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Pediatric Postmarketing Pharmacovigilance

Date:	June 17, 2019
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Product Name:	Rapivab® (peramivir)
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Applicant/Sponsor:	BioCryst Pharmaceuticals, Inc.
OSE RCM #:	2019-1014

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EXECUTIVE SUMMARY

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

FDA approved peramivir on December 19, 2014, and it is currently indicated for the treatment of acute uncomplicated influenza in patients 2 years and older who have been symptomatic for no more than 2 days. This review was prompted by pediatric labeling approved on September 20, 2017, which expanded the indication from adults to pediatric patients 2 years and older. Peramivir has not been presented before the Pediatric Advisory Committee in the past.

Of the pediatric reports reviewed, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and there were no deaths directly attributable to peramivir. Of the four serious and unlabeled adverse event cases in pediatric patients, no specific pattern of adverse events was noted. The four cases were confounded by underlying influenza virus infection which provides an alternative cause for the adverse events described.

DPV did not identify any pediatric safety concerns for peramivir and recommends no regulatory action at this time.

DPV will continue to monitor all adverse events associated with the use of peramivir.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Rapivab® (peramivir) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA).[1,2] This review focuses on serious unlabeled adverse events associated with peramivir in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Peramivir, an influenza virus neuraminidase inhibitor, was first approved on December 19, 2014, for the treatment of acute uncomplicated influenza in patients 18 years and older who have been symptomatic for no more than 2 days.[3] On September 20, 2017, the indication was expanded to include pediatric patients 2 years and older.[2] The recommended dose of peramivir in adult and adolescent patients 13 years of age or older is a single 600 mg dose, administered via intravenous infusion for 15 to 30 minutes. The recommended dose of peramivir in pediatric patients 2 to 12 years of age is a single 12 mg/kg dose (up to a maximum dose of 600 mg), administered via intravenous infusion for 15 to 30 minutes. The peramivir dose should be reduced for patients with baseline creatinine clearance below 50 mL/min (calculated using Cockcroft and Gault equation). Peramivir is supplied in cartons containing three single-use vials; each vial contains 200 mg per 20 mL (10 mg/mL).[4]

DPV has previously evaluated postmarketing adverse event reports for peramivir in pediatric patients. DPV's search of the FAERS database for all pediatric cases from initial U.S. approval (December 19, 2014) through June 30, 2017 was requested by the Division of Antiviral Products (DAVP) in response to a supplemental New Drug Application (NDA), which was submitted to expand the indication to include pediatric patients 2 years and older. The DPV evaluation identified 10 pediatric adverse event cases and no deaths were reported; however, the cases described labeled events or were highly confounded making it difficult to assess a causal relationship between peramivir and the reported unlabeled adverse events. DPV concluded that there was no evidence of a pediatric safety concern with peramivir at that time.[5] Peramivir has not been presented before the Pediatric Advisory Committee in the past.

The safety and effectiveness of peramivir for the treatment of acute uncomplicated influenza in pediatric patients 2 to 17 years of age was supported by partial extrapolation of efficacy from placebo-controlled trials in adults, and efficacy outcomes from a U.S. Phase 3, open-label, randomized, oseltamivir-controlled trial (Study BCX1812-305; Identification No. NCT02369159) conducted in pediatric patients aged 2 to 17 years.[2,6] Although this study was not designed to formally test the efficacy of peramivir in pediatric subjects with acute uncomplicated influenza, the observed trends in clinical and antiviral outcomes were similar between peramivir and the comparator, oseltamivir. Furthermore, the pharmacokinetic data collected in this trial demonstrated that the exposures achieved in pediatric patients with the selected peramivir doses were within the range of exposures shown to be safe and effective in adults, thus permitting partial extrapolation of adult data to support the pediatric indication. Of the 88 patients who enrolled and received peramivir, no new safety signals for peramivir were detected.[2]

1.2 RELEVANT LABELED SAFETY INFORMATION

The peramivir labeling includes the following information under Highlights of Prescribing Information. For further peramivir labeling information, including dosage and administration in adult patients, refer to the full prescribing information.[4]

----------**CONTRAINDICATIONS**----------

Patients with known serious hypersensitivity or anaphylaxis to peramivir or any component of RAPIVAB

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

- Cases of anaphylaxis and serious skin/hypersensitivity reactions such as Stevens-Johnson syndrome and erythema multiforme have occurred with RAPIVAB. Discontinue RAPIVAB and initiate appropriate treatment if anaphylaxis or serious skin reaction occurs or is suspected.
- Neuropsychiatric events: Patients with influenza may be at an increased risk of hallucinations, delirium and abnormal behavior early in their illness. Monitor for signs of abnormal behavior.

8.4 *Pediatric Use*

The safety and effectiveness of RAPIVAB for the treatment of influenza has been established in pediatric patients 2 to 17 years of age. Use of RAPIVAB for this indication is supported by evidence from adequate and well-controlled trials of RAPIVAB in adults with additional data from Study 305, a randomized, active-controlled trial of 110 adolescent and pediatric subjects with acute uncomplicated influenza who received open-label treatment with a single dose of RAPIVAB or 5 days of treatment with oseltamivir administered within 48 hours of onset of symptoms of influenza. Study 305 included:

- 13 to 17 years of age: 21 subjects treated with RAPIVAB 600 mg
- 2 to 12 years of age: 67 subjects treated with RAPIVAB 12 mg/kg (up to a maximum dose of 600 mg)

Safety and effectiveness of RAPIVAB in pediatric patients less than 2 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 1.

Table 1. FAERS Search Strategy[*]

Date of Search	May 9, 2019
Time Period of Search	July 1, 2017[†] - April 30, 2019
Search Type	FAERS Business Intelligence Solution (FBIS) Profile Query, Product-Manufacturer Reporting Summary
Product Terms	Product Name: Rapivab Product Active Ingredient: Peramivir
MedDRA Search Terms (Version 22.0)	All MedDRA Preferred Terms (PTs)

[*] See Appendix A for a description of the FAERS database.
[†] Data lock date from the most recent pediatric review completed by DPV

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 1, 2017 through April 30, 2019 with peramivir.

Table 2. Total Adult and Pediatric FAERS Reports[*] Received by FDA from July 1, 2017 - April 30, 2019 with Peramivir

	All reports (U.S.)	Serious[†] (U.S.)	Death (U.S.)
Adults (≥18 years)	80 (1)	79 (0)	28 (0)
Pediatrics (0 - <18 years)	10 (0)	**10 (0)**	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, and other serious important medical events.

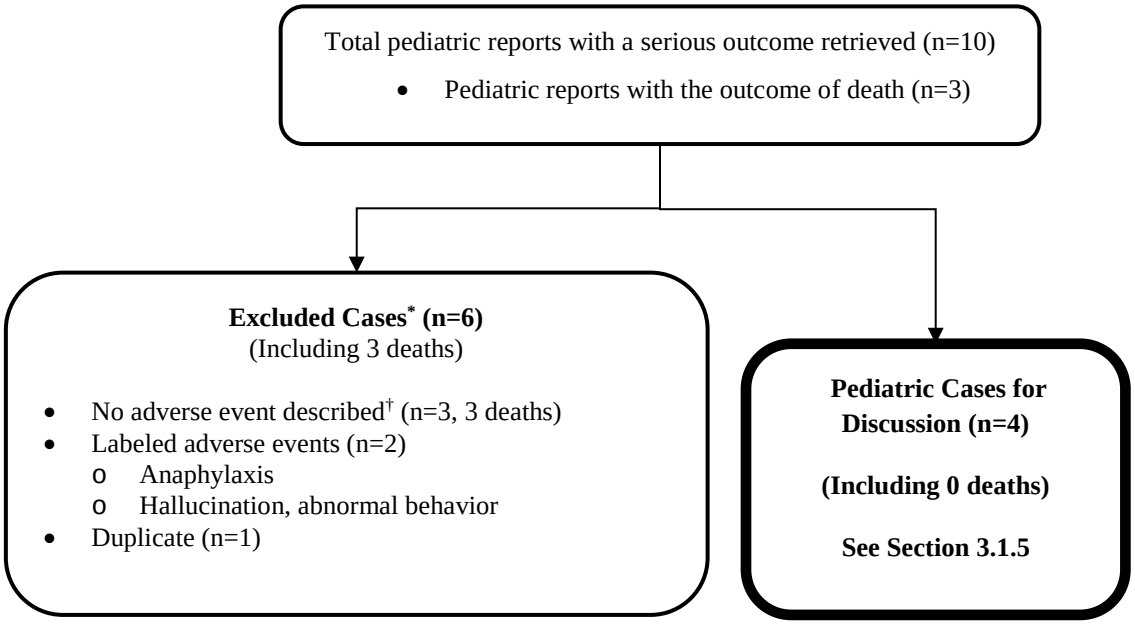
3.1.2 Selection of Pediatric Cases in FAERS

Our FAERS search retrieved 10 pediatric reports from July 1, 2017 through April 30, 2019.

We reviewed all FAERS pediatric reports and excluded duplicate reports, reports describing labeled adverse events, and reports describing peramivir treatment failure. 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 Pediatric Cases with Peramivir



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

† Three cases reported peramivir treatment failure and all three cases had a fatal outcome related to complications from acute influenza infection; one case described a patient with influenza A who received peramivir and experienced persistent fevers and cardiorespiratory arrest 2 days later, and two cases described patients who were diagnosed with severe influenza A encephalitis and received peramivir on day of presentation and died the following day because of encephalitis.

3.1.3 Characteristics of Pediatric Cases

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

3.1.4 Summary of Fatal Pediatric Cases (N=0)

We did not include any fatal pediatric adverse event cases in our case series.

3.1.5 Summary of Non-Fatal Pediatric Serious Cases (N=4)

We identified four FAERS cases with peramivir in the pediatric population reporting a non-fatal serious outcome.

FAERS Case Number: 14694783 (Japan)
Unlabeled Adverse Event: Rhabdomyolysis
A 15-year-old female was diagnosed with influenza B virus infection and received a single dose of intravenous (IV) peramivir (600 mg). Two days after receiving peramivir, it was reported the patient was improving. Four days after receiving peramivir, the patient started to have difficulty walking and visited the reporting physician's hospital where she was noted to have muscular weakness mostly in the thighs and lower back. It was reported that the patient's blood creatine phosphokinase (CPK) "increased to 1,980 IU/L (onset of the event of rhabdomyolysis)"

(baseline CPK values and normal range were not reported). Seven days after receiving peramivir, the patient was able to walk and CPK was 1,982 IU/L. By the next morning, it was reported that symptoms of influenza completely resolved, and the patient was recovering from rhabdomyolysis. The patient's past medical history was not reported, and the only reported concomitant medication was acetaminophen. The reporting physician considered the event of rhabdomyolysis as related to peramivir.
Reviewer's Comment: The onset of rhabdomyolysis four days after receiving a single dose of peramivir supports a possible causal association given peramivir's prolonged elimination half-life; however, the case was confounded by confirmed influenza virus infection, which has been associated with rhabdomyolysis[7,8] and myositis.[9,10]

FAERS Case Number: 14694785 (Japan)
Unlabeled Adverse Event: Shock
A 16-year-old female tested positive for influenza and was prescribed a single dose of IV peramivir (300 mg). The patient began to cry "immediately after the dosing" and "shortly after that," the patient developed queasiness, poor complexion, and "blood pressure and pulse rate were decreased to 75/43 and 59." The administration of peramivir was immediately discontinued and the patient was diagnosed with "shock" and was started on IV fluids. The patient was observed for an hour, and blood pressure and pulse rate improved to 116/72 and 72, respectively. The patient recovered on the same day and returned home. Past medical history and concomitant medications were not reported. The reporting physician considered the reported event of shock as definitely related to peramivir.
Reviewer's Comment: The narrative describes a hypotensive patient who developed bradycardia instead of the expected compensatory increase in heart rate. Hypotension with bradycardia can develop in the setting of neurogenic or cardiogenic shock; however, the narrative lacks information to indicate these conditions were present and rapid symptom resolution after IV fluids argues against this differential. The duration of the episode is unclear, and it is therefore difficult to discern if the event reflected a transient episode of hypotension with bradycardia or if there were sustained findings of circulatory collapse. Alternative etiologies for the event include a vasovagal reaction, dehydration, or symptoms of systemic inflammatory response from the influenza infection. In the absence of additional information, causality assessment remains difficult.

FAERS Case Number: 14974558 (Japan)
Unlabeled Adverse Event: Loss of consciousness
A 16-year-old female was diagnosed with influenza and received a single dose of IV peramivir (dose not reported). After the completion of the peramivir dose, the patient fell down when she stood up and transiently lost consciousness. It was reported that the patient had "symptoms of dehydration" that were considered related to "insufficient water intake due to severe symptoms of influenza." The patient was transferred to another hospital by ambulance and was hospitalized there for several days; she recovered from the event on an unreported date. Past medical history and concomitant medications were not reported. The reporting physician considered the transient loss of consciousness was caused by influenza encephalopathy or dehydration.
Reviewer's Comment: The onset of transient loss of consciousness after the completion of the peramivir infusion supports a possible causal association; however, a vasovagal event following

orthostatic position change is likely in the clinical setting of dehydration in a patient with severe symptoms of influenza.

FAERS Case Number: 16018915 (Japan)
Unlabeled Adverse Event: Seizure
An 8-year-old male with pyrexia (temperature not reported) was diagnosed with influenza A virus infection and received a single dose of oral baloxavir (20 mg); 30 minutes later, the patient developed urticaria and cough, which resolved in 2 to 3 hours. On the same day (time not reported), the patient also received a single dose of IV peramivir (260 mg) and went to bed at 11:00 pm. Around 2:00 am the next day, the patient developed "generalized convulsion" ("status epilepticus") and was hospitalized where he was administered an "anticonvulsant drug." By 9:00 am, convulsion was not observed, but because the patient's consciousness level did not improve, a steroid pulse of methylprednisolone was administered in case the patient had developed influenza-associated encephalopathy. The following day, the patient's body temperature decreased to within normal range and the patient began to improve. An electroencephalogram and head magnetic resonance imaging were performed and both were reported as normal. The patient recovered and was discharged after five days of hospitalization. The reporting physician considered the underlying condition of influenza A virus infection as the causal factor for the event of status epilepticus. Relevant medical history included a "febrile seizure" one month before the reported events.
Reviewer's Comment: The onset of seizure one day after receiving baloxavir and peramivir supports a possible causal association; however, the case was confounded by the patient's history of a recent seizure and confirmed influenza A virus infection. Although the patient is too old to have had a febrile seizure (i.e., greater than 5 years of age),[11] seizure (both febrile and nonfebrile) and decreased consciousness are the most common neurologic complications of influenza.[12,13]

4 DISCUSSION

We reviewed all FAERS reports with peramivir in pediatric patients less than 18 years of age during the period from July 1, 2017 through April 30, 2019. Of the reports reviewed, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events and there were no deaths directly associated with peramivir. The reports described adverse events that were likely associated with underlying influenza infection or were consistent with the known adverse reactions described in labeling (e.g., anaphylaxis, neuropsychiatric events).

Of the four serious and unlabeled adverse event cases in pediatric patients, no specific pattern of adverse events was noted. The four cases were confounded by underlying influenza virus infection which provides an alternative cause for the adverse events described.

5 CONCLUSION

DPV did not identify any pediatric safety concerns for peramivir at this time.

6 RECOMMENDATION

DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of peramivir.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

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 PERAMIVIR PEDIATRIC CASE SERIES (N=4)

	FAERS Case #	Initial FDA Received Date	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	14694783	Mar 29, 2018	3	JP-BIOCRYST PHARMACEUTICALS, INC.-2018BCR00158	Expedited (15-Day)	15	Female	Japan	OT
2	14694785	Mar 29, 2018	3	JP-BIOCRYST PHARMACEUTICALS, INC.-2018BCR00157	Expedited (15-Day)	16	Female	Japan	OT
3	14974558	Jun 5, 2018	2	JP-BIOCRYST PHARMACEUTICALS, INC.-2018BCR00211	Expedited (15-Day)	16	Female	Japan	HO
4	16018915 *Duplicate 15903017*	Feb 28, 2019 *Feb 2, 2019*	2 *3*	US-BIOCRYST PHARMACEUTICALS, INC.-2019BCR00087 *JP-ROCHE-2257315*	Expedited (15-Day) *Expedited (15-Day)*	8 *8*	Male *Male*	Japan *Japan*	HO *HO*

*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, or a congenital anomaly/birth defect, and 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: HO, hospitalization; OT, other medically significant

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