
4. 21 U.S. Code § 355a (e)(2). Identification of certain drugs https://www.law.cornell.edu/uscode/text/21/355a. Accessed May 6, 2021.

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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