CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214460Orig1s000
214461Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA # 214460
Assessment # 1

Drug Product Name	TEMBEXA (brincidofovir)
Dosage Form	suspension
Strength	10 mg/mL
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Chimerix, Inc.
US agent, if applicable	

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 001	10/7/2020	Quality
eCTD 009	12/11/2020	Quality
eCTD 010	12/18/2020	Quality
eCTD 0011	12/23/2020	Quality
eCTD 0013	1/8/2021	Quality
eCTD 0015	1/12/2021	Quality
eCTD 0018	1/27/2021	Quality
eCTD 0020	2/2/2021	Quality
eCTD 0023	2/11/2021	Quality
eCTD 0026	2/17/2021	Quality
eCTD 0028	2/25/2021	Quality
eCTD 0333	3/19/2021	Quality
eCTD 0034	3/25/2021	Quality
eCTD 0039	4/13/2021	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Raymond Frankewich	Paresma Patel
Drug Product	Peter Guerrieri	Erika Englund
Manufacturing	Steven Hertz	Yiwei Li
Microbiology	Peggy Kriger	Elizabeth Bearr

Biopharmaceutics	Gerlie Gieser	Elsbeth Chikhale
Regulatory Business Process Manager	Shamika Brooks	
Application Technical Lead	Erika Englund	
Laboratory (OTR)	NA	
Environmental	Refer to DP review	

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the NDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	IV		(b) (4)	Active	Refer to DP review	
Multiple	III	Refer to DP review				

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	67681	brincidofovir

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	NA			
Pharmacology/Toxicology		Refer to API and DP reviews concerning acceptance criteria for impurities		
CDRH	NA			
Clinical	NA			
Other	NA			

EXECUTIVE SUMMARY

For more details about the items in this template, please see the Executive Summary chapter of the NDA IQA Guide

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ). The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama on 05/11/2021.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Brincidofovir is a phosphonate ester prodrug of cidofovir. The drug product is a lemon-lime flavored oral suspension (10 mg/mL). All excipients are compendial except for the lemon-lime flavor. The product is supplied in an HDPE bottle with an LDPE press-in-bottle adaptor and a child-resistant closure. NDA 214461 for brincidofovir tablets is also currently under review. Products in both NDA 214460 and NDA 214461 are proposed to be indicated for the treatment of smallpox. These products were studied under the Animal Rule.

Proposed Indication(s) including Intended Patient Population	Treatment of smallpox in adult and pediatric patients
Duration of Treatment	Once weekly for 2 doses. The total treatment duration is 2 weeks.
Maximum Daily Dose	200 mg The recommended dose is 20 mL once weekly for patients weighing 48 kg or above, and (b) (4) (b) (4)
Alternative Methods of Administration	enteral

B. Quality Assessment Overview

Drug Substance: Adequate

Brincidofovir is the USAN for the drug substance, which is a white to off-white powder and a crystalline substance. The drug substance module 3.2.S is the same for both NDA 214460 and NDA 214461. Per

the described manufacturing process, brincidofovir is not a salt or a hydrate. The manufacturing process produces (b) (4) Refer to the Drug Product and Biopharmaceutics reviews (b) (4)

The API is manufactured using (b) (4) The manufacturing process is (b) (4)

The API is packaged (b) (4) The retest period for (b) (4) brincidofovir (NDA 214461) is (b) (4) months and for (b) (4) (b) (4) brincidofovir (NDA 214460) is (b) (4) months when stored (b) (4) (b) (4) °C.

This NDA is recommended for approval from an API perspective. For additional details refer to the review by Raymond Frankewich, Ph.D.

Drug Product: Adequate

The drug product is a lemon-lime flavored oral aqueous suspension containing 10 mg/mL of brincidofovir. The suspension is supplied in HDPE bottles, packaged with a press-in bottle adapter (PIBA) with a target fill of 65 mL. Dosing accuracy studies were performed with representative syringes provided by pharmacies and found adequate. Compatibility studies were also conducted with oral/enteral tubing sets and were found adequate.

All excipients in the formulation are compendial except for the (b) (4) Lemon-Lime flavor. DMF (b) (4) was referenced for this flavoring. Sodium benzoate is included in the formulation (b) (4) Although this excipient is included in the Inactive Ingredient Database at higher levels, pharm/tox was consulted concerning if there were any safety concerns with the level of this excipient for children between 0-3 months old. The formulation was found to be adequate.

The drug product specification and analytical methods were found to be adequate. A test for PSD was originally not included in the specification; however, due to limited batch history, the applicant agreed to add PSD

testing to the release and regulatory specifications. During manufacture of the DP, (b) (4) Based on the supporting data, adequate justification was provided to not include a test for the (b) (4) in the drug product specification. The product was also evaluated for elemental impurities. The elemental impurity level was < (b) (4) % of the PDE for each of the Class (b) (4) elements. No additional controls in the specifications were deemed necessary.

The granted shelf life is 30 months when the product is stored at USP controlled room temperature.

The applicant submitted an appropriate claim of categorical exclusion from the requirement to prepare an environmental assessment, including a statement that no extraordinary circumstances exist. This was found adequate.

This NDA is recommended for approval from a drug product perspective. For additional details, refer to the review by Peter Guerrieri, Ph.D.

Labeling: Adequate

The labeling recommendations were communicated to the OND PM.

Manufacturing: Adequate

Brincidofovir Oral Suspension, 10 mg/mL is manufactured (b) (4) (b) (4) The manufacturing process involves the following steps: (b) (4) The applicant proposed (b) (4) and provided a (b) (4) study, but the study did not evaluate PSD. The applicant committed to performing a (b) (4) study (b) (4) (b) (4) that evaluated PSD. This commitment was found adequate.

The applicant provided Executed Batch Records, and the description and controls for the manufacturing process were found adequate.

A 704a4 was performed for the drug product facility, Cambrex Whippany, Inc. After reviewing the facility's 704a4 responses, the primary manufacturing reviewer and lead ORA officer determined that the 704a4 response mitigates the need for a PAI. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama on 05/11/2021.

This NDA is recommended for approval from an OPMA perspective. For additional details, refer to the review by Steven Hertz, PE.

Biopharmaceutics: Adequate

Brincidofovir exhibits the characteristics of a BCS-4 (low solubility, low permeability) drug substance. Both drug substance solubility and drug product dissolution are pH-dependent. The proposed dissolution method and acceptance criteria (Q = (b) (4) % at 30 min) are acceptable.

The applicant did not submit a request to waive the requirement to conduct *in vivo* BA/BE studies because there is only one proposed commercial strength (10 mg/mL) of the to-be marketed drug product. This product was evaluated for clinical PK in healthy subjects. Adequate data was provided to support the bridge between the clinical/stability lots and the final proposed to-be marketed drug product.

This NDA is recommended for approval from a Biopharmaceutics perspective. For additional details, refer to the review by Gerlie Gieser, Ph.D.

Microbiology (if applicable): Adequate

The drug product is a non-sterile suspension that is filled into multi-dose bottles and sealed. The product (b) (4) supporting antimicrobial effectiveness data was found acceptable. The release specification, acceptance criteria (consistent with USP Chapter <1111>), and analytical test methods (USP <61> and <62>) were found acceptable. The risk assessment and internal method for *B. cepacia* control in the drug product specification were also found acceptable. The applicant also responded on 12/23/2020 that antimicrobial effectiveness testing will be performed on at least one primary stability batch at the proposed shelf life of 30 months. This was found acceptable

This NDA is recommended for approval from a microbiology perspective. For additional details, refer to the review by Peggy Kriger, Ph.D.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**

Assay		Low		Acceptable	
Physical State		Low	A test to monitor polymorphic form was included in the drug product specification	Acceptable	
Microbial Limits		Low	Refer to the OPQ microbiology review	Acceptable	
Dissolution		Low	The dissolution method and acceptance criteria were found acceptable	Acceptable	
Leachables		Medium	Acceptable	Test results from extractables and leachables testing were submitted	
Dosing Accuracy		Low	Acceptable	Dosing Accuracy study results were provided	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies *(Deficiencies that affect multiple sub-disciplines)*

NA

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies *(Specify discipline, such as Environmental)*

Application Technical Lead Name and Date:

APPEARS THIS WAY ON ORIGINAL

145 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	TEMBEXA	Adequate.
Established name(s)	Brincidofovir suspension	Adequate.
Route(s) of administration	For oral use	Adequate.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Oral Suspension: 10 mg/mL	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	For patients who cannot swallow, TEMBEXA oral suspension can be administered by enteral tube (naso-gastric or gastrostomy tubes) as follows: • Draw up prescribed dose with a calibrated catheter-tip syringe, and utilize this syringe to administer the dose via the enteral tube. • Refill the catheter-tip syringe with 3 mL of water, shake, and administer the contents via the enteral tube. • Flush with water before and after enteral administration.	Applicant was requested to update with a description/instructions for oral/enteral tube administration of suspension for subjects who cannot swallow tablets or suspension. The language provided was discussed with Clinical and DMEPA and is acceptable.

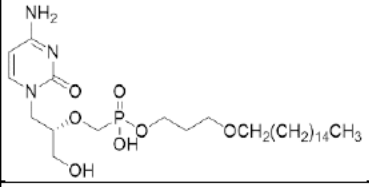
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	TEMBEXA oral suspension is an aqueous based, preserved white to off-white opaque, lemon lime flavored suspension containing 10 mg/mL of brincidofovir	Adequate.
Strength(s) in metric system	Yes.	Adequate.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	aqueous based, preserved white to off-white opaque, lemon lime flavored suspension	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2.3 Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	TEMBEXA (brincidofovir)	Adequate.
Dosage form(s) and route(s) of administration	Suspension, for oral use	Adequate.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Citric Acid Anhydrous, Microcrystalline Cellulose and Carboxymethyl Cellulose Sodium, Lemon Lime Flavor, Purified Water, Simethicone 30% Emulsion, Sodium Benzoate, Sucralose, Trisodium Citrate Anhydrous, and Xanthan Gum	Adequate.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	N/A	

Pharmacological/ therapeutic class	orthopoxvirus nucleotide analog DNA polymerase inhibitor and a lipid conjugate of the deoxynucleotide analog cidofovir and is indicated for the treatment of human smallpox disease	Adequate.
Chemical name, structural formula, molecular weight	The full chemical name is: Phosphonic acid, *P*-[[(1*S*)-2-(4-amino-2-oxo-1(2*H*)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]-, mono[3-(hexadecyloxy)propyl] ester. The molecular formula of brincidofovir is $C_{27}H_{52}N_3O_7P$ and the relative molecular mass is 561.70. The structure is shown below. 	Adequate.
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Brincidofovir is a white to off-white crystalline powder as a free acid and practically insoluble in water	Adequate.

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	

Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity”	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Oral Suspension	Adequate.
Strength(s) in metric system	10 mg/mL	Yes. Adequate.
Available units (e.g., bottles of 100 tablets)	Packaged into a high density polyethylene bottle with a low density polyethylene press-in bottle adaptor (PIBA) inserted into the bottle. The bottle is capped by a child-resistant closure. Each bottle is filled to deliver 65 mL of brincidofovir.	Adequate.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Aqueous based, preserved white to off-white opaque, lemon lime flavored suspension containing 10 mg/mL of brincidofovir (NDC 79622-012-65)	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Avoid direct contact with oral suspension. If contact with skin or mucous membranes occurs, wash thoroughly with soap and water, and rinse eyes thoroughly with water [see Warnings and Precautions (5.6)].	Adequate.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Do not freeze.	Adequate.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	
Include information about child-resistant packaging	Child-resistant closure	Adequate.

1.2.5 Other Sections of Labeling

N/A

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Cambrex Whippany, Inc. Whippany, NJ 07981	Adequate.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

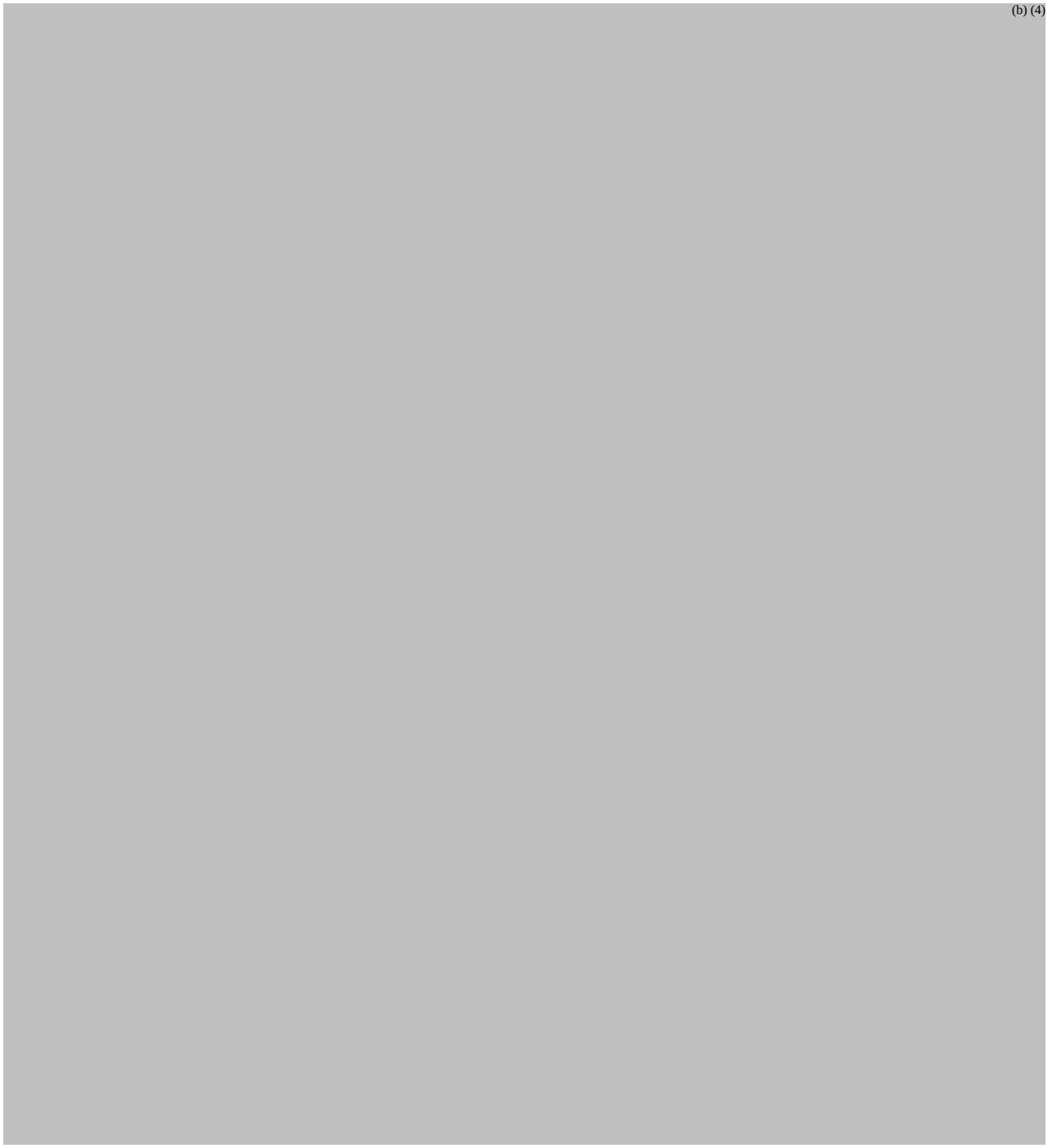
Quality-related information in the Patient Information section is consistent with the information provided above.

3.0 CARTON AND CONTAINER LABELING

The below proposed container and carton labels were submitted with SN 0042 on 04/20/2021.

3.1 Container Label

3.2 Carton Labeling


(b) (4)

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	TEMBEXA (brincidofovir)	Adequate.
Dosage strength	10 mg/mL	Adequate.
Route of administration	For oral use	Adequate.
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	65 mL	Adequate.
"Rx only" displayed on the principal display	Yes.	Adequate.
NDC number	NDC 79622-012-65	Adequate.
Lot number and expiration date	Entries with space included.	Adequate.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 85°F) [see USP Controlled Room Temperature]. Protect from freezing.	Adequate.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Yes.	Adequate.

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Cambrex Whippany, Inc., Whippany, NJ 07981	Adequate.
Medication Guide (if applicable)	N/A	
No text on Ferrule and Cap overseal	No text included.	Adequate.
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available	N/A	

Assessment of Carton and Container Labeling: *Adequate.*
The following IR was sent on 4/29/2021:
Update the excipient listing on the carton to be consistent with the recommended language in the package insert. Note that the commercial names have been removed.

ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Overall Assessment and Recommendation:

Adequate.

Primary Labeling Assessor Name and Date:

Pete Guerrieri, PhD

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Peter Guerrieri

Digitally signed by Peter Guerrieri
Date: 5/07/2021 09:43:19AM
GUID: 54eb8ba100062ea99cbaab7c64143df3

Erika Englund

Digitally signed by Erika Englund
Date: 5/06/2021 09:41:58PM
GUID: 51389ea30003450414230afb8c3e8114

23 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	NDA 214460
Assessment Cycle Number	Original NDA – 505(b)(1)
Drug Product Name/ Strength	TEMBEXA® (brincidofovir) Oral Suspension, 10 mg/mL
Route of Administration	Oral (Immediate Release)
Applicant Name	Chimerix, Inc.
Therapeutic Classification/ OND Division	Viral DNA Synthesis Inhibitor (Pro-Drug of Cidofovir)/ Division of Antivirals
Proposed Indication/ Proposed Dosage	For treatment of human smallpox disease in adult and pediatric patients: • Patients weighing ≥ 48 kg: 200 mg (20 mL suspension) once weekly on Days 1 and 8 (b) (4) Take oral suspension on an empty stomach.

*May not be the same as recommended/approved dosage

Assessment Recommendation: **Adequate**

Assessment Summary:
Brincidofovir exhibits the characteristics of a BCS-4 (low solubility, low permeability) drug substance. Both drug substance solubility and drug product dissolution are pH-dependent.

The proposed dissolution method (USP Apparatus II/paddle at 50 rpm; 900 mL of 0.05 M Sodium Phosphate Monobasic, Monohydrate Buffer, pH 6.4 + 0.05% Tween 80; 37 ± 0.5 °C; 6 mL sample volume) was previously considered adequate for the QC testing of the proposed drug product at batch release and during shelf-life/stability testing. Based on the data provided in the NDA, the proposed dissolution acceptance criterion (Q = (b) (4) % at 30 min) is acceptable.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Dissolution	Medium	BCS-IV	Low	Adequate dissolution specification

Overall, the provided *in vitro* CMC and relative *in vivo* PK data are adequate to support the bridge between the clinical/stability lots and the final proposed to-be-marketed drug product.

List of Submissions Assessed:

Submissions Reviewed	Date Received
SN-9 (Partial Response to Biopharmaceutics Information Request/IR - part 1))	12/11/20
SN-10 (Partial Response to Biopharmaceutics IR - part 2, dissolution datasets)	12/18/20
SN-15 (Response to Follow-up IR regarding (b) (4) (b) (4) XRPD diffractograms)	1/12/21
SN-23 (Complete Response to Biopharmaceutics IR – part 3, dissolution on stability data)	2/11/2021
SN-34 (Response to Quality IR- including suspension particle size)	3/25/2021

Concise Description of Outstanding Issues:

None

B.1 BCS DESIGNATION

The Applicant considers brincidofovir as a BCS-4 (low solubility, low permeability) drug substance.
Brincidofovir (BCV, previously known as CMX001) is a prodrug (lipid conjugate) of cidofovir (CDV).
The proposed drug product is a ready-to-use oral suspension.

Assessment:

Solubility: *Low*

(b) (4) brincidofovir exhibit pH-dependent solubility (i.e., insoluble to almost insoluble up to pH 6.5, then solubility increases at higher pH, being most soluble at pH 7.6/final pH 6.9) without added surfactant. (b) (4) (b) (4) Refer to the pH-solubility data and kinetic solubility profile data tables in the Quality IR Response of SN-9.

Per the Applicant, (b) (4) (b) (4)

Refer to Figure 8 and other XRPD diffractograms provided in the Quality IR Response of SN-9, as well as those provided in the Quality IR Response in SN-15.

Per the Applicant, the quality attributes of the proposed drug product were chosen (b) (4)

(b) (4)

Permeability: *Low*
In Clinical Study CMX001-127, the absolute biovailability of the brincidofovir oral suspension was reported to be low (16.8%), following a 100 mg single oral dose. In SN-9, the Applicant stated that the Caco-2 permeability of brincidofovir could not be determined because of physical incompatibility between the drug substance and Caco-2 cells.

Dissolution: *Slow without added surfactant; Rapid to Very Rapid in medium with added surfactant*
In 0.1N HCl and pH 4.5 acetate buffer without surfactant (900 mL; USP Apparatus 2 at 50 rpm; 37 ℃), NMT 5% and 9% brincidofovir dissolved within 90 minutes of drug product testing. In pH 6.4, 6.6 and 6.8 phosphate buffer media without surfactant, approximately 30%, 60% and ~100%, respectively, of brincidofovir dissolved within 90 minutes.

In the proposed dissolution medium, pH 6.4 buffer with 0.05% Tween 80 (900 mL; USP Apparatus 2 at 50 rpm; 37 ℃), the proposed to-be-marketed oral suspension drug product exhibits rapid to very rapid dissolution (>85% within 30 min).

In biorelevant media, dissolution of the proposed commercial brincidofovir oral suspension followed this rank-order: FaSSIF ≈ FeSSIF>>>FaSSGF. As shown in Table 1 and Figure 9 of the IR Response in SN-23, the suspension was very rapidly dissolving in FaSSIF and FeSSIF, and insoluble in FaSSGF.

Notes:
A formal Food-effect study was not included in the clinical pharmacology program of the proposed brincidofovir oral suspension product. Thus, per the Office of Clinical Pharmacology's recommendation, the oral suspension should be taken on an empty stomach.

Per the Applicant's Population PK report BCV-MMS-02, (and as confirmed by the Clinical Pharmacology Reviewer), concomitant use of proton pump inhibitors (a commonly used gastric pH modulator) was not found to be a

significant covariate of brincidofovir/cidofovir PK and safety parameters of interest. Refer to the Clinical Pharmacology and Pharmacometrics Review (of Drs. Timothy Bensman and Jiajun Liu) for details.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment:

DISSOLUTION METHOD: ***Adequate***

The proposed dissolution method (as tabulated below) for the QC testing of the brincidofovir oral suspension was previously deemed adequate by the Division of Biopharmaceutics; refer to the Biopharmaceutics Review of Drs. Sarah Ibrahim and Elsbeth Chikhale for IND 67681 (SN-641) finalized in DARRTS on 4/16/2020. A suspension sample volume of 6 mL was selected for dissolution testing as it represents the dose most patients would receive based on clinical study designs.

Dissolution Parameters	
Equipment	USP <711> Apparatus II (paddle)
Temperature	37.0°C ± 0.5°C
Rotation Speed	50 rpm through the first 75 minutes followed by 250 rpm for the final 15 min
Medium	0.05M Sodium Phosphate Monobasic, Monohydrate Buffer, pH 6.4 + 0.05% Tween 80
Medium Volume	900 mL
Sampling Volume	10 mL
Sampling Times	Single point: 30 min (specification) Profile: 5, 10, 15, 20, 30, 45, 60, 75, 90 (during development and in support of the NDA)

Discriminating Power

In the 4/16/2020 Biopharmaceutics Review of the dissolution method, it was stated that the proposed dissolution method was shown to be discriminating for differences (b) (4) (b) (4) For details, refer to Figure 17/Table 37 of the Dissolution Method Development Report/DMDR; Figure 17 is excerpted below.

Analytical Method Validation

HPLC with UV detection at 274 nm is used to quantify brincidofovir in the dissolution samples. The Drug Product Reviewer (Dr. Peter Guerrieri) assigned to the NDA confirmed that the analytical method validation for dissolution testing of the oral suspension is adequate.

Sink Conditions

Given that the solubility of BCV in the proposed dissolution medium (50 mM sodium phosphate buffer, pH 6.4 + 0.05% Tween 80) is 1.20 mg/mL at 37 °C, and 6.0 mL is the suspension sample volume used in dissolution testing, sink conditions are anticipated to be achieved and maintained during dissolution testing of the tablet in 900 mL of the proposed dissolution medium.

Dissolution Profiles of Brincidofovir Oral Suspension, 10 mg/mL (Process Validation Batches and Variant Lots), generated using the proposed QC dissolution method

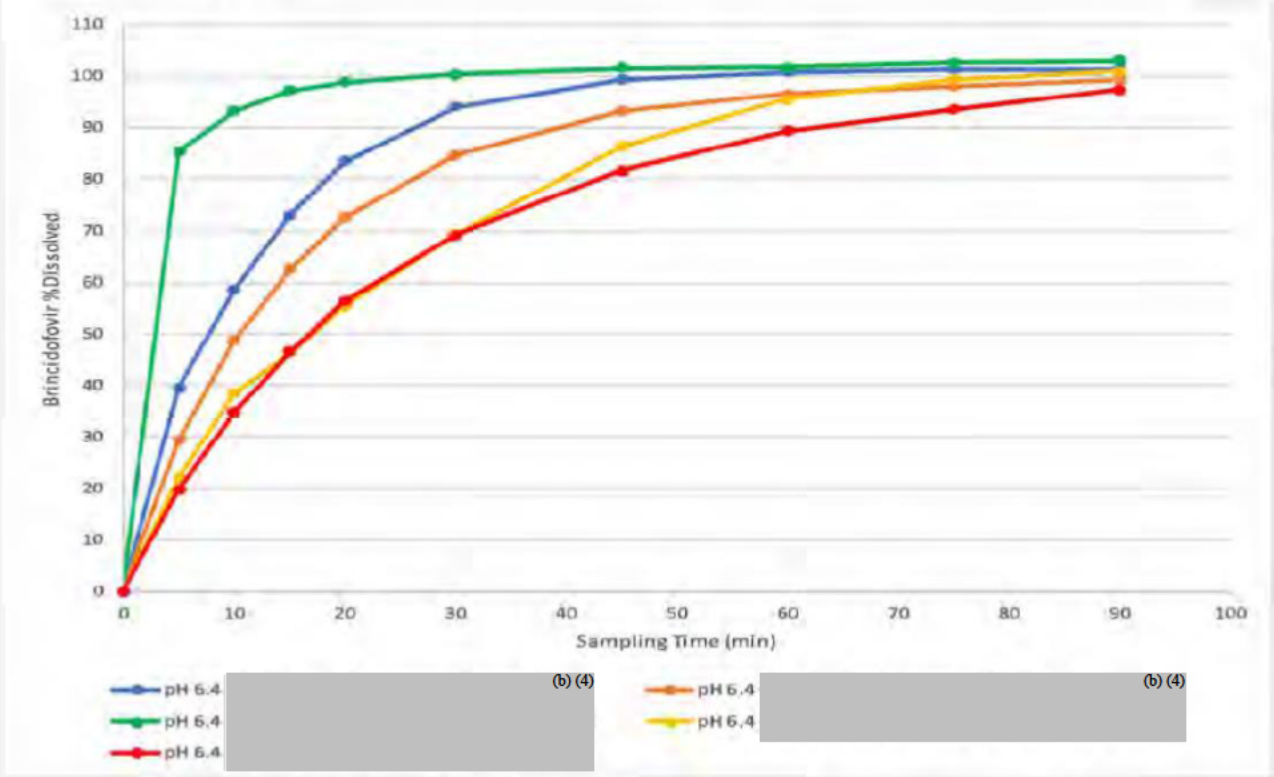


Figure 17 of the Dissolution Method Development Report

DISSOLUTION ACCEPTANCE CRITERIA: *Adequate*

Based on the dissolution profile data from batch release and during stability testing of brincidofovir oral suspension, the proposed dissolution acceptance criterion is "Q = (b) (4)% at 30 minutes". Refer to the dissolution profiles of the two process validation lots of the proposed drug product [Lots 8H12700112 ('112') and 8H12700312 ('312')] in excerpted Figure 17 above.

This Reviewer deems the proposed dissolution acceptance criterion (Q = (b) (4)% at 30 min) acceptable when considering: ***i***) the dissolution profile data of the to-be-marketed suspension formulation (i.e., Lot SB127001691; (b) (4)% at 30 min using the old/penultimate non-discriminating dissolution method) that was evaluated in Absolute BA Study 127, along with the results of the Applicant's cross-over (old/penultimate vs. final) dissolution methods bridging study, ***ii***) the sufficient capability of "Q = (b) (4)% at 30 min" to reject batches with unacceptable quality attributes including those manufactured (b) (4), and those manufactured (b) (4) (as shown in the excerpted Figure 17 above).

Additionally, this Reviewer determines that it is not necessary (b) (4)

(b) (4)

(b) (4)

Dissolution on Stability:

Using the final proposed/recommended dissolution method, dissolution on stability data are available for primary registration/process validation drug product lots starting at Month 12 and until Month 24 of long-term storage. In SN-23, the Applicant also provided the requested dissolution profile data for a new lot that was manufactured using the same formulation, process, and controls as these primary stability/process validation lots. Based on the provided dissolution profile on stability data generated exclusively by the final proposed/approved dissolution method, it appears that there are no storage-time dependent trends in dissolution, specifically when acknowledging that (b) (4) (b) (4) (b) (4) and the dissolution specification time point is at 30 minutes.

Note that an old non-discriminating method (i.e., the old/penultimate dissolution method described in Table 7 of Section 2.7.1 of the cross-referenced NDA 214461) was used to generate the dissolution profile data of the Cambrex-manufactured primary registration lots at the earlier (<Month 12) long-term stability time points. The Applicant provided the results of a cross-over (dissolution methods bridging) study which indicate that the dissolution profiles generated by the old/penultimate dissolution method and the final proposed/recommended dissolution method appear to converge at the 30-minute sampling timepoint. Thus, from (only) a dissolution (at 30 min) perspective, the Applicant's conclusion that for the finished drug product no significant trends were observed for up to 24 months at 25°C/60% RH and 6 months at 40°C/75% RH, is reasonable.

Based on 24 months of long-term (25°C/60% RH) and 6 months of accelerated (40°C/75% RH) stability data for three process validation/NDA registration/stability batches, the proposed expiration dating period for the oral suspension is 30 months when stored at USP Controlled Room Temperature, and when protected from freezing. (b) (4) (b) (4) (b) (4) The Drug Product Reviewer will determine the acceptability of the proposed expiration dating period/shelf life. It is noted that per the Drug Product Reviewer, the syringeability and nasogastric tube related studies are acceptable/adequate.

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

Assessment: *Adequate*

API particle size distribution

The proposed dissolution method produces the correct rank-order relationship with respect to input API's particle size, i.e., oral suspensions (b) (4) showed (b) (4) dissolution at 30 minutes (refer to Figure 17 of the Dissolution Method Development Report/DMDR). The dissolution at 30 minutes data in Table 7 of 3.2.P.2. Pharmaceutical Development Report/PDR demonstrate that the proposed (b) (4) API (b) (4) target and acceptance range (b) (4) are reasonable as the proposed acceptance range encompasses that measured for the clinical lot, and such range would ensure that manufactured oral suspensions exhibit (b) (4) dissolution *in vitro* similar to the reference clinical lot. Note that Lot SB57300169 (manufactured by Cambrex using API (b) (4) DS Lots 24-140828-01/01-45-01-6477 (CMX001-100) was used in Relative BA Study CMX001-124 (versus (b) (4) Lot CMX001-CTM-031). This Reviewer acknowledges that the dissolution profile data in the referenced PDR table appear to have been generated by the old/penultimate dissolution method used during early pharmaceutical development to perform QC testing of the Cambrex drug product lots; thus, refer to the discussion in the section above regarding dissolution methods bridging. *For the final determination regarding the acceptability of the Applicant's proposed* (b) (4) *API particle size QC specification, refer to the Drug Substance and Process Reviews.*

Suspension particle size distribution

The suspension particle size distribution on stability data of (Cambrex-manufactured) clinical lots (e.g., SB57300169 and SB12700169) were similar to those measured during stability testing of the (Cambrex-manufactured) primary registration/process validation and development batches. Altogether, the measured suspension particle size distribution (PSD) values of these historical batches appear within reasonably controlled ranges: d_{10} = (b) (4) µm; d_{50} = (b) (4) µm; d_{90} = (b) (4) µm, (b) (4)

(b) (4) (b) (4) In SN-39, per the Drug Product Reviewer's recommendation, the Applicant added suspension PSD (d_{10}≤ (b) (4) µm; d_{50}≤ (b) (4) µm; d_{90}≤ (b) (4) µm) to the finished product QC specifications of brincidofovir oral suspension. Also in SN-39, per the Process Reviewer's recommendation, the Applicant committed to perform (b) (4) study (b) (4) to evaluate suspension particle size distribution (PSD) based on the FDA-recommended three-tier PSD specification.

B.12 BRIDGING

Assessment: *Adequate*

Bridging to the Final Proposed To-Be-Marketed Drug Product

The FDA Clinical Pharmacology Reviewer confirmed that Clinical BE Study CMX001-124 is adequate to establish the ***PK bridge***, *i.e.,* between the final proposed to-be-marketed formulation/drug product [represented by Clinical Lot SB57300169 and the other (b) (4) clinical/stability/validation batches manufactured by Cambrex (formerly Halo Pharmaceuticals)/New Jersey] versus that used in Phase 2 or Phase 3 clinical studies involving non-orthopoxvirus infected CMV and AdV patients (Lot CMX001-CTM-031 manufactured by (b) (4); used in AdV Clinical Studies 202 and 304). Note that the proposed commercial formulation/drug product was also used in Study CMX001-127 (absolute bioavailability study involving healthy subjects; Lot SB12700169) and in terminated Study CMX001-999 (in AdV HSCTr pediatric patients; Lots SB57300269 and SB57300369). [Note also that Clinical Study CMX001-116 established bioequivalence between the (b) (4) manufactured/Phase 3 clinical suspension and the old/penultimate oral suspension formulation manufactured by (b) (4); Lot 1502022) which was used in clinical trials for pediatric patients.]

The proposed commercial drug product (as represented by the process validation/primary registration lots) will use (used) the ***drug substance source***d from (b) (4) (b) (4) Although Cambrex used (b) (4) API to manufacture suspension lots used in conducted stability/validation/clinical PK/efficacy studies, the input API (b) (4) and the suspension PSD (d_{10}, d_{50}, d_{90}) values of those Cambrex lots appear to be highly similar/matched (as shown in Tables 1 and 2 of 3.2.P.5.4, and Table 2 of 3.2.S.4). Thus, these CMC changes will be covered by the PK bridge established between the non-orthopox clinical lots and the final proposed commercial formulation/drug product.

Although the proposed commercial ***packaging configuration*** (60 mL HDPE bottle with press-in bottle adapter/PIBA and child-resistant/CR closure) is slightly different from the Phase 3 clinical/Cambrex product packaging

configuration ((b) (4) bottles with PIBA and CR closure), the Applicant reported (and the Drug Product Reviewer confirmed) that on stability testing, both proposed commercial and clinical packaging configurations were demonstrated to be capable of preventing decreases in active drug substance assay (b) (4) (over 36 months of long-term storage for the clinical product, and to date, i.e., over at least 18 months of long-term and over 6 months of accelerated storage conditions for the stability/validation batches).

B. 13 BIOWAIVER REQUEST

Assessment: *Not Applicable*

The Applicant did not submit a request to waive the requirement to conduct *in vivo* BA/BE studies because there is only one proposed commercial strength (10 mg/mL) of the to-be-marketed drug product, and such was evaluated for clinical PK in healthy subjects and non-orthopoxvirus infected (CMV/AdV) patients.

Note: Although Section 1.12.13 includes a request for waiver of *in vivo* studies according to 21 CFR 314.126 (c), such request specifically pertains to the requirement to conduct clinical efficacy (not clinical bioavailability) studies, i.e., for the human smallpox indication because such studies are neither feasible nor ethical. Thus, brincidofovir was studied for the smallpox indication under the Animal Rule (21 CFR Part 314 Subpart I). Prior to NDA submission, the Applicant committed to conduct a post-marketing requirement (PMR) field study of brincidofovir for the treatment of smallpox. Additionally, the Applicant reported that the formulations evaluated in nonclinical studies (using animal pox efficacy models) and clinical studies (involving healthy subjects or non-orthopoxvirus infected patients) both have low absolute bioavailabilities (≤17%). Per the FDA's Population PK modeling and simulation [which accounted for differences in formulation (oral solution versus oral tablets/suspension) and species (rabbit/mouse versus humans)], the intracellular (PBMC) CDV-PP exposures in humans receiving the clinical/proposed commercial oral tablet or oral suspension formulations at the FDA recommended clinical dosage are anticipated to be comparable or higher than the exposures found to be efficacious in the animalpox models; refer to the Clinical Pharmacology and Pharmacometrics Reviews for more information. *Refer also to the FDA's Pharmacology/Toxicology Review for the evaluation of the adequacy of the animalpox efficacy studies.* Overall, the FDA determined that the proposed drug product administered at the FDA recommended dosage is not anticipated to be less effective for the treatment of human smallpox than as shown in the conducted animalpox studies.

R. REGIONAL INFORMATION

Post-Approval Commitments

Assessment: *None*

Lifecycle Management Considerations

Assessment: *None*

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date: *Gerlie Gieser, Ph.D. (4/19/2021)*

Secondary Assessor Name and Date: *Elsbeth Chikhale, Ph.D. (4/19/2021)*

Gerlie Gieser

Digitally signed by Gerlie Gieser
Date: 4/19/2021 11:24:44AM
GUID: 507592ba00003d190b2ea34fe8fb8ccb

Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 4/19/2021 11:33:33AM
GUID: 50743ccc000031928b54eba1769a5df9

U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VII: MICROBIOLOGY

Product Information	505(b)(1), Rare disease, Orphan designation
NDA Number	214460
Assessment Cycle Number	1
Drug Product Name/Strength	Brincidofovir (TEMBEXA)/ 10 mg/mL
Route of Administration	Oral
Applicant Name	Chimerix, Inc.
Therapeutic Classification/ OND Division	Type 2 – new active ingredient/ OND/OID/DAV
Manufacturing Site	Cambrex Whippany, Inc., 30 North Jefferson Road, Whippany, NJ 07981
Method of Sterilization	N/A, product is non-sterile

Assessment Recommendation: **Adequate**

Assessment Summary: After compounding, the drug product suspension is filled into bottles and sealed.

List Submissions being assessed:

Document(s) Assessed	Date Received
0001 (1)	10/7/2020
0011 (11)	12/23/2020
0018 (18)	1/27/2021

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The submission was assigned to the reviewer 10/20/20 and is in the eCTD format. The 1/27/21 amendment provides a response to the CMC Information Request (IR) sent by the Agency to the sponsor on 1/19/21. The 12/23/20 amendment provides a response to the Microbiology IR sent to the sponsor on 12/9/20. Amendments dated 10/30/20 (SD 2), 11/6/20 (3), 11/17/20 (4), 12/1/20 (5), 12/7/20 (7), 12/10/20 (8), 1/7/21 (12), 1/11/21 (14), 1/15/21 (16), 1/29/21 (19), 2/5/21 (22), 2/12/21 (24), 2/16/21 (25) and 2/17/21 (26) were IR responses to Non-Clinical, Clin. Pharm. and Clinical IRs. Amendments from 12/11/20 (9), 12/18/20 (10), 1/8/21 (13), 1/12/21 (15), and 2/2/21 (20) were Quality IR responses. Updated information is also reviewed in the following amendments: administrative, 12/2/20 (6); labeling 1/19/21 (17) and 2/3/21 (21); stability 2/11/21 (23). Some tables were copied from the submission.

Concise Description of Outstanding Issues: N/A

Supporting Documents: N/A

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** Non-sterile preserved aqueous liquid suspension, pH (b) (4), filled into multi-dose bottles.

- **Drug product composition –**

Ingredient	Content (mg/mL)	Function
(b) (4) Brincidofovir	10.0	Active
Microcrystalline Cellulose and Carboxymethyl Cellulose Sodium	(b) (4)	
Xanthan Gum		
Simethicone 30% Emulsion		
Citric Acid Anhydrous		
Trisodium Citrate Anhydrous		
Sodium Benzoate		
Sucralose		
(b) (4) Lemon Lime Flavor (b) (4)		
Purified Water		

- **Description of container closure system –**
  60 mL natural colored high density polyethylene round bottle (manufactured by (b) (4)) with a 28 mm low density polyethylene press-in bottle adapter (from (b) (4)) inserted in the bottle opening. The closure is a white (b) (4) 28 mm child resistant cap with a yellow tamper evident ring closure (from (b) (4)).

Assessment: ***Adequate***

P.2 PHARMACEUTICAL DEVELOPMENT
P.2.5 MICROBIOLOGICAL ATTRIBUTES

Container/Closure and Package Integrity

Assessment: ***N/A***

(b) (4)

(b) (4)

[redacted]

Assessment: ***Adequate***

(b) (4)

[redacted]

Notes to reviewer:

(b) (4)

[redacted]

(b) (4)

P.3. MANUFACTURERS
P.3.1 MANUFACTURERS

Manufacturing:
Halo Pharmaceutical Inc., DBA Cambrex Whippany, Inc.
30 North Jefferson Road, Whippany, NJ 07981

Release and stability microbiological testing:
(b) (4)

P.5 CONTROL OF DRUG PRODUCT
P.5.1 SPECIFICATION

The product release specification includes the following tests:

Test	Test method	Acceptance criteria
Total aerobic microbial count	USP <61>	Not more than (b) (4) CFU/g
Total yeast and mold count		NMT (b) (4) CFU/g
Escherichia coli	USP <62>	Should be absent
Burkholderia cepacia complex	Internal	Should be absent
Staphylococcus aureus	USP <62>	Should be absent
Pseudomonas aeruginosa	USP <62>	Should be absent
Salmonella	USP <62>	Should be absent

(b) (4)

Test	Lot results			
	8H12700112	8H12700212	8H12700312	SB57300169
TAMC (CFU/g)	(b) (4)			
TYMC (CFU/g)				
E. coli	Absent	Absent	Absent	Absent
B. cepacia				
S. aureus				
P. aeruginosa				
Salmonella				

(b) (4)

The test results met the acceptance criteria for the executed and bioequivalence batches.

Assessment: *Adequate*

The release specification related to the microbiological tests is acceptable. The acceptance criteria for the microbial tests are consistent with USP Chapter <1111>.

P.5.2 ANALYTICAL PROCEDURES
P.5.3 VALIDATION OF ANALYTICAL PROCEDURES

Note to reviewer: In the original submission, verification of the microbiological methods related to testing according to USP Chapters <60>, <61> and <62> was not described.

The following deficiency was issued in the 12/9/20 IR:

Related to validation of the methods for release and stability testing of the subject drug product for commercial production, the following information is requested:

a) Your submission states that methods described in USP <61> will be utilized in microbial enumeration testing. Provide a description of the routine testing procedures and a summary of corresponding method suitability studies.

b) Your submission states that methods described in USP <62> will be utilized to test for the absence of Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, and Salmonella. Provide a description of the routine testing procedures and a summary of corresponding method suitability studies.

Sponsor's response (12/23/20 amendment): General routine methods for microbial enumeration and testing for specified microorganisms are provided in "quality-response-cmc.pdf", p.1-28/47. Attachments I and II, which are microbial testing flow charts, and Attachments III and IV, which indicate streamlined incubation plate types and times, as well as descriptions of microorganism results on selective agar, are also provided.

The same general information, with the facility protocol and instructions for microbial enumeration and tests for specified microorganisms, is provided in the updated document 3.2.P.5.2 "analytical-procedures.pdf", section 2.2.6, p.32-53/76. Attachments I-IV are not provided in the submission analytical method section. Additional information not used for the subject drug product, such as for transdermal patches, is included.

Method suitability information is provided in the IR response on pp.29-38.

Test procedures: According to USP <61> and <62>

Microbial enumeration testing: One batch of drug product (10 mg/mL) was diluted 1:10 and 1:50 in Tryptic Soy broth with polysorbate and lecithin. Ten mL aliquots of the dilutions were inoculated with ≤ 100 CFU/mL; one mL was then plated in duplicate. Positive and negative controls were used.
Acceptance criterion - recovery of the test organisms must be (b) (4)% when compared to the positive control.

- Total Aerobic Microbial Count (TAMC) – Five compendial microorganisms from USP <61> were tested. The Tryptic Soy Agar plates were incubated at 30-35°C for three days. The positive control results ranged from (b) (4) CFU. Triplicate studies were performed. Overall, the test sample results ranged from (b) (4) CFU, with a recovery of (b) (4)%.

- Total Yeast and Mold Count (TYMC) - Compendial microorganisms *C. albicans* and *A. brasiliensis* noted in USP <61> were tested. The Sabouraud Dextrose Agar plates were incubated at 20-25°C for five days. The positive control results were (b) (4) CFU. Triplicate studies were performed. Overall, the test sample results ranged from (b) (4) CFU, with a recovery of (b) (4)%.

The controls were satisfactory. Test results met the acceptance criterion.

Tests for specified microorganisms: For suitability testing, the equivalent of one gram of product sample was transferred to a tenfold volume of broth. For *E. coli, S. aureus,* and *P. aeruginosa*, Tryptic Soy broth containing 4% Polysorbate 20 and 0.5% Lecithin was used. For *C. albicans*, the product was diluted in Sabouraud Dextrose broth. To test for Salmonella, 1:10 and 1:50 product dilutions in TSB+PL were directly inoculated. The dilutions were inoculated with ≤ 100 CFU of microorganism. The test samples were then incubated before transfer to various selective broths and agars.
The strains, incubation times and temperatures, and selective agars used for testing were as recommended in USP <62>. Each study was performed in triplicate.
Acceptance criterion - Colonies characteristic of the specified microorganisms must be present on the selective agars to demonstrate that the recovery method is suitable.

Results: The inoculums ranged from (b) (4) CFU. The positive and negative controls were satisfactory. The test results for the five specified microorganisms met the acceptance criteria for testing at dilutions of 1:10 and 1:50.

Routine sample testing will be performed by the poured plate microbial enumeration test for TAMC and TYMC. Specified microorganisms testing uses selective media.

Assessment: *Adequate*

The microbial test methods were verified to be suitable for use with the drug product following procedures consistent with those in USP Chapters <61> and <62>.

Note to reviewer: In the original submission, the test method for *B. cepacia* was noted as USP <62>, but should be according to USP <60> if the sponsor used the USP method. See below for a deficiency regarding the method.

The following deficiency was issued in the 12/9/20 IR:

Regarding control for the presence of Burkholderia cepacia complex (BCC) in your product, you should consider the following:

a) Identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled as process controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.

Sponsor's response (12/23/20 amendment): The sponsor provides a description of the risk analysis and the document "risk-assessment.pdf", 3.2.P.5.6, dated 12/15/20. The following potential sources of contamination were discussed:

- Pharmaceutical ingredients selection
- Product formulation including robust antimicrobial preservative system
- Management of pharmaceutical water systems
- Equipment cleaning and sanitization
- Manufacturing processes
- Risk-based microbial testing programs

Risk from the ingredients and formulation is low, as most ingredients are powders, and the product is preserved. One higher risk liquid ingredient is tested upon receipt for bioburden. The water system risk is mitigated through personnel training and use of labels and PPE, cleaning and sanitization of all process equipment prior to use and routine water system testing and quality monitoring. Bioburden is monitored on process equipment and product contact surfaces. Manufacturing follows GMPs and the environment is monitored. The product release specification includes absence of objectionable microorganisms, and specifically evaluates samples for *B. cepacia* and *P. aeruginosa*. Previous testing history has indicated the absence of BCC.

Assessment: ***Adequate***

Overall, the process control strategy, including on-going water testing, and the use of preservative, will support the microbiological quality of the drug product.

b) *The release and stability specifications indicate BCC testing of the drug product according to USP <62>. USP <62> does not describe a method for testing for BCC. The USP BCC test method is USP <60>. Provide revised release and stability specifications that indicate the specific method for testing for the absence of BCC in the drug product. Reference is made to USP <60>; however, suitably validated alternative methods are also acceptable.*

Sponsor's response (12/23/20 amendment): The sponsor provides an updated release and stability specification as Table 29 in the IR response and in 3.2.P.5.1, Table 1; both tables indicate that the sponsor will use an internal method for *B. cepacia* complex release and stability testing.

Assessment: ***Adequate***

c) *Provide a summary of the BCC test method suitability/validation studies.*

Sponsor's response (12/23/20 amendment): The sponsor will use a method other than USP <60> and states that the validation information for the in-house method will be provided to the Agency by February 15, 2021.
The IR response also notes that a BCC test method is currently in use. A method validation study for the recovery of *Burkholderia cepacia* from spiked product samples is summarized in the IR response on p.37-8. The study is similar in design to the studies reviewed above for the suitability testing of other specified microorganisms. Positive and negative controls were stated to be acceptable. Details are described in the table below.

Comparison of *B. cepacia* test methods:

Test	In-house method (12/23/20 amend.)	USP <60>
Organism	*B. cepacia* ATCC 25416	*B. cepacia* ATCC 25416, *B. cenocepacia* and *B. multivorans*
Sample prep.	(b) (4)	10 mL (or suitable amount) of NLT 1 g product in a 1:10 dilution
Challenge		< 100 CFU
Sample media (preincubation)		SCD
Incubation		30-35ºC for 48-72 h
Sample media (selection)		*B. cepacia* selective agar
Incubation		30-35ºC for 48-72 h
Interpretation		Confirm colony characteristics and ID.
Colony media (further selection)		
Incubation		
Interpretation		

An additional BCC method is provided in the 12/23/20 amendment document "analytical-procedures.pdf", section 2.2.7, p.53/76.

Note to reviewer: From the 12/23/20 IR response, it was unclear which analytical method would be used for testing BCC and whether the proposed method was equivalent to the method in USP <60>. Clarification was requested.

The following deficiency was issued in the 1/19/21 IR:

Regarding the Burkholderia cepacia complex (BCC) test method validation, the use of one BCC species, Burkholderia cepacia, during recovery method validation studies is acknowledged. See 1.11 "quality-response-cmc.pdf" submitted 12/23/2020, pp. 37 and 43/47. However, considering the variability of the multiple species among BCC, it is uncertain whether the in-house testing method has a detection capability similar to USP <60>. Provide a summary of a successful validation of the proposed in-house method with additional BCC species, such as the ones identified in USP <60> (B. cenocepacia and B. multivorans). Alternatively, revise the test method for BCC to USP <60> and provide successful study results demonstrating that the USP <60> method is suitable.

Sponsor's response (1/27/21 amendment): The sponsor considers this IR response (see "quality.pdf", pp. 2-3/11) to complete the Microbiology IRs sent on 12/9/20 and 1/19/21 regarding the validation of the method for BCC testing. An updated summary "validation-of-analytical-procedures.pdf" is provided in 3.2.P.5.3, which includes method validation for BCC testing. Section 3.4.2.4.6 notes use of a previous method for testing and is not reviewed further. Section 3.5.1 states that the method for BCC testing meets the requirements in USP <60> and that suitability of the in-house method was demonstrated.

Test for specified microorganisms - *Burkholderia cepacia* complex: The presence/absence procedure is validated by confirming the recovery of the specified microorganism in the presence of the test article. For recovery method validation testing, the equivalent of one mL of product sample was transferred to a tenfold volume of (b) (4) (b) (4) The dilutions were inoculated with ≤ 100 CFU of *Burkholderia cepacia* (ATCC 25416), *B. cenocepacia* (ATCC BAA-245) and *B. multivorans* (ATCC BAA-247). The test samples were incubated at 30-35ºC for 48 hours before transfer to *Burkholderia cepacia* selective agar (BCSA) and incubation of the streaked plates at 30-35ºC for 48 hours. The strains, incubation times and temperatures, and selective agar used for testing were as recommended in USP <60>. Each study was performed in triplicate.

Acceptance criteria - Colonies characteristic of the specified microorganism must be present on selective agar to demonstrate that the recovery method is suitable.

Results: The inoculums ranged from (b) (4) CFU. The positive and negative controls were satisfactory. The test results for the three specified microorganisms met the acceptance criteria for testing at a dilution of 1:10.

For routine testing, the dilution is 1:10. The primary and enrichment diluent is (b) (4) The selective agar is BCSA. Typical growth on selective agar is submitted for microbial identification.

Assessment: *Adequate*

The sponsor performed method validation testing with three *Burkholderia* strains to account for phenotypic variation in the complex. The in-house method is similar to testing according to USP <60> and will be suitable for testing for the presence or absence of BCC.

The following deficiency was issued in the 1/19/21 IR:

The updated document "analytical-procedures.pdf" includes testing procedures for the presence or absence of Burkholderia cepacia complex (BCC). See 12/23/20 amendment, 3.2.P.5, section 2.2.7. The document outlines recovery method validation, as well as analytical testing methods, which substantially differ from the test method described in the document "quality-response-cmc.pdf" (12/23/20 amendment, pp. 37 and 43/47). For example, the method description in the document "analytical-procedures.pdf" notes Burkholderia cepacia Selective agar is used for recovery, while the document "quality-response-cmc.pdf" indicates the use of (b) (4) agar and the possible use of (b) (4) agar. Clarify the routine analytical method proposed for testing for the presence or absence of BCC during commercial production.

Sponsor's response (1/27/21 amendment): The sponsor states that the analytical method in the 12/23/20 amendment, 3.2.P.5.2, section 2.2.7 will be used for routine BCC testing. This internal method (b) (4) (b) (4) then uses *B. cepacia* selective agar plates.

Assessment: *Adequate*

P.8 STABILITY
P.8.1 STABILITY SUMMARY AND CONCLUSION

Proposed expiry: 30 months (2.3 "introduction.pdf", p.69)

Note to reviewer: Related to the original submission,

- The addition of stability testing at the proposed drug product shelf life expiration of 30 months was requested.
- The stability protocol listed the test as "Microbial Enumeration." The stability data provided in 3.2.P.8.3 and the stability specification provided in 3.2.P.5.1 included both microbial enumeration and specified microorganisms testing. Revision of the protocol was requested to include specified microorganisms testing consistent with the stability specification.
- In the 10/7/20 amendment, Table 2 of 'stability-summary.pdf' appeared to indicate that results for microbial enumeration and AET were collected for information only and that these tests were not proposed for future commercial batches. An IR was issued to request the actions to be taken should the stability batches not meet specification for these tests. Additionally, an IR was issued requesting microbial enumeration and specified organism testing for post-approval commercial batches.

The following deficiency was issued in the 12/9/20 IR:

Regarding antimicrobial effectiveness testing, address the following comments:

a) Provide a commitment to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability batch at the end of the proposed shelf life (30 months) and update Section 3.2.P.8.1, accordingly. Reference is made to ICH Q1A Stability Testing of New Drug Substances and Products.

Sponsor's response (12/23/20 amendment): Antimicrobial effectiveness testing will be performed on at least one primary stability batch at the proposed shelf life of 30 months (see 3.2.P.8.1, updated Table 2).

Assessment: ***Adequate***

b) The pre-approval stability protocol (3.2.P.8.1, 'stability-summary.pdf', p. 4, Table 2) appears to indicate that antimicrobial effectiveness test (AET) results are collected for information only. It is acknowledged that acceptable AET results have been obtained for developmental and registration batches; however, acceptable AET results have not been obtained for a stability batch stored under long-term conditions for 30 months. State the actions to be taken should at least one primary stability batch not meet the acceptance criteria for antimicrobial effectiveness at the proposed expiry of 30 months.

Sponsor's response (12/23/20 amendment): The phrase (b) (4) has been removed from the pre-approval stability protocol related to AE testing. Stability testing for AE is planned at 36, 48, and 60 months, in addition to the 30-month timepoint. If one of the registration/validation batches does not meet the

AET acceptance criteria at 30 months, the proposed shelf life will be (b) (4) months, as the AET results met the criteria at (b) (4) months.

Assessment: *Adequate*

c) *Note that if extension of expiry is requested, AET data at the proposed expiry would be requested. Acknowledge this comment in your response.*

Sponsor's response (12/23/20 amendment): The sponsor indicates that AET data at the proposed expiry will be provided to the Agency if an expiry extension is requested.

Assessment: *Adequate*

Note to reviewer: In the original submission,

- the post-approval stability microbial test schedule was not clear. Clarification was requested.
- the post-approval stability protocol indicated "Microbial limits" testing. An IR was issued to revise the protocol to include microbial enumeration and specified microorganisms testing consistent with the stability specification.

The following deficiency was issued in the 12/9/20 IR:

Regarding drug product stability testing, address the following:

a) *The pre-approval stability protocol (3.2.P.8.1, 'stability-summary.pdf', p. 4, Table 2) includes microbial enumeration testing, but does not include testing for specified microorganisms. The post-approval stability protocol (3.2.P.8.2, 'postapproval-stability.pdf', p. 1, Table 1) refers to microbial limits testing that is not defined in the stability specification. Revise the testing protocol for the pre- and post-approval stability batches to include both microbial enumeration and specified microorganisms testing, consistent with the stability specification (see 3.2.P.5.1).*

Sponsor's response (12/23/20 amendment): The updated tables are provided as Table(s) 30, 31 and 32 in the IR response. All tables consistently indicate microbial enumeration and specified microorganisms testing.

Assessment: *Adequate*

b) *The pre-approval stability protocol (3.2.P.8.1, 'stability-summary.pdf', p. 4, Table 2) appears to indicate that microbial tests are not proposed for future commercial batches. Microbial testing is requested for post-approval stability batches at the same testing time intervals as performed for the pre-approval stability batches. Confirm that you intend to perform microbial enumeration*

and specified microorganisms stability testing for post-approval commercial batches stored under long-term conditions and the tests are to be performed at the same testing timepoints indicated in the test schedule for pre-approval stability batches.

Sponsor's response (12/23/20 amendment): Microbial enumeration and specified microorganisms stability testing will be performed for pre-approval samples and post-approval commercial batches stored under long-term conditions on the same intervals in the test schedule.

Assessment: *Adequate*

c) *Commit to perform microbial enumeration and specified microorganisms testing on pre- and post-approval long-term stability batches at the end of the proposed shelf life (30 months).*

Sponsor's response (12/23/20 amendment): The sponsor commits to the testing schedule.

Assessment: *Adequate*

d) *The pre-approval stability protocol (3.2.P.8.1, 'stability-summary.pdf', p. 4, Table 2) appears to indicate that microbial test results are collected for information only. State the actions to be taken should pre- and post-approval stability batches not meet the acceptance criteria for these tests.*

Sponsor's response (12/23/20 amendment): If the acceptance criteria are not met for microbial enumeration, specified microorganisms or AE testing, all impacted batches are placed on hold until an investigation is conducted, and resolution of the issue is complete.

Assessment: *Adequate*

e) *Update Sections 3.2.P.8.1 and 3.2.P.8.2 to reflect the requested microbial and antimicrobial effectiveness tests and test schedules for stability batches.*

Sponsor's response (12/23/20 amendment): The updated tables are provided as Table(s) 30, 31 and 32 in the IR response and in Sections 3.2.P.8.1 and 3.2.P.8.2.
The revised pre- and post-approval stability tables are added to the review below.

Assessment: *Adequate*

Pre-Approval/Registration batch Stability Testing

Test	Time (months)										
	0	3	6	9	12	18	24	30	36	48	60
Microbial enumeration, specified microorganisms	X				X		X	X	X	X	X
Preservative content	X	X	X	X	X	X	X	X	X	X	X
Antimicrobial effectiveness	X				X		X	X*	X	X	X

*AET will be tested on minimally one primary stability batch at the proposed shelf life of 30 months. (3.2.P.8, 2/11/21 amendment)

Assessment: *Adequate*

P.8.2 POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

The product stability specification includes the following tests:

Test	Test method	Acceptance criteria
Total aerobic microbial count	USP <61>	Not more than (b) (4) CFU/g
Total yeast and mold count		NMT (b) (4) CFU/g
Escherichia coli	USP <62>	Should be absent
Burkholderia cepacia complex	Internal	Should be absent
Staphylococcus aureus	USP <62>	Should be absent
Pseudomonas aeruginosa	USP <62>	Should be absent
Salmonella	USP <62>	Should be absent

(b) (4)

Stability storage conditions: 25°C ± 2°C, 60% ± 5% relative humidity

Test	Time (months)							
	0	6	12	24	30*	36	48	60
Microbial enumeration, specified microorganisms	X		X	X	X	X	X	X
Preservative content	X	X	X	X	X	X	X	X
Antimicrobial effectiveness	Not planned							

*Testing at the proposed shelf life (30 months) will no longer be performed if a shelf life extension to 36 months is requested and granted post application approval.

Post Approval Stability Commitment

The applicant placed the three primary stability (full-scale) lots of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot, if available, will be added to the stability program.

Assessment: *Adequate*

P.8.3 STABILITY DATA

For packaged lot #(s) 8H12700184, 8H12700284, and 8H12700384 stored at the long term conditions and tested at the initial, 12 and 24-month points, antimicrobial effectiveness testing results complied with testing requirements. Results for TAMC and TYMC were <(b) (4) CFU/g and the specified microorganisms met the criterion of 'absent.' (b) (4)

(b) (4)

Assessment: ***Adequate***

R REGIONAL INFORMATION

Executed Batch Records

(3.2.R.1 "executed-batch-records.pdf")
Registration/stability/process validation batch #(s): 8H12700112, 8H12700212, 8H12700312; packaged lot #(s): 8H12700184, 8H12700284, 8H12700384, respectively. 60 mL HDPE bottles. Bioequivalence lot #SB57300169, used for study CMX001-124, packaged in 2 oz. PET bottles. Other lots are also listed.

Executed batch records from bulk lot #(s) SB57300100 (for #SB57300169) and 8H12700100 (for #8H12700112) are provided.

Assessment: ***Adequate***

Comparability Protocols - N/A. No CP was included in the application.

2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Prescribing Information

- Storage temperature: 20ºC – 25ºC (68ºF – 77ºF); Route of administration: oral; Container: multi-dose; Post-dilution/constitution hold time - N/A. The drug product is not diluted.

MICROBIOLOGY LIST OF DEFICIENCIES – N/A

Primary Microbiology Assessor: Peggy Kriger, Ph.D., 2/19/21
Senior Pharmaceutical Quality Assessor: Elizabeth Bearr, Ph.D., 2/19/21

Elizabeth Bearr

Digitally signed by Elizabeth Bearr
Date: 4/13/2021 02:41:49PM
GUID: 55370d1e00cfd67fc04d8bfbedbf3096

Peggy Kriger

Digitally signed by Peggy Kriger
Date: 4/13/2021 02:43:16PM
GUID: 534c169d00067f29cedbaa415df21ba2

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/

ERIKA E ENGLUND
05/11/2021 08:42:02 PM

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA # 214461
Assessment # 1

Drug Product Name	TEMBEXA (brincidofovir)
Dosage Form	Tablets
Strength	100 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Chimerix, Inc.
US agent, if applicable	

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 001	5/29/2020	Multiple
eCTD 002	06/30/2020	Multiple
eCTD 003	8/28/2020	Multiple
eCTD 005	10/17/2020	New NDA
eCTD 0013	12/15/2020	Quality
eCTD 0014	12/18/2020	Multiple
eCTD 0016	1/8/2021	Quality
eCTD 0018	1/12/2021	Quality
eCTD 0022	2/2/2021	Quality
eCTD 0027	2/17/2021	Quality
eCTD 0029	2/24/2021	Quality
eCTD 0030	2/25/2021	Quality
eCTD 0035	3/24/2021	Quality
eCTD 0037	3/29/2021	Quality
eCTD 0041	4/13/2021	Quality
eCTD 0042	4/15/2021	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Raymond Frankewich	Paresma Patel
Drug Product	Peter Guerrieri	Erika Englund
Manufacturing	Naveen Kanthamneni	Bo Jiang

Microbiology	NA	
Biopharmaceutics	Gerlie Gieser	Elsbeth Chikhale
Regulatory Business Process Manager	Shamika Brooks	
Application Technical Lead	Erika Englund	
Laboratory (OTR)	NA	
Environmental	Refer to DP review	

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the NDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
multiple	III and IV	Refer to DP review regarding referenced DMFs				

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	67681	brincidofovir

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	NA			
Pharmacology/Toxicology		Refer to API and DP reviews regarding pharm/tox input on acceptance criteria for impurities.		
CDRH	NA			
Clinical	NA			
Other	NA			

EXECUTIVE SUMMARY

For more details about the items in this template, please see the Executive Summary chapter of the NDA IQA Guide

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ). The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama on 5/6/2021.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Brincidofovir is a phosphonate ester prodrug of cidofovir. The drug product is an immediate-release 100 mg blue film coated oral tablet. It is a modified oval shape with BCV debossed on one side, and "100" debossed on the other side. All excipients were listed as compendial, other than (b) (4) *The tablets are supplied in blister packaging consisting of 4 tablets inside a child-resistant blister wallet, to be stored at room temperature.*

NDA 214460 for the oral suspension is also currently under review. Products in both NDA 214460 and NDA 214461 are proposed to be indicated for the treatment of smallpox. These were studied under the Animal Rule.

Proposed Indication(s) including Intended Patient Population	Treatment of smallpox in adult and pediatric patients
Duration of Treatment	Once weekly for 2 doses. The total treatment duration is 2 weeks
Maximum Daily Dose	200 mg The recommended dose is 2 tablets once weekly for patients weighing 48 kg or above
Alternative Methods of Administration	Refer to NDA 214460 for the description of the oral suspension. There are no alternative methods of administration for the tablets.

B. Quality Assessment Overview

Drug Substance: Adequate

Brincidofovir is the USAN for the drug substance, which is a white to off-white powder and a crystalline substance. The drug substance module 3.2.S is the same for both NDA 214460 and NDA 214461. Per the described manufacturing process, brincidofovir is not a salt or a hydrate. The manufacturing process produces (b) (4) (b) (4)

(b) (4) Refer to the Drug Product and Biopharmaceutics reviews (b) (4)

The API is manufactured using (b) (4) (b) (4) The manufacturing process is (b) (4) (b) (4)

The API is packaged (b) (4) (b) (4) The retest period for (b) (4) brincidofovir (NDA 214461) is (b) (4) months and for (b) (4) (b) (4)d brincidofovir (NDA 214460) is (b) (4) months when stored (b) (4) (b) (4) °C.

This NDA is recommended for approval from an API perspective. For additional details refer to the review by Raymond Frankewich, Ph.D.

Drug Product: Adequate

The proposed commercial drug product is a 100 mg blue film coated immediate-release tablet. All excipients are compendial except for (b) (4) (b) (4) No novel or excipients of human or animal origin are used.

As discussed above, the drug substance is manufactured (b) (4) (b) (4)

(b) (4)

The drug product release and stability specifications were found to be adequate. The Elemental Impurities Risk assessment was conducted per ICH Q3D and USP <232>. All tested elemental impurities were measured below the control threshold ((b) (4) % of the PDE). Therefore, no additional elemental impurities controls in the DP specification were considered necessary. The regulatory analytical methods and their validations were also found to be adequate.

The product was not found to be photosensitive in the photostability studies. Long-term stability results of 36 months for 2 registration batches, 24 months for a third registration batch and 60 months for supportive stability batches supported a shelf-life of 48 months when stored at USP controlled room temperature.

The applicant submitted an appropriate claim of categorical exclusion, including a statement that no extraordinary circumstances exist. This was found acceptable.

This NDA is recommended for approval from a drug product perspective. For additional details, refer to the review by Peter Guerrieri, Ph.D.

Labeling: Adequate

Labeling recommendations have been communicated to the OND PM

Manufacturing: Adequate

The drug product is manufactured (b) (4)

(b) (4)

(b) (4) The description of the manufacturing process was found adequate.

Since the product is a solid oral dosage form, OPMA evaluated the microbiological controls for the product. Microbial tests are not included in the drug product specifications at release or during stability. The product was examined for microbiological attributes at release and stability during development according to USP <61> and USP <62>, and the proposed microbiological controls were found adequate.

The facilities were found acceptable based on previous history. The Overall Manufacturing Inspection Recommendation was entered as "Approve" on 5/6/2021.

This NDA is recommended for approval from an OPMA perspective. For additional details, refer to the review by Naveen Kanthamneni, Ph.D.

Biopharmaceutics: Adequate

Brincidofovir exhibits the characteristics of a BCS-4 (low solubility, low permeability) drug substance. Both drug substance solubility and drug product dissolution are pH-dependent. The proposed dissolution method and acceptance criteria (Q = (b) (4) % at 30 min) are acceptable.

The applicant did not submit a request to waive the requirement to conduct *in vivo* BA/BE studies because there is only one proposed commercial strength (100 mg) of the to-be marketed drug product. This product was evaluated for clinical PK in healthy subjects. Adequate data was provided to support the bridge between the clinical/stability lots and the final proposed to-be marketed drug product.

This NDA is recommended for approval from a Biopharmaceutics perspective. For additional details, refer to the review by Gerlie Gieser, Ph.D.

Microbiology (if applicable): N/A

N/A. Refer to OPMA review

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay		Low		Acceptable	
Physical State		medium	The polymorphic form is (b) (4)	Acceptable	

			and monitored in the DP		
Microbial Limits		Low		Acceptable	
Content Uniformity		Low	Tablet composition is (b) (4) % API	Acceptable	
Dissolution		medium	The dissolution method and acceptance criteria were found acceptable in the biopharmaceutics review	Acceptable	
Tablet Water content		Low	Water content is included in the DP specification	Acceptable	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies *(Deficiencies that affect multiple sub-disciplines)*

None

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies *(Specify discipline, such as Environmental)*

Application Technical Lead Name and Date

APPEARS THIS WAY ON ORIGINAL

132 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	TEMBEXA	Adequate.
Established name(s)	Brincidofovir tablets	Adequate.
Route(s) of administration	For oral use	Adequate.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tablets: 100 mg	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not scored.	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	

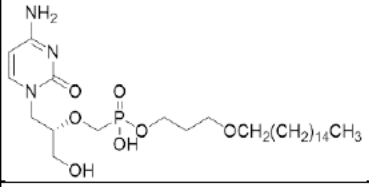
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	TEMBEXA tablets are blue, modified-oval shape, film-coated tablets debossed with BCV on one side and 100 on the other side. Each tablet contains 100 mg of brincidofovir	Adequate.
Strength(s) in metric system	Yes.	Adequate.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	blue, modified-oval shape, film-coated tablets debossed with BCV on one side and 100 on the other side.	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not scored.	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2.3 Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	TEMBEXA (brincidofovir)	Adequate.
Dosage form(s) and route(s) of administration	Tablets, for oral use	Adequate.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Colloidal Silicon Dioxide, Crospovidone, FD&C Blue #1/Brilliant Blue FCF Aluminum Lake, FD&C Blue #2/Indigo Carmine Aluminum Lake, Magnesium Stearate, Mannitol, Microcrystalline Cellulose, Polyethylene Glycol, Polyvinyl Alcohol, Purified Water, Silicified Microcrystalline Cellulose, Talc and Titanium Dioxide	Adequate.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	N/A	

Pharmacological/ therapeutic class	orthopoxvirus nucleotide analog DNA polymerase inhibitor and a lipid conjugate of the deoxynucleotide analog cidofovir and is indicated for the treatment of human smallpox disease	Adequate.
Chemical name, structural formula, molecular weight	The full chemical name is: Phosphonic acid, *P*-[[(1*S*)-2-(4-amino-2-oxo-1(2*H*)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]-, mono[3-(hexadecyloxy)propyl] ester. The molecular formula of brincidofovir is $C_{27}H_{52}N_3O_7P$ and the relative molecular mass is 561.70. The structure is shown below. 	Adequate.
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Brincidofovir is a white to off-white crystalline powder as a free acid and practically insoluble in water	

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	

Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity”	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Tablets	Adequate.
Strength(s) in metric system	100 mg	Yes. Adequate.
Available units (e.g., bottles of 100 tablets)	Packaged into blister cards. Each blister cavity contains one film-coated tablet containing 100 mg of brincidofovir. The blister card is placed in a child-resistant wallet. Each wallet (NDC 79622-010-04) contains one (1) blister card with a total of 4 film-coated tablets.	Adequate.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Tablets are blue, modified-oval shape, film-coated tablets debossed with BCV on one side and 100 on the other side. NDC 79622-010-04	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not scored.	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Do not divide, break, or crush the tablets. Avoid direct contact with broken or crushed tablets. If contact with skin or mucous membranes occurs, wash thoroughly with soap and water, and rinse eyes thoroughly with water [see Warnings and Precautions (b) (4)].	Adequate.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].	Adequate.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	
Include information about child-resistant packaging	Child-resistant wallet	Adequate.

1.2.5 Other Sections of Labeling
N/A

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Penn Pharmaceutical Services, Ltd. Tredegar, Gwent, NP22 3AA, UK	Adequate.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

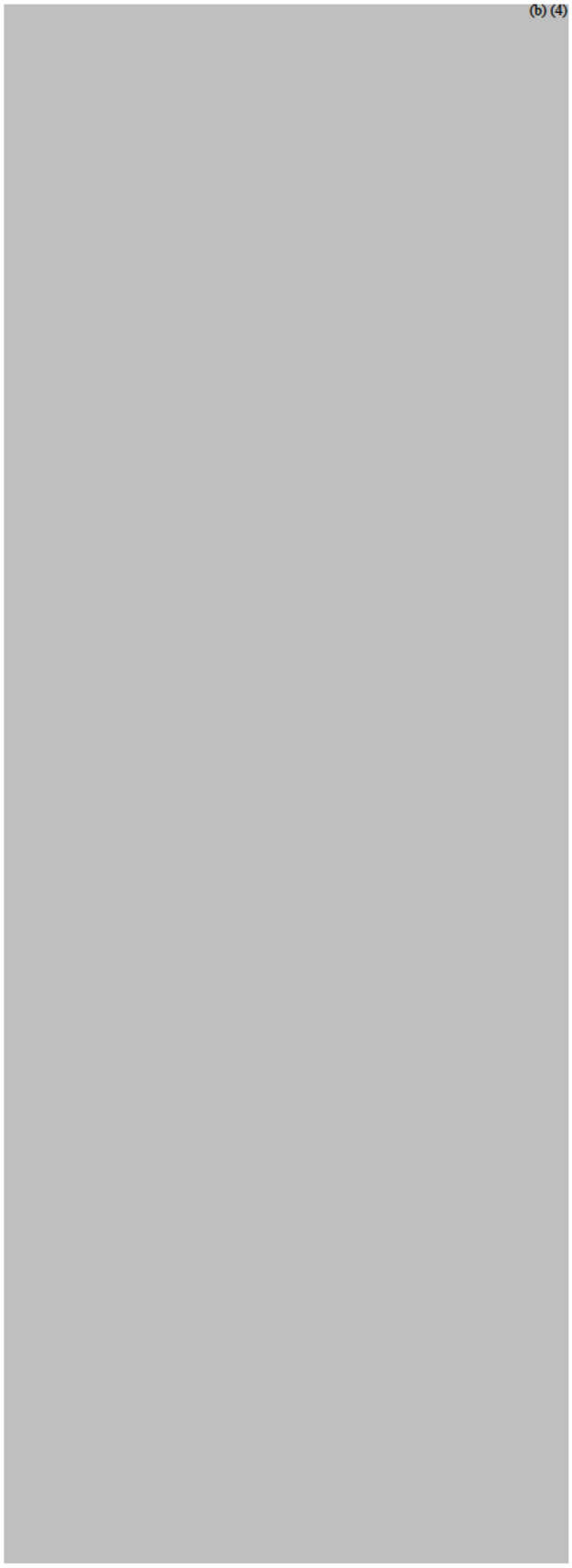
Quality-related information in the Patient Information section is consistent with the information provided above.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label
The below proposed container label was submitted with SN 0045 on 04/20/2021.

3.2 Carton Labeling

The below proposed container label was submitted with SN 0033 on 03/09/2021.



Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	TEMBEXA (brincidofovir)	Adequate.
Dosage strength	100 mg	Adequate.
Route of administration	For oral use.	Adequate.
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	4 Tablets.	Adequate.
"Rx only" displayed on the principal display	Yes.	Adequate.
NDC number	NDC 79622-010-04	
Lot number and expiration date	Entries with space included.	Adequate.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].	Adequate.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Yes.	Adequate.

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Penn Pharmaceutical Services, Ltd. Tredegar, Gwent, NP22 3AA, UK	
Medication Guide (if applicable)	N/A	
No text on Ferrule and Cap overseal	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available	N/A	

Assessment of Carton and Container Labeling: *Adequate.*

ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Overall Assessment and Recommendation:

Adequate.

Primary Labeling Assessor Name and Date:

Pete Guerrieri, PhD

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Peter Guerrieri

Digitally signed by Peter Guerrieri
Date: 5/07/2021 10:59:19AM
GUID: 54eb8ba100062ea99cbaab7c64143df3

Erika Englund

Digitally signed by Erika Englund
Date: 5/10/2021 09:18:06PM
GUID: 51389ea30003450414230afb8c3e8114

23 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	NDA 214461
Assessment Cycle Number	Original NDA – 505(b)(1)
Drug Product Name/ Strength	TEMBEXA® (brincidofovir) Tablets, 100 mg
Route of Administration	Oral (Immediate Release)
Applicant Name	Chimerix, Inc.
Therapeutic Classification/ OND Division	Viral DNA Synthesis Inhibitor (Pro-Drug of Cidofovir)/ Division of Antivirals
Proposed Indication/Proposed Dosage	For treatment of human smallpox disease in adult and pediatric patients: 200 mg (two tablets) once weekly on Days 1 and 8; Take on empty stomach or with a low-fat meal.

Assessment Recommendation: **Adequate**

Assessment Summary:
Brincidofovir exhibits the characteristics of a BCS-4 (low solubility, low permeability) drug substance. Both drug substance solubility and drug product dissolution are pH-dependent.

The proposed dissolution method [USP Apparatus I/basket at 50 rpm; 900 mL of 50 mM Sodium Phosphate Buffer, pH 6.4 + 0.3% sodium dodecyl sulfate (SDS); 37 ± 0.5 °C] was previously deemed adequate for the QC testing of the proposed drug product at batch release and during shelf-life/stability testing. Based on the data provided in the NDA, the proposed dissolution acceptance criterion (Q = (b) (4) % at 30 min) is acceptable.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Dissolution	Medium	BCS-IV	Low	Adequate dissolution specification

Overall, the provided *in vitro* CMC and relative *in vivo* PK data are adequate to support the bridge between the clinical/stability lots and the final proposed to-be-marketed drug product.

List Submissions Assessed

SN-13 (Partial Response to Biopharmaceutics Information Request/IR - part 1))	12/14/20
SN-14 (Partial Response to Biopharmaceutics IR - part 2, dissolution datasets)	12/18/20
SN-18 (Response to Follow-up IR regarding (b) (4) (b) (4) XRPD diffractograms)	1/12/21
SN-29 (Complete Response to Biopharmaceutics IR – part 3, dissolution on stability data)	2/24/2021

Concise Description of Outstanding Issues:
None

B.1 BCS DESIGNATION

The Applicant considers brincidofovir as a BCS-4 (low solubility, low permeability) drug substance.
Brincidofovir (BCV, previously known as CMX001) is a prodrug (lipid conjugate) of cidofovir (CDV).
The proposed drug product is an immediate release oral tablet.

Assessment:

Solubility: *Low*

(b) (4) brincidofovir exhibit pH-dependent solubility (i.e., insoluble to almost insoluble up to pH 6.5, then solubility increases at higher pH, being most soluble at pH 7.6/final pH 6.9) without added surfactant. (b) (4) (b) (4) Refer to the pH-solubility data and kinetic solubility profile data tables in the Quality IR Response of SN-13.

Per the Applicant, (b) (4) (b) (4) (b) (4) Refer to Figure 7 and other XRPD diffractograms provided in the Quality IR Response of SN-13, as well as those provided in the Quality IR Response in SN-18.

Permeability: *Low*
Based on the results of the relative bioavailability study of the oral tablet (versus the oral suspension/submitted under sister NDA 214460), and the Applicant's Population PK modeling, the predicted absolute bioavailability for the brincidofovir oral tablet is ~13.4%. In Clinical Study CMX001-127, the absolute biovailability of the brincidofovir oral suspension was reported to be also low (i.e., 16.8%), following a 100 mg single oral dose. In SN-13, the Applicant stated that the Caco-2 permeability of brincidofovir could not be determined because of physical incompatibility between the drug substance and Caco-2 cells.

Dissolution: *Slow to Not so Rapid without added surfactant; Rapid to Very Rapid in medium with added surfactant*
In pH 1.2 HCl and pH 4.5 acetate buffer without surfactant (900 mL; USP Apparatus 2 at 50 rpm; 37 ℃), 0% brincidofovir dissolved within 90 minutes of drug product testing. In pH 6.8 phosphate buffer without surfactant, approximately 86% and 95 - 100% brincidofovir dissolved within 15 min and 90 minutes, respectively.

In the proposed dissolution medium, pH 6.4 buffer with added surfactant (+ 0.3% SDS; 900 mL; USP Apparatus 1 at 50 rpm; 37 ℃), the proposed to-be-marketed oral tablet drug product exhibits rapid to very rapid dissolution (>85% within 30 min).

In biorelevant media, dissolution of the proposed commercial brincidofovir tablets followed this rank-order: FaSSIF>FeSSIF>>>FaSSGF. As shown in Table 1 and Figure 9 of the IR Response in SN-29, the tablets were very rapidly dissolving in FaSSIF, rapidly dissolving in FeSSIF, and insoluble in FaSSGF.

Notes:
In Food-Effect Study 114 (conducted with the (b) (4)-manufactured brincidofovir tablets used in the pivotal clinical trial), concomitant food decreased the plasma brincidofovir concentrations by 30%, without significantly affecting the intracellular cidofovir-diphosphate (CDV-PP) concentrations.

Per the Applicant's Population PK report BCV-MMS-02, (and as confirmed by the Clinical Pharmacology Reviewer), concomitant use of proton pump inhibitors (a commonly used gastric pH modulator) was not found to be a significant covariate of brincidofovir/cidofovir PK and safety parameters of interest. Refer to the Clinical Pharmacology and Pharmacometrics Review (of Drs. Timothy Bensman and Jiajun Liu) for details.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment:

DISSOLUTION METHOD: ***Adequate***

The proposed dissolution method (as tabulated below) for the QC testing of the brincidofovir oral tablet was previously deemed adequate by the Division of Biopharmaceutics; refer to the Biopharmaceutics Review of Drs. Yang Zhao and Elsbeth Chikhale for IND 67681 (SN-611) finalized in DARRTS on 10/5/2019.

Dissolution Parameters	
Equipment	USP <711> Apparatus I (Basket)
Sample Size	6 tablets
Temperature	37.0°C ± 0.5°C
Rotation Speed	50 rpm through first 75 min followed by 250 rpm for the final 15 minutes
Medium	50 mM Sodium Phosphate buffer, pH 6.4 + 0.3% sodium dodecylsulfate (SDS)
Medium Volume	900 mL
Sampling Volume	10 mL
Sampling Times	Single point: 30 min specification Profile: 5, 10, 15, 20, 30, 45, 60, 75, 90 minutes (during development and in support of the NDA)

Discriminating Power

The 10/5/2019 Biopharmaceutics Review of IND 67681 (SN-611) states that the proposed dissolution method is discriminating for differences (b) (4) (b) (4) (b) (4) refer to Figures 18 and 19 of the Dissolution Method Development Report. Note that in the Biopharmaceutics Review of IND 67681/SN-611, there was a typographical error with respect to the (b) (4) listed to prepare the pH 6.4 phosphate buffer. Additionally, this Reviewer recognizes that in tablet formulations, (b) (4) (b) (4)

This Reviewer determines that the proposed dissolution method was also able to produce the expected rank-order relationships between dissolution profiles and the following quality attributes:

(b) (4)

(b) (4)

Analytical Method Validation
HPLC with UV detection at 274 nm is used to quantify brincidofovir in the dissolution samples. The Drug Product Reviewer (Dr. Peter Guerrieri) assigned to the NDA confirmed that the analytical method validation for dissolution testing of the oral tablet is adequate.

Sink Conditions
Given that the solubility of brincidofovir in the proposed dissolution medium (50 mM sodium phosphate buffer, pH 6.4 + 0.3% SDS) is 7.96 mg/mL at 37 °C, sink conditions are anticipated to be achieved and maintained during dissolution testing of the 100 mg tablet in 900 mL of the proposed dissolution medium.

(b) (4)

DISSOLUTION ACCEPTANCE CRITERIA: *Adequate*
Based on the dissolution profile data of the development and clinical batches at batch release, the proposed dissolution acceptance criterion is "Q = (b) (4)% at 30 minutes".

To support approval of the human smallpox indication, clinical PK/safety studies in healthy subjects and clinical efficacy/safety trials involving non-orthopoxvirus (CMV and AdV) infected patients were submitted. In addition, nonclinical efficacy studies in rabbitpox and mousepox animal models were conducted because human smallpox clinical trials were considered not ethical or feasible. Thus, this Reviewer considered the dissolution profile data of brincidofovir tablet lots that performed successfully in "pivotal" CMV and AdV clinical trials for the determination of the appropriate dissolution

specification of the proposed drug product(s) intended for the treatment of human smallpox in adult and pediatric patients.

Based on the dissolution profile data of the final (b) (4) 'coated' tablet that was shown to be bioequivalent to the pivotal clinical trial formulation/product (i.e., PCI Lot # 014285, as shown in Figure 1/Table 4 on pages 30 and 31 of the Pharmaceutical Development Report/PDR; Figure 1 is excerpted below), this Reviewer determines that the proposed dissolution acceptance criterion (Q = (b) (4)% at 30 min) is justified. Additionally, the proposed dissolution acceptance criteria, 'Q = (b) (4)% at 30 min' is expected to be adequate to reject batches manufactured using (b) (4)

(b) (4)

Brincidofovir Tablets, 100 mg, Mean Dissolution of (b) (4) Clinical Tablets and PCI Clinical Tablets vs. (b) (4) Pivotal Clinical Tablets and Representing Formulation Changes/Site Transfers, generated using the proposed QC dissolution method

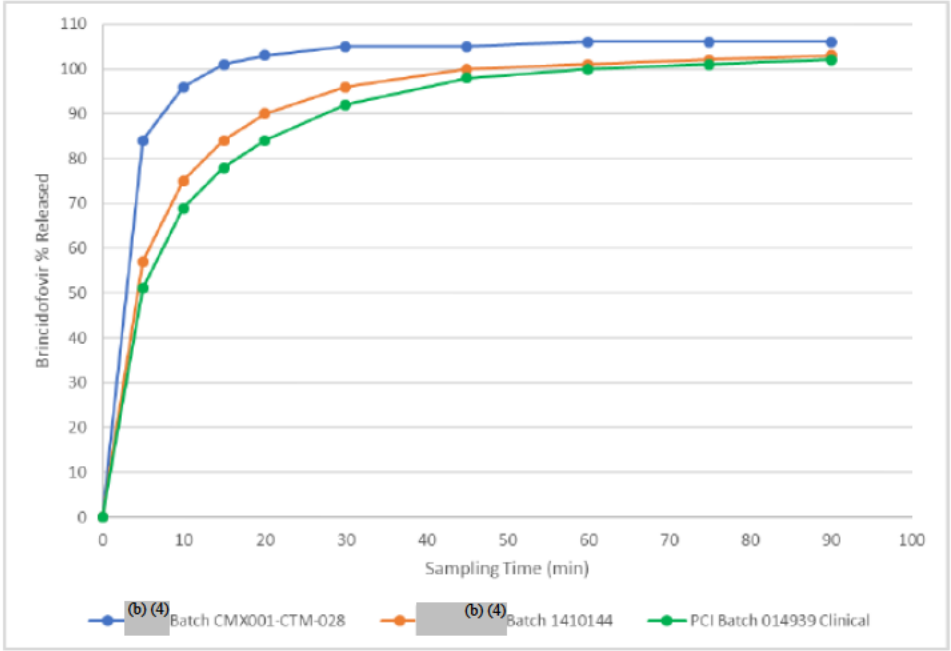


Figure 1 of the Pharmaceutical Development Report

This Reviewer does not consider (b) (4) (b) (4) necessary for the QC testing of the proposed immediate-release drug product based on the following observations: (b) (4)

(b) (4)

(b) (4)

Dissolution on Stability:
Using the final proposed/recommended dissolution method, dissolution on stability data are available for primary registration/process validation drug product lots starting at Month 15 and until Month 24 of long-term storage. In SN-29, the Applicant also provided the requested dissolution profile data for a new lot that was manufactured using the same formulation, process, and controls as these primary stability/process validation lots. Based on the provided dissolution data at 30 minutes of the stability samples, i.e., generated exclusively by the final proposed/approved dissolution method, it appears that there are no storage-time dependent trends in dissolution.

Using the old/penultimate dissolution method (pH (b) (4) buffer, (b) (4) at 50 rpm) for early stability samples and the current/new dissolution method (pH 6.4 buffer + 0.3% SDS, basket at 50 rpm) for stability samples collected after Month 12, the Applicant reported no significant changes in dissolution of the stability batches of the proposed tablet to date. In SN-29, additional crossover dissolution methods bridging data using unexpired proposed commercial formulation tablet and the expired (b) (4) tablet lots, i.e., gathered using the old/penultimate and the final proposed commercial dissolution methods, suggest comparability of the 'dissolution values at 30 minutes' generated by the old and new dissolution methods. Thus, it can be surmised that the primary registration/process validation lots conform to the proposed dissolution acceptance criterion (Q = (b) (4)% at 30 minutes), and there appears to be no dissolution on stability trend over up to 24 months of long-term storage of the drug product.

The proposed tentative expiration dating period for the proposed drug product is 48 months when stored at 15°C to 30°C, based on the 48 months long-term stability studies at 25°C/60% RH and 6 months accelerated studies at 40°C/75%RH for the supportive batches and up to 24 months long-term stability studies at 25°C/60% RH and 6 months accelerated studies at 40°C/75%RH for the primary stability/process validation batches, as well as up to 36 months of long-term and up to 6 months of accelerated stability data for the (b) (4) tablet lot. Based on the available data, the Drug Product Reviewer will recommend an expiration dating period of 36 months, with an option to extend depending on the results of the additional stability data to be submitted at a future time.

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

Assessment: *Adequate*

API particle size distribution

The proposed API particle size distribution (PSD) of the input (b) (4) drug substance raw material is d_{10}: ≤ (b) (4) µm, d_{50}: (b) (4) µm, d_{90}: ≤ (b) (4) µm. Regardless of formulation composition, drug substance manufacturer, presence/absence of coating, and other CMC differences among the developmental formulations or the oral BCV tablet evaluated in clinical studies, the API PSD data of these clinical lots including those that were demonstrated to be bioequivalent to the pivotal clinical trial formulation/product were observed to be contained within the proposed d_{10}, d_{50}, and d_{90} acceptance ranges. However, there are not sufficient complementary API PSD and dissolution profile data for PCI-manufactured clinical lots to be able to explore the adequacy of the proposed upper tolerance limits (e.g., d_{90} NMT (b) (4) µm) from a dissolution perspective. It is noted (b) (4)

(b) (4) per the Process Reviewer (Dr. Naveen Kanthamneni), the Applicant's proposed 3-tiered PSD tolerance limits for the (b) (4) API is acceptable.

API polymorphic form

In SN-13, the Applicant provided kinetic solubility profile data of brincidofovir (BCV) (b) (4)

(b) (4)

Additionally, the following considerations were factored into this Reviewer's overall assessment.

(b) (4)

1 Page has been Withheld in Full as B4 (CCI/TS) immediately following this page

B.12 BRIDGING

Assessment: *Adequate*

Bridging to the Final Proposed To-Be-Marketed Drug Product

The FDA Clinical Pharmacology Reviewer confirmed that Clinical BE Study CMX001-126 is adequate to establish the ***PK bridge***, *i.e.*, between the final proposed to-be-marketed (formulation/process) drug product [represented by Clinical/Registration Stability Bulk Lot 014285/Packaged lot 014939 manufactured by PCI (a.k.a. Penn Pharm/UK) at a smaller scale] versus that used in Phase 3 clinical studies involving non-orthopoxvirus infected CMV and AdV patients (Lot CMX001-CTM-028 manufactured by (b) (4) used in CMV Clinical Study 301 and AdV Clinical Study 304). Note that the proposed commercial formulation/drug product was also used in terminated Study CMX001-999 (in AdV HSCTr pediatric patients; Lot 015204-02). [Note also that Clinical Study CMX001-115 established bioequivalence between the (b) (4)-manufactured/Phase 3 clinical tablet and the penultimate oral tablet formulation manufactured by (b) (4) Lot 01T1410A) which was used in AdV Clinical Study 304, PK in Renal Impairment

Study 118, and terminated Phase 3 CMV Study 307, as well as supportive stability studies.]

The proposed commercial drug product (as represented by Clinical/Stability Lot 014285) will use (used) the ***drug substance source***d from (b) (4) Additionally, the proposed commercial drug product has the same ***appearance*** (shape/color/coating/debossing letters) as the registration stability lots.

The proposed commercial/primary registration ***packaging configuration*** (4-count blister in a child-resistant/CR cardboard wallet) is different from that used to package the AdV clinical trial product (b) (4) (b) (4) but is similar to that used for the Phase 3 CMV clinical trial/supportive stability product ((b) (4) blister in a CR wallet card). Per the Applicant, the assay and impurities on stability profiles of both the primary registration and the supportive registration lots did not significantly change during at least 18 months of long-term and up to 6 months of accelerated stability storage.

B. 13 BIOWAIVER REQUEST

Assessment: *Not Applicable*

The Applicant did not submit a request to waive the requirement to conduct *in vivo* BA/BE studies because there is only one proposed commercial strength (100 mg) of the proposed to-be-marketed drug product, and the proposed product was evaluated for clinical PK in healthy subjects and non-orthopoxvirus infected (CMV/AdV) patients.

Note: Although Section 1.12.13 includes a request for waiver of *in vivo* studies according to 21 CFR 314.126 (c), such request specifically pertains to the requirement to conduct clinical efficacy (not clinical bioavailability) studies, i.e., for the human smallpox indication because such studies are neither feasible nor ethical. Thus, brincidofovir was studied for the smallpox indication under the Animal Rule (21 CFR Part 314 Subpart I). Prior to NDA submission, the Applicant committed to conduct a post-marketing requirement (PMR) field study of brincidofovir for the treatment of smallpox. Additionally, the Applicant reported that the formulations evaluated in nonclinical studies (using animal pox efficacy models) and clinical studies (involving healthy subjects or non-orthopoxvirus infected patients) have low absolute bioavailabilities (≤17%). Per the FDA's Population PK modeling and simulation [which accounted for differences in formulation (oral solution versus oral tablets/suspension) and species (rabbit/mouse versus humans)], the intracellular (PBMC) CDV-PP exposures in humans receiving the clinical/proposed commercial oral tablet or oral suspension formulations at the FDA recommended clinical dosage are anticipated to be comparable or higher than the exposures found to be efficacious in the animalpox models; refer to the Clinical Pharmacology and Pharmacometrics Reviews for more information. *Refer also to the FDA's*

Pharmacology/Toxicology Review for the evaluation of the adequacy of the animalpox efficacy studies. Overall, the FDA determined that the proposed drug product administered at the FDA recommended dosage is not anticipated to be less effective for the treatment of human smallpox than as shown in the conducted animalpox studies.

R. REGIONAL INFORMATION

Post-Approval Commitments

None

Lifecycle Management Considerations

None

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date: Gerlie Gieser, Ph.D. (4/19/2021)

Secondary Assessor Name and Date: Elsbeth Chikhale, Ph.D. (4/19/2021):

Gerlie Gieser

Digitally signed by Gerlie Gieser
Date: 4/19/2021 11:26:19AM
GUID: 507592ba00003d190b2ea34fe8fb8ccb

Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 4/19/2021 11:43:17AM
GUID: 50743ccc000031928b54eba1769a5df9

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/

ERIKA E ENGLUND
05/10/2021 09:33:28 PM