

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208627Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

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

Application Type	NDA 208627
Application Number	208627
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Reviewer Name(s)	Ingrid N. Chapman, Pharm.D., BCPS
Team Leader	Elizabeth Everhart, MSN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	May 11, 2018
Subject	Evaluation of Need for a REMS
Established Name	Tecovirimat
Trade Name	TPOXX
Name of Applicant	Siga Technologies
Therapeutic Class	Antiviral
Formulation(s)	200 mg capsule for oral administration
Dosing Regimen	Adults: 600 mg by mouth twice daily x 14 days Pediatrics: (b) (4) or more: 600 mg by mouth twice daily x 14 days Pediatrics: (b) (4): (b) (4) mg by mouth twice daily x 14 days Pediatrics: (b) (4): 200 mg by mouth twice daily x 14 days

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity TPOXX (tecovirimat) is necessary to ensure the benefits outweigh its risks. Siga Technologies submitted a New Drug Application (NDA 208627) for tecovirimat with the proposed indication: for the treatment of human smallpox disease caused by variola virus in adults and pediatric patients. Because smallpox is a potentially serious threat but does not occur naturally, clinical efficacy trials are not feasible and human challenge studies in healthy subjects are unethical.¹ Therefore, NDA 208627 was submitted for approval under FDA's Animal Rule. The serious risk associated with tecovirimat is hypoglycemia. The applicant did not submit a proposed REMS or risk management plan with this application.

If approved, the labeling will communicate the risks of tecovirimat with Warnings and Precautions specifically highlighting the risk of hypoglycemia. DRISK and the Division of Antiviral Products (DAVP) agree that a REMS is not needed to ensure the benefits of tecovirimat outweigh its risks.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) TPOXX (tecovirimat) is necessary to ensure the benefits outweigh its risks. Siga Technologies submitted a New Drug Application (NDA 208627) for tecovirimat with the proposed indication: for the treatment of human smallpox disease caused by variola virus in adults and pediatric patients. This application is under review in the Division of Antiviral Products (DAVP). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

TPOXX (tecovirimat), a new molecular entity,^a is an antiviral drug with broad activity against orthopoxviruses including variola (smallpox), monkeypox, rabbitpox, and vaccinia. The proposed indication is for the treatment of human smallpox disease. The proposed dosage form is a 200-mg capsule for oral administration. The proposed dose is as follows: 600 mg by mouth twice daily (adults and pediatrics (b) (4) or more); 400 mg by mouth twice daily (pediatrics (b) (4)); 200 mg by mouth twice daily (pediatrics (b) (4)). The treatment duration is 14 days for pediatrics and adults.^b Tecovirimat is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 208627 relevant to this review:

- 11/09/2005: IND 069019 submission received for tecovirimat (ST-246)
- 12/08/2017: NDA 208627 submission for the treatment of smallpox received

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

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

- 03/22/2018: Midcycle telecommunication with the applicant; FDA stated there were no safety issues that require a REMS for tecovirimat.
- 05/01/2018:² The Antimicrobial Drugs Advisory Committee (AMDAC) Meeting was convened to discuss tecovirimat's regulatory considerations, animal efficacy, animal pharmacokinetic data, human safety, and human pharmacokinetic data. The committee voted unanimously, 17/0, that based on the available data, the risk-benefit profile of tecovirimat is acceptable for the treatment of human smallpox.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Smallpox, caused by the variola virus, is a serious, life-threatening, and contagious infectious disease.^c Persons infected with smallpox experience high fevers, head and body aches, pustular rashes and scabs.³ Transmission occurs via face-to-face contact and droplet sharing (coughing and sneezing). The last natural outbreak of smallpox in the U.S. occurred in 1949. The World Health Assembly declared smallpox eradicated in 1980. Current drug research for smallpox focuses on the possibility of it used as an agent of bioterrorism.^d

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The availability of drug therapy for smallpox is limited. Early vaccination attempts began at the end of the 18th century and intensified in 1959 with the Global Smallpox Eradication Program initiated by the World Health Organization (WHO).³ Currently, there is one FDA approved smallpox vaccine indicated for the prevention of smallpox disease, ACAM2000.⁴ There are no FDA approved drugs for the treatment of smallpox. In laboratory tests, the antiviral drugs cidofovir and brincidofovir were effective against the variola virus.³ There is no information regarding the efficacy of these antivirals in persons infected with smallpox.

4 Benefit Assessment^e

The clinical development of tecovirimat was evaluated under FDA's Animal Rule (21 CFR Parts §314.600 through 314.650) with guidance per FDA's Guidance for Industry Product Development Under the Animal Rule.⁵ The two animal models used were non-human primates (NHPs) infected with monkeypox virus (MPXV) and rabbits infected with rabbitpox virus (RPXV). A total of 6 pivotal nonclinical studies (NHPs: 4 studies; rabbits 2 studies) were conducted to evaluate the efficacy of oral tecovirimat in animals. The studies are described in Table 1 below. The clinical reviewer concluded that a statistically significant treatment benefit over placebo was demonstrated for the primary endpoint of survival when

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

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

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

tecovirimat was dosed at 3, 10, and 20 mg/kg/day for 14 days at day 4 post-inoculation (NHP/MPXV) and 20, 40, 80, and 120 mg/kg/day for 14 days at day 4 post-inoculation (rabbit/RPXV).⁶

Table 1:^{5,6} Pivotal In Vivo Efficacy Studies

Study	Type of Study	N	Objective(s)	Results
Nonhuman Primate (cynomolgus monkey)				
FY10-087	<i>Randomized, placebo-controlled, repeat-dose study</i> PK in NHPs infected with MPXV; tecovirimat doses of 3, 10, and 20 mg/kg	24	PK and efficacy in NHPs who received 14 daily doses of tecovirimat or placebo from 4-17 days post-infection with MPXV	<ul style="list-style-type: none"> • Mortality occurred only in subjects receiving placebo. • Doses of at least 3 mg/kg inhibited progression of infection
AP-09-026G	<i>Randomized, double-blind, placebo-controlled, repeat-dose efficacy study</i> To determine the minimum effective therapeutic dose in NHPs infected with MPXV; tecovirimat doses of 0.3, 1, 3, and 10 mg/kg	27	Minimum effective dose of tecovirimat Form I for the treatment of MPXV in the lesional NHP model of smallpox, with tecovirimat or placebo treatment beginning on the day of onset of pox lesions in each animal and continuing for 14 days	<ul style="list-style-type: none"> • Minimum effective dose = 3 mg/kg once daily • 10 mg/kg once daily conferred the greatest protection against mortality
SR10-037F	<i>Randomized, double-blind, placebo-controlled</i> Efficacy of delayed tecovirimat treatment following lethal MPXV challenge in NHPs; tecovirimat dose of 10 mg/kg	21	Maximum delay post MPXV challenge at which 14 daily doses of tecovirimat is effective at preventing mortality in NHPs	<ul style="list-style-type: none"> • Treatment initiated on Day 4 or 5 after viral challenge conferred greater protection against MPXV infection than treatment initiated on Day 6
SR10-038F	<i>Randomized, double-blind, placebo-controlled</i> Efficacy of 3, 5, 7, and 10 daily doses of tecovirimat 10 mg/kg in NHPs infected with MPXV	25	Minimum dose duration post MPXV challenge at which tecovirimat is effective at preventing mortality in NHPs	<ul style="list-style-type: none"> • Treatment durations of at least 7 days conferred the greatest protection against morbidity
Rabbit (New Zealand White rabbit)				
SR13-025F	<i>Randomized, double-blind, repeat-dose efficacy study</i> PK in rabbits infected with RPXV; tecovirimat doses of 40, 80, and 120 mg/kg	24	PK and efficacy in rabbits who received 14 daily doses of tecovirimat from 4-17 days post-infection with RPXV	<ul style="list-style-type: none"> • 40 to 120 mg/kg once daily inhibited progression of infection associated with RPXV infection in rabbits as indicated by the absence of mortality, resolution of lesions, and clearance of RPXV DNA from the peripheral circulation
SR14-008F	<i>Randomized, double-blind, placebo-controlled, repeat-dose efficacy study</i> Dose-response relationship in rabbits infected with RPXV; tecovirimat doses of 20, 40, 80, and 120 mg/kg	50	Minimum efficacious dose that provides maximal survival benefit in rabbits infected with RPXV receiving 14 daily doses of tecovirimat or placebo	<ul style="list-style-type: none"> • No dose-dependent trends were observed, suggesting that the doses used in this study were above the dose-response range for efficacy
MPXV = monkeypox virus; N = sample size; NHP = nonhuman primate; PK = pharmacokinetics; RPXV = rabbitpox virus				

5 Risk Assessment & Safe-Use Conditions

The safety and tolerability of tecovirimat in humans was derived from 11 clinical studies: pivotal study SIGA-246-008, 3 supportive multiple-dose studies (SIGA-246-015, SIGA-246-002, and SIGA-246-004), and 7 supportive single-dose studies (SIGA-246-001, SIGA-246-PO-005, SIGA-246-009, SIGA-246-010, SIGA-246-012, SIGA-246-013, and SIGA-246-018).⁷ Pivotal study SIGA-246-008 and supportive study SIGA-246-015 provide the most relevant safety information as they evaluated the proposed human dosing regimen of tecovirimat (600 mg by mouth twice daily for 14 days).

Study SIGA-246-008 was a Phase 3, multi-center, randomized, double-blind, placebo-controlled study conducted in 452 healthy human subjects to assess the safety, tolerability, and pharmacokinetics of tecovirimat when administered as 600 mg by mouth twice daily for 14 days. Of the 452 randomized subjects, 449 received study drug with tecovirimat (N = 359) or placebo (N = 90). Headache and nausea were the most common treatment emergent adverse events (TEAEs) reported in both groups.⁷

Study SIGA-246-015 was a Phase 1, open-label, parallel, 3-arm, drug-drug interaction study in 78 healthy subjects to evaluate the effect of repeated doses of tecovirimat on the single-dose pharmacokinetics of the probe substrates flurbiprofen, omeprazole, midazolam, bupropion, and repaglinide. All treatments were administered within 30 minutes of consuming a meal of 600 kcal and 25 grams of fat. The dosing regimen was as follows:

- Day 1: single dose of oral flurbiprofen 50 mg, omeprazole 20 mg, and midazolam 2 mg (n = 24) OR repaglinide 2 mg (n = 30) OR bupropion 150 mg (n = 24)
- Days 2-7: washout period
- Days 8 – 21: tecovirimat 600 mg PO BID
- Day 22: single dose of oral flurbiprofen 50 mg, omeprazole 20 mg, and midazolam 2 mg (n = 23) OR repaglinide 2 mg (n = 30) OR bupropion 150 mg (n = 24) in combination with tecovirimat 600 mg PO BID

The serious adverse event (referred to as risk) determined to be associated with tecovirimat is hypoglycemia.^f The Warnings and Precautions section of the proposed tecovirimat label includes this risk and will be discussed below along with the deaths that occurred.

5.1 HYPOGLYCEMIA

Hypoglycemia was identified as an adverse event of special interest in study SIGA-246-015. Ten subjects (33%) reported adverse events of mild hypoglycemia after being administered combination tecovirimat and repaglinide. Four patients (13.3%) experienced further decreases in glucose reading below 50 mg/dL and the adverse event increased to moderate hypoglycemia. It was determined that tecovirimat is a weak inhibitor of cytochrome P450 2C8. The Warnings and Precautions section of the proposed

^f Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

label addresses this risk. The proposed label advises that patients who are co-administered the oral hypoglycemic agent repaglinide should be monitored closely; the label also recommends monitoring patients at risk of hypoglycemia.

5.2 DEATHS

There was a total of 2 deaths in humans throughout tecovirimat clinical development. One subject randomized to tecovirimat in the pivotal study experienced a fatal serious adverse event of pulmonary embolism not considered related to tecovirimat by the FDA. One subject in study SIGA-246-013 (Phase 1, open-label, non-randomized study in patients with varying degrees of hepatic function) with moderate hepatic impairment experienced a fatal serious adverse event of cholecystitis, sepsis, acute myocardial infarction, and acute cardiac arrest determined to be not related to tecovirimat by the FDA.

6 Expected Postmarket Use

Tecovirimat may be prescribed in both the inpatient and outpatient setting. The likely prescribers will potentially be emergency responders during a smallpox public health emergency, general practitioners, and infectious diseases providers. These providers are likely to be familiar with the management of hypoglycemia which is the serious risk associated with tecovirimat. The proposed label currently addresses the associated serious risk and management of hypoglycemia in the Warning and Precautions section.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities beyond labeling and routine pharmacovigilance for tecovirimat.

8 Discussion of Need for a REMS

The Clinical Reviewer concluded that approval of tecovirimat under the FDA's Animal Rule for the treatment of human smallpox disease caused by variola virus infection is fully supported by the available evidence of efficacy and safety.² Smallpox is a serious, life-threatening infection with limited pharmacologic options for treatment and prevention. Tecovirimat is currently available through the Strategic National Stockpile and fills an important unmet medical need.

The serious risk associated with tecovirimat is hypoglycemia. Healthcare providers prescribing tecovirimat are likely to be familiar with managing the risk of hypoglycemia. The labeling will be used to communicate this risk and its associated management. DRISK recommends that, should tecovirimat be approved, a REMS is not necessary to ensure its benefits outweigh its risks.

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 REFERENCES

1. Tecovirimat. FDA Briefing Document. Meeting of the Antimicrobial Drugs Advisory Committee for NDA 208627. . May 1, 2018.
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4. Drugs@FDA: FDA Approved Drug Products. <https://www.accessdata.fda.gov/scripts/cder/daf/>. Accessed March 29, 2018.
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6. Chan-Tack K. Tecovirimat for Treatment of Human Smallpox. Meeting of the Antimicrobial Drugs Advisory Committee for NDA 208627. May 1, 2018.
7. Siga Technologies, Inc. Tecovirimat (TPOXX). Module 2.7.4 - Summary of Clinical Safety. December 8, 2017.

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