



NDA 206426

NDA APPROVAL

BioCryst Pharmaceuticals, Inc.
Attention: Elliott Berger, PhD
Senior Vice President, Regulatory Affairs
4505 Emperor Boulevard, Suite 200
Durham, NC 27703

Dear Dr. Berger:

Please refer to your New Drug Application (NDA) dated December 19, 2013, received December 23, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for RAPIVAB™ (peramivir injection) for intravenous use.

We acknowledge receipt of your amendments dated:

January 7, 2014	February 27, 2014	April 24, 2014	August 5, 2014
January 27, 2014	February 28, 2014	May 8, 2014 (3)	September 12, 2014
January 31, 2014	March 3, 2014	May 19, 2014	October 30, 2014
February 4, 2014	March 5, 2014	May 20, 2014	November 17, 2014
February 7, 2014	March 10, 2014	June 5, 2014	December 3, 2014
February 14, 2014	March 11, 2014	June 11, 2014	December 18, 2014
February 20, 2014	March 26, 2014	June 24, 2014	
February 24, 2014	April 3, 2014	July 18, 2014	

This new drug application provides for the use of RAPIVAB™ (peramivir injection) for intravenous use, for the treatment of acute uncomplicated influenza in patients 18 years and older who have been symptomatic for no more than 2 days.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for*

Content of Labeling Technical Qs and As, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission **“Final Printed Carton and Container Labels for approved NDA 206426.”** Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Elizabeth Thompson, M.S.
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6334
10903 New Hampshire Avenue
Silver Spring, Maryland
*Use zip code **20903** if shipping via United States Postal Service (USPS).*
*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

ADVISORY COMMITTEE

Your application for RAPIVAB™ (peramivir injection) for intravenous use was not referred to an FDA advisory committee because this drug is not the first in its class.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

Your deferred pediatric study required under section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. This required study is listed below.

2831-1 Conduct a clinical trial to evaluate the pharmacokinetics, safety, and antiviral activity of peramivir administration in pediatric subjects with acute uncomplicated influenza infection from birth to less than 18 years of age. Include characterization of peramivir resistance-associated substitutions in viral isolates from subjects with prolonged viral shedding.

Study Completion: 04/30/2018

Final Report Submission: 12/31/2018

Submit the protocol(s) to your IND 69038, with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of emergence of drug resistance to RAPIVAB™ (peramivir injection) for intravenous use and/or the neuraminidase inhibitor drug class.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2831-2 Analyze and submit the remainder of the clinical resistance data that were not included with the NDA. These include both the HA and NA data for trials BCX1812-201, BCX1812-211, and BCX1812-311.

The timetable you submitted on December 18, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/30/2016

- 2831-3 Conduct a study to determine the cross-resistance to oseltamivir and zanamivir for all of the HA peramivir resistance substitutions that have yet to be evaluated (A/H1N1 HA D129S, R208K; A/H3N2 HA G78D, K189E; B HA T139N, G141E, R162M, D195N, T197N, Y319H). Additionally, determine cross-resistance to oseltamivir/zanamivir resistance substitutions (A/H1N1 NA R152K, I122K/T, G248R+I266V, Q312R+I427T, R371K, A/H3N2 NA E41G, I222L/V, Q226H, S247P, HA A28T, K68R, E114K, R124M, N145S, S165N, S186F, N199S, K222T, B NA D198Y, A246D/S/T, G420S).

The timetable you submitted on December 18, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 04/30/2015

Study Completion: 04/30/2016

Final Report Submission: 10/31/2016

Submit the protocols to your IND 69038, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also

include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 2831-4 Evaluate the impact of peramivir resistance-associated substitutions in hemagglutinin (HA) on the effectiveness of influenza vaccine in cell culture assays:
- Titrate the neutralization and hemagglutinin inhibition activity of the serum samples from multiple subjects vaccinated with the influenza virus vaccine against recombinant virus with the peramivir resistance substitutions in the HA and their parental virus. A titration of the serum samples should be evaluated using established methods for determining hemagglutination inhibition (HI) as well as virus neutralization (e.g. plaque number reduction or % infected cells based on nuclear NP staining). We recommend performing neutralization assays using different input concentrations of virus to confirm that assay conditions are such that the EC50 value is independent of virus concentration.
 - Titrate the neutralization and hemagglutinin inhibition activity of the baseline and end of treatment serum samples from multiple subjects treated with peramivir against recombinant virus with the peramivir resistance substitutions in the HA and their parental virus.
 - Compare the antigenicity of wild type (WT) and HA mutants, selected during peramivir treatment in cell culture, against immune serum (convalescent or vaccine-induced) from human subjects and from animal models vaccinated with inactivated WT virus. Antigenicity should be determined using both HI and neutralization assays.

The timetable you submitted on December 18, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/30/2015
Study Completion:	12/31/2018
Final Report Submission:	06/30/2019

- 2831-5 Submit clinical data from an adequate number of subjects to characterize the effectiveness of peramivir administration in patients with acute uncomplicated influenza B virus infection. These data may be collected from the pediatric study required under PREA or from a new stand-alone clinical trial in a different population. Conduct genotypic resistance analysis of neuraminidase and

hemagglutinin using samples directly from subjects without an intervening culture step. Conduct phenotypic analysis, including cross-resistance to approved neuraminidase inhibitors.

The timetable you submitted on December 18, 2014, states that you will conduct this trial according to the following schedule:

Final Analysis Plan Submission:	06/30/2015
Trial Completion:	04/30/2018
Final Report Submission:	12/31/2018

- 2831-6 Conduct a clinical trial to evaluate the pharmacokinetics, safety and antiviral activity of peramivir administration in a predominantly ambulatory setting in elderly subjects aged 65 years or older with influenza infection.

The timetable you submitted on December 18, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	06/30/2015
Trial Completion:	04/30/2018
Final Report Submission:	12/31/2018

- 2831-7 Conduct a clinical trial to evaluate the pharmacokinetics, safety and antiviral activity of peramivir administration in a predominantly ambulatory setting in subjects with influenza infection at higher risk for influenza complications, as defined by the U.S. Centers for Disease Control and Prevention (CDC).

The timetable you submitted on December 18, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	06/30/2015
Trial Completion:	04/30/2018
Final Report Submission:	12/31/2018

Submit clinical protocols to your IND 69038 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at

<http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Elizabeth Thompson, M.S., Chief, Project Management Staff, at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Edward M. Cox, M.D., MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures:

Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EDWARD M COX
12/19/2014