Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	August 4, 2021
Reviewers:	Kate McCartan, MD Division of Pharmacovigilance II
	Ivone Kim, MD, FAAP Division of Pharmacovigilance I
Team Leader:	Rachna Kapoor, PharmD, MBA Division of Pharmacovigilance II
Deputy Division Director:	Ida-Lina Diak, PharmD, MS Division of Pharmacovigilance II
Product Name:	Xofluza (Baloxavir marboxil)
Pediatric Labeling Approval Date:	October 24, 2018
Application Type/Numbers:	NDA 210854, NDA 214410
Applicant:	Genentech, Inc.
OSE RCM #:	2021-574

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Xofluza (baloxavir marboxil) in pediatric patients younger than age 18 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA). This review focuses on serious adverse events associated with Xofluza in U.S. pediatric patients.

The FDA approved Xofluza on October 24, 2018, for the treatment of acute uncomplicated influenza in adult and pediatric patients 12 years of age and older who have been symptomatic for no more than 48 hours. On November 23, 2020, an indication was added for post-exposure prophylaxis of influenza in patients 12 years of age and older following contact with an individual who has influenza.

DPV reviewed all U.S. serious FAERS reports with Xofluza in the pediatric population (ages 0 - < 18 years) received by FDA from October 28, 2018 through March 15, 2021 and identified five cases for inclusion in our case series. Three of the five cases described adverse events that were consistent with known adverse events described in labeling (e.g., hypersensitivity/anaphylactic shock, vomiting). The remaining two cases reported the adverse event of seizure. The adverse event in these two cases had other possible etiologies and both cases had limited information. Of the five cases reviewed, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events and there were no deaths.

This review did not identify any new or unexpected pediatric safety concerns for Xofluza. DPV will continue to monitor all adverse events associated with the use of Xofluza through routine pharmacovigilance.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Xofluza (baloxavir marboxil) in pediatric patients younger than age 18 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA). This review focuses on serious adverse events associated with Xofluza in U.S. pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

FDA approved Xofluza for adults and pediatric patients 12 years of age and older on October 24, 2018. Xofluza is a polymerase acidic endonuclease inhibitor indicated for the treatment of acute uncomplicated influenza in patients who have been symptomatic for no more than 48 hours.[1] Since original approval, supplemental new drug applications (sNDA) received approval to expand the indicated patient population to include individuals at high risk of developing influenza-related complications as well as to include the indication of post-exposure prophylaxis of influenza. On November 23, 2020, FDA approved an oral suspension of Xofluza for these same indications. The labeling changes for INDICATIONS AND USAGE are detailed in Table 1, with the labeling changes underlined.

Table 1. Labeling changes for Xofluza INDICATIONS AND USAGE

Date	Submission	INDICATIONS AND USAGE Labeling
October 24, 2018	NDA 210854 ORIG-1[2]	XOFLUZA™ is a polymerase acidic (PA) endonuclease inhibitor indicated for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours.
October 16, 2019	NDA 210854 SUPPL-1[3]	XOFLUZA™ is a polymerase acidic (PA) endonuclease inhibitor indicated for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours and who are: • otherwise healthy, or • <u>at high risk of developing influenza-related complications</u>.
November 23, 2020	NDA 201854 SUPPL-4 SUPPL-10[4] NDA 214410*[4]	XOFLUZA™ is a polymerase acidic (PA) endonuclease inhibitor indicated for: • Treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours and who are: o otherwise healthy, or o at high risk of developing influenza-related complications.

		• Post-exposure prophylaxis of influenza in patients 12 years of age and older following contact with an individual who has influenza.
*NDA 214410 is Xofluza (baloxavir marboxil) 2 mg/mL oral suspension. This was the labeling on approval. Abbreviations: NDA = new drug application		

Support for the approval of Xofluza applications came from multiple trials that included pediatric patients. Table 2 provides a summary of these trials and their efficacy and safety conclusions. Notably, in trial CP40563, the frequency of treatment-emergent resistance to baloxavir was found to be substantially higher in pediatric subjects (1 to < 12 years old) than in adults and adolescents and therefore, due to concerns for decreased efficacy and the possibility of increased influenza transmission associated with this high frequency of baloxavir-resistance, the risks of baloxavir use in patients < 12 years of age was thought to outweigh the benefits[5]. Xofluza was therefore not approved for treatment of acute, uncomplicated influenza in patients 1 to < 12 years of age. Similarly, it was not approved for post-exposure prophylaxis in pediatric patients 1 to < 12 years of age.

Table 2. Xofluza (baloxavir marboxil) Trials Including Pediatric Patients

Application# / Trial Number	Trial Design	Patient Population and Number of Pediatric Patients	Efficacy and Safety Results
NDA 210854[6]/ Trial 1601T0831	Phase 3, randomized, double-blind, active (oseltamivir) and placebo-controlled, safety and efficacy trial	Otherwise healthy patients 12 to 64 years of age with influenza Conducted in Japan and North America (U.S. and Canada) ITTI population: 118 patients ages ≥ 12 and ≤ 19 years • Baloxavir marboxil n=80 • Placebo n=38 • No patients in this age group received oseltamivir because of concerns of neuropsychiatric adverse events by the Japanese regulatory authorities	• Efficacy (adolescents): Time to alleviation of symptoms was 39 hours shorter in adolescents (12 to < 18 years of age) who received baloxavir marboxil compared to those who received placebo (p=0.0055) • Safety: No severe or serious adverse events were reported in the adolescent subject population. No increase in incidence or severity of adverse events in adolescents and the types of adverse events observed with the adolescent population were similar to those observed in adult subjects.
NDA 210854[6]/ Trial 1618T0822 (non-IND pediatric study)	An open-label, single arm, safety, pharmacokinetic (PK), and efficacy study	Otherwise healthy Japanese pediatric patients (6 months to < 12 years of age) with uncomplicated influenza treated with single dose of baloxavir marboxil Randomized subjects n=107	• Conclusions could not be drawn in the 6 months to < 2 years old cohort due to the small number of subjects. Noted that appropriate dose not yet identified for specific pediatric weight or age ranges. • Efficacy: Overall median time to alleviation of symptoms was 45

Table 2. Xofluza (baloxavir marboxil) Trials Including Pediatric Patients			
Application# / Trial Number	**Trial Design**	**Patient Population and Number of Pediatric Patients**	**Efficacy and Safety Results**
		• Ages 2 to 12 years n=105 • Ages 6 months to < 2 years n=2	hours, compared to the Phase 3 trial result of 54 hours. It was therefore concluded that baloxavir marboxil was efficacious in pediatric patients. • Safety: No deaths or serious adverse events. Adverse drug reactions were reported in 4 subjects (4%) including diarrhea or soft feces (n=3) and increased alanine aminotransferase (n=1). Overall, it was assessed that the safety results reported in this pediatric trial were similar to those reported in the trials with adults.
NDA 210854 SUPPL-1[7]/ Trial 1602T0832 (T032)	Phase 3, randomized, double-blind, active-(oseltamivir) and placebo-controlled, safety and efficacy trial	Adults and adolescents 12 years of age and older who were at high risk of influenza complications and who had acute, uncomplicated influenza Conducted in North America, Asia, and South America ITTI population: 58 patients ages ≥ 12 and ≤ 19 years • Baloxavir marboxil n=19 • Oseltamivir n=22 • Placebo n=17	• Efficacy: The median time to improvement of influenza symptoms in the adolescent subjects (12 to 17 years of age) infected with influenza virus was similar for subjects who received baloxavir marboxil (188 hours) and placebo (191 hours), however, the small number of adolescents in this subgroup (13 subjects in the baloxavir marboxil arm and 12 in the placebo arm) precluded accurate analysis of the median time to improvement of influenza symptoms in this age group. Despite these inconclusive results, it was assessed that baloxavir marboxil could be approved for use in adolescents with acute, uncomplicated influenza who are at high risk of influenza complications based on extrapolation of efficacy from Trial T0831. • Safety: There were too few adolescent subjects to analyze safety in this population compared to adults, however, there were no serious adverse events or Grade 3 or Grade 4 adverse events reported in adolescents in the trial, regardless of the treatment arm.

Table 2. Xofluza (baloxavir marboxil) Trials Including Pediatric Patients			
Application# / Trial Number	**Trial Design**	**Patient Population and Number of Pediatric Patients**	**Efficacy and Safety Results**
NDA 214410 and NDA 210854/S-10[5]/ Trial CP40563	Phase 3 randomized, double-blind, active-(oseltamivir) controlled safety, pharmacokinetic (PK) and effectiveness trial	Otherwise healthy pediatric patients from 1 to <12 years of age with influenza ITTI population: 123 patients • Baloxavir marboxil n=80 • Oseltamivir n=43	• Efficacy: Time to alleviation of symptoms was similar for patients who received baloxavir marboxil and for those who received oseltamivir. Treatment-emergent baloxavir resistance-associated amino acid substitutions were identified in 22.4% of pediatric patients 1 to < 12 years of age. • Safety: No serious adverse events or deaths. Vomiting was the most commonly observed treatment-emergent adverse event.
NDA 214410 and NDA 210854/S-10[5]/ Trial T0822 (non-IND trial)	Open-label, uncontrolled trial	Pediatric patients < 12 years of age with acute, uncomplicated influenza Conducted in Japan Total patients n=107 patients	• Safety: No serious adverse events or deaths. No Grade 3 or Grade 4 treatment-emergent adverse events reported; Treatment-emergent adverse events observed in >2% of subjects were vomiting, diarrhea, pharyngitis. Adverse events assessed by investigator to be drug-related were diarrhea (n=2) and soft feces (n=1).
NDA 214410 and NDA 210854/S-10[5]/ Trial T0833 (non-IND trial)	Open-label, uncontrolled trial	Pediatric patients < 12 years of age with acute, uncomplicated influenza and weighing < 20 kg Conducted in Japan Total patients n=33 patients	• Safety: No serious adverse events or deaths. No Grade 3 or Grade 4 treatment-emergent adverse events. Treatment-emergent adverse events observed in more than one patient included vomiting, nasopharyngitis, upper respiratory tract infection, and otitis media. One drug-related adverse event, thrombocytosis, was reported.
NDA 214410 and NDA 210854/S-04,S-10[5]/ Trial T0834 (Post-exposure Prophylaxis of Influenza in Household Contacts)	Phase 3 randomized, double-blind, placebo-controlled safety and efficacy trial	Healthy subjects who lived with index patient with influenza symptoms for ≥ 48 hours prior to providing informed consent and who were judged not to have influenza Pediatric subjects of any age could be enrolled • No pediatric subjects < 1 year of age were enrolled	• Efficacy: Demonstrated efficacy in pediatric subjects < 12 years of age, but not approved for post-exposure prophylaxis in this group due to high frequency of treatment-emergent baloxavir resistance. • Safety: No serious adverse events or deaths in the baloxavir marboxil arm. All treatment-emergent adverse events in baloxavir marboxil arm were mild in intensity. No Grade 3

Table 2. Xofluza (baloxavir marboxil) Trials Including Pediatric Patients			
Application# / Trial Number	**Trial Design**	**Patient Population and Number of Pediatric Patients**	**Efficacy and Safety Results**
		mITT population: 179 patients less than 20 years of age (107 patients less than 10 years of age) • Baloxavir marboxil n=85 (< 10 years of age n=55) • Placebo n=94 (< 10 years of age n=52)	or Grade 4 adverse events in baloxavir marboxil arm. The most common treatment-emergent adverse events in pediatric patients were respiratory adverse events, headache and pyrexia.
Abbreviations: ITTI = Intent-to-treat-infected population, IND = investigational new drug, mITT = modified intent-to-treat			

This review was triggered by the original approval for Xofluza in October 24, 2018. DPV has not previously presented a Xofluza pediatric evaluation to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Xofluza labeling provides the following safety information (excerpted from the pertinent sections). For further Xofluza labeling information, please refer to the full prescribing information.[1]

----------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)
- 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. (5.2)

----------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)

----------DRUG INTERACTIONS----------

- Avoid coadministration of XOFLUZA with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids, or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc). (2.1, 7.1)
- Live attenuated influenza vaccines may be affected by antivirals. (7.2)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Treatment of Acute Uncomplicated Influenza in Pediatric Subjects

The safety and effectiveness of XOFLUZA for the treatment of acute uncomplicated influenza in pediatric 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 2) and one trial in subjects at high risk of developing influenza-related complications (Trial 3) *[see Clinical Studies (14.1)]*. A total of 117 otherwise healthy adolescents 12-17 years old were randomized and received either XOFLUZA (N=76) or placebo (N=41) in Trial 2; 38 adolescents aged 12 to 17 years at high risk for influenza complications were randomized and received either XOFLUZA (N=21) or placebo (N=17) in Trial 3. The median time to alleviation of symptoms in influenza-infected adolescent subjects aged 12 to 17 years in Trial 2 was comparable to that observed in adults. In Trial 3, 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)]*.

The safety and efficacy of XOFLUZA in pediatric subjects less than 12 years of age have not been established for the treatment of acute uncomplicated influenza. For information on baloxavir resistance in subjects less than 12 years of age *[see Microbiology (12.4)]*.

Post-Exposure Prophylaxis of Influenza in Pediatric Subjects

The safety and effectiveness of XOFLUZA for post-exposure prophylaxis in adolescents (12 years to < 18 years) is supported by one randomized, double-blind, controlled trial conducted in Japan (Trial 4) *[see Clinical Studies (14.3)]*. Subjects in this trial were randomized in a 1:1 ratio to receive XOFLUZA or placebo. A total of 12 subjects from ≥ 12 to < 18 years of age received XOFLUZA. The incidence of RT-PCR-confirmed symptomatic influenza was similar in the XOFLUZA and placebo arms in the limited number of adolescent subjects aged 12 to 17 years of age *[see Clinical Studies (14.3)]*. Adverse events reported in adolescent subjects were similar to those reported in adults in the same trial *[see Adverse Reactions (6.1)]*.

The safety and efficacy of XOFLUZA for post-exposure prophylaxis of influenza in pediatric subjects less than 12 years of age have not been established.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 3.

Table 3. FAERS Search Strategy*	
Date of search	March 16, 2021
Time period of search	October 24, 2018† - March 15, 2021
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Query
Product terms	Product name: Xofluza Product Active Ingredient (PAI): Baloxavir, Baloxavir Marboxil
MedDRA search terms (Version 23.1)	All PTs

* See Appendix A for a description of the FAERS database.
† U.S. approval date and approval date of pediatric labeling for Xofluza
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 4 presents the number of adult and pediatric FAERS reports from October 24, 2018 through March 15, 2021 with Xofluza.

Table 4. Total Adult and Pediatric FAERS Reports* Received by FDA From October 24, 2018 to March 15, 2021 With Xofluza			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	602 (182)	458 (46)	75 (5)
Pediatrics (0 - <18 years)	395 (279)	115‡ **(8)**	3 (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.
‡ 105 of the 115 total reports with a serious outcome were from Japan. Xofluza was first approved in Japan in February 2018, prior to the U.S. approval date of October 2018. Xofluza is also approved in Japan for treatment in patients < 12 years of age who weigh ≥ 10 kg and for prevention in patients < 12 years of age who weigh ≥ 20 kg.

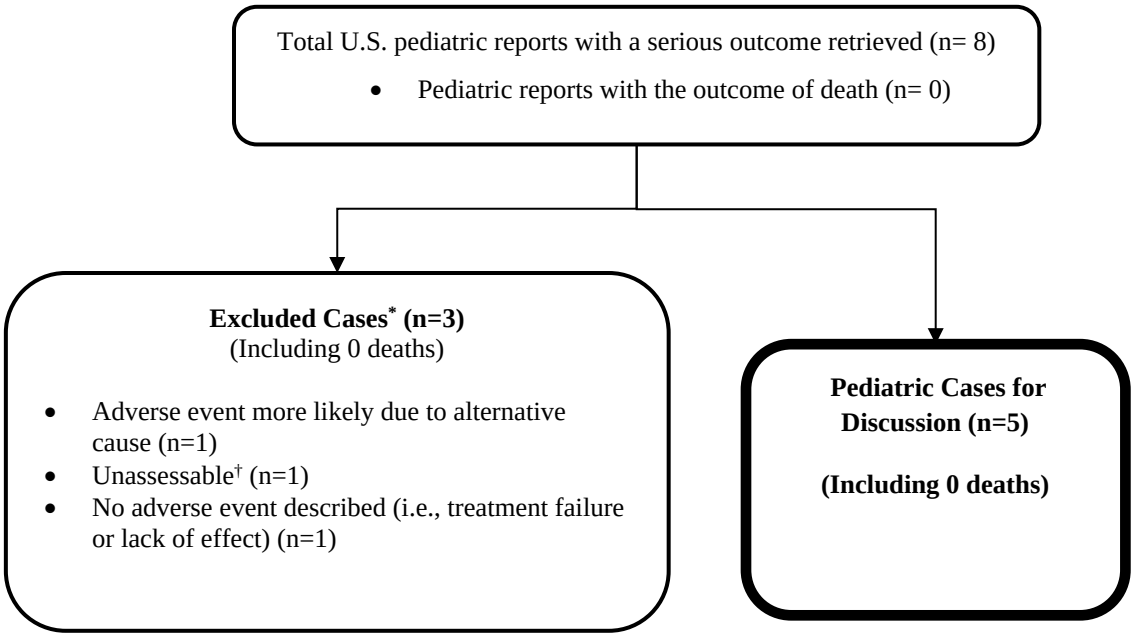
3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 8 U.S. serious pediatric reports from October 24, 2018 to March 15, 2021.

We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded reports from the case series for various reasons, such as if the adverse event was more likely due to an alternative cause (n=1; pneumonia secondary to influenza infection), if there was no adverse event described (n=1; treatment failure), or if the report was unassessable due to limited information (n=1). We summarize the remaining cases in the sections below.

Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious U.S. Pediatric Cases with Xofluza



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above

† Unassessable: Case 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) or the information is contradictory, or information provided in the case cannot be supplemented or verified.

3.1.3 Characteristics of Pediatric Cases

Appendix B contains a line listing of the 5 pediatric cases.

Table 5 summarizes the 5 FAERS cases in U.S. pediatric patients with Xofluza reporting a serious outcome received by FDA from October 24, 2018 through March 15, 2021.

Table 5. Characteristics of the FAERS U.S. Serious Pediatric Cases With Xofluza Received by FDA From October 24, 2018 – March 15, 2021 (N=5)

Age	12 years	1
	13 years	1
	14 years	1
	15 years	1
	17 years	1
Sex	Male	1
	Female	4
Reported reason for use	Influenza/flu	5
Serious outcome*	Other Serious	4
	Life-threatening	1

* 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.

3.1.4 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal U.S. pediatric adverse event reports associated with Xofluza.

3.1.5 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=5)

We identified five serious FAERS cases with Xofluza in the U.S. pediatric population reporting a non-fatal serious outcome. Three of these five cases reported labeled adverse events including hypersensitivity/anaphylactic shock (n=2) and vomiting (n=1). The remaining two cases reported a serious unlabeled event (i.e., seizure) and are summarized below.

FAERS Case #17468805, United States, 2020, Expedited Report, Serious Outcome: Other Serious

A 14-year-old female with no reported past medical history was treated with an unspecified dose of baloxavir marboxil "two times in total" on the same day for influenza A. Her only reported concomitant medication was ibuprofen. Four days after taking baloxavir marboxil, she developed a seizure. An ambulance was called, and she was taken to the hospital for blood work. She was not admitted. She recovered from the seizure on the same day.

FAERS Case #17422065, United States, 2020, Expedited Report, Serious Outcome: Other Serious

A 17-year-old female with no reported past medical history was treated with baloxavir marboxil 40 mg once a day for the flu. Two days later, she experienced a seizure. No concomitant medications were reported. Outcome of the seizure was unknown. No further information was provided.

Reviewers' Comments: The long half-life of baloxavir marboxil (79.1 hours) supports a temporal relationship in these cases with the 4 day and 2 day periods between treatment with baloxavir marboxil and the seizure events. In the first case, the only reported concomitant medication was ibuprofen, which is also not labeled for seizures. The second case did not report any concomitant medications. A possible alternative etiology of the seizure in both cases is fever associated with influenza and influenza infection itself as seizures are a recognized complication of influenza, including in pediatric patients.[8] Causality in both cases was assessed as possible. However, assessment of both cases was limited by the lack of details regarding the seizure workup, described only as "blood work" in the first case and not described at all in the second case, and the absence of any reported past medical history.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with Xofluza in the pediatric population (ages 0 - < 18 years) received by FDA from October 28, 2018 through March 15, 2021 and identified five cases for inclusion in our case series. Three of the five cases described adverse events that were consistent with known adverse events described in labeling (e.g., hypersensitivity/anaphylactic shock, vomiting). The remaining two cases reported the adverse event of a seizure. The adverse event in these two cases had other possible etiologies and both cases had limited information. Of the five cases reviewed, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events and there were no deaths.

5 CONCLUSION

DPV did not identify any new or unexpected pediatric safety concerns for Xofluza.

6 RECOMMENDATION

DPV will continue to monitor all adverse events associated with the use of Xofluza through routine pharmacovigilance.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

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 (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

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 or not 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.

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=5)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	2/3/2020	17369270	1	-	Direct	13	Female	U.S.	LT
2	2/14/2020	17422065	1	US-ROCHE-2549186	Expedited	17	Female	U.S.	OT
3	2/18/2020	17430870	2	US-ROCHE-2544589	Expedited	15	Female	U.S.	OT
4	2/27/2020	17468805	2	US-ROCHE-2557981	Expedited	14	Female	U.S.	OT
5	4/27/2020	17713639	1	US-ROCHE-2543049	Expedited	12	Male	U.S.	OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome.
Abbreviations: LT=life-threatening, OT=other medically significant

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08/04/2021 01:17:00 PM

IDA-LINA DIAK
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