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:	June 4, 2025
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Product Name:	Xofluza (baloxavir marboxil)
Pediatric Labeling Approval Dates:	November 23, 2020; August 11, 2022
Application Type/Numbers:	NDA 210854, NDA 214410
Applicant:	Genentech, Inc.
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Xofluza (baloxavir marboxil) 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). This review focuses on United States (U.S.) serious unlabeled adverse events associated with baloxavir in pediatric patients.

Xofluza (baloxavir) is a polymerase acidic endonuclease inhibitor and was initially approved in the U.S. on October 24, 2018. Baloxavir is currently indicated for (1) the treatment of acute uncomplicated influenza in patients 5 years of age and older who have been symptomatic for no more than 48 hours and who are otherwise healthy or at high risk of developing influenza-related complications, and (2) for post-exposure prophylaxis of influenza in persons 5 years of age and older following contact with an individual who has influenza.

This pediatric postmarketing safety review was prompted by pediatric labeling on November 23, 2020, and August 11, 2022, where indications for post-exposure prophylaxis in adolescent patients (12 years and older), and the treatment and post-exposure prophylaxis of influenza in pediatric patients (5 years and older) were added, respectively. Adverse events reported in the pediatric and adolescent trials were similar to adults except for vomiting and diarrhea, which were both more commonly reported in pediatric patients.

On August 4, 2021, DPV completed a review of postmarketing adverse event reports in the U.S. with a serious outcome for baloxavir in pediatric patients. DPV's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with baloxavir. DPV's evaluation was presented to the Pediatric Advisory Committee via webposting on September 3, 2021.

DPV searched FAERS for all U.S. serious reports with baloxavir in pediatric patients less than 18 years of age from March 16, 2021 - May 7, 2025, and identified 10 reports; however, all reports were excluded from further discussion because they described labeled adverse events, did not contain sufficient information to assess causality, or were a duplicate report.

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

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Xofluza (baloxavir marboxil) 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). This review focuses on United States (U.S.) serious unlabeled adverse events associated with baloxavir in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Xofluza (baloxavir) is a polymerase acidic endonuclease inhibitor and was initially approved in the U.S. on October 24, 2018. Baloxavir is currently indicated for (1) the treatment of acute uncomplicated influenza in patients 5 years of age and older who have been symptomatic for no more than 48 hours and who are otherwise healthy or at high risk of developing influenza-related complications, and (2) for post-exposure prophylaxis of influenza in persons 5 years of age and older following contact with an individual who has influenza[1, 2].

This pediatric postmarketing safety review was prompted by pediatric labeling on November 23, 2020[3], and August 11, 2022[4], where indications for post-exposure prophylaxis in adolescent patients (12 years and older), and the treatment and post-exposure prophylaxis of influenza in pediatric patients (5 years and older) were added, respectively. Adverse events reported in the pediatric and adolescent trials were similar to adults except for vomiting and diarrhea, which were both more commonly reported in pediatric patients.

On August 4, 2021, DPV completed a review of postmarketing adverse event reports in the U.S. with a serious outcome for baloxavir in pediatric patients[5]. DPV's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with baloxavir. On September 3, 2021, DPV's evaluation was presented to the Pediatric Advisory Committee via webposting.

1.2 RELEVANT LABELED SAFETY INFORMATION

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

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

XOFLUZA is contraindicated in patients with a history of hypersensitivity to baloxavir marboxil or any of its ingredients. (4)

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

- Hypersensitivity such as anaphylaxis, angioedema, urticaria, and erythema multiforme: Initiate appropriate treatment if an allergic-like reaction occurs or is suspected. (5.1)
- Increased incidence of Treatment-Emergent Resistance in Patients Less Than 5 Years of Age: XOFLUZA is not indicated in patients less than 5 years of age due to increased incidence of treatment-emergent

resistance in this age group. In clinical trials, incidence of virus with treatment-emergent substitutions associated with reduced susceptibility to baloxavir (resistance) was higher in pediatric subjects younger than 5 years of age than older subjects. (5.2)

- Risk of bacterial infection: Serious bacterial infections may begin with influenza-like symptoms or may coexist with, or occur as, a complication of influenza. XOFLUZA has not been shown to prevent such complications. Prescribers should be alert to potential secondary bacterial infections and treat them as appropriate. (5.3)

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

Adverse events reported in at least 1% of adult and adolescent influenza subjects treated with XOFLUZA included diarrhea (3%), bronchitis (3%), nausea (2%), sinusitis (2%), and headache (1%). (6.1)

Adverse events reported in at least 5% of pediatric subjects (5 to < 12 years) treated with XOFLUZA included vomiting (5%) and diarrhea (5%).

8.4 Pediatric Use

Treatment of Acute Uncomplicated Influenza in Adolescent Subjects (≥ 12 Years of Age)

The safety and effectiveness of XOFLUZA for the treatment of acute uncomplicated influenza in adolescent subjects 12 years of age and older weighing at least 40 kg is supported by one randomized, double-blind, controlled trial in otherwise healthy subjects Trial T0831 and one trial in subjects at high risk of developing influenza-related complications Trial T0832 [see Clinical Studies (14.1)]. A total of 117 otherwise healthy adolescents 12 to17 years of age were randomized and received either XOFLUZA (N=76) or placebo (N=41) in Trial T0831; 38 adolescents 12 to 17 years of age at high risk for influenza complications were randomized and received either XOFLUZA (N=21) or placebo (N=17) in Trial T0832. The median time to alleviation of symptoms in influenza-infected adolescent subjects aged 12 to 17 years in Trial T0831 was comparable to that observed in adults. In Trial T0832, the median time to improvement of symptoms in the limited number of influenza-infected adolescent subjects aged 12 to 17 years was similar in the XOFLUZA and placebo arms [see Clinical Studies (14.1)]. Adverse events reported in adolescents in both trials were similar to those reported in adults [see Adverse Reactions (6.1)].

Treatment of Acute Uncomplicated Influenza in Pediatric Subjects (5 to < 12 Years of Age)

The safety and effectiveness of XOFLUZA in pediatric subjects 5 to less than 12 years of age is supported by one randomized, double-blind, controlled trial Trial CP40563 with a primary endpoint of safety. In this trial, 118 pediatric subjects were randomized and treated in a 2:1 ratio and received either XOFLUZA (N=79) or oseltamivir (N=39). Efficacy was extrapolated from adults and adolescents based on comparable PK exposures in adults, adolescents and pediatric subjects 5 to less than 12 years of age. The median time to alleviation of signs and symptoms in influenza-infected subjects was comparable in the XOFLUZA and oseltamivir arms. Adverse events reported with XOFLUZA in pediatric subjects were similar to those observed in adults and adolescents except for vomiting and diarrhea, which were both more commonly reported in pediatric subjects [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1)].

Post-Exposure Prophylaxis of Influenza in Pediatric and Adolescent Subjects (5 to < 18 Years of Age)

The safety and effectiveness of XOFLUZA for post-exposure prophylaxis in pediatric and adolescent subjects 5 to less than 18 years of age is supported by one randomized, double-blind, controlled trial conducted in Japan Trial T0834 [see Clinical Studies (14.3)]. Subjects in this trial were randomized in a 1:1 ratio to receive XOFLUZA or placebo. A total of 69 subjects from 5 to <18 years of age in Trial T0834 received XOFLUZA. The incidence of RT-PCR-confirmed symptomatic influenza in pediatric subjects 5 to <18 years of age was similar to that observed in adult subjects [see Clinical Pharmacology (12.3), and Clinical Studies (14.3)]. Efficacy was extrapolated from adults based on comparable PK exposures in adults, adolescents and pediatric subjects 5 to <18 years of age.

Adverse events reported in pediatric and adolescent subjects were similar to those reported in adults in the same trial [see Adverse Reactions (6.1)].

Pediatric Subjects (< 5 Years of Age)

The safety and effectiveness of XOFLUZA for treatment and post-exposure prophylaxis of influenza in pediatric subjects less than 5 years of age, including neonates, have not been established [see Warnings and Precautions (5.2) and Microbiology (12.4)].

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 8, 2025
Time period of search	March 16, 2021† - May 7, 2025
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product Active Ingredient: baloxavir, baloxavir marboxil
MedDRA search terms (Version 28.0)	All Preferred Terms
Other criteria	Case Seriousness: Serious‡ Country Derived: USA
* See Appendix A for a description of the FAERS database. † The FAERS search period for the most recently completed DPV pediatric postmarketing pharmacovigilance review for baloxavir ended on March 15, 2021. ‡ 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. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, USA=United States of America	

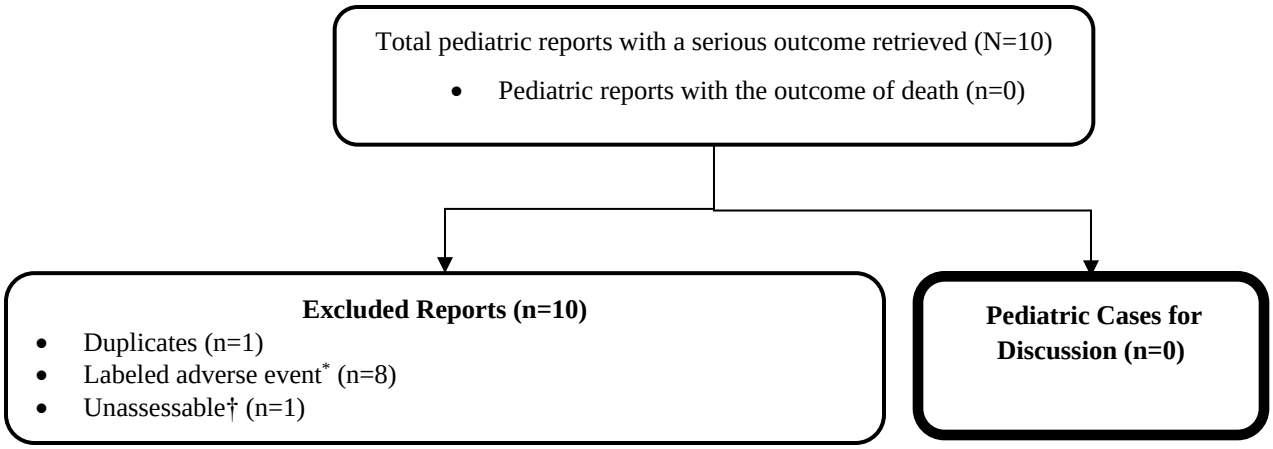
3 RESULTS

3.1 FAERS

3.1.1 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 10 U.S. serious pediatric reports for patients less than 18 years old from March 16, 2021 - May 7, 2025. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all 10 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 Baloxavir



* Labeled adverse event does not represent increased severity.
† 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.

3.1.2 Summary of U.S. Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.3 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 baloxavir in pediatric patients less than 18 years of age from March 16, 2021 - May 7, 2025, and identified 10 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 baloxavir in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

[1] Xofluza (baloxavir marboxil) tablet, for oral use [package insert]. South San Francisco, CA: Genentech USA, Inc.
[2] Xofluza (baloxavir marboxil) suspension, for oral use [package insert]. South San Francisco, CA: Genentech USA, Inc.
[3] Food and Drug Administration. Integrated Review for NDA 214410/Original 1 & NDAs 210854/S-04, 10; NDA 214410/Original 2 & NDAs 210854/S-05, 09 Xofluza (baloxavir marboxil). November 23, 2020.
[4] Food and Drug Administration. Approval Letter for Xofluza (baloxavir marboxil) NDA 210854/S-05 and NDA 210854/S-09. August 11, 2022.
[5] McCartan K, Kim I, Kapoor R, Diak IL. Food and Drug Administration. Office of Surveillance and Epidemiology. Pediatric Postmarketing Pharmacovigilance Review for Xofluza (baloxavir marboxil). August 4, 2021.

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.