

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214460Orig1s000

214461Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 5, 2021
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 214460 NDA 214461
Product Name and Strength:	Tembexa (brincidofovir) Tablet, 100 mg; Tembexa (brincidofovir) Oral Suspension, 10 mg/mL
Applicant/Sponsor Name:	Chimerix Inc.
OSE RCM #:	2020-2101-2
DMEPA Safety Evaluator:	Melina Fanari, RPh
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on April 20, 2021 for Tembexa. The Division of Antivirals (DAV) requested that we review the revised container labels and carton labeling for Tembexa (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review^a.

2 CONCLUSION

The Applicant implemented all of our recommendations. We have no additional recommendations.

^a Fanari, M. Label and Labeling Review for Tembexa (NDA 214460 NDA 214461). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Mar 18. RCM No.: 2020-2101-1.

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/

MELINA N FANARI
05/05/2021 01:09:14 PM

SEVAN H KOLEJIAN
05/05/2021 02:25:51 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 18, 2021
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 214460 NDA 214461
Product Name and Strength:	Tembexa (brincidofovir) Tablet, 100 mg; Tembexa (brincidofovir) Oral Suspension, 10 mg/mL
Applicant/Sponsor Name:	Chimerix Inc.
OSE RCM #:	2020-2101-1
DMEPA Safety Evaluator:	Melina Fanari, RPh
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on March 9, 2021 for Tembexa. In addition, Chimerix submitted draft labeling for product intended for the Strategic National Stockpile (SNS). The Division of Antivirals (DAV) requested that we review the revised container labels and carton labeling for Tembexa (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review^a and an Information request from the Office of Pharmaceutical Quality.

2 CONCLUSION

The Applicant implemented all of our recommendations. However, we have additional recommendations related to the revised labels and labeling (see section 3 below). In addition, we note the SNS labels and labeling are identical to the proposed commercial product labels and labeling with minor exceptions of 1) a new NDC #, 2) contain the statement “For Strategic

^a Fanari, M. Label and Labeling Review for Tembexa (NDA 214460 NDA 214461). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Jan 25. RCM No.: 2020-2101.

3 RECOMMENDATIONS FOR CHIMERIX INC.

We recommend the following be implemented prior to approval of these NDAs:

A. Blister Foil Container Labels (Commercial and SNS)

- 1- To improve the readability and prominence of the product name and strength, please revise the proprietary name, established name and strength presentation as displayed below. In addition, this statement should be the most prominent on the blister foil label and should be relocated away from the product NDC# and manufacturer information.

‘Tembexa (brincidofovir) 100 mg per tablet’

B. Oral Suspension Container Label (Commercial and SNS)

- 1- Increase the prominence of the strength presentation statement.

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/s/

MELINA N FANARI
03/18/2021 08:39:02 AM

SEVAN H KOLEJIAN
03/18/2021 09:11:08 AM

Clinical Inspection Summary

Date	03/18/2021
From	Jenn Sellers, M.D., Ph.D., Medical Officer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Andrew Gentles, Pharm.D., Regulatory Project Manager Kirk Chan-Tack, M.D., Clinical Reviewer Kimberly Struble, M.D., Clinical Team Leader Division of Antiviral Products (DAV)
NDA #	214461 and 214460
Applicant	Chimerix, Inc.
Drug	Brincidofovir (Tembexa)
NME	No
Therapeutic Classification	Inhibitor of Viral DNA Synthesis
Proposed Indication	Treatment of Human Smallpox Disease
Consultation Request Dates	11/17/2020
Summary Goal Date	02/08/2020
Updated Summary Goal Date	03/18/2020
Action Goal Date	04/07/2021
PDUFA Date	04/07/2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigators Drs. Boeckh, Winston, Papanicolaou, Marty, Chemaly and Grimley were inspected in support of this application.

To demonstrate efficacy, studies were conducted in the rabbitpox and the mousepox models. In order to assess the safety of brincidofovir, the sponsor relied on the data from randomized, double-blind, placebo-controlled, multi-center clinical trials to assess the safety and tolerability of brincidofovir compared to placebo for the prevention of cytomegalovirus (CMV) infection in CMV-seropositive (R+) hematopoietic stem cell transplant recipients (Protocols CMX001-301, CMX001-201) and for the prevention of adenovirus disease following hematopoietic stem cell transplantation (Protocol CMX001-202). The applicant submitted the safety data from all three studies in order to support the indication of brincidofovir in the treatment of smallpox.

Except for the site of Dr. Winston, the safety data were verifiable for all reviewed subjects, and there was no evidence of underreporting of adverse events. For Dr. Winston, most of the adverse events were verifiable. However, a number of adverse events were not reported (see Tables 1 and 2). The review division should consider these unreported adverse events in their safety evaluation of brincidofovir.

Of note, the inspection results for Dr. Chemaly are based on a summary provided by the FDA field investigator and are therefore preliminary. If significantly new or different information is contained in the final FDA Establishment Inspection Report, an addendum to this clinical inspection summary will be filed.

II. BACKGROUND

Brincidofovir (proprietary name: Tembexa; code name: CMX001) is a selective inhibitor of viral DNA synthesis. It has broad antiviral activity against double-stranded DNA (dsDNA) viruses including herpesviruses, adenoviruses, orthopoxviruses, and polyomaviruses.

The sponsor, Chimerix, has been developing brincidofovir for the treatment of human smallpox disease caused by variola virus. It was granted Fast Track designation by FDA in July 2005. brincidofovir was granted Orphan Designation for the treatment of smallpox in June 2018. For efficacy, studies were conducted in the rabbitpox and the mousepox models because adequate and well-controlled field trials in human have not been feasible and inducing smallpox disease in humans to study the efficacy of the drug is not ethical.

To assess the safety of brincidofovir, the sponsor relied on the data from randomized, double-blind, placebo-controlled, multi-center clinical trials to assess the safety and tolerability of brincidofovir compared to placebo for the prevention of CMV infection in CMV-seropositive (R+) hematopoietic stem cell transplant recipients (Protocols CMX001-301, CMX001-201) and for the prevention of adenovirus disease following hematopoietic stem cell transplantation (Protocol CMX001-202). The applicant submitted the safety data from all three studies in order to support the indication of brincidofovir in the treatment of smallpox.

The review division (DAV) requested clinical investigator (CI) inspections for the purpose of verifying the safety data (only) for these three studies. The following briefly describes the Protocols CMX001-301, CMX001-201 and CMX001-202.

Protocol CMX001-301

Title: “A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Phase 3 Study of the Safety, Tolerability, and Efficacy of CMX001 for the Prevention of Cytomegalovirus (CMV) Infection in CMV-seropositive (R+) Hematopoietic Stem Cell Transplant Recipients”

Subjects: 458 subjects were randomized

Study Sites: 44 centers in the USA (39), Canada (3), and Belgium (2).

Study Initiation and Completion Dates: 22 Aug 2013 and 12 Nov 2015

The primary study objective was to compare the safety and tolerability of brincidofovir to placebo for the prevention of clinically significant CMV infection in R+ allogeneic Hematopoietic Stem Cell Transplant (HSCT) recipients.

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter, Phase 3 study of the safety, tolerability, and efficacy of brincidofovir for the prevention of CMV in the CMV-seropositive HSCT population.

Main inclusion criteria included:

- Allogeneic HSCT recipient who had prior evidence of CMV exposure (CMV-seropositive) before transplantation and who was CMV viremia negative at screening and at any other assessments performed prior to the first dose day.
- Aged ≥ 18 years

Main exclusion criteria included:

- Subjects who had a positive CMV viremia test (at the designated central virology laboratory or a local virology laboratory) at any time between transplant and the first dose day;
- Subjects who had received (or who were anticipated to need treatment with) any of the following: ganciclovir, valganciclovir, foscarnet, intravenous cidofovir, or any other anti-CMV therapy (including CMV immune globulin, cell-based therapies, and investigational anti-CMV drugs, e.g., leflunomide, letermovir, or maribavir) at any time post-transplant; any anti-CMV vaccine at any time;
- Subjects who were receiving: acyclovir orally at >2000 mg total daily dose or intravenously at 15g/kg total daily dose, valaciclovir at >3000 mg total daily dose, or leflunomide at any dose

Eligible subjects were randomized 2:1 to brincidofovir 100 mg or placebo twice-weekly (BIW). During randomization, subjects were stratified within center, based on their likelihood for progression to clinically significant CMV infection. Subjects who had received a matched, related, non-T cell-depleted graft, who did not have acute graft-versus-host disease, who had not received anti-thymocyte globulin or Campath (alemtuzumab), and who were not receiving high-dose (≥ 1 mg/kg prednisone equivalent) systemic steroids were stratified in the “lower likelihood” group. All other subjects were stratified in the “higher likelihood” group. Dosing for all subjects was initiated as soon as individual subjects could ingest tablets after transplant (but no later than Day 28 post-transplant).

The planned duration of the treatment phase varied for individual subjects from a minimum of 10 weeks, up to a maximum of 14 weeks, depending on when treatment was initiated relative to the date of transplant. All subjects were followed to 24 weeks post-transplant.

Study assessments were performed weekly from randomization through completion of the first post-treatment follow-up assessment at Week 15 post-transplant, and every three weeks thereafter through Week 24.

Major subject discontinuation criteria included:

- Persistent neutropenia without an alternative explanation. “Persistent” was to be defined by the investigator using standard site definitions, as applicable,
- Decrease in eGFR to <15 mL/min or a new or persistent requirement for renal dialysis if the eGFR change or the requirement for dialysis was study drug-related.

Safety Endpoint Assessments:

- Discontinuation from study drug due to adverse events (AEs)
- Treatment emergent adverse events (TEAEs), in particular TEAEs of $\geq$ Grade 3 severity, as defined by the NIH/NCI Common Terminology Criteria for Adverse Events (CTCAE)
- TEAEs leading to dose interruption, dose reduction, or dose discontinuation
- Gastrointestinal (GI)-related events, in particular diarrhea
- Acute graft versus host disease, in particular acute gut graft versus host disease, as adjudicated by the graft versus host disease adjudication committee
- Hepatobiliary events, liver-related laboratory abnormalities
- New onset (i.e., post-first dose day) renal dysfunction through Week 14 and through Week 24

Protocol CMX001-201

Title: “A multicenter, randomized, double-blind, placebo-controlled, dose-escalation study of the safety, tolerability, and ability of CMX001 to prevent or control CMV infection in R+ hematopoietic stem cell transplant recipients”

Subjects: 239 subjects were enrolled

Study Sites: 26 centers in the USA

Study Initiation and Completion Dates: 24 December 2009 and 15 November 2011

This was a multicenter, randomized, double-blind, placebo-controlled, dose escalation study of CMX001 administered once weekly for 12 weeks. The study was planned to have Part 1 and Part 2. Part 2 was not conducted following the safety and antiviral activity analyses of the 5 cohorts in Part 1. The following describes Part 1 only.

The primary objectives were to determine the safety and tolerability of CMX001 in Hematopoietic Stem Cell Transplant (HSCT) recipients and to determine the ability of CMX001 to prevent or control infection in CMV seropositive (R+) HSCT recipients during the treatment period.

The main criteria included allogeneic HSCT recipients ≥ 18 years of age who were CMV seropositive at the time of transplant; transplant occurred ≤ 30 days before first dose of study medication; transplant recipients must have engrafted (i.e., had an increase in absolute neutrophil count [ANC] for 3 consecutive days up to ≥ 500 cells/mm³ by the third day or 3 consecutive days with an ANC ≥ 500 cells/mm³) ≤ 30 days after the transplant. Cohorts of recipients were randomized 3:1 to CMX001 or matching placebo.

Below is a summary of the 5 cohorts enrolled in this study:

- Cohort 1 = CMX001 40 mg or matching placebo administered once weekly (QW)
- Cohort 2 = CMX001 100 mg or matching placebo administered QW
- Cohort 3 = CMX001 200 mg or matching placebo administered QW
- Cohort 4 = CMX001 200 mg or matching placebo administered twice weekly (BIW) and then reduced to 200 mg QW for ongoing subjects following the recommendation of the Data and Safety Monitoring Board (DSMB)
- Cohort 4A = 100 mg CMX001 or matching placebo administered BIW

Subjects were to receive their first dose of study drug (Week 1) within 14 to 30 (+5) days posttransplant, inclusive. Subjects were to take QW or BIW doses of study drug through posttransplant Week 13 (between 84- and 90-days post-transplant). Due to an excess of serious adverse events (SAEs), primarily associated with AEs of diarrhea during the dosing of Cohort 4, an ad hoc DSMB meeting was convened. After review of the data from this cohort, the DSMB decided to dose reduce the subjects in Cohort 4 still on study drug to 200 mg QW. No new subjects were enrolled into this cohort following the decision to reduce the dose. In addition, a program-wide safety monitoring and management plan (SMMP) was implemented during Cohort 4 and in Cohort 4A. The SMMP directed investigators to carefully monitor subjects for gastrointestinal (GI) and hepatic events and systematically interrupt study drug for subjects with $\geq$ Grade 3 GI-associated AEs and certain hepatic laboratory abnormalities.

Subject Discontinuation Criteria

Subjects who experienced any one of the following criteria after dosing were to be discontinued from the study:

- persistent neutropenia without an alternative explanation, or
- emergence of CMV disease as evidenced by pneumonia, gastrointestinal disease or organ pathology, or
- treatment with an excluded medication, or
- decrease in glomerular filtration rate [GFR] to < 30 mL/min that is drug related or persistent, pregnancy.

Safety monitoring

Subjects in this study were to undergo safety monitoring as indicated below:

Prior to study: Baseline hematology and biochemistry, urinalysis, ECG and physical examination. Following the first dose of study medication, subjects were to remain in the clinic for 4 hours for observation and safety evaluations. Vital signs were to be recorded pre-dose and at 3.5 hours post dose.

Every two weeks during the treatment phase, blood and urine samples were to be collected to evaluate organ function. Clinical evaluations including vital sign measurements were to be performed to monitor for changes from baseline.

The DSMB chairman were to immediately review all SAEs considered possibly related to study drug, and the DSMB were to have ongoing review of all safety assessments and AEs. The DSMB were to approve the dose for the subsequent cohort and were to review complete data from each cohort after the completion of the cohort.

After 20 subjects had completed 4 doses in any one cohort, the unblinded study statistician was to begin biweekly monitoring of the safety data to verify that the incidence of drug-related grade 4 AEs and SAEs in CMX001 treated subjects was not statistically significantly greater than the incidence of these events in placebo subjects. If there was a significant increase in CMX001 treated subjects, then the DSMB chairman was to be notified immediately. Plasma samples were to be collected before each dose to monitor CMX001 and cidofovir levels. Plasma samples were to be collected weekly throughout the study to monitor for CMV; urine and/or plasma samples were to be collected once every 2 weeks for BK virus, adenovirus, and Epstein Barr virus DNA analysis. Adverse events and the requirement for concomitant medication and/or changes in concomitant medications were to be monitored throughout the study.

Safety Endpoint Assessment

Safety endpoints included AEs, SAEs, AEs of special interest (including nephrotoxicity, neutropenia, ocular hypotony, graft versus host disease-related gastrointestinal symptoms, and glomerular filtration rate [GFR] <30 mL/min), development or progression of graft versus host disease, laboratory evaluations (biochemistry, hematology, urinalysis, viral load measurements, etc.), vital signs, electrocardiograms (ECGs), and physical examination.

Protocol CMX001-202

Title: *“A randomized, placebo-controlled, multi-site Phase 2 study evaluating the safety and efficacy of preemptive treatment with CMX001 for the prevention of adenovirus disease following hematopoietic stem cell transplantation”*

Subjects: 48 subjects randomized

Study Sites: 17 centers in the USA

Study Initiation and Completion Dates: 22 June 2011 and 28 February 2013

The primary objective was to evaluate the safety and efficacy of preemptive treatment with CMX001 versus placebo for the prevention of adenovirus disease in recipients of hematopoietic cell transplant with asymptomatic adenovirus viremia.

This was a Phase 2, randomized, multicenter, placebo-controlled study for pediatric and adult subjects who had undergone hematopoietic cell transplant and who had been identified as having asymptomatic adenovirus viremia. These subjects had detectable adenovirus DNA in plasma based on polymerase chain reaction (PCR) testing performed at the local laboratory but did not have adenovirus disease symptoms.

Main inclusion criteria included:

- Male or female, ≥ 3 months to ≤ 75 years of age.
- Received an allogeneic hematopoietic cell transplant.
- Positive serum adenovirus PCR (≥ 100 copies/mL) as measured by the central virology laboratory (unless the subject developed adenovirus disease while participating in prescreening activities and after concurrence from the Chimerix medical monitor or designee).
- Subject was on dialysis during treatment if he/she had an estimated glomerular filtration rate (eGFR) ≤ 30 mL/minute.

Main exclusion criteria included:

- Subject had possible, probable, or definitive adenovirus disease (unless the subject developed probable or definitive adenovirus disease while participating in prescreening activities and after concurrence from the Chimerix medical monitor or designee).
- Subject was diagnosed with adenovirus disease within 60 days prior to randomization (unless the subject developed a new onset of adenovirus disease while participating in prescreening activities and after concurrence from the Chimerix medical monitor or designee).
- Suspected gut graft versus host disease that was not biopsy-proven (subjects with a biopsy performed may have been included in the study); subjects with suspected gut graft versus host disease for whom biopsy was contraindicated may have been enrolled on a case-by-case basis if approved by the Chimerix medical monitor or designee.
- Subject had an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 5 times the upper limit of normal ($> 5 \times \text{ULN}$), total bilirubin $\geq 2 \times \text{ULN}$, or conjugated (direct) bilirubin $\geq 1.5 \times \text{ULN}$.

For randomization, subjects were stratified based on absolute lymphocyte count (ALC; < 300 or ≥ 300 cells/mm³) at screening. Subjects were randomized 1:1 to dosing frequency (QW: BIW, unblinded) and 2:1 to study treatment (CMX001: placebo, blinded). Following randomization, subjects received their first dose of study drug on Day 0. Subjects were assessed twice weekly for the first two weeks (Days 0, 3, 7, and 10) and then once a week thereafter for the duration of treatment

for safety and virology assessments. Subjects were to have remained on study treatment for at least six, but no more than 12 weeks, followed by four weeks of posttreatment follow-up.

Main discontinuation criteria included any subject in the study who had increasing adenovirus viremia (≥ 1 log₁₀ increase from baseline, as confirmed by two measurements performed one week apart) or who developed probable or definitive adenovirus disease at any time during the study was considered a treatment failure with respect to the primary endpoint. These subjects were offered open-label treatment with CMX001 for a period of up to 12 weeks. Subjects who cleared viremia during open-label CMX001 therapy were followed for four weeks after the end of therapy to assess the potential for relapse.

Safety Endpoint Assessment

Safety assessment included AEs, SAEs, AEs of special interest (including nephrotoxicity, neutropenia, ocular hypotony, gastrointestinal (GI) symptoms, and hepatic symptoms), development or progression of graft versus host disease, laboratory evaluations (biochemistry, hematology, and urinalysis), vital signs, and physical examination.

Rationale for Site Selection

The clinical investigator (CI) sites were selected based on enrollment, participation in multiple studies, and inspection history.

III. RESULTS

1. Michael J. Boeckh, M.D.

Site number #7 for both Protocol CMX001-301 & CMX001-201

1100 Fairview Avenue North, E4-100

Seattle, WA 98109, USA

Inspection dates: 01/04/2021 to 01/08/2021

At this site for Protocol CMX001-301, a total of 38 subjects were screened, 31 were enrolled, and 27 subjects completed the study. Four subjects discontinued the study for the following reasons: one withdrew consent and three died (one due to multi-system organ failure considered unrelated to study drug in a subject with graft versus host disease and CMV reactivation, one due to leukemia relapse, and one due to relapsed leukemia and multi-system organ failure considered unrelated to study drug). The number of discontinuations and the reasons for them as described in the source documents matched those in the data line listings provided by the sponsor.

For Protocol CMX001-201, a total of 19 subjects were screened, 14 were enrolled, and 5 completed the study. Nine subjects discontinued the study for the following reasons: five subjects due to CMV reactivation requiring treatment, two were due to adverse events of diarrhea, one due to relapse and persistent neutropenia, and one due to death from acute graft versus host disease and methicillin susceptible *Staphylococcus aureus* sepsis. The number of discontinuations and the reasons for them as described in the source documents matched those in the data line listings provided by the sponsor.

For Protocol CMX001-301, the inspection reviewed the informed consent forms for all 38 screened subjects, adverse events for all 31 enrolled subjects, and other study records (eligibility, protocol deviations, concomitant medications, randomization, study drug administration, and drug accountability) for 13 enrolled subjects. For Protocol CMX001-201, the inspection reviewed the informed consent forms for all 19 screened subjects, adverse events for all 14 enrolled subjects, and other study records (eligibility, protocol deviations, concomitant medications, randomization, study drug administration, and drug accountability) for 12 enrolled subjects. In addition, the review included, but was not limited to, case report forms; medical records for office visits, hospital visits, consultations, and outside medical records; laboratory reports; and ECG tracings. Trial records reviewed included drug accountability records; site correspondence with the sponsor, monitor, and Institutional Review Board (IRB); and regulatory records including FDA 1572s and financial disclosure records.

The safety data for all enrolled subjects for both studies were verifiable. There was no evidence of underreporting of adverse events.

2. Drew Winston, M.D.

Site number #25 for both Protocol CMX001-301 & CMX001-201
757 Westwood Plaza
Los Angeles, CA 90095, USA
Inspection dates: 2/4, 5, 8-12, 17, 18, 22, 2021

At this site for Protocol CMX001-301, 52 subjects were screened, 45 were enrolled, and 14 subjects completed the study. Thirty-one subjects discontinued the study. For Protocol CMX001-201, 51 subjects were screened, 39 were enrolled, and 21 subjects completed the study. Eighteen subjects discontinued the study. For both studies, the number of discontinuations and the reasons for them as described in the source documents matched those in the data line listings provided by the sponsor.

The inspection reviewed 12 study records for Protocol CMX001-301 and 15 study records for Protocol CMX001-201. Records reviewed included, but were not limited to, study eligibility, the safety endpoint data, medication administration reports, progress notes, research notes, and labs. Regulatory documents reviewed included informed consent forms, monitoring logs, study personnel signature/responsibility list, Institutional Review Board (IRB) correspondence and approvals, drug accountability, subject-specific binder source documentation, unblinding log, and electronic case report forms (eCRFs).

Based on the Establishment Inspections Report, most of the adverse events were verifiable. However, a number of adverse events were not reported. Tables 1 and 2 below list the subjects and their unreported adverse events

Table 1: Adverse Events Not Reported for Protocol CMX-301 for Site #25

Subject Number	Treatment Group	Adverse Event
(b) (6)	CMX001	Vomiting after study drug dose
		Abdominal distension
		Yeast infection
		Bilateral rash on armpits and groin
		Swelling in legs
	CMX001	Difficulty thinking/focusing
		Decrease in appetite
		Worsening overall condition
		Vomiting after study drug dose
	CMX001	Mild mucositis pain
		Decrease in appetite
		Bilateral lower back pain
	CMX001	Lack of concentration
		Weakness
		Shortness of breath
	CMX001	Tired/lethargic
		Poor appetite/anorexia
	CMX001	Neutropenia
	CMX001	Weakness
		Pressure ulcer
		Blurry vision
	CMX001	Productive cough
		Intermittent tremors/chills
		Pain from buttocks
	CMX001	Lethargic
	CMX001	Migraines
		Headache

Table 2: Adverse Events Not Reported for Protocol CMX-201 for Site #25

Subject Number	Treatment Group	Adverse Event
(b) (6)	brincidofovir 200mg BIW	Malaise
		Weakness
	brincidofovir 40mg QW	Vomiting from constipation
	brincidofovir 200mg BIW	Hyponatremia
	brincidofovir 200mg QW	Recurrent decrease in po intake
		Recurrent fatigue
		Anterior pericardial effusion
		Pericardial thick
		Diastolic dysfunction on ECHO
		Pulmonic resurgence on ECHO
		Graft versus host disease
		Recurrent vomiting
		Dry skin
		Rash to trunk
		Recurrent intermittent diarrhea
		Increased liver enzymes
		Failure to thrive
		Urinary tract infection
		Recurrent hypertension

Reviewer's comment: The review division should consider these unreported adverse events in their safety evaluation of brincidofovir.

3. Genovefa Papanicolaou, M.D.

Site number #30 for both Protocol CMX001-301 & CMX001-201

Site number #1140 for Protocol CMX001-202

1275 York Avenue

New York, NY 10065

Inspection dates: 1/4-8/21 and 1/26-27/21

At this site for Protocol CMX001-301, 30 subjects were screened, 21 were enrolled, and 5 subjects completed the study. Sixteen subjects discontinued this study. At this site for Protocol CMX001-201, 13 subjects were screened, 12 were enrolled, and 5 subjects completed the study. Seven subjects discontinued this study. At this site for Protocol CMX001-202, 4 subjects were screened and 2 were enrolled, all of whom discontinued the study. For both studies, the number of discontinuations and the reasons for them as described in the source documents matched those in the data line listings provided by the sponsor.

The inspection reviewed subject study records for 21 enrolled subjects for Protocol CMX001-301, 12 enrolled subjects for Protocol CMX001-201, and 2 enrolled subjects for Protocol CMX001-202. Records reviewed included, but were not limited to, subject eligibility, informed consent, study approvals, study monitoring, adverse events, case report forms, protocol deviations, concomitant medications, laboratory reports, electrocardiogram tracings, investigational product accountability, randomization, blinding procedures, site correspondence, regulatory records, FDA form 1572 and financial disclosure and the training of study staff.

The safety data for all enrolled subjects for the three studies were verifiable. There was no evidence of underreporting of adverse events.

4. Francisco Marty, M.D.

Site number# 036 for both Protocol CMX001-301 & CMX001-201

75 Francis Street, PBB-A4

Boston, Massachusetts 02115

Inspection dates: Jan 26, 2021 – Feb 5, 2021

At this site for Protocol CMX001-301, 51 subjects were screened, 45 were enrolled, and 30 subjects completed the study. Fifteen subjects were discontinued. The number of discontinuations and the reasons for them as described in the source documents matched those in the data line listings provided by the sponsor.

At this site for Protocol CMX001-201, 68 subjects were screened, 40 were enrolled, and 19 subjects completed the study. Twenty-one subjects discontinued this study. The number of discontinuations and the reasons for them as described in the source documents matched those in the data line listings provided by the sponsor.

The inspection reviewed subject study records for 15 enrolled subjects for Protocol CMX001-301 and 15 enrolled subjects for Protocol CMX001-201. Records reviewed included, but were not limited to, informed consent forms, screening and study eligibility, discontinuation, adverse events, concomitant medications, protocol deviations, ECG tracings, individual drug dispensing logs,

administration records, drug accountability, and provider notes as well as FDA Form 1572, financial disclosures, IRB approvals, and monitoring reports.

The safety data were verifiable for all reviewed subjects for both studies, and there was no evidence of underreporting of adverse events.

5. Roy Chemaly, M.D.

Site number #046 for both Protocols CMX001-301 & CMX001-201

Site number #1104 for Protocol CMX001-202

1515 Holcombe Boulevard

Houston, TX 77030

Inspection dates: 02/23-26/2021

At this site for Protocol CMX001-301, 41 subjects were screened, 33 were enrolled, and 8 subjects completed the study. Twenty-five subjects discontinued the study. At this site for Protocol CMX001-201, 14 subjects were screened, 10 were enrolled, and one subject completed the study. Nine subjects discontinued the study. At this site for Protocol CMX001-202, 6 subjects were screened, 5 were enrolled, and one subject completed the study. Four subjects discontinued the study. For all three studies, the number of discontinuations and the reasons for them as described in the source documents matched those in the data line listings provided by the sponsor.

The inspection reviewed 17 out of 33 enrolled subjects for Protocol CMX001-301, 9 out of 10 enrolled subjects for Protocol CMX001-201, and 5 out of 5 enrolled subjects for Protocol CMX001-202. Records reviewed included, but were not limited to, study eligibility criteria, discontinuations, vital signs, physical examinations, progress notes, concomitant medications, the safety endpoint data, adverse events, and protocol deviations. The inspection also reviewed the regulatory binders for the protocols, which included Independent Review Board (IRB) approvals, delegation of authority logs, financial disclosures, test article accountability records, correspondence between the sponsor and the clinical investigator, and correspondence between monitors and the clinical investigator.

The safety data were verifiable for all reviewed subjects for the three studies, and there was no evidence of underreporting of adverse events.

There were two findings for Study CMX001-301:

- Subject # (b) (6) (CMX001) was on prohibited medication (Cidofovir) for BK Virus-associated cystitis.
- Subject # (b) (6) (Placebo), the preemptive therapy should have been implemented on (b) (6) when CMV PCR result was <150 copies/mL per central lab. Treatment was not started until (b) (6) based on local lab results.

Reviewer's comment: These two unreported protocol deviations are unlikely to have an effect on the safety evaluation of brincidofovir.

6. Michael Grimley, M.D.

Site number #069 for Protocol CMX001-301
Site number #1100 for Protocol CMX001-202
3333 Burnet Avenue
Cincinnati, OH 45229
Inspection dates: 1/13-15, 1/19-22, 1/25-28/2021

At this site for Protocol CMX001-301, 10 subjects were screened and enrolled, and 5 subjects completed the study. Five subjects discontinued the study. The number of discontinuations and the reasons for them as described in the source documents matched those in the data line listings provided by the sponsor.

At this site for Protocol CMX001-202, 27 subjects were screened and 17 were enrolled. The inspection reported that 6 subjects completed the study and 11 subjects discontinued the study. The inspection verified the reasons for these 11 discontinuations. The number of discontinuations and the reasons for them as described in the source documents matched those in the clinical study report (there appears to have been an error in the BIMO discontinuation line listings for this site, which is why we relied on the listings in the clinical study report).

For Protocol CMX001-301, the inspection reviewed all 10 enrolled subject study records. For Protocol CMX001-202, the inspection reviewed subject source records for 15 out of the 17 enrolled subjects. Records reviewed during the inspection included, but were not limited to, study eligibility criteria, the safety endpoint data, adverse events, protocol deviations, vital signs, physical examinations, and concomitant medications. The inspection also reviewed the regulatory files for both protocols, which included Independent FDA form 1572, financial disclosures, Review Board (IRB) approvals, delegation of authority logs, test article accountability records, and correspondence between the sponsor and the clinical investigator.

The safety data were verifiable for all reviewed subjects for both studies, and there was no evidence of underreporting of adverse events.

{ See appended electronic signature page }

Jenn W. Sellers, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Rm. NDA 214461 and 214460
DAVP/Project Manager/Andrew Gentles
DAVP/Medical Officer/Kirk Chan-Tack
DAVP/Clinical Team Leader/Kimberly Struble
OSI/Office Director/David Burrow
OSI/Deputy Office Director/Laurie Muldowney
OSI/DCCE/Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Jenn Sellers
OSI/GCP Program Analyst/Yolanda Patague

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/s/

JENN W SELLERS
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PHILLIP D KRONSTEIN
03/18/2021 01:05:16 PM

KASSA AYALEW
03/18/2021 01:21:20 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: 3/16/2021

To: CDR Andrew Gentles, PharmD, BCPS AQ-ID
Senior Regulatory Project Manager
Division of Antivirals (DAV)

From: Nima Ossareh, PharmD, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for TEMBEXA (brincidofovir) tablets, for oral use, TEMBEXA (brincidofovir) suspension, for oral use

NDA: 214660, 214661

In response to DAV's consult request dated September 28, 2020, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for TEMBEXA (brincidofovir) tablets, for oral use, TEMBEXA (brincidofovir) suspension, for oral use.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAVP on March 2, 2021, and are provided below.

PPI: A combined OPDP and Division of Medical Policy Programs (DMPP) review of the PPI will be completed under a separate cover.

Thank you for your consult. If you have any questions, please contact Nima Ossareh at (240) 402-2769 or nima.ossareh@fda.hhs.gov.

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/s/

NIMA OSSAREH
03/16/2021 10:28:35 AM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: March 15, 2021

To: Andrew Gentles, PharmD, BCPS
Regulatory Project Manager
Division of Antivirals (DAV)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA, CPH
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Nima Ossareh, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): TEMBEXA (brincidofovir)

Dosage Form and Route, Application Type/Number: oral suspension, for oral use, NDA 214460
oral tablets, for oral use, NDA 214461

Applicant: Chimerix

1 INTRODUCTION

On October 7, 2020, Chimerix submitted for the Agency's review an original New Drug Application (NDA) 214460 and (NDA) 214461 for TEMBEXA (brincidofovir) tablets and oral suspension, respectively. TEMBEXA (brincidofovir) tablets and oral suspension is indicated for the treatment of human smallpox disease caused by variola virus in adult and pediatric patients.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antivirals (DAV) on September 25, 2020 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TEMBEXA (brincidofovir) tablets and oral suspension.

2 MATERIAL REVIEWED

- Draft TEMBEXA (brincidofovir) tablets and oral suspension PPI received on October 7, 2020, and received by DMPP and OPDP on March 2, 2021.
- Draft TEMBEXA (brincidofovir) tablets and oral suspension Prescribing Information (PI) received on October 7, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on March 2, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

5 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

MORGAN A WALKER
03/15/2021 03:26:19 PM

NIMA OSSAREH
03/15/2021 04:02:52 PM

LASHAWN M GRIFFITHS
03/15/2021 11:03:01 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health Review

Date: 3/12/2021 **Date consulted:** 10/13/2020

From: Wenjie Sun, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health (DPMH)

To: Division of Antivirals (DAV)

Drug: Tembexa (brincidofovir) 100mg Tablets
Tembexa (brincidofovir) 10mg/mL oral suspension

NDA: 214460
214461

Applicant: Chimerix

Subject: New NDA

Proposed Indication: For the treatment of human smallpox disease in adult and pediatric patients.

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 214460 and 214461
- DAV consult form for DPMH, DARRTS Reference ID 4684777

Consult Question:

- DAAP is seeking assistance from DPMH in developing Sections 8.1, 8.2, and 8.3 of the product's labeling.

INTRODUCTION AND BACKGROUND

On October 7, 2020, the applicant (Chimerix) submitted two new original NDAs 214460 and 214461 for brincidofovir tablet and oral suspension for approval. The Division of Antivirals (DAV) consulted the Division of Pediatric and Maternal Health (DPMH) on October 13, 2020, to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- On October 7, 2020, the applicant submitted an NDA for brincidofovir tablets and powder with the proposed indication for the treatment of human smallpox disease in adult and pediatric patients in accordance with 21 CFR Part 314, subpart I (Animal Rule).
- On July 8, 2015, brincidofovir (BCV) was granted Fast Track Designation which allows a rolling NDA submission.
- On June 5, 2018, BCV was granted Orphan Designation for the treatment of smallpox.
- On July 22, 2019, the proprietary name Tembexa was deemed conditionally acceptable by FDA.
- On May 29, 2020, the applicant requested Priority Review, but it was not granted as BCV is not consider as a new molecular entity. BCV contains the same active moiety as the previously approved drug Vistide (cidofovir)¹, which was first approved on June 26, 1996.
- On October 13, 2020, DAV consulted DPMH to assist with updating the Pregnancy and Lactation subsections of brincidofovir labeling.
- On January 7, 2021, FDA send an information request (IR) to the applicant to obtain pregnancy outcome information for Tembexa use in the clinical trials.
- On January 15, 2021, the applicant replied to the IR with a Labeling Supplement.

Drug Characteristics²

Drug Class	antiviral-variola virus
Mechanism of action ³	Brincidofovir is a lipid conjugate of cidofovir, which is a nucleotide analog. The lipid conjugate is designed to mimic a natural lipid, lysophosphatidylcholine, and thereby uses endogenous lipid uptake pathways. Once inside cells, the lipid ester linkage of brincidofovir is cleaved to liberate cidofovir, which is then phosphorylated to produce the active antiviral, cidofovir diphosphate. Cidofovir diphosphate inhibits orthopoxvirus replication by inhibiting viral DNA polymerase-mediated synthesis of viral DNA.
Proposed Dose and Administration ⁴	• Adult and pediatric patients weighing 48 kg or above: 200 mg (two 100 mg tablets or 20 mL oral suspension for patients who cannot swallow tablets) once weekly for 2 doses.

¹ Vistide was not discontinued for safety or efficacy reasons.

² Based on Applicant's Proposed Labeling with DAI Review Team Input.

³ Based on discussion with DAI Pharmacology Toxicology Team. 1/25/21

⁴ Based on discussion with DAI Clinical Pharmacology Team. 1/29/21

Metabolism ⁴	Hydrolysis, CYP4F2: Brincidofovir is metabolized by hydrolysis of the phosphoester bond to form cidofovir. One enzyme involved in brincidofovir hydrolysis is acid sphingomyelinase. Cidofovir is subsequently phosphorylated to form cidofovir diphosphate. Brincidofovir is also hydroxylated at the terminal carbon by CYP4F2, followed by subsequent CYP-mediated oxidations and multiple cycles of fatty acid beta-oxidation. The major inactive metabolites formed via these pathways are CMX103 (3-hydroxypropyl ester of cidofovir) and CMX064 (4-(3-propoxy) butanoic acid ester of cidofovir). 51% of the dose is excreted in urine and 40% excreted in feces as metabolites.
Molecular weight ⁴	561.69 Dalton
Half life ⁴	19.3 hours (mean terminal half-life), cidofovir diphosphate has half-life of 113 hours.
Protein Binding ⁴	>99.9%
Bioavailability ⁴	16.8% (suspension); 13.4% (tablet)
Serious Adverse Reactions ⁵	- Elevations in hepatic transaminases and bilirubin: Rare cases (<1%) of severe hepatobiliary adverse events including hyperbilirubinemia, acute hepatitis, hepatic steatosis, and venoocclusive liver disease have been reported. - Diarrhea and other gastrointestinal adverse events - Increased risk for mortality when used for longer duration in diseases other than human smallpox TEMBEXA is not indicated for use in diseases other than human smallpox. An increase in mortality was observed in a randomized, placebo-controlled Phase 3 trial when TEMBEXA was evaluated in another disease. An increased risk in mortality is possible if TEMBEXA is used for a duration longer than at the recommended dosage on Days 1 and 8. - Cyclosporine: The concomitant use of TEMBEXA with cyclosporine has resulted in increased brincidofovir exposures and increased serum bilirubin - Cidofovir: TEMBEXA should not be co-administered with IV cidofovir - Embryo-fetal toxicity Based on findings from animal reproduction studies, TEMBEXA may cause fetal harm when administered to pregnant individuals. TEMBEXA administration to pregnant rats and rabbits resulted in embryotoxicity, decreased embryo-fetal survival and/or structural malformations. These effects occurred in animals at systemic exposures less than the expected human exposure based on the recommended dose of TEMBEXA. Use an alternative therapy to treat smallpox during pregnancy, if available. Advise individuals of

⁵ Based on discussion with DAIClinical Team. 1/25/21

	childbearing potential to avoid becoming pregnant and to use effective contraception during treatment with TEMBEXA and for (b) (4) months after the last dose • Carcinogenicity • Male infertility
--	--

REVIEW

PREGNANCY

Smallpox and Pregnancy

Variola virus is the causative agent of smallpox, a highly infectious disease characterized by fever, rash, and a high mortality rate. In 1979, the global eradication of smallpox was announced.⁶ Although there have been no reported cases since eradication, continued interest in this virus remains because of the concern regarding smallpox as a potential agent of bioterrorism.

- Smallpox occurred in two forms caused by different strains: variola major, which was a serious illness with a mortality rate of 30 to 50 percent in the unvaccinated individual, and variola minor, which was a milder infection with a mortality rate of less than 1 percent.⁷
- Transmission can be spread through humans only, via respiratory route, contact of fluid either directly or via contaminated materials, and airborne route.
- Clinical presentation can be characterized into five categories: ordinary, modified, flat, hemorrhagic, and variola sine eruptione. All the forms have a characteristic rash, except for variola sine eruptione. In general, smallpox was most severe in infants, the elderly, and in the impaired host, particularly those with T cell deficits. Milder forms of infection were observed in patients with a history of smallpox immunization.
- The mainstay of treatment for smallpox is supportive care, which includes maintenance of fluid and electrolyte balance, skin care, and observing for complications related to infections. The only approved antiviral therapy in United States through Government's Strategic National Stockpile is tecovirimat, which is an oral drug that is taken twice daily for 14 days and targets the viral envelope protein required for viral maturation and inhibits release of the infectious orthopoxvirus from infected cells. Tecovirimat has been administered to approximately 360 human volunteers in an expanded safety trial, which found an adverse effect profile similar to placebo.⁶ It was also given as an Emergency Investigational Drug to patients who developed complications from the smallpox vaccine, including a severely ill child with eczema vaccinatum and a military recruit with progressive vaccinia.⁶ In both of these cases, tecovirimat was administered in conjunction with vaccinia immune globulin, and both patients survived. In the event of an exposure to smallpox, administration of smallpox live attenuated vaccine within the first 4 days of exposure may reduce the severity of disease.

⁶ Friedman HM, Issacs SN. Variola virus (smallpox). UpToDate, https://www.uptodate.com/contents/variola-virus-smallpox?search=smallpox%20and%20pregnancy&source=search_result&selectedTitle=1~54&usage_type=default&display_rank=1 Accessed 10/14/2020.

⁷ Fenner F, Henderson DA, Arita I, et al. Smallpox and its eradication, World Health Organization, Geneva 1988.

Maternal mortality in smallpox affected pregnancies was reported disproportionately high compared with that of the overall population.⁸ Both vaccinated and unvaccinated pregnant women experience significant perinatal and maternal morbidity and mortality in pregnancy with smallpox infection.

- The largest series by Rao et al.⁹ consists of 389 pregnant women with smallpox in the 1960s in India. The authors reported an overall case-fatality rate of 33%, with a 27% rate of fatality among the vaccinated and 61% rate of fatality among the unvaccinated. The authors also reported that smallpox acquired before 24 weeks' gestation was associated with a 75% rate of miscarriage or preterm delivery. When smallpox was acquired between 24 to 37 weeks' gestation, 55% of these pregnancies delivered prematurely. When smallpox was acquired at term, 9% of women died before delivery and 45% of women delivered during the acute phase of disease. Hemorrhagic type smallpox was seven times more frequent in pregnant women and case-fatality rate was 100% among pregnant Indian women.¹⁰ Nearly 55% of the live births died within 15 days after birth (the majority during the first 72 hours of life). The rate of congenital smallpox among the live births was 9%; all of them died.⁹

Treatment in pregnancy is the same as the general population. There are no human data on the use of tecovirimat, an antiviral therapy, in pregnancy. Tecovirimat has not been shown to be associated with embryofetal developmental toxicity in animal reproduction studies.¹¹ Although vaccination with live attenuated virus in general is not recommended in pregnancy and smallpox vaccination (with live vaccinia virus) is contraindicated as pre-exposure prophylaxis; the recommendation is different post-exposure. For pregnant women who have had a definite direct exposure, vaccination is recommended due to high fatality related to smallpox infection in pregnancy.¹² Primary vaccination during pregnancy has been associated with a slight but measurable risk of vertical transmission to the fetus, which is known as vaccinia fetalis and is fatal to the neonate.¹³ Breastfeeding is contraindicated during active smallpox infection because vaccinia virus can be transmitted in breastmilk.¹¹

Nonclinical Experience

In animal reproduction studies, oral administration of brincidofovir to pregnant rats and rabbits during the period of organogenesis resulted in embryotoxicity and structural malformations. These effects occurred in animals at systemic exposures less than the expected human exposure based on the recommended dose of TEMBEXA.

For a review from the Pharmacology Toxicology team, the reader is referred to the Nonclinical comments within the integrated review.

⁸ Surarez VR, et al. Smallpox and Pregnancy: From Eradicated Disease to Bioterrorist Threat. *Obstetric and Gynecology* 2002;100(1): 87-93.

⁹ Rao AR. Smallpox. Bombay, India: The Kothari Book Depot, 1972.

¹⁰ Rao AR, Prahlad I, Swaminathan M, Lakshmi A. Pregnancy and smallpox. *J Indian Med Assoc* 1963; 40:353-63.

¹¹ Approved labeling for TPOXX (tecovirimat) capsule for oral use. Drugs@FDA. Accessed 1/28/21.

¹² Yawetz S. Immunizations during pregnancy. UpToDate. Accessed 2/4/2021.

¹³ Hassett DE. Smallpox infections during pregnancy, lessons on pathogenesis from nonpregnant animal models of infection. *Journal of Reproductive Immunology* 2003;60: 13-24.

Review of Clinical Trials

There were no pregnant women exposed to BCV in the clinical trials.

Review of Literature

DPMH's Review of Literature

DPMH conducted a literature review in Embase, Pubmed, Micromedex,¹⁴ and ReproTox.¹⁵

Embase and Pubmed were searched for “brincidofovir” or “cidofovir” and “pregnancy,” “brincidofovir” or “cidofovir” and “fetal malformations/congenital malformations/birth defects/stillbirth/spontaneous abortion/miscarriage.”

- There is no published literature on brincidofovir or cidofovir use in pregnancy.

Micromedex¹⁴ and ReproTox¹⁵ contain no information on brincidofovir.

Micromedex¹⁴ and ReproTox¹⁵ states that no human studies of pregnancy outcomes after exposure to cidofovir have been published. Micromedex¹⁴ gives “Pregnancy Rating: Fetal risk cannot be ruled out.”

Reviewer comment:

There are no data on the use of brincidofovir or cidofovir in pregnancy. Brincidofovir is teratogenic in animals at systemic exposures less than the expected human exposure based on the recommended dose of TEMBEXA. Therefore, brincidofovir may cause fetal harm. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data, submission and recommendations.

LACTATION

Nonclinical Experience

When brincidofovir was administered to lactating rats (4 mg/kg/day or 15 mg/kg twice weekly), brincidofovir was detected in milk but not in the plasma of nursing pups.

For a review from the Pharmacology Toxicology team, the reader is referred to the Nonclinical comments within the integrated review.

Review of Clinical Trials

There were no lactating women in any of the clinical trials.

Review of Literature

DPMH's Review of Literature

A search was performed using the sources noted below, and the following findings were retrieved:

A search in PubMed and Embase was performed using the search terms “brincidofovir” or “cidofovir” AND “lactation” and “brincidofovir” or “cidofovir” AND “breastfeeding.”

¹⁴ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 10/14/2020.

¹⁵ Reprotox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 10/14/2020.

- No articles were found on the use of brincidofovir or cidofovir during lactation.

Smallpox is highly contagious. Current practice recommends that breastfeeding mothers with smallpox avoid breastfeeding to prevent transmission through direct contact with the infant.¹⁶ In addition, a report of documents tertiary contact vaccinia in a breastfeeding infant exist in the literature of lesions developed in his wife and the breastfeeding infant after he received vaccinia despite observing appropriate precautions. Sepkowitz¹⁷ reported 27 cases of secondary vaccinia in household between 1931 to 1981 and CDC reported 30 suspected cases of secondary/tertiary vaccinia with 18 of those confirmed by culture or PCR related to vaccinated military personnel.¹⁸

LactMed,¹⁹ Briggs,²⁰ and Hale²¹ contain no information on brincidofovir or cidofovir.

Reviewer comment:

Smallpox is highly contagious and current practice recommends avoiding breastfeeding to prevent transmission of smallpox through direct contact with the infant. It is not known if brincidofovir is present in breastmilk. Brincidofovir is present in animal milk. When a drug is present in animal milk, it is likely to be present in human milk. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Carcinogenesis and Mutagenesis

Palpable masses occurred in rats with high frequency after as few as 26 doses of brincidofovir at systemic exposures less than the expected human exposure based on the recommended dose of TEMBEXA. The masses diagnosed as mammary adenocarcinomas, carcinoma in squamous cell, Zymbal's gland, uterus and small intestine and hemangiosarcomas in mesenteric and mediastinal lymph node, liver and abdominal cavity were observed in rats following long term (13-weeks and 26-weeks) dosing studies. No tumors occurred in rats after 9 twice-weekly IV doses, although rats were only followed for 14 days after the last administration. Based on these data

¹⁶ Lawrence R. Transmission of Infectious Diseases Through Breast Milk and Breastfeeding. Breastfeeding. 2011: 406–473.

¹⁷ Sepkowitz KA: How contagious is vaccinia? N Engl J Med 348:439, 2003.

¹⁸ Centers for Disease Control and Prevention: Secondary and tertiary transfer of vaccinia virus among U.S. military personnel—United States and worldwide, 2002–2004, MMWR Morb Mortal Wkly Rep 53(5):103, 2004.

¹⁹ <http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed data base provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfeeding infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility. Accessed 10/15/2020.

²⁰ Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th Ed. 2015. Online, accessed 10/15/20

²¹ Hale, Thomas. Hale's Medications and Mother's Milk 2019. Springer Publishing Company, New York, NY. Accessed 10/15/20

and the unknown translation of nonclinical findings to clinical risk, TEMBEXA should be considered a potential human carcinogen.

Brincidofovir was negative in a bacterial mutagenicity (Ames) assay and an in vivo micronucleus assay in mice. Brincidofovir was positive for increased structural chromosomal aberrations in the absence of metabolic activation in an in vitro assay.

Reviewer comment:

In discussion with the DAI Pharmacology Toxicology Team, it was noted that although brincidofovir did not meet the criteria to be genotoxic according to the Oncology Reproductive Toxicity Testing and Labeling Recommendations Guidance, it is genotoxic according to the ICH S2(R1) (in the absence of clearly negative results in two well-conducted in vivo assays). Brincidofovir is a carcinogen, and it is tumorigenic in rats at a dose that is associated with systemic exposures less than the expected human exposure. Therefore, the use of contraception during treatment and for a period of 4 months (5 half-lives plus 3 months) after cessation of therapy is recommended in males. According to the Oncology Reproductive Toxicity Testing and Labeling Recommendations guidance, this drug is aneugenic, a substance that causes a daughter cell to have an abnormal number of chromosomes or aneuploidy, and the use of contraception during treatment and for a period of 2 months (5 half-lives plus 1 month) after cessation of therapy is generally acceptable because only dividing oocytes are affected by aneugenicity.

Impairment of Fertility

In chronic dosing studies with orally administered brincidofovir, testicular effects were seen in both rats and monkeys. Monkeys administered twice weekly doses of brincidofovir via oral gavage for 9 months exhibited atrophy of the seminiferous tubules and hypospermia in the epididymides. Based on sperm analysis and histopathology, these findings demonstrated a trend towards recovery after a 6-month, post-dosing period. Rats administered brincidofovir via oral gavage twice weekly for 13 weeks exhibited decreased testes weights, depletion of spermatogenesis and hypospermia. Unlike in the monkey, recovery was not demonstrated in the rats following a 12-week post-dosing period.

In a rat fertility and early embryonic development study, administration of brincidofovir once daily beginning 15 days before cohabitation, during cohabitation and continuing through GD 7 resulted in decreased embryonal viability at 0.25 mg/kg/day, a dose that did not cause maternal toxicity. Male rats dosed twice weekly by oral gavage for 10 to 19 weeks had reduced sperm motility and a decrease in total sperm count. These effects resulted in reduced fertility during the first cohabitation period, and infertility during the second cohabitation period.

Brincidofovir exposures in both monkeys and rats were less than exposures seen in humans administered 200 mg brincidofovir. Studies conducted using IV brincidofovir to achieve clinically relevant exposures demonstrated diminished but ongoing spermatogenesis in the tubules of rats 15 weeks after administration of 3 doses of brincidofovir administered once weekly. The testicular pathology appears to be an effect on the mitotic spermatogonia.

For a review from the Pharmacology Toxicology team, the reader is referred to the Nonclinical comments within the integrated review.

Reviewer comment:

In discussion with DAI Pharmacology Toxicology Team, it was noted that minimal germ cell depletion and minimal tubular atrophy were also observed in rats that only received a total of 3 doses of intravenous infusions once weekly (i.e., Day 1, Day 8, and Day 15) followed by a 6-month recovery period. This represents incomplete/partial recovery. Therefore, based on animal data, brincidofovir may impair male fertility even with short term use and it may be irreversible. This was confirmed in an email communication with the DAI Pharmacology Toxicology Team.

In discussion with the DAI Pharmacology Toxicology Team, it was noted that although brincidofovir does not meet the criteria for a mutagen, it does cause tumors in rats.

Review of Clinical Trials

There are no specific reports of fertility issues noted in any of the clinical trials.

Review of Literature

DPMH's Review of Literature

DPMH conducted a published literature review by using the sources noted below, and the following findings were retrieved:

DPMH conducted a published literature review on PubMed and Embase using term “brincidofovir” or “cidofovir” and “fertility,” “brincidofovir” or “cidofovir” AND “reproduction,” “brincidofovir” or “cidofovir” AND “contraception.” No relevant articles were retrieved.

ReproTox²² contains contain no information on brincidofovir. ReproTox²² notes that in the product labeling of cidofovir, fertility was not affected in male rats given treatments approximately equal to those recommended for humans on a plasma concentration basis in spite of findings that sperm concentration was decreased by cidofovir exposure in rats and dogs.²³

Reviewer comment:

There are no data on the effect of brincidofovir on fertility in humans. Based on animal data, brincidofovir may irreversibly impair male fertility. Although brincidofovir does not meet the criteria to be categorized as a mutagen, it is tumorigenic and aneugenic. The Pharmacology Toxicology team recommends contraceptive use in both males and females of reproductive potential. Four months was recommended for males due to a length of time of spermatogenesis (3 months) plus 1 month for the 5 half-lives and two months was recommended for females, based on length of time to avoid the dividing oocytes and 5 half-lives. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data, submission and recommendations.

²² Reprotox Website: www.Reprotox.org. REPROTOX dytem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 10/14/2020.

²³ Vistide product labeling. 9/24/13. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=90639fc6-0295-4115-98f0-054b783850ce>

DISCUSSION AND CONCLUSIONS

Pregnancy

There are no data on the use of brincidofovir in humans during pregnancy. In animal reproduction studies, brincidofovir administered in pregnancy resulted in embryotoxicity and structural malformation. Therefore, based on animal reproduction studies, brincidofovir may cause fetal harm. Based on historic data, smallpox in pregnancy is associated with significant morbidity and mortality to the mother and the unborn child; therefore, brincidofovir should not be contraindicated for use in pregnant women if an outbreak occurs. DPMH recommends including a Warning and Precaution statement to inform the prescribers about the potential drug-related harm to the fetus. There is a safer treatment for smallpox in pregnant women. The effectiveness of tecovirimat²⁴ was established in studies in animals infected with viruses closely related to the variola virus. Additionally, there was no embryofetal developmental toxicity observed with administration of tecovirimat in mice (during organogenesis at doses 23 times the MRHD) and rabbits (during organogenesis at doses less than the MRHD), and in a mouse pre-/post-natal development study (at doses 24 times the MRHD). Since tecovirimat is a reasonable treatment for smallpox in pregnant women and since brincidofovir may cause fetal harm, DPMH recommends including language in brincidofovir labeling that instructs prescribers to consider an alternative therapy for treatment of small pox infection in pregnant women.

Smallpox has been eradicated in the world since 1978. There are no data on the use of brincidofovir in pregnancy. Brincidofovir will likely not be the drug of choice in the pregnant population given the associated embryotoxicity; therefore, a postmarketing study of brincidofovir use in the pregnant population will not be feasible. DPMH does not recommend any postmarketing pregnancy studies at this time.

Lactation

Smallpox is highly contagious. Current practice recommends that breastfeeding mothers with smallpox avoid breastfeeding to prevent transmission through direct contact with the infant.²⁵ There are no data on the presence of brincidofovir in human milk. Brincidofovir is present in animal milk. When a drug is present in animal milk, it is likely to be present in human milk. There are no data on the effects of the drug on the breastfed infant, or on milk production. DPMH does not recommend a lactation study because breastfeeding during active infection with smallpox is not recommended.

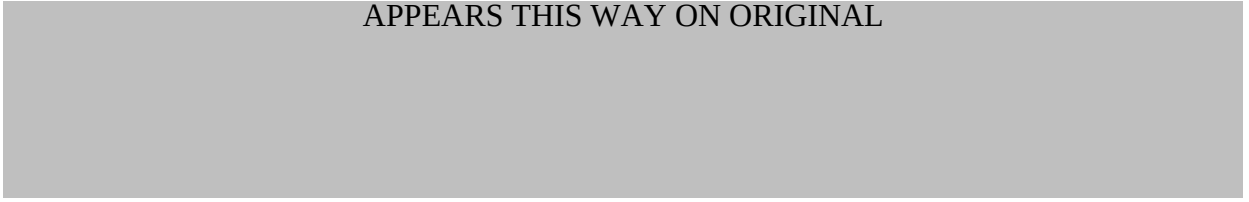
Females and Males of Reproductive Potential

Based on animal studies, brincidofovir may irreversibly impair male fertility. There are no human data. There are no data to suggest brincidofovir interacts with systemic hormonal contraceptive. This was confirmed in discussion with the DAI Clinical Pharmacology Team. Brincidofovir is aneugenic. The Pharmacology Toxicology Team recommends contraceptive use for 4 months in males and 2 months in females of reproductive potential. DPMH recommends including information about the effect of brincidofovir on male fertility under Highlights, Warning and Precautions, Males and Females of Reproductive Potential, and Patient Counseling Information.

²⁴ Product Information: TPOXX, tecovirimat capsules for oral use. Siga Technologies. 2018

²⁵ Lawrence R. Transmission of Infectious Diseases Through Breast Milk and Breastfeeding. Breastfeeding. 2011: 406–473.

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MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: March 5, 2021

TO: Debra Birnkrant, M.D.
Director
Division of Antivirals (DAV)
Office of Infectious Diseases (OID)
Office of New Drugs (OND)

FROM: Gajendiran Mahadevan, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

Yiyue Zhang, Ph.D.
DNDSI
OSIS

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDSI
OSIS

SUBJECT: Recommendations for Remote Record Review (RRR) and
Directed Inspection (b) (4)

1. RRR and Inspection Summary

(b) (4)



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(b) (4)

6. Conclusion

After review of the RRR and inspectional findings, we conclude that analytical data from the reviewed Animal Rule specific studies are reliable.

Based on the inspectional findings, studies of similar design conducted between the previous inspection (b) (4) and the

end of the current surveillance interval should be considered
reliable without an inspection or inspection alternative.

Gajendiran Mahadevan, Ph.D.
Pharmacologist
DNDSI/OSIS

Yiyue Zhang, Ph.D.
Senior Staff Fellow
DNDSI/OSIS

Final Classification for On-site ORA's inspection:

NAI: (b) (4)

FEI #: (b) (4)

cc:
OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/Haidar/Mirza/Irier
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas/Chen/Mahadevan/
Zhang
OTS/OSIS/DGDSI/Cho/Benson/Skelly/Au/Lewin
ORA/OMPTO/OBIMO/DBIMC (b) (4)
ORA/ORA/ORS/OFFLO/ (b) (4)
OND/OID/DAV/Birnkrant
OND/ORO/DROID/Gentles/Moruf

Draft: GM 02/16/2021, 03/01/2021, 03/03/2021, 03/04/2021,
03/05/2021; YZ 02/16/2021, 03/04/2021, 03/05/2021
Edits: RCA 3/02/2021, 3/03/2021, 3/4/2021; ZC 3/4/2021; AD
3/04/2021

ECMS:
<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f883cb52a2>

FACTS#: (b) (4)
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	January 25, 2021
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 214460 NDA 214461
Product Name, Dosage Form, and Strength:	Tembexa (brincidofovir) Tablet, 100 mg; Tembexa (brincidofovir) Oral Suspension, 10 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Chimerix, Inc.
FDA Received Date:	August 28, 2020, October 7, 2020 and January 19, 2021
OSE RCM #:	2020-2101
DMEPA Safety Evaluator:	Melina Fanari, RPh
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 REASON FOR REVIEW

As part of the 505(b)(1) NDAs for Tembexa (brincidofovir) Tablet and Oral Suspension, the Division of Antivirals (DAV) requested that we review the proposed Tembexa Prescribing Information (PI), Patient Prescribing Information (PPI), container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tembexa will be available in an oral tablet (100 mg) and oral suspension (10 mg/mL) formulation. The proposed oral suspension packaging configuration contains an overfill and potential for overdose. We note in product labeling that the recommended adult dose is 200 mg (20 mL of oral suspension) on Day 1 and 8, however, the packaging configuration (bottle/adaptor) contains 65 mL and there is a risk of patients misinterpreting that the bottle only contains the required 2 doses and taking the remainder of the bottle as a second dose. This concern was shared with the clinical team in DAV and based on feedback provided, the clinical impact of a patient administering a wrong dose would be GI toxicities (diarrhea, nausea, vomiting, abdominal pain leading to dehydration) and hepatotoxicity (mainly LFT abnormalities) and that these toxicities were related to dose and duration. Given the course of treatment (2 doses) the clinical consequences are not considered to be significant. Further, we note that the bottle will contain an adaptor which will require insertion of a syringe and measuring of the prescribed dose. We consider that this step will minimize a patient from inadvertently ingesting the remainder of the bottle contents as a second dose. Thus, we determined that the

residual risk association with potential wrong dose medication errors associated with the design of this product is minimal. Furthermore, we note that the residual risk can be further mitigated through appropriate labeling of the product.

Our evaluation of the prescribing information identified areas of vulnerability to medication error and we collaborated with the review team to revise the prescribing information (see Appendix F.3, Annotated Prescribing Information with DMEPA revisions and comments) to address the following identified medication error concerns:

1. Improve clarity and readability of recommended dosage information in chart format.
2. Advise prescribers and patients to utilize an oral syringe to measure prescribed doses and to discard unused portions of the oral suspension after treatment.

We also reviewed Patient Prescribing Information (PPI) and recommended to add information on how to properly measure dose of oral suspension to decrease risk for wrong dose medication errors (See Appendix F.3).

Table 3 below include the identified medication error issues with the submitted container labels and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Chimerix, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Carton Labeling and Container Label (Oral Suspension)			
1.	Net quantity statement is in close proximity to strength statement.	Minimize confusion between the strength and net quantity statement.	Relocate the net quantity statement away from the product strength.
2.	Strength statement lacks prominence.	Improve readability.	Increase the prominence of the strength statement and relocate it to a more prominent location such as to follow the established name. In addition, consider removal (b) (4) on the carton label so that the strength statement is on one line (b) (4) Additionally,

Table 2. Identified Issues and Recommendations for Chimerix, Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			the unit of measure (mg/mL) should appear on the same line as the numerical part of the strength statement (e.g. 10 mg/mL)
3.	The product identifier required under the drug supply chain security act (DSCSA) is missing.	DSCSA requires manufacturers and repackages, respectively, to affix or imprint a product identifier to each package and homogeneous case of a product intended to be introduced in a transaction in (to) commerce beginning November 27, 2017, and November 27, 2018, respectively.	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf
4.	Discard after 30 days statement requires revisions.	Avoid administration of expired drug product.	Revise the (b) (4) to read as follows: “Date of first opening __/__/__. Discard unused portion 30 days after first opening.” in bold font under storage information. In addition, this statement should be added to the container label.
5.	Storage information is missing (container label only).	Minimize risk of improper storage.	Revise the container label to include storage information. Consider condensing and minimizing the manufacturer logo and information to allow for adequate room.
Carton Label (Oral Suspension)			
1.	Bullets 2 and 3 on side panel under Dosage and Administration section should be removed.	Minimize wrong dose errors and ensure consistency with the Prescribing Information.	Bullets 2 and 3 under Dosage and Administration section should be removed and replaced with the following statement: “Recommended Dosage: See prescribing information.”

Table 2. Identified Issues and Recommendations for Chimerix, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	Measuring device recommendation statement is missing.	Minimize risk of wrong dose medication errors.	Add the following statements to the dosage and administration section of the carton labeling: “Use the appropriate measuring device for your total prescribed dose. Only take the volume prescribed. Discard unused portion.”
Container label (Blister foil label)			
1.	The following product identification information is missing: • Proprietary name • Established name • Name of manufacturer	Per 21 CFR 201.10(i)	Add the following: • Proprietary name • Established name • Name of manufacturer
Wallet Carton Labeling (Tablets)			
1.	Product strength is not expressed in mg per single unit and missing from several panels.	To avoid wrong dose errors and to clarify the designated strength is per unit.	Revise the strength presentation statement as follows: “100 mg per tablet”. In addition, the strength presentation should be added to follow each instance of the proprietary and established name presentation (i.e. open, wallet and back panels).
2.	Net quantity statement is in close proximity to strength statement.	Minimize confusion between the strength and net quantity statement.	Relocate the net quantity statement away from the product strength, such as to the bottom of the principal display panel.
3.	The product identifier required under the drug supply chain	DSCSA requires manufacturers and repackages, respectively, to	We recommend that you review the draft guidance to determine if the

Table 2. Identified Issues and Recommendations for Chimerix, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	security act (DSCSA) is missing.	affix or imprint a product identifier to each package and homogeneous case of a product intended to be introduced in a transaction in (to) commerce beginning November 27, 2017, and November 27, 2018, respectively.	product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf
4.	Product strength is not expressed in mg per single unit and missing from several panels.	To avoid wrong dose errors and to clarify the designated strength is per unit.	Revise the strength presentation statement as follows: "100 mg per tablet". In addition, the strength presentation should be added to follow each instance of the proprietary and established name presentation (i.e. open, wallet and back panels).

4 CONCLUSION

Our evaluation of the proposed Tembexa Prescribing Information (PI), Patient Prescribing Information (PPI), container labels and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations to the container labels and carton labeling for the Applicant and have collaborated with DAV during internal labeling meetings recommendations to the PI and PPI. We ask that the Division convey Table 3 in its entirety to Chimerix, Inc. so that recommendations are implemented prior to approval of these NDAs.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tembexa received on October 7, 2020 from Chimerix, Inc.

Product Name	Tembexa
Initial Approval Date	N/A
Active Ingredient	brincidofovir
Indication	treatment of human smallpox disease caused by variola virus in adult and pediatric patients
Route of Administration	oral
Dosage Form	Tablet; Oral Suspension
Strength	100 mg; 10 mg/mL
Dose and Frequency	<u>Adults and pediatric patients weighing at least 48 kg: 200 mg (two 100 mg tablets or 20 mL oral suspension) once weekly for 2 doses (on Days 1 and 8)</u> (b) (4)
How Supplied	Tablets – Blister wallets containing one (1) blister strip of 4 tablets. Each blister cavity contains one (1) tablet Oral Suspension – high density polyethylene bottle with a low density polyethylene press-in-bottle-adapter inserted into the bottle. Each bottle contains 65 mL of brincidofovir.
Storage	Store at (b) (4) 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F). (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 6, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, Tembexa and brincidofovir. Our search did not identify any relevant reviews.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Tembexa labels and labeling submitted by Chimerix, Inc.

- Container labels and carton labeling received on August 28, 2020
- Prescribing Information and Patient Prescribing Information (Images not shown) received on October 7, 2020 and available January 19, 2021 from
<\\CDSESUB1\evsprod\NDA214461\0005\m1\us\114-labeling\114a-draft-label>
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F.2 Label and Labeling Images

(b) (4)



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/s/

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PHARMACOLOGIST REVIEW OF DATA INTEGRITY INSPECTION EIR

Firm Name: (b) (4)

City, State: (b) (4)

Assignment Date: August 17, 2020

EI Start Date: (b) (4)

EI End Date: (b) (4)

FDA Participants: (b) (4) ORA Investigator
(b) (4) ORA Investigator

Inspection Summary

(b) (4)

Recommendations:

- Data from audited Animal Rule studies are reliable for Agency review.
- The next inspection should be scheduled (b) (4)
- Final classification: Voluntary Action Indicated (VAI).

Justification for classification change: Two discussion items (b) (4) were upgraded to observations. Both observations can be related to violation of 21CFR, (b) (4)

cc: via DARRTS NDA 214461

OSIS/Kassim/Folian/Fenty-Stewart/Haidar/Mirza/Johnson

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NDA 214461

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OID/Andrew A. Gentles (Program Coordinator)

Draft: (ZC 10/25/2020)

Edits: (CRB 10/29/2020)

ECMS: Cabinets/CDER OTS/Office of Study Integrity and Surveillance/INSPECTIONS/GLP

Program (b) (4)/Post-Inspection

Folder/EIR & EIR Review

OSIS File #: GLP File number: 1220

FACTS: (b) (4)

FEI: (b) (4)

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