CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

214460Orig1s000
214461Orig1s000

Trade Name:	TEMBEXA
Generic or Proper Name:	brincidofovir
Sponsor:	Chimerix, Inc.
Approval Date:	June 4, 2021
Indication:	For the treatment of human smallpox disease in adult and pediatric patients, including neonates

CENTER FOR DRUG EVALUATION AND RESEARCH

214460Orig1s000
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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 214460
NDA 214461

NDA APPROVAL – ANIMAL EFFICACY

Chimerix, Inc.
Attention: A. Heather Knight-Trent, PharmD
Vice President, Regulatory Affairs
2505 Meridian Parkway, Suite 100
Durham, NC 27713

Dear Dr. Knight-Trent:[1]

Please refer to your new drug applications (NDAs) dated October 7, 2020, received October 7, 2020, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NDA 214460, Tembexa (brincidofovir), 10 mg/ml, oral suspension, and NDA 214461,Tembexa (brincidofovir), 100 mg tablets.

We acknowledge receipt of your major amendment dated January 29, 2021, which extended the goal date by three months.

These new drug applications provide for the use of Tembexa (brincidofovir), oral suspension and Tembexa (brincidofovir) tablets for the treatment of human smallpox disease caused by variola virus in adult and pediatric patients, including neonates.

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

FDA.gov.[2] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert) as well as annual reportable changes not included in the enclosed labeling. 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 FDA.gov.[3]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate these submission "**Final Printed Carton and Container Labeling for approved NDA 214460 or "Final Printed Carton and Container Labeling for approved NDA 214461**." Approval of these submissions by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Tembexa (brincidofovir), 10 mg/ml oral suspension shall be 30 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F) and for Tembexa (brincidofovir), 100 mg tablets for oral use shall be 48 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F).

MATERIAL THREAT MEDICAL COUNTERMEASURE PRIORITY REVIEW VOUCHER

Your request for a material threat medical countermeasure priority review voucher for NDA 214461, Tembexa (brincidofovir) tablet, is denied. This application is not eligible for a material threat medical countermeasure priority review voucher because, at the time of approval, it is not an application "for a human drug, no active moiety (as defined by the Secretary in section 314.3 of title 21, Code of Federal Regulations (or any successor regulations) of which has been approved in any other application under section 505(b)(1) or for a biological product, no active ingredient of which has been

[2] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[3] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htmhttps://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

approved in any other application under section 351 of the Public Health Service Act." We reference the June 26, 1996 approval of Vistide (cidofovir) Injection (NDA 020638), which contains the same active moiety as that contained in Tembexa (brincidofovir) tablet. See section 565A(a)(4)(D) of the FD&C Act.

SUBPART I APPROVAL REQUIREMENTS

Approvals under 21 CFR Part 314, Subpart I (Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible) are subject to three requirements:

(1) *Approval with restrictions to ensure safe use.* This subsection permits the Agency to require postmarketing restrictions as are needed to ensure safe use of the drug product, commensurate with the specific safety concerns presented by the drug product. We have concluded that TEMBEXA (brincidofovir) can be safely used without restrictions on distribution or use.

(2) *Information to be provided to patient recipients.* This subsection requires applicants to prepare labeling to be provided to patient recipients for drug products approved under this subpart. We have concluded that the FDA-Approved Patient Package Insert meets the requirements of this subsection.

(3) *Postmarketing Studies.* This subsection requires you to conduct postmarketing studies, such as field studies, to verify and describe the drug's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical. We remind you of your postmarketing requirement specified in your submissions dated March 30, 2021 and April 16, 2021, stating that you agree to conduct a field study in the event of a smallpox outbreak. This requirement, along with any agreed upon completion dates, is listed below.

4050-1 Conduct a field study to evaluate the clinical response, drug concentrations, and safety profile of brincidofovir (BCV) when used for the treatment of human smallpox disease due to variola virus infection. This trial should evaluate BCV vs. standard-of-care (i.e. active control) vs. BCV as an add-on-therapy to standard-of-care.

Draft Protocol Submission: 02/2022
Final Protocol Submission: 07/2022

Submit final reports to these NDAs as supplemental applications. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart I Postmarketing Requirements**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4050-2 Conduct cell culture studies to characterize brincidofovir antiviral activity against recombinant vaccinia viruses encoding specific amino acid substitutions that emerged in ectromelia virus in brincidofovir-treated animals in mouse study CMX001-VIR-044.

The timetable you submitted on April 19, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 01/2022
Final Protocol Submission: 07/2022
Study Completion: 07/2023
Final Report Submission: 12/2023

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 067681 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to these NDAs. 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 these NDAs. 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

Under 21 CFR 314.640, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796 1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.640, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see the final guidance for industry Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.

REPORTING REQUIREMENTS

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

If you have any questions, call Andrew Gentles, PharmD, BCPS AQ-ID, Senior Regulatory Project Manager at (240) 402-5708 or the mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antivirals
Office of Infectious Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DEBRA B BIRNKRANT
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