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RESEARCH**

APPLICATION NUMBER:

206426Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	(electronic stamp)
From	Edward Cox, MD MPH
Subject	Office Director Decisional Memo
NDA/BLA #	NDA 206426
Applicant Name	BioCryst Pharmaceuticals, Inc.
Date of Submission	December 23, 2013
PDUFA Goal Date	December 23, 2014
Proprietary Name	Rapivab
Established (USAN) Name	peramivir
Dosage Forms / Strength	200 mg per 20 mL (10 mg/mL) solution for injection in a single-use vial
Indication	Rapivab is indicated for the treatment of acute uncomplicated influenza in patients 18 years and older who have been symptomatic for no more than 2 days.
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Peter Miele
Product Quality	Fuqiang Liu, Stephen Miller, Neal Sweeney, John Metcalfe, Fuqiang Liu, Stephen Miller, Rapti Madurawe (12/18/2014 addendum)
Statistical Review	Thomas Hammerstrom, Guoxing Soon, Dionne L Price
Pharmacology Toxicology Reviews	Kuei Meng Wu, Hanan Ghantous, Abigail Jacobs
Clinical Virology	Takashi Komatsu, Julian O'Rear
Clinical Pharmacology Review	Islam Younis, Leslie Chinn, Jeffry Florian,
OSI	Antoine El-Hage, Susan Thompson, Kassa Ayalew, Chuck Bonapace, William Taylor
CDTL Review	Linda Lewis
Division Director's Review	Debbie Birnkrant

OND=Office of New Drugs
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader

Rapivab (peramivir) is an influenza neuraminidase inhibitor antiviral drug. It has been developed as a single dose intravenous infusion for the treatment of adults with acute uncomplicated influenza who are symptomatic for less than two days. There are two previously approved influenza virus neuraminidase inhibitors, Tamiflu (oseltamivir) and Relenza (zanamivir); they are approved for the treatment of acute uncomplicated influenza with symptoms of two days duration or less. A trial designed to evaluate peramivir as a

treatment for patients with serious influenza who are hospitalized has not shown efficacy for peramivir treatment in this patient population. During the 2009 H1N1 influenza pandemic, peramivir was available under an Emergency Use Authorization.

The review team has reviewed the issues in detail in their respective disciplines with regard to the safety and efficacy of peramivir for the treatment of patients with acute uncomplicated influenza. For a detailed discussion of NDA 206426, the reader is referred to the individual discipline specific reviews. In addition, the Cross-Discipline Team Leader's review and the Division Director's review summarize key issues in the NDA submission. This memorandum will focus on select issues from the review.

The NDA is recommended for approval from the CMC perspective (12/18/2014 addendum). The Product Quality Microbiology Review identifies no product quality microbiology deficiencies and recommends approval. The manufacturing facilities inspection summary of December 18, 2014 finds the facilities to be acceptable.

The recommendation from the Pharmacology/Toxicology Reviewers is for approval. The key target organs of toxicity identified in toxicology studies were the kidney and liver. In studies in rabbit, a species sensitive to the nephrotoxic effects of peramivir, kidney toxicity was noted. Renal toxicity was also noted in monkeys that received high drug exposures and in rats that received longer durations of exposure. Abnormal liver function was also noted in rabbits that had nephrotoxic effects. Peramivir is categorized as pregnancy category C. The available carcinogenicity study data (included a completed oral carcinogenicity studies in rats), were reviewed by the Executive Carcinogenicity Assessment Committee. Their conclusion was that the study was acceptable and that there were no drug-related neoplasms in the study.

The Clinical Virology Reviewer recommends that the data in NDA 206426 support approval. Peramivir is an inhibitor of influenza neuraminidase, an enzyme that releases virus from the plasma membrane of infected cells. The product labeling describes resistance mutations associated with reduced influenza virus susceptibility from cell culture studies and clinical isolates. In addition, amino acid substitutions with cross-resistance between peramivir and oseltamivir, or peramivir and zanamivir, are described in the product labeling. The labeling also includes a statement under Limitations of Use in the Indications and Usage section noting that Prescribers should consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use peramivir.

The Clinical Pharmacology Reviewers find there is sufficient clinical pharmacology information to support approval of the application for a single dose of peramivir 600 mg administered as an intravenous infusion over at least 15 minutes. Plasma protein binding of peramivir is low (<18%). It is not extensively metabolized and is excreted primarily as unchanged peramivir (90%). Dose adjustment is specified in the product labeling for patients with impaired renal function with creatinine clearance less than 50 mL/min. Peramivir is not a substrate for CYP enzymes, it is not a substrate or inhibitor of P-glycoprotein mediated transport and it does not affect glucuronidation.

A randomized, double-blind, multi-center trial conducted in Japan (study 621) evaluated the time to alleviation of influenza symptoms for peramivir 600 mg, peramivir 300 mg or placebo in patients with acute uncomplicated influenza with symptoms of 48 hours or less duration. The subjects receiving peramivir 600 mg experienced alleviation of symptoms 21 hours sooner than those receiving placebo. In addition, there were three additional placebo controlled trials in patients with acute uncomplicated influenza that provided supportive information. The statistical reviewer conducted a sensitivity analysis that combined data from across these three trials and study 621 and found that peramivir 600 mg was associated with a shorter time to alleviation of symptoms. This sensitivity analysis provides additional supportive information on the efficacy of peramivir in acute uncomplicated influenza. As noted in the product labeling there were insufficient numbers of subjects infected with influenza B virus to determine efficacy against influenza B.

The product labeling also describes that the efficacy of peramivir could not be established in patients with serious influenza requiring hospitalization. The Clinical Studies section provides additional information on the trial in serious influenza requiring hospitalization. Inclusion of this information in the product labeling is important so that healthcare providers are aware that efficacy has not been demonstrated for peramivir intravenous injection in this patient population.

A total of 1,399 subjects with acute uncomplicated influenza received a single dose of peramivir intravenously or intramuscularly. The most common adverse reactions reported among 664 subjects receiving doses of peramivir at 600 mg intravenously or intramuscularly were diarrhea reported in 8% of peramivir recipients and 7% of placebo recipients. The product labeling includes a statement in the Warnings and Precautions section on serious skin and hypersensitivity reactions based on reports in clinical studies and postmarketing experience. There is also a Warnings and Precautions statement on neuropsychiatric events in patients with influenza who were receiving neuraminidase inhibitors. The statements on neuropsychiatric events are similar for each of the neuraminidase inhibitors. Similar to other influenza neuraminidase inhibitors, the product labeling notes that prescribers should be alert to the potential for secondary bacterial infections.

The Office of Scientific Investigations summarizes inspections of five clinical trial sites. One of the five sites received a preliminary classification of OAI and the other four sites were classified as either NAI or pending NAI. The data the trial involved were analyzed removing the data from the one site classified as OAI.

NDA 206426 was not presented before the Antiviral Drugs Advisory Committee. There were no particular issues with safety, efficacy, or trial design that warranted presenting the application to an Advisory Committee.

We are deferring submission of pediatric studies until December 31, 2018, because this product is ready for approval for use in adults and the pediatric study has not been completed.

In summary, I agree with the review team, CDTL, and the Division Director, that the overall benefits and risks support the approval of NDA 206426 for Rapivab (peramivir) for the

treatment of patients with acute uncomplicated influenza with symptoms of less than 2 days duration as described in the product labeling. The benefits of peramivir for the treatment of acute uncomplicated influenza outweigh the risk of treatment with peramivir. The approval of Rapivab (peramivir) provides for an intravenous treatment for acute uncomplicated influenza that is administered as a single dose. The product labeling adequately describes the safety and efficacy findings. Postmarketing requirements include studies that will provide additional information on resistance mutations and pediatric safety and activity data in children ages birth to less than 18 years of age.

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OND/CDER/FDA

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EDWARD M COX
12/19/2014