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:	October 7, 2024
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Product Name:	Entresto (sacubitril/valsartan) tablets
Pediatric Labeling Approval Date:	October 1, 2019
Application Type/Number:	NDA 207620
Applicant:	Novartis Pharmaceuticals Corporation
TTT Record ID:	2024-9738

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Entresto (sacubitril/valsartan) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with sacubitril/valsartan in pediatric patients.

Entresto (sacubitril/valsartan) is a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker. Sacubitril/valsartan was initially approved in the U.S. on July 7, 2015, as tablets for use in adult patients. On October 1, 2019, the use of sacubitril/valsartan was expanded to treat symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older and on April 12, 2024, the FDA approved a new dosage form, Entresto Sprinkle oral pellets. Sacubitril/valsartan is currently indicated:

- to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.
- for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. ENTRESTO reduces NT-proBNP and is expected to improve cardiovascular outcomes.

This pediatric postmarketing safety review was stimulated by pediatric labeling on October 1, 2019, which expanded the use of sacubitril/valsartan to treat symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older.

DPV reviewed all U.S. serious FAERS reports with sacubitril/valsartan in pediatric patients less than 18 years of age from July 7, 2015, through August 5, 2024. DPV identified 21 reports; however, all reports were excluded from further discussion.

There were no new safety signals, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with sacubitril/valsartan in pediatric patients less than 18 years of age. DPV did not identify any new pediatric safety concerns for sacubitril/valsartan at this time.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Entresto (sacubitril/valsartan) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with sacubitril/valsartan in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY[1]

Entresto (sacubitril/valsartan) is a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker. Sacubitril/vasartan was initially approved in the U.S. on July 7, 2015, as tablets for use in adult patients. On October 1, 2019, the use of sacubitril/valsartan was expanded to treat symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. On April 12, 2024, the FDA approved a new dosage form, Entresto Sprinkle oral pellets. Sacubitril/valsartan is currently indicated:

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This pediatric postmarketing safety review was stimulated by pediatric labeling on October 1, 2019, which expanded the use of sacubitril/valsartan to treat symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older.

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

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

The sacubitril/valsartan labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional sacubitril/valsartan labeling information, please refer to the full prescribing information.

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

- Hypersensitivity to any component.
- History of angioedema related to previous ACE inhibitor or ARB therapy.
- Concomitant use of ACE inhibitors.
- Concomitant use of aliskiren in patients with diabetes.

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

- Observe for signs and symptoms of angioedema and hypotension.
- Monitor renal function and potassium in susceptible patients.

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

- Adverse reactions occurring greater than or equal to 5% are hypotension, hyperkalemia, cough, dizziness, and renal failure.

8.4 Pediatric Use

The safety and effectiveness of ENTRESTO have been established for the treatment of heart failure in pediatric patients 1 year to less than 18 years. Use of ENTRESTO was evaluated in a multinational, randomized, double-blind trial comparing ENTRESTO and enalapril in 375 patients aged 1 month to less than 18 years (ENTRESTO n = 187; Enalapril n = 188) (PANORAMA-HF) [see Clinical Studies (14.2)]. The safety profile in pediatric patients (1 year to less than 18 years) receiving ENTRESTO was similar to that seen in adult patients.

Limited safety and efficacy data in patients aged 1 month to less than 1 year were inadequate to support conclusions on safety and efficacy in this age group.

Juvenile Animal Toxicity Data

Sacubitril given orally to juvenile rats from postnatal day (PND) 7 to PND 35 or PND 70 (an age approximately equivalent to neonatal through pre-pubertal development or adulthood in humans) at doses greater than or equal to 400 mg/kg/day (approximately 2-fold the AUC exposure to the active metabolite of sacubitril, LBQ657, at an ENTRESTO pediatric clinical dose of 3.1 mg/kg twice daily) resulted in decreases in body weight, bone length, and bone mass. The decrease in body weight was transient from PND 10 to PND 20 and the effects for most bone parameters were reversible after treatment stopped. Exposure at the No-Observed-Adverse-Effect-Level (NOAEL) of 100 mg/kg/day was approximately 0.5-fold the AUC exposure to LBQ657 at the 3.1 mg/kg twice daily dose of ENTRESTO. The mechanism underlying bone effects in rats and the translatability to pediatric patients are unknown.

Valsartan given orally to juvenile rats from PND 7 to PND 70 (an age approximately equivalent to neonatal through adulthood in humans) produced persistent, irreversible kidney damage at all dose levels. Exposure at the lowest tested dose of 1 mg/kg/day was approximately 0.2-fold the exposure at 3.1 mg/kg twice daily dose of ENTRESTO based on AUC. These kidney effects in neonatal rats represent expected exaggerated pharmacological effects that are observed if rats are treated during the first 13 days of life. This period coincides with 36 weeks of gestation in humans, which could occasionally extend up to 44 weeks after conception in humans. In humans, nephrogenesis is thought to be complete around birth; however, maturation of other aspects of kidney function (such as glomerular filtration and tubular function) may continue until approximately 2 years of age. It is unknown whether post-natal use of valsartan before aturation of renal function is complete has long-term deleterious effects on the kidney.

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	August 6, 2024
Time period of search	July 7, 2015† - August 5, 2024
Search type	RxLogix Pediatric Focused Review Alert - DPV
Product terms	Product Active Ingredient: sacubitril/valsartan
MedDRA search terms (Version 27.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database. † U.S. approval date for Entresto (sacubitril/valsartan) Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

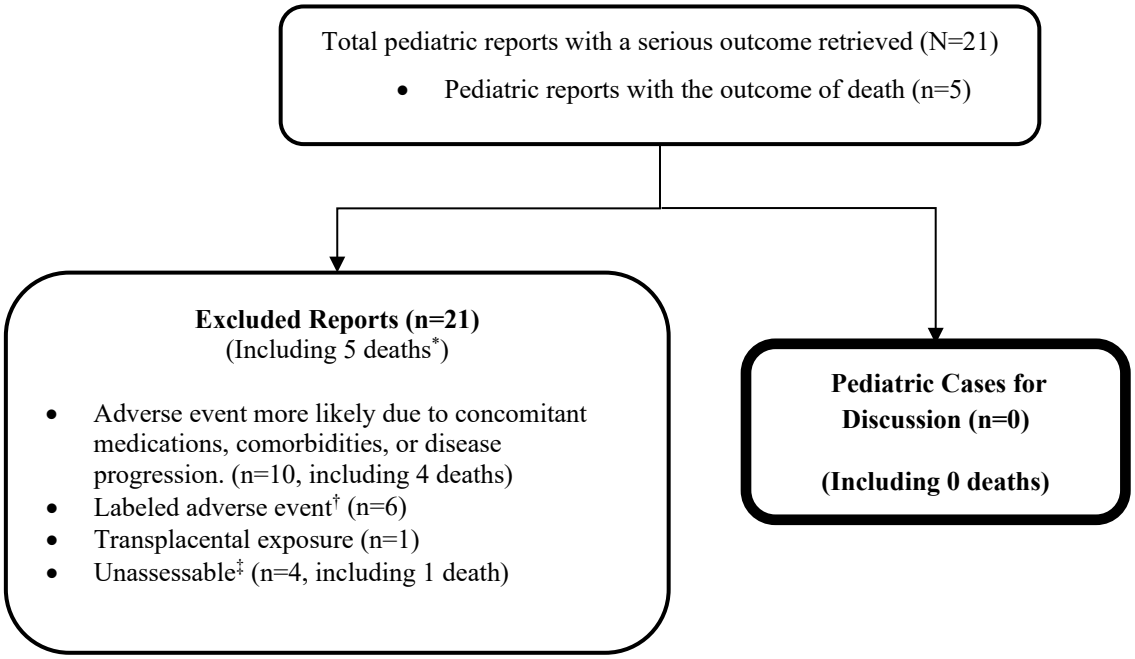
Table 2 presents the number of adult and pediatric FAERS reports from July 7, 2015, through August 5, 2024, with sacubitril/valsartan.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From July 7, 2015, through August 5, 2024, With Sacubitril/Valsartan			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	34,613 (19,298)	23,981 (8,845)	6,831 (2,015)
Pediatrics (0 - < 18 years)	69 (30)	60 (21)	10 (5)
* 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 U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 21 U.S. serious pediatric reports from July 7, 2015, through August 5, 2024. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all 21 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 Sacubitril/valsartan



* Five excluded U.S. FAERS reports described fatal outcomes. None of the deaths were determined to be attributed to sacubitril/valsartan. Four cases described fatal outcomes due to disease progression [cardiac failure (n=3) and Duchenne Muscular Dystrophy (n=1)]. The remaining case contained insufficient information to determine cause of death or attribute death to sacubitril/valsartan exposure.
† 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 sacubitril/valsartan in pediatric patients less than 18 years of age from July 7, 2015, through August 5, 2024. DPV identified 21 reports; however, all reports were excluded from further discussion.

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

5 CONCLUSION

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

6 REFERENCES

1. Entresto (sacubitril/valsartan) [package insert]. East Hanover, NJ. Novartis Pharmaceuticals Corporation. 2024.

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.