CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214460Orig1s000
214461Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	NDA
Application Number	214461 and 214460
PDUFA Goal Date	July 7, 2021
OSE RCM #	2020-2102/2103-2129
Reviewer Name(s)	Naomi Boston, Pharm.D.
Deputy Division Director	Doris Auth, Pharm.D.
Review Completion Date	May 17, 2021
Subject	Evaluation of the Need for a REMS
Established Name	Brincidofovir
Trade Name	Tembexa
Name of Applicant	Chimerix Inc.
Therapeutic class	DNA polymerase inhibitor
Formulation	100 mg tablets or 10mg/ml oral suspension
Dosing Regimen	200mg orally (or 20ml orally) taken once weekly for 2 doses (on Days 1 and 8)

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Tembexa (brincidofovir) is necessary to ensure the benefits outweigh its risks. Chimerix Inc. submitted a New Drug Application (NDA) 214460 (oral suspension) and NDA 214461 (oral tablet) for brincidofovir with the proposed indication for the treatment of human smallpox disease caused by variola virus. The FDA approved indication will be for the treatment of human smallpox disease in adult and pediatric patients, including neonates. The risks associated with brincidofovir include diarrhea, nausea and elevations in hepatic transaminases and bilirubin. There is also the risk for increased mortality when brincidofovir is used for longer durations than what is recommended for the treatment of human smallpox disease. The applicant did not submit a proposed REMS or risk management plan with this application.

The DRM and the Division of Antivirals (DAV) believes that a REMS is not needed to ensure the benefits of brincidofovir outweigh its risks in the treatment of human smallpox disease. Although smallpox is a serious disease with a high mortality rate, currently, there are no active infections due to elimination of this disease in 1980. Brincidofovir would only be manufactured for the Strategic National Stockpile (SNS) for possible variola virus outbreak(s). If necessary, brincidofovir would only be dispensed by authorities in the SNS in case of a bioterrorism attack or individual variola outbreak cases that meet CDC guidelines for potential smallpox infections. The adverse events reported for brincidofovir for the treatment of human smallpox disease are not new or unusual events and can be adequately communicated in labeling.

1 Introduction

This review by the DRM evaluates whether a REMS for the NME Tembexa (brincidofovir) is necessary to ensure the benefits outweigh its risks. Chimerix Inc. submitted NDAs 214461 (100mg tablet) and 214460 (10mg/ml suspension) for brincidofovir with the proposed indication for the treatment of human smallpox disease caused by variola virus. This application is under review in the DAV, Office of Infectious Diseases. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Brincidofovir is an orthopoxvirus nucleotide analog DNA polymerase inhibitor. The Applicant's proposed indication is for the treatment of human smallpox disease caused by variola virus. The FDA approved indication will be for the treatment of human smallpox disease in adult and pediatric patients, including neonates.[1] Brincidofovir is a lipid-conjugate prodrug that is converted intracellularly to cidofovir diphosphate. Cidofovir diphosphate selectively inhibits orthopoxvirus DNA polymerase-mediated viral DNA synthesis which results in reductions in the rate of the production of virus. Brincidofovir is supplied as a 100mg oral tablet or 10mg/ml oral solution. The dose is 200mg (two 100mg tablets) orally (or 20ml orally for patients who can not swallow) taken once weekly for 2 doses on Day 1 and Day 8.[a]

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

Brincidofovir will only be manufactured for the Strategic National Stockpile (SNS) for possible variola virus outbreak(s).

Brincidofovir is an NME[b] and was granted Fast Track Designation for the treatment of human smallpox disease caused by variola virus on July 8, 2005. Orphan Designation for the same indication was granted on June 5, 2018. Brincidofovir is currently not marketed in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDAs 214460 and 214461 relevant to this review:

- 10/07/2020: NDAs 214460 and 214461 submitted for the proposed treatment of adult and pediatric patients with human smallpox disease caused by variola virus.
- 07/07/2021: Prescription Drug User Fee Act (PDUFA) date for approval.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Smallpox disease is a highly contagious disease unique to humans. Caused by a variant of poxvirus, variola, the mortality rate for an infected person can be as high as 30%.[c,2] The incubation period of the virus in its host is 10-14 days, at which time the patient is usually asymptomatic and noncontagious. Initial symptoms include flu-like symptoms, which progress to body aches, open sores in the mouth, throat, and pustular rashes and lesions on the skin. The patient is most contagious during this time. Eventually scabs form over the lesions and fall off after about three weeks of infection. This often leaves deep pockmarks on the patient's skin, commonly on the face.[3] The last widespread outbreak of smallpox was in 1949, and the last case was documented in 1977.[3] Small pox disease was eradicated in 1980 with the development of widespread vaccination.[d,2] However, there remains a risk that variola virus could be developed as a bioterrorism agent. Though the risk is deemed to be low, there are concerns that this virus may exist outside of the two World Health Organization (WHO)-designated collaborating centers. Any risk of this virus being accidentally or intentionally released could result in devasting effects on an individual or collective circumstance.[3] There is a need for the development of agents that would be readily available to treat variola cases should someone be exposed, in the case of a natural re-emergence of smallpox disease, or a bioterrorism attack.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

At the time of this writing, tecovirimat (TPOXX) is the only drug approved for treatment of human smallpox disease. Tecovirimat was approved by the FDA under 21 CFR part 314, subpart I, known as the Animal Rule, in July 2018. The dose is 600mg twice daily for 14 days in adults or those weighing more than 40kg and is weight-based in pediatric patients 13kg to 40kg. Tecovirimat must be taken within 30 minutes after a full meal of moderate or high fat. Adverse reactions reported in more than 2% of healthy adults were headache, nausea, abdominal pain and vomiting. Hypoglycemia may occur with co-administration of repaglinide; recommendations are to monitor blood glucose and for hypoglycemic symptoms during co-administration.[4]

4 Benefit Assessment

Because of the devastating and severe nature of smallpox disease, and the eradication of smallpox in 1980, there are no clinical trials to determine the efficacy of antiviral agents for the treatment of this disease. Therefore, brincidofovir was evaluated under the Animal Rule for the treatment of smallpox disease in humans. The human dose selection, duration for brincidofovir, and clinical outcomes result from two animal efficacy trials, one using the rabbit/RPXV model (Study VIR-106) and one using the mouse/ECTV model (Study VIR-044).[5]

The primary efficacy endpoint was the proportion of animals that survived to the pre-specified end of study date (day 42). Brincidofovir blood levels were collected, as well as viral DNA levels, laboratory details including hematology and clinical chemistry, clinical observations of skin lesions, vital signs and other signs of illness. Pathologies on deceased animals were also evaluated. Please see Dr. Chan-Tack's review in DARRTS[5] of detailed analysis and outcomes of these non-clinical trials. The table below is from the draft Tembexa label as of May 7, 2021.

Table 1: Survival Rates in Brincidofovir Treatment Studies in the Rabbitpox and Mousepox Models[1]

Dose Regimen (mg/kg)	Treatment Initiation Day	Survival % (# survived/n)		Survival Rate Difference (95% CI)[a]	p-value[b]
		Placebo	Brincidofovir		
Rabbitpox[c]					
Study 1	Day 4	29% (8/28)	90% (26/29)	61% (36%, 79%)	<0.0001
	Day 5		69% (20/29)	40% (12%, 63%)	0.0014
	Day 6		69% (20/29)	40% (12%, 63%)	0.0014
Mousepox[d]					
Study 2	Day 4	13% (4/32)	78% (25/32)	66% (44%, 82%)	<0.0001
	Day 5		66% (21/32)	53% (29%, 72%)	<0.0001
	Day 6		34% (11/32)	22% (1%, 43%)	0.0233[e]

[a.] Survival percentage with brincidofovir-treated animals minus survival percentage in placebo-treated animals. Exact confidence intervals are presented.
[b.] P-value is from 1-sided Boschloo test compared with placebo.
[c.] 20/5/5 mg/kg (fully effective dose in the rabbitpox model)
[d.] 10/5/5 mg/kg (fully effective dose in the mousepox model)
[e.] P-value is not significant at the one-sided alpha of 0.0125.

The DAV recommends the regulatory action of Approval for brincidofovir (Tembexa) for the treatment of human smallpox disease in adult and pediatric patients, including neonates based on the information currently available.[1,5,e]

5 Risk Assessment & Safe-Use Conditions

The safety of brincidofovir has not been studied in human smallpox disease. The safety information for brincidofovir was evaluated in 392 adults aged 18 to 77 years in Phase 2 and 3 randomized, placebo-controlled clinical trials. Of these 392 adults, 85% received a 200 mg total weekly dose of brincidofovir for at least 2 weeks.[1] Diarrhea, nausea and elevations in hepatic transaminases and bilirubin were adverse events reported in 2% or more of patients. Because brincidofovir is a lipid-derivative prodrug of cidofovir, intravenous cidofovir should not be given concomitantly with brincidofovir.[1,f] The following are risks of brincidofovir noted in the review of this application:

5.1 INCREASED RISK FOR MORTALITY WHEN USED FOR LONGER DURATION

Brincidofovir is only indicated for human smallpox disease and should not be used for more than two doses, each given one week apart. In a study for the prevention of cytomegalovirus (CMV) infection (CMX001-301), 303 subjects received brincidofovir 100mg twice weekly and 149 subjects received matching placebo for up to 14 weeks. The primary endpoint was evaluated at week 24, in which all-cause mortality was seen in 16% in the brincidofovir-treated group compared to 10% in the placebo group. The prescribing information for brincidofovir includes a Boxed Warning, as well as labeling in Warnings in Precautions stating that the safety and effectiveness has not been established for diseases other than human smallpox disease, and that there is an increased risk for mortality when used for longer duration. Furthermore, the prescribing information will also contain this information under Limitations of Use.

5.2 ELEVATIONS IN HEPATIC TRANSAMINASES AND BILIRUBIN

In the 392 adults who received brincidofovir in Phase 2 and Phase 3 trials, 7% experienced elevations in alanine aminotransferase (ALT) greater than three times the upper limit of normal, and bilirubin elevations greater than two times the upper limit of normal were reported in 2%

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

during the first two weeks of therapy. These adverse events were reversible and did not require discontinuation of therapy. Recommendations in the prescribing information will be in Warnings and Precautions and will advise performing hepatic laboratory testing in all patients prior to initiating therapy with brincidofovir, and while receiving therapy as clinically appropriate. Recommendations will also include to monitor patients who develop abnormal hepatic laboratory tests during therapy and clinically evaluate and treat as appropriate.

5.3 DIARRHEA AND OTHER GASTROINTESTINAL ADVERSE EVENTS

In the first 2 weeks of brincidofovir therapy in 392 adults, diarrhea of all grades and causes occurred in 40% of adults compared with 25% of adults in the placebo group. Treatment was discontinued in 5% of adults for diarrhea compared to 1% in the placebo group. Other gastrointestinal related events included nausea, vomiting, and abdominal pain; some of which required discontinuation of brincidofovir. Recommendations for monitoring gastrointestinal events in patients who receive brincidofovir will be communicated in the Warnings and Precautions section of the prescribing information.

5.4 EMBRYOFETAL TOXICITY

In nonclinical reproduction studies, brincidofovir may cause fetal harm. Embryotoxicity, decreased embryo-fetal survival and/or structural malformations occurred when brincidofovir was given to pregnant rats and rabbits. These effects occurred at systemic exposures less than the expected human dose. Recommendations are to use an alternative therapy to treat smallpox during pregnancy if feasible, and to advise individuals of childbearing potential to avoid becoming pregnant, by using effective contraception during treatment and for at least 2 months after the last brincidofovir dose. Pregnancy testing in individuals of childbearing potential before commencing brincidofovir treatment is also recommended and will be communicated in the Warnings and Precautions section of the prescribing information.

5.5 CARCINOGENICITY

Brincidofovir is considered a potential human carcinogen. Mammary adenocarcinomas and squamous cell carcinomas occurred in rats at systemic exposures less than the expected human exposure based on the recommended dose of brincidofovir given for human smallpox disease. Recommendations are not to crush or divide brincidofovir tablets and avoid direct contact with broken or crushed tablets or oral suspension. This information will be communicated in the Warnings and Precautions of the prescribing information.

5.6 MALE INFERTILITY

Brincidofovir may irreversibly impair fertility in individuals of reproductive potential. These effects were based on testicular toxicity in animal studies. Testicular effects were seen in rats and monkeys who received brincidofovir. Atrophy of the seminiferous tubules and hypospermia in the epididymides were testicular adverse effects seen in monkeys, however, it appeared there was a trend towards recovery after a 6-month post-dosing period. In rats, decreased testicular weight, depletion of spermatogenesis and hypospermia were seen, however, recovery was not

demonstrated in rats following a 12-week dosing period. Brincidofovir exposures in these animals were less than exposures seen in humans.

6 Expected Postmarket Use

If approved, brincidofovir (Tembexa) will only be indicated for the treatment of human smallpox disease given at 1 dose per week for 2 doses. In communication during the review of these NDAs, the Applicant stated that their intent is to only manufacture Tembexa for the SNS for potential variola virus outbreak(s). The Applicant stated that there was no plan or intent to manufacture or maintain stockpiles of brincidofovir for other indications. Therefore, we do not expect Tembexa to be prescribed or dispensed unless there is a case of variola virus exposure. In all potential or possible smallpox cases, a prescriber must contact the Centers for Disease Control (CDC), and submit an evaluation of the case in order to receive treatment for a patient who may potentially have this disease. Currently, TPOXX is the only FDA approved therapy for human smallpox disease and is held in the SNS.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for brincidofovir beyond routine pharmacovigilance and labeling when these NDAs were initially submitted. During the NDA review, the Applicant agreed to conduct a post-marketing requirement (PMR) and a post-marketing commitment (PMC) described as follows:

- PMR – a field study to evaluate the clinical response, drug concentrations, and safety profile of brincidofovir when used for the treatment of human smallpox disease due to variola virus infection. The trial should evaluate brincidofovir vs. standard-of-care vs. brincidofovir as an add-on-therapy to standard-of-care.
- PMC – conduct cell culture studies to characterize brincidofovir antiviral activity against recombinant orthopoxviruses (vaccinia virus or ectromelia virus) encoding specific amino acid substitutions that emerged in ectromelia virus in brincidofovir-treated animals in mouse study CMX001-VIR-044.

8 Discussion of Need for a REMS

When evaluating the need for a REMS, this reviewer, in collaboration with the clinical review team for brincidofovir, assessed factors such as the estimated size of population, seriousness of disease, expected benefit, expected duration of treatment, seriousness of known or potential adverse events and whether this drug is a NME. These factors are based on The Food and Drug Administration Amendments Act of 2007 (FDAAA), section 505-1 of the Food, Drug, and Cosmetics Act, which establishes FDA's REMS authority. Here is a summary of this reviewer's evaluation for the need of a REMS for brincidofovir:

A. Estimated size of population: The last natural smallpox outbreak was in 1949, and the last documented case was in 1977. Due to global vaccination efforts, smallpox disease was eradicated in 1980. There are only two places in the world that are approved to have the

smallpox virus for research: The Centers for Disease Control and Prevention (CDC) in the United States and the Russian State Centre for Research on Virology and Biotechnology in the Russian Federation.[3] Although there have been no reported cases in over 40 years, there is a concern that the virus may be used with criminal intent if it were obtained by terrorists. By 1972, the smallpox vaccine was no longer given routinely in the United States, and as a result, people who were born after this time period would be at risk of becoming infected. Because the disease has been deemed eradicated since 1980, the current size of the population is zero, however, if there is a bioterrorist attack with the variola virus, the population would vary, but could be massive based on the extent of the release of the virus.

B. Seriousness of the disease – Smallpox disease has a mortality rate as high as 30%, and the incubation can be several days up to two weeks before the patient exhibits symptoms. Clinical manifestations include flu-like symptoms, body aches, and pustular wide-spread body rashes and lesions in which the patient is highly contagious. Upwards of 80% of people who survive smallpox disease are left with pockmarks (deep pitted scars) on the face.

C. Expected benefit – Because of the eradication of smallpox disease, and the risk of infection just from vaccination alone, there are no human clinical trials. The efficacy of brincidofovir is based on the Animal Rule [21 CFR part 314, subpart I] for the treatment of smallpox disease in humans. The clinical review team in the DAV, Office of Infectious Diseases recommends approval of Tembexa (brincidofovir) based on the efficacy and safety information currently available.

D. Expected duration of treatment – The expected duration is to be given at two doses, spread one week apart. The recommended dose is 200mg (two 100mg tablets) orally (or 20ml orally for patients who cannot swallow) taken once weekly for 2 doses on Day 1 and Day 8. Any adverse events that the patient might experience would be limited this treatment duration.

E. Seriousness of known or potential adverse events – The adverse event profile of brincidofovir was evaluated in 392 human subjects in Phase 2 and Phase 3 randomized clinical trials. Common adverse events were elevations in hepatic transaminases, bilirubin, diarrhea and other gastrointestinal effects including nausea and diarrhea which often resolved on their own, or in the cases of gastrointestinal events, upon discontinuation. The extent of these adverse events are duration dependent. Nonclinical markers such as carcinogenicity (lower than the human brincidofovir dose) and embryofetal toxicity (at lower exposures seen in humans) have been reported with brincidofovir administration.

   There is an increased risk of mortality when brincidofovir is used for longer durations than what is currently recommended for the treatment of human smallpox disease. In a study where brincidofovir was evaluated for CMV prophylaxis, a 16% increase in mortality was seen in patients who received brincidofovir 100mg twice weekly for 14 weeks compared to 10% of patients who received placebo.[1] According to some literature resources, brincidofovir has been studied in other disease states such as adenovirius, CMV prophylaxis in allogeneic hematopoietic cell transplantation, and potentially parovirus B19; all of which require longer treatment durations.[6,7,8,9,10] The risk of increased mortality is serious and severe, and if given in other disease states where the safety and effectiveness of brincidofovir has not been established could result in an unfavorable benefit:risk profile. Given that there are primary literature sources documenting the evaluation of brincidofovir in other disease states that

would require prolonged treatment with brincidofovir, the DRM and the DAV were concerned about the potential off-label use of brincidofovir in other disease states. Over the course of this NDA review, we expressed concerns to the Applicant regarding the potentiality of off-label use in the post-market setting. DAV requested the Applicant provide details of their manufacturing and distribution plan prior to the planned action date for brincidofovir.

On February 23, 2021, the Applicant provided documentation in a follow-up to a teleconference held with members of the DAV and DRM on their manufacturing plan and distribution strategy for Tembexa. The Applicant stated the intent for Tembexa drug product in the United States is for exclusive manufacturing and delivery to the SNS, and that the Applicant has no plan or future intent to manufacture or maintain stockpiles of oral brincidofovir for use or study in other indications, nor do they have any plans to use a vendor managed inventory process for storage or deployment of Tembexa outside of the SNS.[11] On March 2, the Applicant submitted another correspondence discussing the treatment courses of Tembexa that they had at the time in preparation for possible approval. The Applicant stated that (b) (4) bottles of the suspension (10mg/ml, 65ml fill) and approximately (b) (4) four-count blister packs were in their current inventory. These were unlabeled and manufactured based on the draft labeling with a two-dose regimen for one treatment for the tablets or the suspension. The Applicant stated that they also plan to supply approximately (b) (4) additional bottles of brincidofovir suspension and approximately (b) (4) additional four-count blister packs to the SNS by the end of 2021.[12] During labeling negotiations, the Applicant agreed to having a Boxed Warning for the risk of increased mortality in longer treatment durations, as well as placing this information in the Warnings and Precautions and Limitations of Use.

F. Whether the drug is an NME – Brincidofovir is an NME but will not be the first drug approved for the treatment of human smallpox virus. Tecovirimat (TPOXX) was approved by the FDA in July 2018 for the treatment of human smallpox disease in adults and pediatric patients weighing at least 13kg. Tecovirimat appears to have a better safety profile than brincidofovir, with its primary adverse event being hypoglycemia due to a drug interaction with repaglinide. Gastrointestinal events have also been reported with tecovirimat use. However, tecovirimat's dosing requirements include twice daily dosing for 14 days compared to only once weekly for 2 weeks for brincidofovir. Furthermore, tecovirimat has a low resistance barrier, which can lead to reductions in its antiviral activity.[4] Cross-resistance between brincidofovir and tecovirimat is not expected based on their different mechanism of actions. Orthopoxvirus isolates resistant to tecovirimat have not been resistant to brincidofovir and vice versa.[1]

In summary, although smallpox is a serious disease with a high mortality rate, currently, there are no active infections for smallpox disease, as the infection has been eradicated since 1980. Brincidofovir would only be manufactured for the SNS and if needed, would be dispensed by authorities in the SNS in case of a bioterrorism attack or individual cases that meet CDC criteria for potential smallpox infections. The adverse events for brincidofovir when given for the treatment of smallpox disease are not new or unusual events and can be adequately managed in labeling. However, during the review of this application, it was noted that there are sources of information where brincidofovir has been studied in other antiviral infections. In a clinical trial program for CMV prophylaxis, there was an 16% increased risk of mortality in patients who received brincidofovir 100mg twice weekly for 14 weeks compared to 10% in the placebo arm. The risk of increased mortality is serious and severe and would provide an unfavorable benefit:risk profile if given than longer than the recommended treatment duration. The

safety and effectiveness of brincidofovir has not been established for diseases other than human smallpox disease. Because there is a risk of mortality if brincidofovir is given more than the recommended dose for human smallpox disease, and the fact that there are already studies evaluating the potential use of brincidofovir in other disease states that would include a longer treatment duration, DRM and DAV considered whether there was a need to require risk mitigation measures beyond prescribing information that would mitigate the risks of exposing a patient to increased mortality for potentially using this product in other diseases where the safety and efficacy has not been established.

The most serious concern the Agency had was uncertainty regarding the Applicant's manufacturing and distribution plan for brincidofovir, and whether there would be the ability for brincidofovir to be procured outside of the SNS for off-label use. These concerns were raised with the Applicant, who also provided documentation of their manufacturing and distribution plan, as well as the current and planned inventory that they held. The Applicant confirms that brincidofovir will only be manufactured in two-doses (as it relates to either the suspension or oral tablets) as per product labeling. The Applicant has confirmed that there are no plans to manufacture brincidofovir for other uses and will only make the product available for the SNS. Furthermore, the Applicant has agreed to maximized labeling which includes a Box Warning, Limitations of Use, as well as Warnings and Precautions that state the risk of increased mortality when used for longer treatment durations.

In addition, DRM considered how approval under the Animal Rule for brincidofovir might further mitigate the risk of increased mortality when used in longer treatment durations. Under the Animal Rule, 21 CFR Subpart I (314.610), approval is subject to three requirements:

1) **Post-marketing studies** – The Applicant must conduct post-marketing 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. Such post-marketing studies would not be feasible until an exigency arises. When such studies are feasible, the Applicant must conduct such studies with due diligence Applicants must include as part of their application a plan or approach to post-marketing study commitments in the event such studies become ethical and feasible.

   Reviewer comment: *The Applicant has agreed to perform the following post-marketing requirement and commitments:*
   - *PMR – a field study to evaluate the clinical response, drug concentrations, and safety profile of brincidofovir when used for the treatment of human smallpox disease due to variola virus infection. The trial should evaluate brincidofovir vs. standard-of-care vs. brincidofovir as an add-on-therapy to standard-of-care.*
   - *PMC – to conduct cell culture studies to characterize brincidofovir antiviral activity against recombinant orthopoxviruses (vaccinia virus or ectromelia virus) encoding specific amino acid substitutions that emerged in ectromelia virus in brincidofovir-treated animals in mouse study CMX001-VIR-044.*

2) **Approval with restrictions to ensure safe use** – If the FDA concludes that a drug product shown to be effective under this subpart can be safely used only if distribution or use is restricted, FDA will require such post-marketing restrictions as are needed to ensure safe

use of the drug product, commensurate with the specific safety concerns presented by the drug product such as:

a. Distribution restricted to certain facilities or health care practitioners with special training or experience;
b. Distribution condition on the performance of specified medical procedures, including medical follow-up; and
c. Distribution condition on specified record-keeping requirements.

Reviewer comment: *The Applicant has provided a manufacturing and procurement plan that is agreeable with the Agency. The Applicant has submitted documentation stating that brincidofovir will only be manufactured for the use of human smallpox disease, in packaging that is consistent with the two-dose regimen described in the prescribing information for both the oral tablets and suspension. Brincidofovir will only be held and dispensed by the SNS.*

3) **Information to be provided to patient recipients** - For drug products or specific indications approved under this subpart, applicants must prepare, as part of their proposed labeling, labeling to be provided to patient recipients. The patient labeling must explain that, for ethical or feasibility reasons, the drug's approval was based on efficacy studies conducted in animals alone and must give the drug's indication(s), directions for use (dosage and administration), contraindications, a description of any reasonably foreseeable risks, adverse reactions, anticipated benefits, drug interactions, and any other relevant information required by FDA at the time of approval. The patient labeling must be available with the product to be provided to patients prior to administration or dispensing of the drug product for the use approved.

Reviewer comment: *there is a Patient Information Guide that will be approved as part of the prescribing information that patients will be given with brincidofovir treatment.*

The DRM and the DAV agree that in combination with the Applicants manufacturing and distribution plan, maximized labeling, as well as conditions for approval under the Animal Rule, that any potential risk for off label use which may expose a patient to an increased risk of mortality, are mitigated by these resources, and that no other additional mitigation measures are necessary at this time. In the event of an individual case of smallpox, there is a protocol that prescribers must follow mandated by the CDC in order to get treatment from the SNS for possible smallpox cases. Brincidofovir is an NME, and while there may be more adverse events reported with brincidofovir as compared to the currently approved drug tecovirimat, the dosing frequency and duration is lower compared to tecovirimat. In addition, brincidofovir may be an option for tecovirimat-resistant cases.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile for Tembexa for the treatment of human smallpox disease in adult and pediatric patients, including neonates is favorable therefore, a REMS is not necessary for Tembexa (brincidofovir) to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

[1] Tembexa (brincidofovir) DRAFT US Prescribing Information, May 7, 2021

[2] Theves C, Biagini P, Crubezy E. The rediscovery of smallpox. Clin Microbiol Infect. 2014 Mar;20(3):210-8

[3] www.cdc.gov/smallpox accessed April 30, 2021

[4] TPOXX US Prescribing Information, 2018 https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208627s000lbl.pdf accessed April 30, 2021

[5] Chan-Tack K. Clinical review Tembexa (brincidofovir) NDA 214461 and NDA 214460. Entered in DARRTS May 10, 2021

[6] Frange P, Leruez M. Maribavir, brincidofovir and letermovir: efficacy and safety of new antiviral drugs for treating cytomegalovirus infections. *Med Mal Infect.* 2018 Dec;48(8):495-502

[7] Marty FM, et al. A randomized, double-blind, placebo-controlled phase3 trail of oral brincidofovir for cytomegalovirus prophylaxis in allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2019 Feb;25(2):369-381

[8] Sulejmani N, et al. Brincidofovir as salvage therapy for adenovirus disease in intestinal transplant recipients. *Pharmacotherapy.* 2018 April;38(4):470-475

[9] Alvarez-Cardona JJ et al. Brincidofovir: understanding its unique profile and potential role against adenovirus and other viral infections. *Future Microbiology* 2020 April;15:389-400

[10] Bua G et al. Antiviral activity of brincidofovir on parovirus B19. *Antiviral Res.* 2019Feb;162:22-29

[11] General correspondence, Chimerix Inc. Distribution Plan. Final February 23, 2021

[12] General correspondence, Chimerix Inc., Response to current treatment courses available March 2, 2021

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/s/

NAOMI S BOSTON
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DORIS A AUTH
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