CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206426Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	September 8, 2014
Reviewers:	Bob Pratt, Pharm.D. Division of Risk Management
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Subject:	Review evaluates if a REMS is needed for peramivir
Drug Name:	Rapivab (peramivir)
Therapeutic Class:	Neuraminidase inhibitor
Dosage and route:	600 mg intravenous given once
Application Type/Number:	NDA 206426
Applicant/sponsor:	BioCryst Pharmaceuticals
OSE RCM #:	2013-2845

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1 INTRODUCTION

This review documents the Division of Risk Management (DRISK)'s evaluation of NDA 206426 for Rapivab (peramivir) to assess the need for a risk evaluation and mitigation strategy (REMS). An application for Rapivab was received by the Division of Antiviral Products (DAVP) from BioCryst Pharmaceuticals on December 23, 2013. The Applicant did not propose a REMS for peramivir.

1.1 BACKGROUND

Peramivir is an antiviral drug that inhibits influenza virus neuraminidase. The proposed indication is for the treatment of adult patients with acute uncomplicated influenza infection (b) (4). Peramivir is available as an intravenous (IV) infusion, whereas other approved antiviral treatment options for influenza patients are currently limited to oral or inhaled products. The proposed dosing regimen for peramivir is a single 600 mg IV dose. Throughout its development, peramivir has been evaluated as single-dose treatment (IV or intramuscular [IM]) for uncomplicated influenza and as multiple-dose, multi-day treatment IV for seriously ill hospitalized patients. The use of a single dose of peramivir for outpatient therapy would be presumed to result in improved patient compliance while maintaining sufficient drug exposure for antiviral activity and possibly minimizing the development of viral resistance.

Influenza viruses are RNA viruses that historically cause between three to fifty thousand deaths annually during the influenza season. Patients typically experience fevers, chills, myalgias, and upper respiratory symptoms which may lead to hospitalization. From 2012 to 2013, approximately 137,000 patients were hospitalized due to influenza-related complications. Prevention strategies include vaccination and antiviral drugs. Treatment goals include reduction in illness duration, expedition of recovery, and reduction in the risk of complications.

On the following page, Table 1 lists the drugs used for the treatment of influenza. Ideally, these drugs (including peramivir) should be administered early in the disease, that is, within 48 hours of symptom onset. The neuraminidase inhibitors are recommended as first line treatment for patients in need of antiviral drug therapy, as the currently circulating influenza viruses are resistant to the class of adamantane antivirals.

Table 1. Drugs used to treat patients with acute, uncomplicated influenza

Therapy	Recommended dosage	Comments
Tamiflu (oseltamivir)	75 mg orally twice daily for 5 days	Neuraminidase inhibitor; Warnings and Precautions: serious skin reactions, neuropsychiatric events (confusion or abnormal behavior)
Relenza (zanamivir)	10 mg inhaled twice daily for 5 days	Neuraminidase inhibitor; Warnings and Precautions: bronchospasm; allergic reactions; neuropsychiatric events; high-risk underlying medical conditions
Symadine (amantadine)	200 mg orally once daily for 7 days	Adamantane; minor dose-related CNS and GI adverse effects; many influenza strains are resistant
Flumadine (rimantadine)	100 mg orally twice daily for 7 days	Adamantane; minor dose-related CNS and GI adverse effects; many influenza strains are resistant

1.2 REGULATORY HISTORY

June 28, 2013: Pre-NDA meeting held to obtain agreement on the content of the planned NDA.

December 23, 2013: BioCryst Pharmaceuticals submitted a NDA for Rapivab (peramivir). The submission did not include a proposed REMS.

June 13, 2014: The Agency provided the Applicant with a Mid-Cycle Communication where it stated there were no major safety concerns identified at that time that warrant the need for a REMS.

2 MATERIALS REVIEWED

The following is a list of internal materials that informed our review:

- DAVP Draft Prescribing Information for Rapivab (peramivir), August 27, 2014
- Peter Miele, M.D. Clinical review for Rapivab (peramivir), Division of Antiviral Products, August 22, 2014
- BioCryst Corporation. Proposed Prescribing Information for Rapivab (peramivir), received December 23, 2013
- BioCryst Corporation. Clinical Overview for Rapivab (peramivir), received December 23, 2013

Below is a list of other materials that informed our review:

- Amanda Kamali and Mark Holodniy, Influenza treatment and prophylaxis with neuraminidase inhibitors: a review. Infection and Drug Resistance 2013; 6 187–198.
- World Health Organization, Influenza Seasonal Factsheet, March 2014.
- Dipiro, et al. Pharmacotherapy: A Pathophysiologic Approach. 9th Edition, February 2014.

3 REVIEW FINDINGS FOR PERAMIVIR

3.1 NEURAMINIDASE INHIBITOR CLASS ADVERSE EVENT PROFILE

As displayed in Table 1 above (Section 1.1), approved neuraminidase inhibitors include Tamiflu and Relenza. Included in the Warnings and Precautions section of the Tamiflu and Relenza product labels is an increased risk of psychiatric adverse events. However, these events can also be associated with the underlying disease state, influenza. Exposure to Tamiflu is associated with an increased risk of serious skin reactions and exposure to Relenza is associated with an increased risk of bronchospasm and allergic reactions.

Peramivir is approved in Japan and was authorized for use in the United States (U.S.) under an Emergency Use Authorization in the wake of the H1N1 influenza pandemic in 2009. During the pandemic, data on 344 patients who were exposed to peramivir were made available via a MedWatch reporting reminder survey. Although serious adverse events, including death, renal complications, and neuropsychiatric events were reported, they may have been related to influenza severity, comorbid underlying disease, or concomitant medications (this could not be determined due to the lack of a comparison group).

3.1.1 Efficacy

The pivotal study for the use of IV peramivir to treat subjects with acute, uncomplicated influenza was a Phase 2 double-blind, placebo-controlled, single dose study. A total of 300 Japanese subjects with confirmed influenza were randomized to receive placebo, 300 mg peramivir, or 600 mg peramivir. The primary efficacy endpoint was time to alleviation of influenza symptoms (nasal congestion, sore throat, cough, aches and pains, fatigue, headache, feeling feverish). Secondary efficacy endpoints included time to resolution of fever, time to resumption of usual activities, decrease in viral titers from baseline, and decrease in viral shedding, among other endpoints.

Peramivir was found to be efficacious in the pivotal trial. For the primary endpoint, both dosages of peramivir (single IV doses of 300 or 600 mg) significantly shortened the time to alleviation of influenza symptoms (TTAS) compared with placebo, with a median improvement of approximately 1 day for peramivir treatment. The median TTAS was 59.1 hours in the 300 mg IV group, 59.9 hours in the 600 mg IV group, and 81.1 hours in the placebo group. The difference in duration of influenza symptoms in comparison with placebo was -22.7 hours and -21.9 hours for peramivir 300 mg and 600 mg, respectively, both of which were statistically significant (pooled peramivir group vs. placebo p value: 0.0010). A consistent peramivir treatment effect was also observed across multiple secondary endpoints. Efficacy data from three placebo-controlled Phase 2 and 3 trials of IM peramivir, in comparable adult populations with acute influenza, further supported the efficacy findings of the pivotal trial. (A Phase 1 study demonstrated the bioequivalence of the IM and IV formulations of peramivir, enabling use of data collected with the IM formulation to support the IV formulation results.)

Selection of the 600 mg dose for approval was based on observation of a dose response in time to alleviation of symptoms and in virologic outcomes, and on results of pharmacokinetic modeling that suggested the 600 mg dose would result in more patients exceeding a pharmacodynamic endpoint of time above viral IC_{50}.

3.1.2 Safety

The evaluation of IV peramivir safety in adults was based primarily on data from the pivotal trial and supported by data from three Phase 2 and Phase 3 placebo-controlled trials of IM peramivir, as well as a Phase 3 clinical study that compared IV peramivir with oral oseltamivir therapy. In addition, safety data from a Phase 3 non-controlled study of patients with high-risk factors was included in the analysis.

Serious adverse events

The rates of serious adverse events (SAE) were evaluated in the six adult trials of influenza mentioned above. Similar rates were observed between the peramivir groups (0.5% [7/1453]) and the two control groups (placebo 0.5% [2/442]; oseltamivir 0.5% [2/365]). Pneumonia was the most frequently reported SAE in peramivir treated subjects (2 subjects, 0.1%). The clinical review noted that none of the SAEs in peramivir-treated subjects was considered related to study drug.

One adult subject with acute uncomplicated influenza died of meningitis after receiving treatment with peramivir. The clinical review noted that the cause of death (meningitis) was not considered related to study drug. In clinical trials of hospitalized patients, 24 patients (4%) died in the peramivir group and 3 (2%) died in the placebo group. The most common causes of death in subjects treated with peramivir were respiratory failure (6 subjects), acute respiratory distress syndrome (ARDS) (5 subjects), and septic shock (4 subjects). In most cases, the cause of death was related to progressive influenza or disease complications. The clinical review noted that none of the deaths was considered related to study drug by the investigators.

Class-related adverse events of interest

In a Phase 3 open-label clinical trial of hospitalized subjects with influenza, one subject with a history of herpes simplex infection developed ARDS, sepsis, and a significant skin reaction. After completing a 10-day course of peramivir, she experienced a mild case of erythema multiforme. The investigator believed the event could have been possibly related to peramivir. The clinical review noted the event was mild and not serious and causality was heavily confounded. No other severe skin reactions were observed in the clinical development program of peramivir.

There were no neuropsychiatric treatment emergent adverse events reported in any adult trials of acute uncomplicated influenza consistent with delirium, suicidal behavior, or other abnormal behaviors described in the postmarketing experience of other neuraminidase inhibitors.

Allergic-type adverse events showed a minimally higher incidence of urticaria, rash, pruritus, and other hypersensitivity events in subjects who received peramivir compared with placebo. One peramivir-treated subject developed a nonserious but severe (Grade 3) allergic reaction considered possibly related to treatment by the investigator.

4 DISCUSSION

In the clinical trials, peramivir was found to be efficacious versus placebo with an acceptable safety profile that is comparable to the other approved neuraminidase inhibitors, none of which are approved with a REMS. Peramivir use was associated with a low incidence of serious safety issues.

DRISK does not recommend a REMS as necessary to ensure the benefits of peramivir outweigh the risks. Influenza causes significant morbidity and mortality in the U.S. population annually. Although other drugs are approved to treat influenza, there is a need for additional treatments that can be administered IV (in addition to orally) as well as because of the potential for resistance to approved antiviral drugs. None of the currently approved antiviral drugs for acute, uncomplicated influenza require a REMS to ensure the benefits of treatment outweigh the risks, and the safety profile of peramivir does not present new concerns in comparison with the approved agents.

5 CONCLUSION AND RECOMMENDATIONS

In conclusion, risk mitigation measures beyond professional labeling are not warranted for peramivir. Peramivir has proven efficacy in the treatment of acute, uncomplicated influenza. There were few SAEs reported of peramivir exposed patients in the clinical trials pertaining to the proposed indication. Thus, the benefit-risk profile for peramivir is favorable and the risks can be effectively communicated though the professional labeling.

Should DAVP have any concerns or questions, feel that a REMS may be warranted for this product, or new safety information becomes available, please send a consult to DRISK.

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/s/

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09/08/2014

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09/08/2014