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 8, 2023
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Product Name:	Symtuza (cobicistat; darunavir; emtricitabine; tenofovir alafenamide)
Pediatric Labeling Approval Date:	March 2, 2020
Application Type/Number:	NDA 210455
Applicant:	Janssen
TTT Record ID:	2023-6410

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Symtuza (cobicistat; darunavir; emtricitabine; tenofovir alafenamide) 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 Symtuza in pediatric patients.

Symtuza is a four-drug combination of darunavir, a human immunodeficiency virus (HIV-1) protease inhibitor, cobicistat, a CYP3A inhibitor, and emtricitabine and tenofovir alafenamide, both HIV-1 nucleoside analog reverse transcriptase inhibitors. Symtuza was initially approved in the United States (U.S.) on July 17, 2018, and is currently indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 40 kg who have no prior antiretroviral treatment history or who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months and have no known substitutions associated with resistance to darunavir or tenofovir.

This pediatric postmarketing safety review was stimulated by pediatric labeling on March 2, 2020, that expanded the Symtuza 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 Symtuza in pediatric patients less than 18 years of age from July 17, 2018, through September 18, 2023, and we identified two reports; however, we excluded both 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 Symtuza in pediatric patients less than 18 years of age.

DPV will continue routine pharmacovigilance monitoring for Symtuza.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Symtuza (cobicistat; darunavir; emtricitabine; tenofovir alafenamide) 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 Symtuza in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Symtuza is a four-drug combination of darunavir, a human immunodeficiency virus (HIV-1) protease inhibitor, cobicistat, a CYP3A inhibitor, and emtricitabine and tenofovir alafenamide, both HIV-1 nucleoside analog reverse transcriptase inhibitors. Symtuza was initially approved in the United States (U.S.) on July 17, 2018, and is currently indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 40 kg who have no prior antiretroviral treatment history or who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months and have no known substitutions associated with resistance to darunavir or tenofovir.[1]

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

No clinical trials with Symtuza were performed in pediatric patients. The approval for the use of Symtuza in the pediatric population was based on the pharmacokinetics (PK), safety, and efficacy data from two trials evaluating components of Symtuza in pediatric subjects of 12 to less than 18 years of age: clinical trials GS-US-216-0128 (virologically-suppressed, N=7 with weight ≥40 kg) for darunavir co-administered with cobicistat and other antiretroviral agents, and GS-US-292-0106 (treatment-naïve, N=50 with weight ≥35 kg) for a fixed-dose combination regimen containing cobicistat, emtricitabine, tenofovir alafenamide, and elvitegravir.[1,3,4] Pharmacokinetic results and safety analyses of the trials in these pediatric subjects did not identify new safety concerns compared to the known safety profile of Symtuza in adult subjects.[1,3,4]

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

1.2 RELEVANT LABELED SAFETY INFORMATION

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

CONTRAINDICATIONS:

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

WARNINGS AND PRECAUTIONS:

- Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) including some fatalities can occur with Symtuza. 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.
- Severe skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis may occur with Symtuza. Discontinue treatment if severe skin reaction develops.
- Patients receiving Symtuza may develop new onset or exacerbations of immune reconstitution syndrome.
- Monitor in patients with a known sulfonamide allergy.
- Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity.
- Patients receiving Symtuza may develop new onset or exacerbations of diabetes mellitus/hyperglycemia and redistribution/accumulation of body fat.
- Patients with hemophilia may develop increased bleeding events.

ADVERSE REACTIONS:

- The most common adverse reactions (all grades, incidence greater than or equal to 2%) were diarrhea, rash, nausea, fatigue, headache, abdominal discomfort, and flatulence.

Pediatric Use:

- The safety and effectiveness of Symtuza for the treatment of HIV-1 infection in pediatric patients weighing at least 40 kg was established through studies with components of Symtuza. Use of Symtuza in this group is supported by evidence from adequate and well-controlled studies of Symtuza in adults with additional pharmacokinetic, safety, and virologic data from studies of components of Symtuza (Trials GS-US-216-0128 and GS-US-292-0106) in pediatric subjects with HIV-1 infection aged 12 to less than 18 years.
- The safety and effectiveness of Symtuza have not been established in pediatric patients weighing less than 40 kg. Darunavir, a component of Symtuza is not 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	July 17, 2018† - September 18, 2023
Search type	RxLogix Post-Market Cases
Product terms	Product Active Ingredients: cobicistat\darunavir\emtricitabine\tenofovir alafenamide
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 July 17, 2018, through September 18, 2023, with Symtuza.

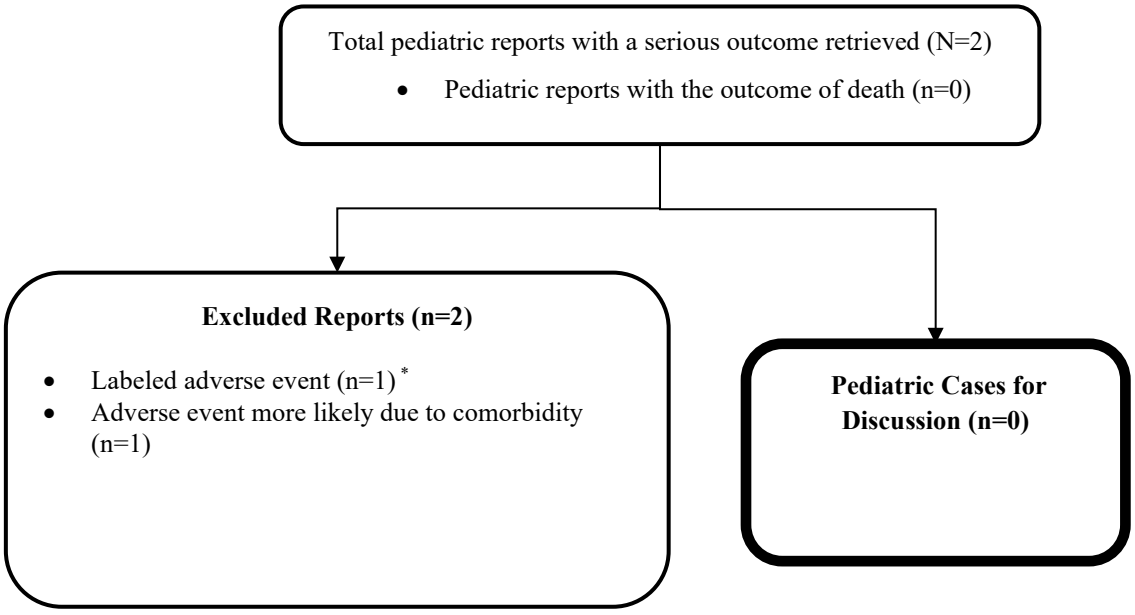
Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From July 17, 2018, through September 18, 2023, With Symtuza			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	335 (204)	233 (103)	41 (25)
Pediatrics (0 - < 18 years)	5 (4)	2 (1)	0 (0)

* 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 two serious pediatric reports from July 17, 2018, through September 18, 2023. We reviewed and excluded both 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 Symtuza



* Labeled adverse event does not represent increased severity or frequency.

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 Symtuza in pediatric patients less than 18 years of age from July 17, 2018, through September 18, 2023, and we identified two reports; however, we excluded both 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 Symtuza in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Symtuza (cobicistat; darunavir; emtricitabine; tenofovir alafenamide) [Package Insert]. Horsham, PA: Janssen Products.; Revised March 2023. Accessed on September 19, 2023 at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/210455s023lbl.pdf

2. Birnkrant D. NDA 210455 Supplement 09 Approval Letter. March 2, 2020. Accessed on October 4, 2023 at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/210455Orig1s009ltr.pdf

3. Sampson M., Arya V. Symtuza Clinical Pharmacology Review. NDA 210455 Supplement 9. February 13, 2020. Accessed on October 4, 2023 at: https://www.fda.gov/media/136676/download?attachment

4. Boyd S., Sherwat A. Symtuza Clinical and Cross Discipline Team Leader Review. NDA 210455 Supplement 9. February 5, 2020. Accessed on October 4, 2023 at: https://www.fda.gov/media/136675/download?attachment

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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