CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214518Orig1s000

OTHER REVIEW(S)

Division of Antivirals

REGULATORY PROJECT MANAGER LABELING REVIEW

Applications: NDA 208627/S-007
NDA 214518

Name of Drug: TPOXX (tecovirimat) 200 mg capsules, for oral use
TPOXX (tecovririmat) 200 mg injection for intravenous use

Applicant: SIGA Technologies, Inc

Labeling Reviewed

Submission Date: May 17, 2022

Receipt Date: May 17, 2022

Background and Summary Description:

On April 30, 2021, SIGA Technologies, Inc submitted New Drug Application (NDA), NDA 214518 for TPOXX (tecovirimat) 200 mg injection. This new NDA allows for the administration of tecovirimat injection for intravenous use in pediatric patients weighing at least 3 kg and adults who are unable to take oral tecovirimat. Dosing for this new patient population was supported by clinical pharmacology study reports of two phase 1 clinical studies that evaluated the IV tecovirimat formulation in healthy subjects: Study SIGA-246-IV-202 (Single dose comparative bioavailability (200 mg IV vs. 600 mg oral) and multiple dose PK study (240 mg IV BID for 7 days) and Study SIGA-246-IV-201 (Single ascending dose PK study, dose range: 37.5 -200 mg). In addition, population PK analyses reports were submitted to support the proposed tecovirimat IV regimen.

Additionally, on April 18, 2022, SIGA Technologies, Inc submitted a supplemental New Drug Application (sNDA) efficacy supplement to NDA 208627 for TPOXX (tecovirimat) oral capsule. This efficacy supplement was submitted to update the labeling with this pharmacokinetic data that will support the new dosage form, TPOXX (tecovirimat) injection for use in adults and pediatric patients weighing at least 3 kg who are unable to tolerate oral dosing. As both formulations share one label, on May 17, 2022, the Sponsor submitted revised labels to NDA 214518 and NDA 208627/S-007 to ensure alignment across the oral and IV formulation of TPOXX.

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Review

General Changes: Throughout the labeling, formatting changes were made such as spacing, edits in the titles of subheadings, renumbering of tables and grammatical edits. Additionally, for each recent major change (RMC) listed in the HIGHLIGHTS, the modified text in the FULL PRESCRIBING INFORMATION was marked with a vertical line on the left edge.

HIGHLIGHTS OF PRESCRIBING INFORMATION

- TPOXX (tecovirimat) injection for intravenous use was added to the reflect the new dosage form.

RECENT MAJOR CHANGES (RMC)

Under Recent Major Changes the following changes were noted:

- Indications and Usage (1.1)
- Dosage and Administration (2.1, 2.2, 2.3, 2.4, 2.5)
- Contraindications (4)
- Warnings and Precautions (5.2)

Note:

- Previous RMC changes made in November 2021 under S-006 are now summarized concisely under Dosage and Administration.

INDICATIONS AND USAGE

- Indication statement for the TPOXX was revised from 13 kg to now reflect dosing down to adults and pediatric patients weighing at least 3 kg

DOSAGE AND ADMINISTRATION

This section was revised into three categories of dosing recommendations for patient populations based on their weight (kg and those who cannot swallow capsules. In addition, the dosing frequencies for TPOXX oral dosing was revised (please see below)

- Pediatric and Adult Patients weighing 40 kg or more (2.3) (Oral Dosing):
    - Dosing frequency changed from twice daily to now every 12 hours and from three times daily to every 8 hours
- Pediatrics and adult patients weighing 13 kg or more and those who cannot swallow capsules (2.3) (Oral Dosing):
    - Dosing frequency changed from twice daily to now every 12 hours and from three times daily to every 8 hours
    - Additional examples provided to describe moderate or high-fat meal
- Patients weighing 3 kg and above (2.5) (Intravenous Dosing):

DOSAGE FORMS AND STRENGTHS

Intravenous dosage formulation added in this section

- A single-dose vial containing 200 mg of tecovirimat in 20 mL for further dilution prior to intravenous infusion. (3)

CONTRAINDICATIONS

The following statement was added:

- TPOXX injection: TPOXX Injection is contraindicated in patients with severe renal impairment (defined as creatinine clearance below 30 mL/min) (4,5.2)

ADVERSE REACTIONS

This section was revised as follows:

- TPOXX Capsules (incidence ≥ 2%): headache, nausea, abdominal pain, and vomiting. (6.1)
- TPOXX Injection (incidence ≥ 4%): administration site reactions and headache. (6.1)

USE IN SPECIFIC POPULATIONS

This is a new heading in Highlights with the following language added:

- Lactation: Breastfeeding is not recommended in patients with smallpox. (8.2)

Revision Date

Date has been revised and will be updated to reflect when action is taken

FULL PRESCRIBING INFORMATION: Contents*

New subsections added are:

DOSAGE AND ADMINISTRATION

- 2.4 – Renal Impairment
- 2.5 – Dosage and Administration of TPOXX Injection for Intravenous Infusion

WARNINGS AND PRECAUTIONS

- 5.2 - Risks of Hydroxypropyl-β-Cyclodextrin Excipient for Patients with Renal Insufficiency and Pediatric Patients < 2 Years of age

FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

1.1 Treatment of Human Smallpox Disease

Dosing modified from 13kg to reflect dosing down to adults and pediatric patients weighing at least 3 kg

DOSAGE AND ADMINISTRATION

2.1 Important Dosing Instructions

Subheading title was changed and language added to provide dosing and administration instructions based on the indication for oral capsules vs intravenous (IV) infusion and timing of missed oral TPOXX dose

2.2 Testing Before Initiating and During Treatment with TPOXX Injection

	Subheading title was changed and language added on monitoring creatinine clearance prior to starting and during TPOXX injection **2.3 TPOXX Oral Dosage for Pediatric Patients Weighing at Least 13 Kg and Adults** Subheading title was changed and dosing table 2 on recommended oral TPOXX capsules in pediatric patients weighing at least 13 kg and adults renumbered. Additional edits made to dosing frequency and drug food preparation for patients who cannot swall capsules **2.4 Renal Impairment** New subsection added to indicate that TPOXX injection is contraindicated in patients with creatinine clearance below 30 mL per minute **2.5 DOSAGE and Administration of TPOXX Injection for Intravenous Infusion** New subsection and Table added to provide dosing and administration information for the new formulation, TPOXX injection
3	**DOSAGE FORMS AND STRENGTHS** Additional information added for TPOXX injection
4	**CONTRAINDICATIONS** New contraindication information added for TPOXX injection as it relates to the excipient hydroxypropyl-β-cyclodextrin
5	**WARNINGS AND PRECAUTIONS** **5.2 Risks of Hydroxypropyl-β-Cyclodextrin Excipient for Patients with Renal Insufficiency and Pediatric Patients < 2 Years of age** New subsection added to provide information on the risk of the excipient hydroxypropyl-β-cyclodextrin with TPOXX injection in patients with renal insufficiency and pediatric patients less than 2 years of age
6	**ADVERSE REACTIONS** **6.1 Clinical Trials Experience** Edits made include: o New heading titled “TPOXX Clinical Trial (Oral Administration) along with edits to Table 3 in the title. o New heading titled “TPOXX Clinical Trial (Intravenous Administration) with the addition of adverse reaction data of TPOXX injection data from the Phase 1 clinical studies, Study SIGA-246-IV- 202 and Study SIGA-246-IV-201 along with a new Table on Treatment- Related Adverse Reactions
7	**DRUG INTERACTIONS** Table renumbering noted
8	**USE IN SPECIFIC POPULATIONS** **8.1 Pregnancy** Edits and additional language added in the Risk Summary section **8.2 Lactation** Additional language added describing the potential for variola virus

	transmission through direct contact with the breastfed infant and that breastfeeding is not recommended in patients with smallpox.
8.3	**Females and Males of Reproductive Potential** Language revised to remove “female and male reproductive potential” and add “human fertility”
8.4	**Pediatric Use** New section added “TPOXX Injection” describing the limited data on the use of hydroxypropyl-β-cyclodextrin, an ingredient in TPOXX injection, in pediatric patients less than 2 years of age and the potential for drug accumulation in this population
8.6	**Renal Impairment** New section added “TPOXX Injection” describing hydroxypropyl-β-cyclodextrin, an ingredient in TPOXX injection and warnings based on the level or renal impairment due to creatinine clearance.
11	**DESCRIPTION** Additional language added to describe new formulation, TPOXX (tecovirimat) injection
12	**CLINICAL PHARMACOLOGY**
	This section was revised with updated pharmacokinetic information from healthy adults based on results from the two Phase 1 clinical studies, Study SIGA-246-IV-202 and Study SIGA-246-IV-201 SIGA-246-022 and Table 6 which summarizes the pharmacokinetic properties of Tecovrimat. In addition, information on the elimination of Hydroxypropyl-β-cyclodextrin through glomerular filtration was added in this section.
16	**HOW SUPPLIED/STORAGE AND HANDLING** Additional information was added to describe how the new formulation, TPOXX injection is supplied and stored and handled.
17	**PATIENT COUNSELING INFORMATION** This section was revised to provide information on the following: Important Dosage and Administration Information for oral TPOXX Information on Hydroxypropyl-β-cyclodextrin, a required component of TPOXX injection and warnings based on the level or renal impairment due to creatinine clearance.
PATIENT INFORMATION	
	Patient information was also revised as follows: o New patient information for the new dosage form, TPOXX injection for intravenous use. This new information was added to ensure alignment with the USPI o New language was also added to clarify the dosing intervals for TPOXX capsules that should be used by adults and children who weigh at least 7 pounds (3 kg)
INSTRUCTIONS FOR USE	

	Instructions for use was updated to align with changes in the USPI. This includes edits to the oral dosing frequency located in the TPOXX Dosing Table (Figure A)
	Please Note: The Sponsor indicated that they do not intend to dispense the IFU with TPOXX injection. As a result it was not included in the approval letter for NDA 214518.

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The changes as proposed in the new drug application (NDA 214518) and efficacy supplement (NDA 208627/S-007) are acceptable.

Andrew Gentles	5/17/2022
Regulatory Project Manager	Date
Karen Winestock	5/18/2022
Chief, Project Management Staff	Date

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/s/

ANDREW A GENTLES
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KAREN D WINESTOCK
05/18/2022 04:14:57 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 9, 2022
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 214518
Product Name and Strength:	Tpoxx (tecovirimat) injection, 200 mg/20 mL (10 mg/mL)
Applicant/Sponsor Name:	Siga Technologies (SIGA)
OSE RCM #:	2021-895-1
DMEPA 1 Safety Evaluator:	Melina Fanari, RPh
DMEPA 1 Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on March 2, 2022 for Tpoxx (tecovirimat) injection, 200 mg/20 mL (10 mg/mL).The Division of Antivirals (DAV) requested that we review the revised container label and carton labeling for Tpoxx (tecovirimat) injection, 200 mg/20 mL (10 mg/mL) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations with the exception of our recommendations related to the product expiration date and the drug supply chair security act (DSCSA). We note that the Applicant requested labeling exception for expiration date and for (DSCSA) because Tpoxx injection is for the strategic national stockpile. We have no additional recommendations at this time.

[a] Fanari, M. Label and Labeling Review for Tpoxx (tecovirimat) injection, 200 mg/20 mL (10 mg/mL) (NDA 214518). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 SEPT 28. RCM No.: 2021-895.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MARCH 2, 2022

Container labels

Carton labeling

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/s/

MELINA N FANARI
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SEVAN H KOLEJIAN
03/09/2022 12:27:40 PM

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

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

Memorandum

Date: 3/3/2022

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

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

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for TPOXX (tecovirimat) injection for intravenous use

NDA: 214518

In response to DAV's consult request dated May 14, 2021, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for TPOXX (tecovirimat) injection for intravenous use.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAV on February 17, 2022 and are provided below.

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

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

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/s/

NIMA OSSAREH
03/03/2022 11:49:04 AM

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

PATIENT LABELING REVIEW

Date:	March 2, 2022
To:	Andrew Gentles, PharmD Regulatory Project Manager **Division of Antivirals (DAV)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nima Ossareh, PharmD, RAC Regulatory review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	TPOXX (tecovirimat)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	NDA 214518
Applicant:	SIGA Technologies, Inc.

1 INTRODUCTION

On April 30, 2021, SIGA Technologies, Inc., submitted for the Agency's review an original New Drug Application (NDA) 214518 for TPOXX (tecovirimat) injection, for intravenous use. The proposed indication is for the treatment of human smallpox disease caused by variola virus in adults and pediatric patients.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antivirals (DAV) on May 14, 2021 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for TPOXX (tecovirimat) injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft TPOXX (tecovirimat) injection, PPI and IFU received on April 30, 2021, and received by DMPP and OPDP on February 17, 2022.
- Draft TPOXX (tecovirimat) injection, Prescribing Information (PI) received on April 30, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 17, 2022.
- TPOXX (tecovirimat) capsules DMPP PPI and IFU review dated June 07, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and the target reading level is at or below an 8th grade level.

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

In our collaborative review of the PPI and we:

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

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
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NIMA OSSAREH
03/02/2022 03:48:23 PM

BARBARA A FULLER
03/02/2022 04:01:18 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: 11/22/2021 **Date consulted:** 5/14/2021

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

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

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

To: Division of Antivirals (DAV)

Drug: TPOXX (tecovirimat) injection

NDA: 214518

Applicant: SIGA Technologies Inc

Subject: New NDA

Proposed Indication: For the treatment of human smallpox disease caused by variola virus in adults and pediatric patients.

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 214518
- DAV consult form for DPMH, DARRTS Reference ID 4795526

- DPMH review of Tembexa by Wenjie Sun, MD on March 12, 2020, DARRTS Reference ID 4761093[1]

Consult Question:

- DAV is seeking assistance from DPMH in revising subsections 8 of the draft USPI.

INTRODUCTION AND BACKGROUND

On April 30, 2021, the applicant (SIGA Technologies, Inc) submitted a new original NDA 214518 for tecovirimat injection for approval. The Division of Antivirals (DAV) consulted the Division of Pediatric and Maternal Health (DPMH) on May 14, 2021, to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- Tecovirimat capsules, NDA 208627, was initially approved in the U.S. on July 13, 2018 for the treatment of human smallpox disease in adults and pediatric patients.
- On April 30, 2021, the applicant submitted an NDA for TPOXX injection with the proposed indication for the treatment of human smallpox disease in adult and pediatric patients in accordance with 21 CFR Part 314.600 through 314.650 (Animal Rule). The applicant is relying on Tpoxx capsule, NDA 208627, as the listed drug relied upon.
- On November 1, 2012, tecovirimat was granted Fast Track Designation, which allows a rolling NDA submission.
- Tecovirimat has obtained orphan drug designation for the following:
    - 06-2335 Post Exposure Prophylaxis against smallpox
    - 06-2298 Treatment of Smallpox
    - 10-3162 Treatment of Orthopoxvirus Infections
- Upon submission the applicant also requested Priority Review since smallpox is a serious and life-threatening condition and, if approved, Tpoxx injection would represent the only intravenous drug to treat smallpox.
- On May 14, 2021, DAV consulted DPMH to assist with updating the Pregnancy and Lactation subsections of tecovirimat labeling.

Drug Characteristics[2]

Drug Class	Antiviral-variola virus
Mechanism of action	Tecovirimat targets and inhibits the activity of the orthopoxvirus VP37 protein (encoded by and highly conserved in all members of the orthopoxvirus genus) and blocks its interaction with cellular Rab9 GTPase and TIP47, which prevents the formation of egress competent enveloped virions necessary for cell to cell and long-range dissemination of virus.
Dose and Administration[3]	• 200 mg every 12 hours by intravenous (IV) infusion over 6 hours up to 14 days (with the option to switch to TPOXX Capsules 600mg every 12 hours to complete the treatment course) • 600 mg (3 x 200 mg capsules) orally every 12 hours

[1] The Tembaxa review was part of the materials reviewed for smallpox background information only but was not a source relied upon for the labeling recommendations below.
[2] Based on the approved TPOXX Labeling and discussion with DAV Clinical, Pharmacology Toxicology, and Clinical Pharmacology Review Team.
[3] Based on discussion with DAV Clinical Pharmacology Review Team.

	Pediatric Patients (IV Dosing): The dosage of TPOXX Injection for pediatric patients should be determined by weight: (b) (4)
Metabolism[3]	Hydrolysis, UGT1A1d, UGT1A4 for the 600mg oral dose
Molecular weight	394.35 Dalton
Half life[3]	(b) (4) hours for the 200mg intravenous dose hours for the 600mg oral dose
Protein Binding	77-82%
Bioavailability	100% for the intravenous dose

Tecovirimat injection contains 200mg of tecovirimat in 20 mL of hydroxypropyl β-cyclodextrin[4] (HP-β-CD), hydroxypropyl betadex, and water for injection. IV tecovirimat contains 40% w/v (weight of solution in total volume of solution) of HP- β -CD.

The amount of excipient HP-β-CD (8g of HP-β-CD per 200mg tecovirimat/20 ml solution, 16g per day according to proposed dosing) exceeds the approved formulation concentration for other IV products listed in the FDA Inactive Ingredient Search for Approved Drug Products (1333mg per day or 20% w/v[5]). The Sponsor notes the amount HP-β-CD in the proposed maximum recommended human daily dose (MRHD) for IV tecovirimat is the same as the FDA approved product, Sporanox (itraconazole) injection, NDA 020966, which was discontinued not for reasons of safety. Although Sporanox contained an equal amount of HP-β-CD as IV tecovirimat, Sporanox was not recommended for use during pregnancy secondary to the teratogenic effects of itraconazole found in animal reproduction studies. Sporanox was also not recommended to be used during lactation to reduce the potential transmission of HIV in the indicated population.

Although the oral HP-β-CD is considered Generally Regarded as Safe (GRAS), there are concerns regarding the safety of IV HP-β-CD. IV HP-β-CD is not recommended in patients with severe renal impairment because HP-β-CD is eliminated through glomerular filtration and clearance of HP-β-CD is reduced in patients with renal impairment resulting in accumulation of HP-β-CD until steady state is reached. Regarding the pediatric population, the European Medicines Agency (EMA) notes that "Because of their lower renal function, children less than 2 years old may theoretically be less vulnerable to renal toxicity (due to HP-β-CD), whereas it is likely to lead to higher blood levels (slower elimination) … The major concern in children under 2 is the risk of osmotic nephrosis, because they have a lower renal function than adults … leading to an increase in extra-renal adverse effects." Based on a threshold of 20mg/kg/day of HP-β-CD, the EMA concludes that "there is insufficient information on the effects of

[4] Cyclodextrins (CDs) are cyclic oligosaccharides. Cyclodextrins are made up of six, seven or eight dextrose units, including α-, β, and γ-CDs.
[5] See "hydroxypropyl betadex" intravenous in the FDA Inactive Ingredient Search for Approved Drug Products. https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm?event=BasicSearch.page Accessed 8/19/21.

cyclodextrins in children <2 years old. Therefore, a case-by-case judgement should be made regarding the risk/benefit for the patient."[6]

Reviewer comment:
Although there is a concern regarding the use of HP-β-CD in children due to immaturity of the renal system, this does not apply to an unborn fetus where the placenta functions as the renal system and eliminates wastes.

Serious Adverse Reaction
Serious adverse reactions of tecovirimat injection includes hypoglycemia with coadministration with repaglinide. This was confirmed in discussion with the DAV Clinical Pharmacology and the Clinical Review Team.

REVIEW
PREGNANCY
Smallpox and Pregnancy[7]
Variola virus is the causative agent of smallpox, a highly infectious disease characterized by fever, rash, and a high mortality rate. In 1979, the global eradication of smallpox was announced.[8] Although there have been no reported cases since eradication, continued interest in this virus remains because of the concern regarding smallpox as a potential agent of bioterrorism.

- Smallpox occurred in two forms caused by different strains: variola major, which was a serious illness with a mortality rate of 30 to 50 percent in the unvaccinated individual, and variola minor, which was a milder infection with a mortality rate of less than 1 percent.[9]
- Transmission can be spread through humans only, via respiratory route, contact of fluid either directly or via contaminated materials, and airborne route.
- Clinical presentation can be characterized into five categories: ordinary, modified, flat, hemorrhagic, and variola sine eruptione. All the forms have a characteristic rash, except for variola sine eruptione. In general, smallpox was most severe in infants, the elderly, and in the impaired host, particularly those with T cell deficits. Milder forms of infection were observed in patients with a history of smallpox immunization.
- Treatment:
    - Supportive care includes maintenance of fluid and electrolyte balance, skin care, and observing for complications related to infections.
    - Antivirals approved for the treatment of smallpox in U.S. include tecovirimat capsule, brincidofovir tablets, and brincidofovir oral suspension.
    - Smallpox vaccination

[6] Questions and answers on cyclodextrins used as excipients in medical products for human use. EMA 2017. https://www.ema.europa.eu/en/documents/report/cyclodextrins-used-excipients-report-published-support-questions-answers-cyclodextrins-used_en.pdf
[7] DPMH review of Tembexa on March 12, 2021, DARRTS Reference ID 4761093
[8] Friedman HM, Issacs SN. Variola virus (smallpox). UpToDate, https://www.uptodate.com/contents/variola-virus-smallpox?search=smallpox%20and%20pregnancy&source=search_result&selectedTitle=1~54&usage_type=default&display_rank=1 Accessed 10/14/2020.
[9] Fenner F, Henderson DA, Arita I, et al. Smallpox and its eradication, World Health Organization, Geneva 1988.

Maternal mortality in smallpox affected pregnancies was reported disproportionately high compared with that of the overall population.[10] Both vaccinated and unvaccinated pregnant people experience significant perinatal and maternal morbidity and mortality in pregnancy with smallpox infection.

- The largest series by Rao et al.[11] consists of 389 pregnant people with smallpox in the 1960s in India. The authors reported an overall case-fatality rate of 33%, with a 27% rate of fatality among the vaccinated and 61% rate of fatality among the unvaccinated. The authors also reported that smallpox acquired before 24 weeks' gestation was associated with a 75% rate of miscarriage or preterm delivery. When smallpox was acquired between 24 to37 weeks' gestation, 55% of these pregnancies delivered prematurely. When smallpox was acquired at term, 9% of subjects died before delivery and 45% of subjects delivered during the acute phase of disease. Hemorrhagic type smallpox was seven times more frequent in pregnant people and case-fatality rate was 100% among pregnant Indian people.[12] Nearly 55% of the live births died within 15 days after birth (the majority during the first 72 hours of life). The rate of congenital smallpox among the live births was 9%; all of them died.[9]

Treatment of smallpox in pregnancy is similar to treatment in the general population.

- Supportive care
- Antivirals
    - Brincidofovir is associated with embryotoxicity and structural malformations following oral administration to rats and rabbits during period of organogenesis.
    - Tecovirimat has not been shown to be associated with embryofetal developmental toxicity in mouse and rabbits after oral administration during organogenesis at up to 23 and 0.4 times the recommended human dose (RHD), respectively.[13]
- Vaccination
    - Although vaccination with live attenuated virus in general is not recommended in pregnancy and smallpox vaccination (with live vaccinia virus) is contraindicated as pre-exposure prophylaxis, the recommendation is different post-exposure. For pregnant people who have had a definite direct exposure, vaccination is recommended due to high fatality related to smallpox infection in pregnancy.[14]
    - Primary vaccination during pregnancy has been associated with a slight but measurable risk of vertical transmission to the fetus, which is known as vaccinia fetalis and is fatal to the neonate.[15]

[10] Surarez VR, et al. Smallpox and Pregnancy: From Eradicated Disease to Bioterrorist Threat. Obstetric and Gynecology 2002;100(1): 87-93.
[11] Rao AR. Smallpox. Bombay, India: The Kothari Book Depot, 1972.
[12] Rao AR, Prahlad I, Swaminathan M, Lakshmi A. Pregnancy and smallpox. J Indian Med Assoc 1963; 40:353–63.
[13] Approved labeling for Tembexa, NDA 414460 and NDA 214461. Drugs@FDA. Accessed 6/17/21.
[14] Yawetz S. Immunizations during pregnancy. UpToDate. Accessed 2/4/2021.
[15] Hassett DE. Smallpox infections during pregnancy, lessons on pathogenesis from nonpregnant animal models of infection. Journal of Reproductive Immunology 2003;60: 13-24.

- Breastfeeding is not recommended during active smallpox infection due to the potential for variola virus transmission through direct contact with the breastfed infant.[13,16,17,18]

Current State of the Labeling for the approved labeling for TPOXX (tecovirimat) oral capsule, NDA 208627

- Approved labeling is in Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) format.
- There is no boxed warning.
- There is no contraindication for use.
- Serious Adverse Reactions:
  - Hypoglycemia: Co-administration with repaglinide may cause hypoglycemia. Monitor blood glucose and monitor for hypoglycemic symptoms during co administration.

8.1 Pregnancy notes the following:

Risk Summary

No adequate and well controlled studies in pregnant women were conducted; therefore, there are no human data to establish the presence or absence of TPOXX associated risk.

In animal reproduction studies, no embryofetal developmental toxicity was observed in mice during the period of organogenesis at tecovirimat exposures (area under the curve [AUC]) up to 23 times higher than human exposure at the recommended human dose (RHD). In rabbits, no embryofetal developmental toxicity was observed during organogenesis at tecovirimat exposures (AUC) less than human exposures at the RHD. In a mouse pre-/post-natal development study, no toxicities were observed at maternal tecovirimat exposures up to 24 times higher than human exposure at the RHD (see Data).

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Tecovirimat was administered orally to pregnant mice at doses up to 1,000 mg/kg/day from gestation Days 6-15. No embryofetal toxicities were observed at doses up to 1,000 mg/kg/day (approximately 23 times higher than human exposure at the RHD).

Tecovirimat was administered orally to pregnant rabbits at doses up to 100 mg/kg/day from gestation Days 6 19. No embryofetal toxicities were observed at doses up to 100 mg/kg/day (0.4 times the human exposure at the RHD).

In the pre-/post-natal development study, tecovirimat was administered orally to pregnant mice at doses up to 1,000 mg/kg/day from gestation Day 6 to post-natal

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

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

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

Day 20. No toxicities were observed at doses up to 1,000 mg/kg/day (approximately 24 times higher than human exposure at the RHD).

8.2 Lactation notes the following:

Risk Summary

There are no data to assess the effect on milk production, the presence of the drug in human milk, and/or the effects on the breastfed child. When administered to lactating mice, tecovirimat was present in the milk *(see Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TPOXX and any potential adverse effects on the breastfed child from TPOXX or from the underlying maternal condition.

Data

In a lactation study at doses up to 1,000 mg/kg/day, mean tecovirimat milk to plasma ratios up to approximately 0.8 were observed at 6 and 24 hours post dose when administered orally to mice on lactation Day 10 or 11.

8.3 Females and Males of Reproductive Potential Infertility notes the following:

There are no data on the effect of tecovirimat on female and male reproductive potential in humans. Decreased fertility due to testicular toxicity was observed in male mice.

- There are no existing pregnancy testing/contraception recommendations.
- There are known drug-drug interactions with hormonal contraceptives.

REVIEW

Nonclinical Experience

No new animal reproduction studies were conducted for this submission. This submission relies on the genotoxicity, reproductive and developmental toxicity data for oral tecovirimat, NDA 208627, which were described above in the approved labeling for NDA 208627.

The reader is referred to the May 5, 2018 Pharmacology Toxicology review for NDA 208627 by David McMillian, Ph.D., L. Peyton Myers, Ph.D., and Hanan Ghantous, Ph.D.

Regarding HP-β-CD

The following is taken from the Review of Pharmacology and Toxicology Data for Sporanox Injection[19]:

> No primary embryotoxic effect was evidenced in rats or rabbits exposed to HP-β-CD during organogenesis. In pregnant rats administered oral (2000 and 5000 mg/kg) and IV (400 mg/kg) HP-β-CD, there was maternal toxicity, decreased pup survival, and reduced pup birth weight and body weight. In pregnant rabbits, administered oral (100mg/kg) HP-β-CD, there was maternal toxicity and increased skeletal variations. No adverse effects in pregnant rabbits were observed after administration of IV HP-β-CD (400mg/kg). No clear teratogenic effects were noted in any study.

[19] Review of Pharmacology and Toxicology Data, NDA 20966, Drugs@FDA. Page 13-14. https://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20-966_SPORANOX%20INJECTION%2010MG%20PER%20ML_PHARMR.PDF Accessed 10/22/21.

Reviewer comment:
Doses of 400 mg/kg IV HP-β-CD in rats and rabbits, which corresponds to approximately 0.3 times and 0.5 times the recommended human dose (RHD), respectively, have not demonstrated any clear teratogenic effects. This was confirmed in discussion with the Pharmacology Toxicology Team.[20]

Review of Clinical Trials
There were no pregnant females exposed to tecovirimat (orally or intravenously) in the clinical trials.

Review of Literature
DPMH's Review of Literature
Tecovirimat
DPMH conducted a literature review in Embase, Pubmed, Micromedex,[21] and TERIS.[22]

Embase and Pubmed were searched for "tecovirimat" and "pregnancy," "tecovirimat" and "fetal malformations/congenital malformations/birth defects/stillbirth/spontaneous abortion/miscarriage."

- There is no published literature on tecovirimat use in pregnancy.

Micromedex[21] and TERIS[22] both cite the labeling. Micromedex[21] gives "Pregnancy Rating: Fetal risk cannot be ruled out."

HP-β-CD
A search was also conducted on HP-β-CD and pregnancy in Embase, Pubmed, and Google. There are no data on HP-β-CD use in pregnant people.

Reviewer comment:
There are no data on the use of tecovirimat during human pregnancy. There are no new animal reproduction studies submitted during this submission. According to the approved labeling, oral tecovirimat is not teratogenic in animals; embryofetal toxicities were not observed at systemic exposure up to 23 times the RHD in mice and 0.4 times the RHD in rabbits.

There are no data on intravenous use of HP-β-CD during human pregnancy. In discussion with the Pharmacology Toxicology team, it was noted that there were no primary embryotoxic effect with a HP-β-CD *intravenous dose of 400 mg/kg administered to rats or rabbits during organogenesis.*[23] *The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data, submission, and recommendations.*

[20] Personal communication with DAI Pharmacology Toxicology Team on 8/19/21
[21] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 5/17/2021.
[22] TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 5/17/21.
[23] Personal communication with the Pharmacology Toxicology Team on 10/14/21.

LACTATION

Nonclinical Experience

Tecovirimat

In a lactation study at doses up to 1,000 mg/kg/day, mean tecovirimat milk to plasma ratios up to approximately 0.8 were observed at 6 and 24 hours post dose when administered orally to mice on lactation Day 10 or 11.

HP-β-CD

It is not known if HP-β-CD is present in animal milk.
The reader is referred to the May 5, 2018 Pharmacology Toxicology review for NDA 208627 by David McMillian, Ph.D., L. Peyton Myers, Ph.D., and Hanan Ghantous, Ph.D.

Review of Clinical Trials

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

Review of Literature

DPMH's Review of Literature

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

Tecovirimat

A search in PubMed and Embase was performed using the search terms "tecovirimat" AND "lactation" and "tecovirimat" AND "breastfeeding."

- No articles were found on the use of tecovirimat during lactation.

LactMed,[24] Briggs,[25] and Hale[26] do not contain any information on tecovirimat. Micromedex[21] gives a Lactation Rating of "Infant risk cannot be ruled out."

HP-β-CD

A search was also conducted on HP-β-CD and lactation in PubMed, Embase, and Google. There are no data on HP-β-CD use during lactation.

Current practice

Smallpox is highly contagious. Current practice recommends that breastfeeding mothers with smallpox avoid breastfeeding to prevent transmission through direct contact with the infant.[27] In

[24] http;//toxnet nlm nih.gov/newtoxnet/lactmed htm. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed data base provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfeeding infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility. Accessed 5/17/2021.
[25] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th Ed. 2015. Online, accessed 5/17/21.
[26] Hale, Thomas. Hale's Medications and Mother's Milk 2019. Springer Publishing Company, New York, NY. Accessed 5/17/21
[27] Lawrence R. Transmission of Infectious Diseases Through Breast Milk and Breastfeeding. Breastfeeding. 2011: 406–473.

addition, a case report documents tertiary contact vaccinia in a lactating female and her breastfed infant following the administration of the smallpox vaccine in the father despite observing appropriate precautions. Sepkowitz[28] reported 27 cases of secondary vaccinia in households between 1931 to 1981, and CDC reported 30 suspected cases of secondary/tertiary vaccinia with 18 of those confirmed by culture or PCR related to vaccinated military personnel.[29]

Reviewer comment:
Smallpox is highly contagious and current practice recommends avoiding breastfeeding to prevent transmission of smallpox through direct contact with the infant. It is not known if tecovirimat is present in human breastmilk. Tecovirimat is present in animal milk. When a drug is present in animal milk, it is likely to be present in human milk. There are no data on the presence of HP-β-CD in animal or human milk, the effect on the breastfed infant or milk production. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data, submission, and recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Tecovirimat

Approved labeling states the following:

> *Carcinogenesis and Mutagenesis*
>
> Carcinogenicity studies have not been conducted with tecovirimat.
>
> Tecovirimat was not genotoxic in in vitro or in vivo assays, including a bacterial reverse mutation assay, a mammalian mutagenicity assay in mouse lymphoma L5178Y/TK± cells, and in an in vivo mouse micronucleus study.
>
> *Impairment of Fertility*
>
> In a fertility and early embryonic development study in mice, no effects of tecovirimat on female fertility were observed at tecovirimat exposures (AUC) approximately 24 times higher than human exposure at the RHD. In male mice, decreased male fertility associated with testicular toxicity (increased percent abnormal sperm and decreased sperm motility) was observed at 1,000 mg/kg/day (approximately 24 times the human exposure at the RHD).

HP-β-CD

The following is taken from the approved labeling for Sporanox Injection[30]:

> Hydroxypropyl-β-cyclodextrin (HP-β-CD) was found to produce pancreatic exocrine hyperplasia and neoplasia when administered orally to rats at doses of 500, 2000 or 5000 mg/kg/day for 25 months.

The following is taken from the Review of Pharmacology and Toxicology Data for Sporanox Injection[31]:

[28] Sepkowitz KA: How contagious is vaccinia? N Engl J Med 348:439, 2003.
[29] Centers for Disease Control and Prevention: Secondary and tertiary transfer of vaccinia virus among U.S. military personnel—United States and worldwide, 2002-2004, MMWR Morb Mortal Wkly Rep 53(5):103, 2004.
[30] Approved labeling for Sporanox Injection, NDA 20966, Drugs@FDA. Last updated 4/23/2009.
[31] Review of Pharmacology and Toxicology Data, NDA 20966, Drugs@FDA. Page 13-14.

No mutagenic potential was evidenced in any of the studies performed to investigate the potential of HP-β-CD to induce DNA-damage, point and or gene mutations, and chromosome aberrations in in vivo and in vitro test systems.

The reproductive function of male and female rats, dosed orally up to 5000mg/kg, and intravenously up to 400 g/kg, with HP-β-CD, was not adversely affected.

The reader is referred to the May 5, 2018 Pharmacology Toxicology review for NDA 208627 by David McMillian, Ph.D., L. Peyton Myers, Ph.D., and Hanan Ghantous, Ph.D.

Reviewer Comment:
In discussion with the Pharmacology Toxicology Team, it was noted that the fertility study on mice did not have a no-observed-adverse-effect level (NOAEL) for testicular toxicity. Spermatological effects were seen at the high dose and were not evaluated at the lower doses, so a NOAEL could not be defined. In addition, toxicokinetics were not evaluated, and the exposure multiples were based on another rat study with identical dose levels. Therefore, NOAEL cannot be established.

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

Review of Literature
DPMH's Review of Literature
DPMH conducted a published literature review by using the sources noted below, and the following findings were retrieved:

Tecovirimat
DPMH conducted a published literature review on PubMed and Embase using term "tecovirimat" and "fertility," "tecovirimat" AND "reproduction," "tecovirimat" AND "contraception." No relevant articles were retrieved.

There is no information regarding tecovirimat and reproduction in Micromedex[21] or TERIS.[22]

HP-β-CD
A search was also conducted on HP-β-CD and fertility on PubMed, Embase, and Google. There are no data on HP-β-CD and effects on human fertility.

Reviewer comment:
There are no data on the effects of tecovirimat on fertility in humans. Based on animal data, tecovirimat decreased male fertility in mice at a dose 24 times the RHD. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data, submission, and recommendations.

DISCUSSION AND CONCLUSIONS
Pregnancy
There are no data on the use of tecovirimat during human pregnancy. In animal reproduction studies, embryofetal toxicity was not observed in mice (during organogenesis at doses up to 23

times the RHD) or rabbits (during organogenesis at doses less than the RHD). There was no embryofetal toxicity observed in mice during pre-/postnatal development studies (at doses approximated 24 times the RHD).

There are no data on HP-β-CD use in pregnant people. Animal reproductive toxicity studies with HP-β-CD in rats and rabbits at IV doses of 400 mg/kg, which are 0.3 times and 0.5 times the RHD, respectively, have not demonstrated any clear teratogenic effects. Because smallpox can be life threatening and tecovirimat injection is the only drug available intravenously, pregnant people should be allowed access to this formulation of drug despite the lack of data with HP-β-CD use in pregnancy.

Smallpox has been eradicated in the world since 1978. Oral tecovirimat has been approved since 2018, and there are no data on the use of tecovirimat in pregnancy. A postmarketing study of IV tecovirimat use in the pregnant population will not be feasible; therefore, DPMH does not recommend a postmarketing pregnancy study for tecovirimat injection at this time.

Lactation

Smallpox is highly contagious. Current practice recommends that breastfeeding mothers with smallpox avoid breastfeeding to prevent transmission through direct contact with the infant.[32] There are no data on the presence of tecovirimat in human milk. Tecovirimat is present in animal milk. When a drug is present in animal milk, it is likely to be present in human milk. There are no data on the effects of the drug on the breastfed infant, or on milk production.

There are no data on the presence of HP-β-CD in animal or human milk, the effect on the breastfed infant or milk production.

DPMH does not recommend a lactation study because breastfeeding during active infection with smallpox is not recommended.

Females and Males of Reproductive Potential

Based on animal studies, tecovirimat may impair male fertility at dose that is 24X MRHD. Spermatological effects were seen at the high dose, and were not evaluated at the lower doses, so a NOAEL could not be defined. Because no NOAEL was established, the Pharmacology Toxicology Team recommends including this information under subsection 8.3. There are no human data regarding effects of tecovirimat on fertility. There are no data to suggest tecovirimat interacts with systemic hormonal contraceptive. There are no data on HP-β-CD use and effects on fertility.

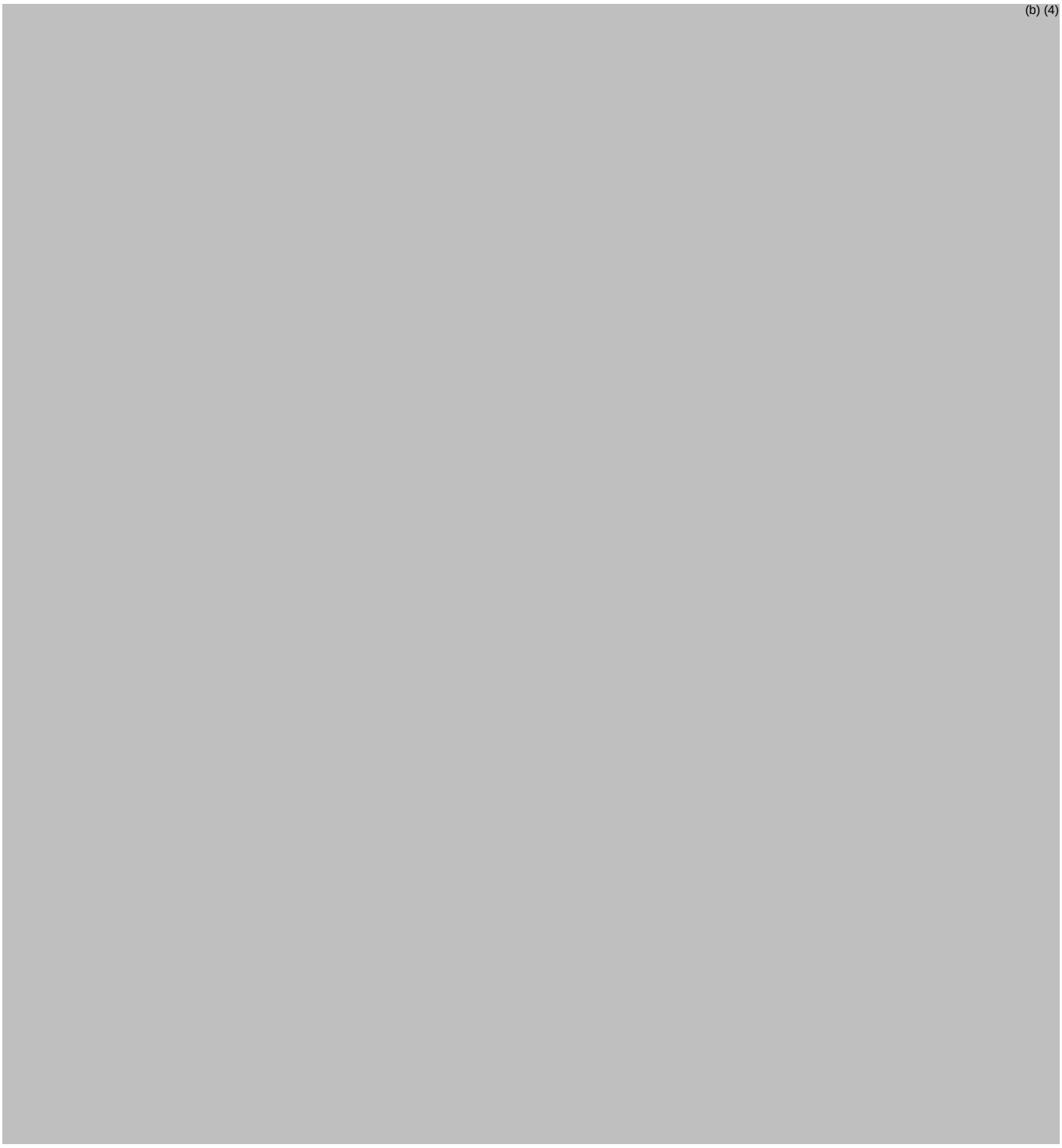
LABELING RECOMMENDATIONS

DPMH proposes edits to subsections 8.1, 8.2, and 8.3 of labeling for the new NDA and in compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

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

DPMH Proposed Pregnancy and Lactation Labeling

(b) (4)



Reviewer's Comments: The Pharmacology/Toxicology review was not finalized at the time the DPMH review was completed. The current labeling recommendations do not reflect input from the Pharmacology/Toxicology team.

8.2 Lactation

Risk Summary

Because of the potential for variola virus transmission through direct contact with the breastfed infant, breastfeeding is not recommended in patients with smallpox. There are no data on the presence of tecovirimat in human milk, the effects of the drug on the breastfed infant, or on milk production. Tecovirimat is present in animal milk. When a drug is present in animal milk, it is likely to be present in human milk.

8.3 Females and Males of Reproductive Potential

Infertility

There are no data on the effect of tecovirimat on human fertility. Decreased fertility due to testicular toxicity was observed in male mice *[see Nonclinical Toxicology (13.1)]*.

17 PATIENT COUNSELING INFORMATION

Lactation

Instruct individuals with smallpox not to breastfeed their infant because of the risk of passing variola virus to the breastfed infant *[see Use in Specific Populations (8.2)]*.

APPEARS THIS WAY ON ORIGINAL

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/

WENJIE SUN
11/22/2021 05:25:35 PM

MIRIAM C DINATALE
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LYNNE P YAO
11/29/2021 11:06:29 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	September 28, 2021
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 214518
Product Name and Strength:	Tpoxx (tecovirimat) injection, 200 mg/20 mL (10 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Siga Technologies (SIGA)
FDA Received Date:	April 20, 2021
OSE RCM #:	2021-895
DMEPA 1 Safety Evaluator:	Melina Fanari, RPh
DMEPA 1 Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 REASON FOR REVIEW

As part of the approval process for Tpoxx (tecovirimat) injection, the Division of Antivirals (DAV) requested that we review the proposed Tpoxx prescribing information (PI), patient prescribing information (PPI), instruction for use (IFU), container label and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Tpoxx (tecovirimat) (b) (4) was approved on July 13, 2018 under NDA 208627 for the treatment of human smallpox disease in adults and pediatric patients weighing 13 kg.

SIGA is now pursuing an injection formulation for intravenous administration in adult and pediatric patients (weighing 3 kg and up), under NDA 214518 submitted on April 30, 2021.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

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

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed PI, PPI and container label and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Siga Technologies (SIGA). We will collaborate with DAV to incorporate the necessary changes as outlined below to the PI.

4 RECOMMEDATIONS FOR DIVISION OF ANTIVIRALS (DAV)

Table 2. Identified Issues and Recommendations for Division of Antivirals (DAV)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	The abbreviation 'iv' is utilized throughout labeling.	Minimize misinterpretation and confusion	Consider replacing the abbreviation 'iv' with its intended meanings.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	References made to (b) (4) are ambiguous.	Ensure proper product preparation.	Replace the statements (b) (4) (b) (4) with 'Tpoxx 10 mg/mL injection solution'.
2.	Section 2.5 lacks a bullet stating further dilution is required.	Ensure proper product preparation.	Add a bullet (bullet 2) to section 2.5 to state the following: 'For Intravenous infusion after dilution.'
3.	Section 2.5 is unclear with respect to the need to utilize one syringe of adequate size to draw up both the Tpoxx injection and required diluent.	Ensure proper product preparation.	Add a bullet (as bullet 3) to section 2.5 to state the following: 'Obtain one syringe of adequate size to draw up both the prescribed volume of Tpoxx injection and required diluent. In addition, bullet 2 requires revisions as outlined above (see comment 1) and to include details related to the preparation of the syringe.
Patient Prescribing Information			
1.	The abbreviation 'iv' is utilized throughout labeling.	Minimize misinterpretation and confusion	Consider replacing the abbreviation 'iv' with its intended meanings.

5 RECOMMENDATIONS FOR SIGA TECHNOLOGIES (SIGA)

Table 3. Identified Issues and Recommendations for Siga Technologies (SIGA) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	The expiration date is missing and the format is not defined.	Clearly define the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2.	Total drug content strength statement is of equal prominence to mg/mL strength statement.	Minimize risk of wrong dose medication errors.	The prominence of the total drug content statement (200 mg/20 mL) should be increased in prominence in comparison

Table 3. Identified Issues and Recommendations for Siga Technologies (SIGA) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			to the 10 mg/mL strength statement.
Carton Labeling			
1.	Usual dosage statement requires revisions.	21 CFR 201.55	To ensure consistency with the Prescribing Information, revise the statement, (b) (4) (b) (4) (b) (4) to read "Recommended Dosage: See prescribing information."
2.	The product identifier required under the drug supply chair security act (DSCSA) is missing.	DSCSA requires manufacturers and repackages, respectively, to affix or imprint a product identifier to each package and homogeneous case of a product intended to be introduced in a transaction in (to) commerce beginning November 27, 2017, and November 27, 2018, respectively.	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf
3.	Net quantity statement requires revision and includes product strength.	21 CFR 201.51	Remove the statement (b) (4) (b) (4) (b) (4) and revise the net quantity statement as follows: 'Contains 7 x 20 mL single dose vials. Discard unused portion.'

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Tpoxx that Siga Technologies (SIGA) submitted on April 30, 2021.

Table 4. Relevant Product Information for Tpoxx

	Tpoxx capsule	**Tpoxx Injection**
Initial Approval Date	July 13, 2018	N/A
Active Ingredient	tecovirimat	
Indication	Tpoxx is indicated for the treatment of human smallpox disease in adults and pediatric patients.	
Dosage Form	Capsule	Injection
Route of Administration	Oral	Intravenous
Strength	200 mg	200 mg/20 mL (10 mg/mL)
Dose and Frequency	(b) (4)	

	(b) (4)	
How Supplied	Bottles of 42 capsules	Provided in a clear type I glass 30 mL vial with a (b) (4) stopper, aluminum seal and flip off cap. The vials are supplied as 200 mg single dose tecovirimat vial; packed in cartons of 7 vials.
Storage	Store in original bottle at 20°C to 20°C (68°F to 77°F)	Store at 2°C to 8°C (36°F to 46°F). Store in a refrigerator. Do not freeze.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 14, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, Tpoxx. Our search identified did not identify any relevant reviews.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Tpoxx labels and labeling submitted by Siga Technologies (SIGA).

- Container label and carton labeling received on April 30, 2021
- Prescribing Information, Patient prescribing Information, and Instructions for Use (Images not shown) received on April 30, 2021, available from \\CDSESUB1\evsprod\NDA214518\0001\m1\us\114-label\1141-draft-label

F.2 Label and Labeling Images

Container label

Carton labeling

1 Page of Draft Labeling has been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MELINA N FANARI
09/28/2021 07:14:04 AM

SEVAN H KOLEJIAN
09/28/2021 12:54:45 PM

Memorandum (Neonatal-Perinatal Medicine Consultation)

To: Andrew Gentles, PharmD; Senior Regulatory Project Manager
Kimberly Struble, PharmD; Cross-Discipline Team Leader, DAV/OID/OND/CDER

From: An Massaro, MD
Medical Officer, Office of Pediatric Therapeutics, OCPP/OC

Through: Gerri R. Baer, MD
Supervisory Medical Officer, Office of Pediatric Therapeutics, OCPP/OC

Dionna Green, MD
Director (Acting), Office of Pediatric Therapeutics, OCPP/OC

Date: September 15, 2021

Subject: Neonatal-Perinatal Medicine Consultation Memo for NDA 214518 TPOXX IV (tecovirimat)
Neonatal Labeling

MATERIALS REVIEWED:

1. NDA 214518 TPOXX IV (tecovirimat) - EDR Link: \\CDSESUB1\evsprod\NDA214518\0001
   - Cover letter (Section 1.2)
   - Clinical overview (Section 2.5)
   - *Hydroxypropyl Betacyclodextrin Use with Tecoririmat Injection, 10mg/mL* "white paper"
2. Current labeling for TPOXX capsules for oral use: https://elist.fda.gov/prpllr/public/spl/638105d6-2895-4ab5-b1ef-3b5d95c196fa/638105d6-2895-4ab5-b1ef-3b5d95c196fa.view#section-1.1

Published Literature
The reference list is included at the end of the consultation, following the recommendations.

NEONATAL-PERINATAL MEDICINE CONSULTATION QUESTION(S):

SIGA technologies, Inc. submitted an NDA for TPOXX (tecovirimat) IV for the treatment of smallpox disease caused by variola virus in adults and pediatric patients.

- For hydroxypropyl betadex, IV tecovirimat (8 g dose of hydroxypropyl-β-cyclodextrin per 200 mg tecovirimat/20 mL solution) exceeds the approved formulation concentration for other IV products.
- IV formulation allows for administration of tecovirimat in adults and pediatric patients who are unable to take PO tecovirimat. IV formulation also allows dosing down to neonates weighing at least 3 kg. However, dosing recommendations for PO tecovirimat are constrained to 13 kg cut-off due to absence of approved pediatric formulation.
- For pediatric patients 3 kg to <13 kg: Would use up to 14 days of IV tecovirimat (and do not have the option to convert to PO) – is this acceptable given HPBCD issue?
- Also, please provide your perspective on at what age GFR is "matured" enough, i.e., should an age cutoff be considered for the above HPBCD issue?
- Based on OPT's assessments of the above issues, DAV may also request that OPT provide specific labeling recommendations.

BACKGROUND:

Description of the Disease Process

Smallpox is caused by the variola virus (VARV), is highly communicable and caries a case-fatality rate of 1% for variola minor and 30% for variola major. After widespread vaccination, global eradication of smallpox was declared by the World Health Organization in 1980, with no cases reported in the world since that time.[1] However, with the advent of bioterrorism, concerns regarding weaponization of smallpox have led to the development of medical countermeasures to address the potential public health emergency of a smallpox attack leading to outbreak.

Available Therapeutics

Current therapies for smallpox include smallpox vaccines and antiviral chemotherapeutics. Smallpox vaccines licensed for *prevention* of smallpox disease in the U.S. include ACAM2000 (approved 2007) and Jynneos (approved 2019). For *treatment* of human smallpox disease, TPOXX (tecovirimat) oral capsules was approved in 2018 for treatment of human smallpox disease in adults and pediatric patients weighting at least 13 kg. The current submission represents development of an intravenous formulation to provide a therapeutic option for adult and pediatric patients who are unable to take the product orally. Most recently, TEMBEXA (brincidofovir) oral suspension, an orthopoxvirus nucleoside analog DNA polymerase inhibitor, was approved in June 2021 for treatment of human smallpox disease in adult and pediatric patients, including neonates. The availability of at least 2 antiviral drugs that work by different molecular mechanisms has been recommended by the Institute of Medicine for protection against a potential smallpox outbreak.[1]

Product Description

TPOXX (tecovirimat) is an inhibitor of the orthopoxvirus VP37 envelope wrapping protein, which is required for exit of the enveloped virions from the infected cell. Given the highly conserved nature of the VP37 protein, tecovirimat has antiviral activity not only against VARV, the etiologic agent of smallpox, but also against other members of the orthopoxvirus genus such as vaccinia virus (VACV) and monkeypox virus (MPXV). It was developed as a new molecular entity under the FDA Animal Rule for biodefense.

The drug substance, tecovirimat monohydrate, (b) (4) hydroxypropyl β-cyclodextrin (b) (4), and water for injection. Prior to infusion, IV tecovirimat is diluted with 0.9% normal saline solution.

Regulatory History

8 DEC 2005	The original IND application (IND 69,019) in support of tecovirimat was opened
22 DEC 2005	Fast track status was granted for IND 69,019
18 DEC 2006	Orphan-drug designation (06-2335) granted for “use for post-exposure prophylaxis of smallpox”
27 DEC 2006	Orphan-drug designation (06-2298) granted for “use for post-exposure treatment of smallpox”
29 SEP 2010	Orphan-drug designation (10-3162) granted for “use for treatment of orthopoxvirus infections”
1 NOV 2012	Fast track status granted for the intravenous formulation under IND 111,390

Between 2017-2020, a series of FDA interactions occurred during the Pre-IND stage, including discussion of the following key regulatory issues:

- Since traditional drug development and approval based on clinical demonstration of efficacy is not possible, tecovirimat has been developed under the “Animal Rule” (21 CFR §314.600 through §314.650).
- Efficacy discussion will reference NDA 208,627 for Tecovirimat oral dosage (approved for “treatment of human smallpox disease in adults and pediatric patients weighing at least 13 kg” on July 13, 2018).
- Given orphan-drug designation, Tecovirimat is exempt from PREA.

Proposed Labeling

Relevant sections from Sponsor draft prescribing information:

NDA 214518 TPOXX IV (tecovirimat)

1 Page of Draft Labeling has been Withheld in Full as B4(CCI/TS) Immediately Following this Page

Available Study Data

In this submission, evidence of efficacy for the proposed IV regimen is drawn from the tecovirimat oral submission (oral tecovirimat NDA 208,627), whereas pharmacokinetic (PK), pharmacodynamic, and safety data are drawn from clinical trials of IV tecovirimat in human subjects. Clinical development of oral tecovirimat was conducted under FDA's Animal Rule. *In vivo* efficacy data for the oral formulation were collected from 6 pivotal animal studies: 4 studies in nonhuman primates (NHPs) and 2 studies in rabbits. Clinical development of IV tecovirimat is further supported by clinical trials in healthy adult human subjects with the IV formulation. Two human clinical pharmacology studies were conducted (with doses infused over 6 hours) to evaluate dose ranging and tolerability, single-dose and multiple-dose PK, dose linearity, comparative PK between IV and oral formulations, and oral bioavailability:

- Pivotal Study SIGA-246-IV-202: Phase 1, single-dose PK comparison (IV vs oral) 3-period study: 2-period crossover, followed by a double-blind, randomized, placebo-controlled 7-day multiple IV dose study in n=32 healthy adult subjects
    - Period 1: IV tecovirimat 200mg
    - Period 2: Oral tecovirimat 600mg
    - Period 3: IV tecovirimat 240mg (n=26) or placebo (n=6) BID for 7 days
- Supportive Study SIGA-246-IV-201: Phase 1, double-blind, randomized, placebo-controlled, single ascending dose-finding study
    - IV tecovirimat 37.5, 75, 150, or 200 mg (n=6/cohort) or placebo (n=8)

Key findings of clinical pharmacology studies:

- Oral bioavailability was estimated to be ~48% of IV infusion.
- Targeted dosage regimen for IV tecovirimat is 200mg BID for patients >40 kg to achieve similar exposure to the approved oral dose (600mg).
- Population PK (POP PK) analyses indicated that age and gender did not affect IV tecovirimat PK.
- POP PK modeling was used to simulate exposures for patients ranging 3 to 150 kg.

Safety and tolerability of IV tecovirimat were evaluated in the 2 clinical studies mentioned above, with supportive data from the 11 clinical studies performed with the oral formulation. In the multiple-dose period of pivotal Study SIGA-246-IV-202, adverse events (AEs) and treatment-related AEs were each reported by 22 subjects (84.6%) in the tecovirimat group and 6 subjects (100.0%) in the placebo group. Most AEs are mild or moderate, and the most common AEs are infusion-related AEs (infusion site pain, infusion site swelling, infusion site erythema, and infusion site extravasation), headache, and dizziness. No deaths or SAEs were reported during the study.

No pediatric studies have been conducted due to ethical concerns. Pediatric dosing is based on POP PK modeling which provided 5 IV dose levels for pediatric patients ranging 3 to 40 kg.

Hydroxylpropyl Betacyclodextrin (HP-β-CD)

The IV tecovirimat formulation contains HP-β-CD as the primary excipient (Table 1).

Table 1: Tecovirimat Injection, 10 mg/mL – Formula per vial

Ingredient	Quality Standard	mg/mL	%w/v
Tecovirimat Monohydrate (b) (4)	In-House Standard	10.0	1
Hydroxypropyl-β-cyclodextrin (Hydroxypropyl Betadex, (b) (4))	(b) (4)	400	40
Water for Injection	USP	q.s.	q.s.

At the clinical dose of 200 mg/infusion twice a day (400 mg/day), patients will receive a total of 8 g/infusion (16 g/day) of HP-β-CD. This quantity is equivalent to 114-160 mg/kg/dose or 228-320 mg/kg/day for a 70 or 50 kg patient, respectively. HP-β-CD exposure for the recommended weight-based dosing for pediatric patients is summarized in Table 2.

Table 2. HP-β-CD exposure for pediatric doses

(b) (4)

Safety of HP-β-CD:

The non-clinical PK and safety profile of IV HP-ß-CD has been well-characterized in several animal species including rats, mice, dogs, rabbits, and NHP in single and multiple doses.[2,3] IV HP-ß-CD is cleared rapidly from the plasma by renal excretion, with clearance directly correlated to glomerular filtration rate (GFR). Overall observed toxicity has been minimal and is characterized by mild biochemical changes (liver function) and mild to moderate histopathological changes including foamy cells in the liver and lungs, and vacuolation of cells in the liver, kidneys and bladder. These changes were largely reversible following cessation of therapy. Histopathological changes are most notable in the kidneys, with renal tubular cell swelling and micovacuolation resulting in an "osmotic nephrosis" morphological pattern that is similar between adult and juvenile animals. Nephrotic changes are generally not correlated to biochemical markers of renal impairment, although slight elevation of urinary N-Acetyl-ß-d-Glucosaminidase (NAG), protein, and occult blood were observed in juvenile rats (females>males) exposed to 400mg/kg/day dosing for 28 days.[3] The **NOAEL is 50mg/kg in rats and 100mg/kg in dogs** for 3 months of therapy[2] and the **LD_{50} in rats has been reported to range between 450-790mg/kg**. **Ototoxicity in mice, rats and cats has been observed after 2000mg/kg to 8000mg/kg provided as a single dose**.[4-7]

Clinical experience in adult patients has demonstrated reduced clearance and accumulation in patients with renal impairment, although major toxicity (including nephrotoxicity) has not been reported. Intravenous studies with Sporanox (itraconazole) in pediatric patients 7 months to 17 years demonstrated no significant age-dependence of estimated PK parameters and no AEs after single dose exposure of 100mg/kg HP-ß-CD.[8] At high doses (>2000mg/kg), HP-ß-CD has been investigated as a neuroprotective therapy for Nieman-Pick disease and has been generally well tolerated. However, intrathecal dosing of HP-ß-CD has been associated with hearing loss in pediatric and young adult patients with Nieman Pick and **hearing outcomes have not been systematically evaluated in most reports of high-dose HP-ß-CD treatment**.[4] The Sponsor also cites human experience in adults from the multiple dose IV tecovirmat study (SIGA-246-IV-202) that evaluated a dose of 240mg IV BID x 7days (HP-ß-CD 9.6g/dose; ~137-192mg/kg/dose; total exposure 1918-2688mg/kg) that reported tolerability and no SAEs associated with HP-ß-CD exposure.

According to EMA reports on cyclodextrins used as excipients (EMA/CHMP/333892/2013 and EMA/CHMP/302620/2017), **the dose of HP-ß-CD of 250mg/kg/day administered up to 21 days is considered safe in patients 2 years of age or older. PK and safety data of IV HP-ß-CD in children less than 2 years old are limited (and in neonates no data are available).** The report concludes that precautions regarding risk for nephrotoxicity should be included in labeling for doses >200mg/kg/day and use >2 weeks and that for children "a case by case judgement should be made regarding the risk/benefit for the patient."

ANALYSIS/RESPONSE:

General Comments:

The development of Tecovirimat to treat smallpox infection in the event of a bioterrorism-related outbreak has clear public health benefit. Only one other agent with antiviral activity against VARV is approved and it is important to have additional therapeutic options available. It is important to provide dosing and administration information to address all populations, including neonates, for which the potential benefits of the product outweigh potential risks in the case of an outbreak or bioterrorism event. We defer to the clinical pharmacology reviewers regarding whether the POP PK-based pediatric dosing proposed by the Sponsor is appropriate. The preparation instructions (i.e. dilution with 0.9% normal saline or 5% dextrose solution to a volume that will not exceed 3mL/kg) are appropriate for the neonatal population. The main concern regarding the product relates to the exposure to the excipient, HP-ß-CD, which may be addressed in labeling.

Responses to Consult Questions:

- For pediatric patients 3 kg to <13 kg: Would use up to 14 days of IV tecovirimat (and do not have the option to convert to PO) – is this acceptable given HPBCD issue?

Reviewer response: *The risks of HP-ß-CD largely relate to non-clinical safety concerns of nephrotoxicity and ototoxicity. At the recommended doses of Tecovirimat, the HP-ß-CD exposure will exceed the NOAEL and LD_{50} thresholds from animal studies and the suggested "safe" dose of IV HP-ß-CD for patients greater than 2 years of age according to the EMA. The "safe" dose of IV HP-ß-CD in pediatric patients less than 2 years of age is unknown given the limited clinical PK and safety data available and the knowledge that developmental changes in GFR may lead reduced clearance and higher blood levels in younger patients. This unclear risk needs to be weighed against the clinical benefit of treating a disease with high transmissibility and associated morbidity/ mortality. While the availability of Tembexa may offer a potentially safer alternative for neonatal patients, it is only available as an oral solution and may not be appropriate for patients that are unable to tolerate oral medications. Additionally, as viral resistance may emerge, it is important to have alternative therapies available.[1] We recommend that if the data submitted supports the safety and efficacy of Tecovirimat for treatment of smallpox infection, that clear warnings and precautions be included in labeling regarding the risk for nephrotoxicity and ototoxicity with prolonged HP-ß-CD exposure in pediatric patients.*

- Also, please provide your perspective on at what age GFR is "matured" enough, i.e., should an age cutoff be considered for the above HPBCD issue?

Reviewer response: *Glomerular filtration rate (GFR) is low at birth and increases over the first year of life. "Healthy" preterm and term neonates have GFR as low as 10-20 mL/min/m^2 at birth (~15-20% of adult) with a rapid increase to 20-30ml/min/m^2 within the first 2 weeks of life (~30-40% of adult) and levels reading adult levels by 6 months of age.[9,10] Renal tubular function rapidly matures over the first 1-3 years of life. This developmental immaturity of renal function contributes to the risk of HP-ß-CD accumulation and toxicity in young pediatric patients and should be included in labeling.*

- Based on OPT's assessments of the above issues, DAV may also request that OPT provide specific labeling recommendations.

Reviewer response: *We recommend the following labeling modifications:*

1. We recommend inclusion of non-clinical toxicology information for HP-ß-CD to include observed nephrotic changes in rats, rabbits and dogs and ototoxicity observed in cats and rats.
2. The concern for HP-ß-CD accumulation in pediatric patients less than 2 years of age due to renal immaturity should be included in section 5 (Warnings and Precautions) and section 8.4 (Pediatric Use) of labeling.
3. Monitoring renal function and hearing after treatment is recommended in pediatric patients less than 2 years of age given the limited PK and safety data in this population, the potential accumulation of HP-ß-CD due to developmental renal immaturity, and the non-clinical safety concerns observed with exposure to HP-ß-CD in the cumulative dose range of Tecovirimat.

4. The appropriateness of the footnote In Table 3 should be discussed with the clinical pharmacology reviewers; the following revision may be considered: (b) (4)

(b) (4)

REFERENCES:

1. Meyer H, Ehmann R, Smith GL. Smallpox in the Post-Eradication Era. *Viruses.* 2020;12(2).
2. Gould S, Scott RC. 2-Hydroxypropyl-beta-cyclodextrin (HP-beta-CD): a toxicology review. *Food Chem Toxicol.* 2005;43(10):1451-1459.
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4. Crumling MA, King KA, Duncan RK. Cyclodextrins and Iatrogenic Hearing Loss: New Drugs with Significant Risk. *Front Cell Neurosci.* 2017;11:355.
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6. Liu X, Ding D, Chen GD, Li L, Jiang H, Salvi R. 2-Hydroxypropyl-beta-cyclodextrin Ototoxicity in Adult Rats: Rapid Onset and Massive Destruction of Both Inner and Outer Hair Cells Above a Critical Dose. *Neurotox Res.* 2020;38(3):808-823.
7. Ding D, Jiang H, Manohar S, et al. Spatiotemporal Developmental Upregulation of Prestin Correlates With the Severity and Location of Cyclodextrin-Induced Outer Hair Cell Loss and Hearing Loss. *Front Cell Dev Biol.* 2021;9:643709.
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9. Kastl JT. Renal function in the fetus and neonate - the creatinine enigma. *Semin Fetal Neonatal Med.* 2017;22(2):83-89.
10. Ku LC, Smith PB. Dosing in neonates: special considerations in physiology and trial design. *Pediatr Res.* 2015;77(1-1):2-9.

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M E M O R A N D U M

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

DATE: 6/25/2021

TO: Division of Antivirals (DAV)
Office of Infectious Diseases (OID)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 214518

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS inspected the site in (b) (4), which falls within the surveillance interval. The inspection was conducted under the following submissions: NDAs (b) (4)

The final classification for the inspection was Voluntary Action Indicated (VAI) for the following observations related to NDA (b) (4) only:

- (b) (4)

After review of the inspectional findings and the firm's written response, OSIS recommended that data from NDAs (b) (4) be accepted. (OSIS Final EIR Review – (b) (4)).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

James J. Lumalcuri -S

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