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 13, 2023
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Product Name:	Prezcobix (cobicistat; darunavir)
Pediatric Labeling Approval Date:	July 31, 2020
Application Type/Number:	NDA 205395
Applicant:	Janssen
TTT Record ID:	2023-6411

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Prezcobix (cobicistat; darunavir) 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). We focused on serious unlabeled adverse events associated with Prezcobix in pediatric patients.

Prezcobix is a two-drug combination of darunavir, a human immunodeficiency virus (HIV-1) protease inhibitor, and cobicistat, a CYP3A inhibitor. Prezcobix was initially approved in the United States (U.S.) on January 29, 2015, and is currently indicated for the treatment of HIV-1 infection in treatment-naïve and treatment-experienced adults and pediatric patients weighing at least 40 kg with no darunavir resistance-associated substitutions.

This pediatric postmarketing safety review was stimulated by pediatric labeling on July 31, 2020, that expanded the Prezcobix indication from use in adult patients to use in adult and pediatric patients weighing at least 40 kg.

DPV reviewed all serious FAERS reports with Prezcobix in pediatric patients less than 18 years of age from January 29, 2015, through September 18, 2023, and identified 24 reports; however, we excluded all reports 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 Prezcobix in pediatric patients less than 18 years of age.

DPV will continue routine pharmacovigilance monitoring for Prezcobix.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Prezcobix (cobicistat; darunavir) 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). We focused on serious unlabeled adverse events associated with Prezcobix in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Prezcobix is a two-drug combination of darunavir, a human immunodeficiency virus (HIV-1) protease inhibitor, and cobicistat, a CYP3A inhibitor. Prezcobix was initially approved in the United States (U.S.) on January 29, 2015 and is currently indicated for the treatment of HIV-1 infection in treatment-naïve and treatment-experienced adults and pediatric patients weighing at least 40 kg with no darunavir resistance-associated substitutions.[1]

This pediatric postmarketing safety review was stimulated by pediatric labeling on July 31, 2020, that expanded the Prezcobix indication from use in adult patients to use in adult and pediatric patients weighing at least 40 kg.[1,2]

No clinical trials with Prezcobix were performed in pediatric patients. The pharmacokinetics, safety, and efficacy of the components of Prezcobix, darunavir and cobicistat, were established in clinical trial GS-US-216-0128 where seven virologically-suppressed HIV-1 pediatric subjects of 12 to less than 18 years of age, weighing at least 40 kg, received treatment with darunavir, cobicistat, and two nucleoside reverse transcriptase inhibitors through Week 48.[1,3,4]

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

1.2 RELEVANT LABELED SAFETY INFORMATION

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

CONTRAINDICATIONS:

- Prezcobix is contraindicated in patients receiving certain co-administered drugs for which altered plasma concentrations are associated with serious and/or life-threatening events or loss of therapeutic effect.

WARNINGS AND PRECAUTIONS:

- Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis), liver injury, including some fatalities can occur with Prezcobix. Monitor liver function before and during therapy, especially in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases.
- Skin reactions ranging from mild to severe, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms and acute

generalized exanthematous pustulosis, can occur with Prezcobix. Discontinue treatment if severe reaction develops.
- When Prezcobix is used in combination with a tenofovir disoproxil fumarate (tenofovir DF) containing regimen, cases of acute renal failure and Fanconi syndrome have been reported.
- Prezcobix is not recommended in combination with other antiretroviral drugs that require pharmacokinetic boosting.
- Monitor in patients with a known sulfonamide allergy.
- Patients receiving Prezcobix may develop new onset or exacerbations of diabetes mellitus/hyperglycemia, redistribution/accumulation of body fat, and immune reconstitution syndrome.
- Patients with hemophilia may develop increased bleeding events.

ADVERSE REACTIONS:
- The most common adverse reactions to darunavir, a component of Prezcobix (incidence greater than or equal to 5%) of at least moderate severity (greater than or equal to Grade 2) were diarrhea, nausea, rash, headache, abdominal pain, and vomiting.

Pediatric Use:
- The safety and effectiveness of Prezcobix for the treatment of HIV-1 infection in pediatric patients weighing at least 40 kg was established through a trial with components of Prezcobix. Use of Prezcobix in this group is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic, safety, and virologic data from a study of components of Prezcobix (Trial GS-US-216-0128) in pediatric subjects with HIV-1 infection aged 12 to less than 18 years.
- The safety and effectiveness of Prezcobix have not been established in pediatric patients weighing less than 40 kg. Darunavir, a component of Prezcobix is recommended in pediatric patients below 3 years of age because of toxicity and mortality observed in juvenile rats dosed with darunavir.
  Juvenile Animal Toxicity Data:
  - Darunavir: In a juvenile toxicity study where rats were directly dosed with darunavir (up to 1000 mg/kg), deaths occurred from post-natal day 5 at plasma exposure levels ranging from 0.1 to 1.0 of the human exposure levels. In a 4-week rat toxicology study, when dosing was initiated on post-natal day 23 (the human equivalent of 2 to 3 years of age), no deaths were observed with a plasma exposure (in combination with ritonavir) 2 times the human plasma exposure levels.

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 19, 2023
Time period of search	January 29, 2015† - September 18, 2023
Search type	RxLogix Post-Market Cases
Product terms	Product Active Ingredient: cobicistat\darunavir ethanolate
MedDRA search terms (Version 26.0)	All Preferred Terms

* See Appendix A for a description of the FAERS database.
† 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 January 29, 2015, through September 18, 2023, with Prezcobix.

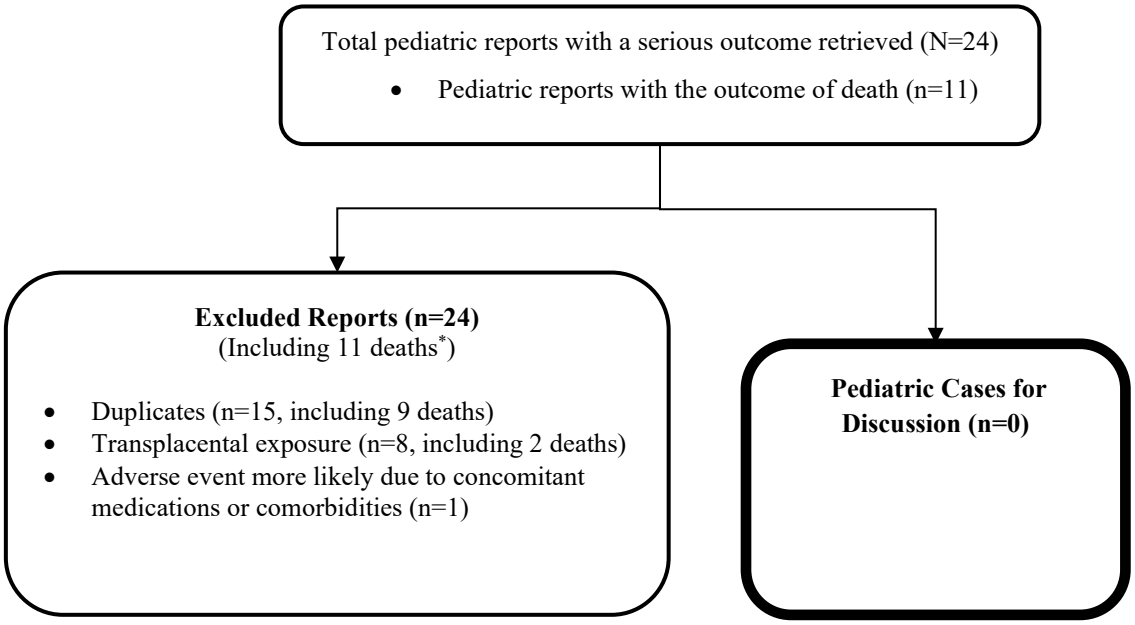
Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From January 29, 2015, through September 18, 2023, With Prezcobix			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	873 (389)	659 (188)	70 (34)
Pediatrics (0 - < 18 years)	24‡ (9)	24‡ (9)	11‡ (6)

* 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.
‡ This table includes two additional reports of pediatric deaths that were identified among U.S. reports not reporting an age. These reports are reflected in the counts of pediatric reports.

3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved 24 serious pediatric reports from January 29, 2015, through September 18, 2023. We reviewed all FAERS pediatric reports with a serious outcome. We excluded all reports from the case series for the reasons listed in **Figure 1**, which presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious Pediatric Cases With Prezcobix



* Eleven excluded reports described fatal outcomes. None of the deaths were determined to be attributed to Prezcobix. These eleven reports included two unique transplacental cases. One case described death following elective pregnancy termination, and the other case reported death secondary to a combination of unspecified conditions including "toxicity" and "osteoporosis" without further clinical context.

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 reviewed all serious FAERS reports with Prezcobix in pediatric patients less than 18 years of age from January 29, 2015, through September 18, 2023, and identified 24 reports; however, we excluded all reports 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 Prezcobix in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Prezcobix (cobicistat; darunavir) [Package Insert]. Horsham, PA: Janssen Products.; Revised March 2023. Accessed on September 19, 2023 at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/205395s025lbl.pdf

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3. Sampson M., Arya V. Prezcobix Clinical Pharmacology Review. NDA 205395 Supplement 16. June 19, 2020. Accessed on October 4, 2023 at: https://www.fda.gov/media/142206/download?attachment

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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.

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/s/

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