Department of Health and Human Services
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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:	June 10, 2024
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Product Name:	Diovan (valsartan) tablets
Pediatric Labeling Approval Date:	April 19, 2021
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Applicant:	Novartis
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Diovan (valsartan) tablets 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 valsartan in pediatric patients.

Diovan (valsartan) tablets is an angiotensin II receptor blocker first approved in the U.S. on July 18, 2001. At initial approval, Diovan was indicated for use in adult patients for the treatment of hypertension alone or in combination with other antihypertensive agents.

On November 29. 2007, FDA approved expanding the valsartan indication to include treatment of hypertension in pediatric patients aged 6 – 16 years of age. On April 19, 2021, FDA approved expanding the valsartan indication to include treatment of hypertension in children aged 1 year and older.

Currently, valsartan is approved for use in the following indications:[4]

- Hypertension, to lower blood pressure in adults and children 1 year and older. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions
- Heart failure (NYHA class II-IV), to reduce hospitalization for heart failure in adults
- Post-myocardial infarction, for the reduction of cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction in adults

This pediatric postmarketing pharmacovigilance review was prompted by the April 19, 2021, pediatric labeling.

DPV previously conducted a pediatric postmarketing pharmacovigilance review of valsartan on February 9, 2009. DPV's review did not identify any new safety concerns with valsartan and recommended continued routine pharmacovigilance. DPV's findings were presented to the Pediatric Advisory Committee (PAC) on June 23, 2009, and the PAC agreed with DPV's recommendations.

DPV reviewed all U.S. serious FAERS reports with valsartan in pediatric patients less than 17 years of age from September 9, 2008 – May 13, 2024. DPV identified 23 reports; however, all reports were excluded from further discussion.

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

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Diovan (valsartan) tablets 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 valsartan in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Diovan (valsartan) tablets is an angiotensin II receptor blocker first approved in the U.S. on July 18, 2001. At initial approval, Diovan was indicated for use in adult patients for the treatment of hypertension alone or in combination with other antihypertensive agents.[1]

On November 29, 2007, FDA approved expanding the valsartan indication to include treatment of hypertension in pediatric patients aged 6 – 16 years of age.[2] On April 19, 2021, FDA approved expanding the valsartan indication to include treatment of hypertension in children aged 1 year and older.[3]

Currently, valsartan is approved for use in the following indications:[4]

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1.2 RELEVANT LABELED SAFETY INFORMATION

The Diovan (valsartan) tablets labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Diovan tablet labeling information, please refer to the full prescribing information.[4]

WARNING: FETAL TOXICITY

See full prescribing information for complete boxed warning.

- **When pregnancy is detected, discontinue Diovan as soon as possible. (5.1)**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1)**

---------- CONTRAINDICATIONS ----------
Known hypersensitivity to any component. Do not coadminister aliskiren with Diovan in patients with diabetes (4)

---------- WARNINGS AND PRECAUTIONS ----------
Observe for signs and symptoms of hypotension (5.2)
Monitor renal function and potassium in susceptible patients (5.3, 5.4)

---------- ADVERSE REACTIONS ----------
Hypertension: Most common adverse reactions are headache, dizziness, viral infection, fatigue and abdominal pain (6.1)
Heart Failure: Most common adverse reactions are dizziness, hypotension, diarrhea, arthralgia, back pain, fatigue and hyperkalemia (6.1)
Post-Myocardial Infarction: Most common adverse reactions which caused patients to discontinue therapy are hypotension, cough and increased blood creatinine (6.1)

8.4 Pediatric Use
The antihypertensive effects of Diovan have been evaluated in 5 clinical studies in pediatric patients from 1-16 years of age [see Clinical Studies (14.1)]. The pharmacokinetics of Diovan have been evaluated in pediatric patients 1 to 16 years of age [see Clinical Pharmacology (12.3)]. The adverse experience profile of Diovan was similar to that described for adults [see Adverse Reactions (6.1)].

In children and adolescents with hypertension where underlying renal abnormalities may be more common, renal function and serum potassium should be closely monitored as clinically indicated.

Use of Diovan is not recommended in children less than 1 year of age. [see Nonclinical Toxicology 13.2)]. It is not known whether post-natal use of valsartan, before maturation of renal function is complete, has a long-term deleterious effect on the kidney.

No data are available in pediatric patients either undergoing dialysis or with a glomerular filtration rate less than 30 mL/min/1.73 m2.

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	May 14, 2024
Time period of search	September 9, 2008† - May 13, 2024
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product Active Ingredient: Valsartan, valsartan disodium
MedDRA search terms (Version 27.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database. † Data lock date from DPV's last pediatric postmarketing pharmacovigilance review for valsartan 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 September 9, 2008 – May 13, 2024, with valsartan.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From September 9, 2008 – May 13, 2024, With Valsartan

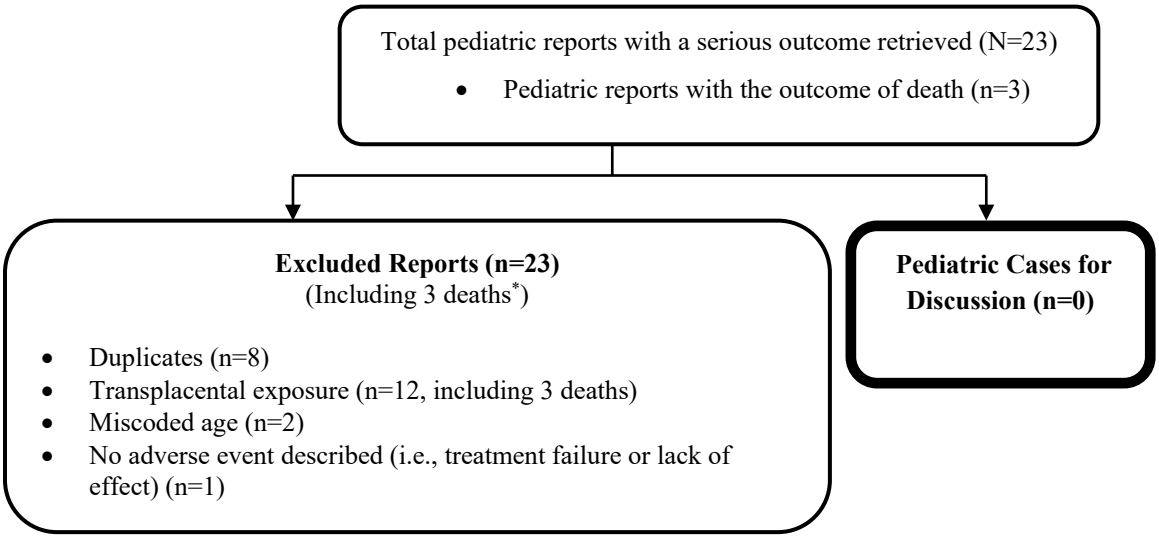
	All Reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	16,879 (3,621)	15,914 (2,770)	2,087 (332)
Pediatrics (0 - < 17 years)	216‡ (23)	216‡ (23)	23‡ (3)

* 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.
‡ See Figure 1. Two 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 23 U.S. serious pediatric reports from September 9, 2008 – May 13, 2024, with valsartan. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all 23 reports from the case series for the reasons listed in **Figure 1**. **Figure 1** presents the selection of cases for the pediatric case series.

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



* Three excluded U.S. FAERS reports described fatal outcomes. The reports described stillbirth (n=1) and neonatal deaths (n=2) following prenatal exposure to valsartan and other products with known fetal toxicity. None of the reports provided clinical information to determine cause of death.
† 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 valsartan in pediatric patients less than 17 years of age from September 9, 2008 – May 13, 2024. DPV identified 23 reports; however, all reports were excluded from further discussion.

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

5 CONCLUSION

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

6 REFERENCES

1. Diovan (valsartan) tablets. [Prescribing information]. East Hanover, NJ; Novartis Pharmaceuticals Corp.: June 2001.
2. Approval letter. NDA 21283/S024. November 29, 2007. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2007/021283s024ltr.pdf
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5. Houstoun M. Pediatric Postmarketing Adverse Event Review. NDA 21283. February 9, 2009. Available at: https://wayback.archive-it.org/7993/20170405195603/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM166796.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.