PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr TPOXX®

Tecovirimat Capsules

Capsules, 200 mg tecovirimat (as tecovirimat monohydrate), Oral

Antiviral Agent (ATC: J05AX24)

"HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS EXTRAORDINARY USE NEW DRUG FOR TREATMENT OF HUMAN SMALLPOX DISEASE IN ADULTS AND PEDIATRIC PATIENTS WEIGHING AT LEAST 13KG BASED ON LIMITED CLINICAL TESTING IN HUMANS"

Sponsor:

SIGA Technologies, Inc.

4575 Research Way, Ste. 110

Corvallis, OR 97333

USA

Distributor:

Innomar Strategies, Inc

Oakville, ON L6L 0C4

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RECENT MAJOR LABEL CHANGES

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Sections or subsections that are not applicable at the time of authorization are not listed.

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1. INDICATIONS

EUND TPOXX (tecovirimat capsules) is indicated for the treatment of human smallpox disease in adults and pediatric patients weighing at least 13kg.

1.1. Pediatrics

Pediatrics (≥13 kg): Health Canada has authorized an extraordinary use indication for pediatric patients weighing ≥13 kg. No clinical studies in pediatric patients are available. Pharmacokinetic simulation was used to derive the dosing regimens of TPOXX in pediatric patients that are predicted to be comparable to adult exposure from the recommended dose of TPOXX.

Pediatrics (<13 kg): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2. Geriatrics

Geriatrics (≥65 years of age): Clinical studies of TPOXX did not include sufficient numbers of subjects aged 65 and over to determine whether the safety profile of TPOXX is different in this population compared to younger subjects.

2. CONTRAINDICATIONS

TPOXX is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition and Packaging.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

EUND

4.2 Recommended Dose and Dosage Adjustment

The recommended dosage of TPOXX in adults and pediatric patients weighing at least 40 kg is 600 mg (three 200 mg capsules) taken twice daily orally for 14 days. TPOXX should be taken within 30 minutes after a full meal of moderate or high fat.

Dosage for Pediatric Patients and Those Who Cannot Swallow Capsules

The recommended dosage for pediatric patients is based on weight starting at 13 kg as shown in Table 1. The dose should be given twice daily orally for 14 days and should be taken within 30 minutes after a full meal of moderate or high fat.

Preparation Instructions:

- Carefully open the capsule so that the contents do not spill or escape into the air.
- Hold the capsule with the cap facing up and pull the cap away from the body of the capsule.
- Use a small container for mixing.
- Mix the entire contents of the capsule with 30 mL of liquid (e.g. milk, chocolate milk) or soft food (e.g. yogurt, applesauce).
- The mixture should be taken within 30 minutes after mixing and within 30 minutes of eating a meal.

Table 1: Recommended Pediatric and Adult Dosage and Preparation Instructions

Body Weight	Dosage	Number of Capsules	Drug-Food Preparation
13 kg to less than 25 kg	200 mg twice daily	Contents of 1 Capsule twice daily	Mix 1 capsule of TPOXX with 30 mL of liquid (e.g. milk, chocolate milk) or soft food (e.g. yogurt, applesauce). Administer the whole mixture.
25 kg to less than 40 kg	400 mg twice daily	Contents of 2 Capsules twice daily	Mix 2 capsules of TPOXX with 30 mL of liquid (e.g. milk, chocolate milk) or soft food (e.g. yogurt, applesauce). Administer the whole mixture.
40 kg and above	600 mg twice daily	Contents of 3 Capsules twice daily	Mix 3 capsules of TPOXX with 30 mL of liquid (e.g. milk, chocolate milk) or soft food (e.g. yogurt, applesauce). Administer the whole mixture.

Renal Impairment

No dose adjustment of TPOXX is required for patients with renal impairment (see Pharmacokinetics, Special Populations and Conditions).

Hepatic Impairment

No dose adjustment of TPOXX is required for patients with hepatic impairment (see Pharmacokinetics, Special Populations and Conditions).

4.4 Administration

The recommended dose should be administered orally and should be taken within 30 minutes after a full meal of moderate or high fat (containing approximately 25 grams of fat) to ensure proper tecovirimat absorption.

4.5 Missed Dose

If a dose of TPOXX is missed, the patient should be advised to take it as soon as the patient remembers, and then continue with the next dose at the proper time interval.

5 OVERDOSAGE

There is no clinical experience with overdosage of TPOXX. In case of overdosage, monitor patients for any signs or symptoms of adverse effects. Hemodialysis will not significantly remove TPOXX in overdosed patients.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Tecovirimat capsules are orange/black opaque hard gelatin capsule, size “0”, containing 200 mg of tecovirimat (as tecovirimat monohydrate). The capsules are imprinted with white ink with “SIGA” and the SIGA symbol followed by “®” on an orange body and with “ST-246®”on the black cap. TPOXX capsules are supplied in an HDPE plastic bottle containing 42 opaque hard-shell capsules.

Table 2: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsule, 200 mg	Colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, lactose monohydrate magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate. The capsule shell contains gelatin, FD&C Blue No. 1, FD&C Red No. 3, FD&C Yellow No. 6, and titanium dioxide. The printing ink contains ammonium hydroxide, isopropyl alcohol, n-butyl alcohol, propylene glycol, simethicone, shellac, and titanium dioxide.

7 WARNINGS AND PRECAUTIONS

General

The efficacy of TPOXX for treatment of smallpox disease has not been determined in humans because adequate and well-controlled field trials have not been feasible, and inducing smallpox disease in humans to study the drug's efficacy is not ethical. The efficacy of TPOXX is based solely on efficacy studies in animal models of orthopoxvirus disease (see Clinical Trials).

Endocrine and Metabolism

Co-administration of repaglinide and TPOXX may cause mild to moderate hypoglycemia. Monitor blood glucose and monitor for hypoglycemic symptoms when administering TPOXX with repaglinide.

In a drug interaction study, 10 of 30 healthy subjects experienced mild (6 subjects) or moderate (4 subjects) hypoglycemia following co-administration of repaglinide (2 mg) and TPOXX. Symptoms resolved in all subjects after intake of food and/or oral glucose.

Taking TPOXX may reduce the effects of the medicine midazolam, a medicine used for the treatment of seizures, anxiety, or sleeping problems. Talk to your doctor or pharmacists before taking TPOXX if you are taking midazolam.

Immune

TPOXX efficacy may be reduced in immunocompromised patients based on studies demonstrating reduced efficacy in immunocompromised animal models.

Live animal studies have indicated that co-administration of TPOXX at the same time as live smallpox vaccine (vaccinia virus) may reduce the immune response to the vaccine. The clinical impact of this is unknown.

QTc Interval Prolongation

TPOXX has been reported to cause prolongation of the QTc interval (see CLINICAL PHARMACOLOGY, Cardiac Electrophysiology). Caution should be observed if TPOXX is administered to patients who are considered to be at a high risk of the torsade de pointes arrhythmia, including, but not limited to, those with congenital or acquired long QT syndrome, other cardiac disease, electrolyte depletion (e.g., hypokalemia, hypomagnesemia, or hypocalcemia) or conditions that can lead to electrolyte depletion, or in situations of concomitant treatment with Class IA or Class III antiarrhythmics or other QTc-prolonging drugs (see DRUG INTERACTIONS, QT/QTc Prolonging Drugs). Torsade de pointes can be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

Reproductive Health - Fertility

There is no data on the effects on fertility in humans. In male mice decreased fertility associated with testicular toxicity (increased percent abnormal sperm and decreased

sperm motility) was observed at 1000 mg/kg/day (approximately 24 times the human exposure at RHD) (see Non-Clinical Toxicology).

7.1 Special Populations

7.1.1 Pregnant Women

TPOXX has not been studied in pregnant women. TPOXX should not be used during pregnancy unless the benefits outweigh the risks.

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 Non-Clinical Toxicology).

The background risk of major birth defects and miscarriage for the indicated population is unknown.

7.1.2 Breast-feeding

It is unknown if TPOXX is excreted in human milk. Because many drugs are excreted in human milk, precaution should be exercised. When administered to lactating mice, tecovirimat was present in the milk. 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.

7.1.3 Pediatrics

Based on the data submitted and reviewed, Health Canada has authorized an extraordinary use indication for pediatric populations ≥13 kg.

As in adults, the effectiveness of TPOXX in pediatric patients is based solely on efficacy studies in animal models of orthopoxvirus disease. As exposure of healthy pediatric subjects to TPOXX with no potential for direct clinical benefit is not ethical, pharmacokinetic simulation was used to derive dosing regimens that are predicted to provide pediatric patients with exposures comparable to the observed exposure in adults receiving 600 mg twice daily. The dosage for pediatric patients is based on weight.

7.1.4 Geriatrics

Clinical studies of TPOXX did not include sufficient numbers of subjects aged 65 and over to determine whether the safety profile of TPOXX is different in this population compared to younger subjects. Of the 359 subjects in the TPOXX clinical study, 10%

(36/359) were ≥ 65 years of age, and 1% (4/359) were ≥ 75 years of age. No alteration of dosing is needed for patients ≥ 65 years of age

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

EUND Because clinical trials are conducted under very specific conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of TPOXX has not been studied in patients with smallpox disease.

8.2 Clinical Trial Adverse Reactions

The safety of TPOXX was evaluated in 359 healthy adult subjects ages 18-79 years in a Phase 3 clinical trial. Of the subjects who received at least one 600 mg dose of TPOXX, 59% were female, 69% were White, 28% were Black/African American, 1% were Asian, and 12% were Hispanic or Latino. Ten percent of the subjects who participated in the study were age 65 or older. Of these 359 subjects, 336 subjects received at least 23 of 28 doses of 600 mg TPOXX in a twice daily regimen for 14 days.

Most Frequently Reported Adverse Reactions

The most frequently reported adverse reactions were headache and nausea. Adverse reactions that occurred in at least ≥1% of subjects in the TPOXX treatment group are shown in Table 3.

Table 3: Adverse Reactions Reported in ≥1% of Healthy Adult Subjects Receiving at Least One Dose of TPOXX® 600 mg

Adverse Reaction	**TPOXX 600 mg N = 359 (%)**	**Placebo N = 90 (%)**
Very Common (≥10%) Headache	12	8
Common (≥1%) Nausea	5	4
Abdominal pain[a]	2	1
Vomiting	2	0

[a]Includes abdominal pain, abdominal pain upper, abdominal distension, abdominal discomfort, abdominal pain lower, epigastric pain

Adverse Reactions Leading to Discontinuation of TPOXX

Six subjects (2%) had their treatment with TPOXX discontinued due to adverse reactions. Each of these subject's adverse reactions (with severity) is listed below:

- EEG change, abnormal
- Mild upset stomach, dry mouth, decreased concentration and dysphoria
- Mild nausea and fever, moderate diarrhea, severe headache
- Mild palpable purpura
- Mild nausea, fever and chills
- Mild facial redness, facial swelling and pruritus

8.2.1 Clinical Trial Adverse Reactions (Pediatrics)

Since conducting studies in healthy children is unethical, pediatric safety studies have not been conducted.

8.3 Less Common Clinical Trial Adverse Reactions

Clinically significant adverse reactions that were reported in <1% of subjects exposed to TPOXX and at rates higher than subjects who received placebo are listed below:

- Gastrointestinal: dry mouth, chapped lips, dyspepsia, eructation, oral paresthesia
- General and administration site: pyrexia, pain, chills, malaise, thirst
- Investigations: abnormal electroencephalogram, hematocrit decreased, hemoglobin decreased, heart rate increased
- Musculoskeletal and connective tissue: arthralgia, osteoarthritis
- Nervous system: migraine, disturbance in attention, dysgeusia, paresthesia
- Psychiatric: depression, dysphoria, irritability, panic attack
- Respiratory, Thoracic and Mediastinal Disorders: oropharyngeal pain
- Skin and subcutaneous tissue: palpable purpura, rash, pruritic rash, facial redness, facial swelling, pruritus

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

No abnormal laboratory findings have been found in clinical trials with TPOXX. Clinical trials were only conducted in healthy adults so these findings may not be reflective of use in the target patient population.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Tecovirimat is a weak inducer of cytochrome P450 (CYP) 3A4 and a weak inhibitor of CYP2C8 and CYP2C19. However, the effects are not expected to be clinically relevant for most substrates of those enzymes based on the magnitude of interactions and the duration of treatment of TPOXX. Tecovirimat is a substrate of UGT1A1 and UGT1A4. Tecovirimat inhibited Breast Cancer Resistance Protein (BCRP) *in vitro*. See Table 4 for clinical recommendations for select sensitive substrates.

9.3 Drug-Behavioral Interactions

No studies on the effects on the ability and use of machines have been performed. However, there is no evidence from the available data that TPOXX treatment affects the ability to drive and use machines.

9.4 Drug-Drug Interactions

The following table provides a list of established drug interactions. Interactions with other drugs have not been studied at this time.

Table 4: Established or Potential Drug-Drug Interactions

Concomitant Drug Class: Drug Name	Source of Evidence	Effect on Concentration[a]	Clinical Comment
Blood Glucose-Lowering Agent:			
Repaglinide[b]	Clinical Trial	↑ repaglinide	Monitor blood glucose and monitor for hypoglycemic symptoms in patients when TPOXX is co-administered with repaglinide.
CNS Depressant:			
Midazolam[b]	Clinical Trial	↓ midazolam	Monitor for effectiveness of midazolam.

[a] ↓ = decrease, ↑ = increase
[b] These interactions have been studied in healthy adults.

QT/QTc Prolonging Drugs

Caution should be observed if TPOXX is administered in combination with drugs that cause QT/QTc interval prolongation (see WARNINGS AND PRECAUTIONS, QTc Interval Prolongation & CLINICAL PHARMACOLOGY, Cardiac Electrophysiology). Current information sources should be consulted for lists of drugs that cause QT/QTc prolongation.

Drugs that Can Reduce Serum Electrolyte Levels

Caution should be observed if TPOXX is administered with drugs that can decrease serum levels of potassium, magnesium, and/or calcium because of potential augmentation of the QTc prolongation effect (see WARNINGS AND PRECAUTIONS,

Cardiovascular & CLINICAL PHARMACOLOGY, Cardiac Electrophysiology). Drugs that can decrease serum electrolyte levels include, but are not limited to, loop, thiazide, and related diuretics.

9.5 Drug-Food Interactions

Absorption of tecovirimat increased by approximately 40-50% (as measured by C_{max} and AUC_{0-24}) when TPOXX was administered with a full meal of moderate or high fat (containing approximately 25 grams of fat), as compared to administration in the fasted state.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10. 1 Mechanism of Action

Tecovirimat targets and inhibits the activity of the orthopoxvirus VP37 protein (encoded by a highly conserved gene in all members of the orthopoxvirus genus). Tecovirimat blocks the interaction of VP37 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.

10.2 Pharmacodynamics

Cardiac Electrophysiology

In a double-blind, placebo- and positive-controlled, randomized, crossover ECG assessment study in healthy subjects (N=48), tecovirimat administered as a single supratherapeutic dose of 1000 mg was associated with a maximum difference from placebo in mean change from baseline QTcF of 5.1 ms (90% CI 2.9, 7.3) at 4 h post-dosing. Following the 1000 mg single dose of tecovirimat, the mean C_{max} values were 2500 ng/mL for tecovirimat, 710 ng/mL for the M4 metabolite, 121 ng/mL for the M5 metabolite, and 4250 ng/mL for the TFMBA metabolite.

This ECG assessment study did not achieve therapeutic plasma concentrations of the metabolites of tecovirimat. In healthy subjects (N=48) receiving the therapeutic 600 mg BID dose for 14 days under fed conditions, the mean C_{max} values were reported to be 2209 ng/mL for tecovirimat, 1290 ng/mL for the M4 metabolite, 665 ng/mL for the M5 metabolite, and 7956 ng/mL for the TFMBA metabolite.10.3 Pharmacokinetics

Comparison of Animal and Human PK Data to Support Effective Human Dose Selection

Because the effectiveness of TPOXX cannot be tested in humans, a comparison of tecovirimat exposures achieved in healthy human subjects to those observed in animal models of orthopoxvirus infection (nonhuman primates and rabbits infected with monkeypox virus and rabbitpox virus, respectively) in therapeutic efficacy studies was necessary to support the dosage regimen of 600 mg twice daily for treatment of smallpox disease in humans. Humans achieve greater systemic exposure (AUC, C_{max}, and C_{min}) of tecovirimat following a twice daily dose of 600 mg when compared to the therapeutic exposures in these animal models.

Human pharmacokinetic data from a Phase 3 safety study (SIGA-246-008) is presented in Table 5. The data presented is taken from healthy, fed, male and female subjects, 18-72 years of age who had taken TPOXX 600 mg twice daily for 14 days.

Table 5: Summary of TPOXX Pharmacokinetic Parameters in Healthy Adults

	C_{max} (ng/mL) N=48	**C_{min}** N=48	**T_{max} (h)** N=48	**$t_{½}$ (h)** N=48	**AUC_{0-24h} (ng.h/mL)** N=48	**$AUC_{0-\infty}$ (ng.h/mL)** N=16	**CL (CL/F, L/h)** N=167	**Vd (Vz/F, L)** N=16
Steady State (mean)[a]	2209[d]	690	4[b]	19.3[c]	30632	50975[d]	20.8	572

[a]Values listed are arithmetic mean values
[b]Value reflects administration of drug with food.
[c]Value refers to mean terminal plasma half-life.
[d]600 mg BID on Day 14 in fed subjects.

Absorption: Tecovirimat reaches maximum plasma concentrations 4 to 6 hours after oral administration.

Distribution: Tecovirimat is 77.3-82.2% bound to human plasma proteins at concentrations between 0.03 and 50 µM. After a single 600 mg dose of [^{14}C]-tecovirimat in healthy subjects, concentrations of total radioactivity were lower in whole blood compared to plasma at all time points, with ratios of whole blood to plasma ranging from 0.62-0.90 across all time points. Tecovirimat has a high volume of distribution (572 L).

Metabolism: Tecovirimat is metabolized by hydrolysis of the amide bond and glucuronidation. The following inactive metabolites were detected in plasma: M4 (N-{3,5-dioxo-4-azatetracyclo[5.3.2.0{2,6}.0{8,10}]dodec-11-en-4-yl}amine), M5 (3,5 dioxo-4-aminotetracyclo[5.3.2.0{2,6}.0{8,10}]dodec-11-ene), and TFMBA (4 (trifluoromethyl) benzoic acid).

Elimination: After a single dose of [^{14}C]-tecovirimat in healthy subjects, approximately 95% of the [^{14}C]-radioactivity was recovered in urine and feces over the 192-hour post-dose period, with approximately 73% of the [^{14}C]-radioactivity administered being recovered in urine and 23% being recovered in feces, indicating that the renal pathway is the major route of excretion. The renal excretion of parent compound was minimal, accounting for less than 0.02%. The majority of drug excreted by the renal system is in

a glucuronidated form of drug and metabolite. In feces, the excretion was mainly unchanged tecovirimat. The terminal half-life was 19.3 hours.

Special Populations and Conditions

No clinically significant differences in the pharmacokinetics of tecovirimat in healthy adults were observed based on age, gender, or race.

TPOXX pharmacokinetics has not been evaluated in pediatric patients.
The recommended pediatric dosing regimen is expected to produce tecovirimat exposures that are comparable to those in adult subjects based on a population pharmacokinetic modeling and simulation approach.

Pregnancy and Breast-feeding*:* Studies have not been performed in pregnant and/or breast-feeding women. Therefore, no pharmacokinetic data are available in this specific population.

Hepatic Insufficiency*:* In a dedicated study in subjects with mild, moderate, or severe hepatic insufficiency (based on Child Pugh Scores A, B, or C), no clinically significant differences in the pharmacokinetics of tecovirimat were observed. No dosage adjustment is required for patients with mild, moderate, or severe hepatic insufficiency (Child Pugh Class A, B, or C).

Renal Insufficiency*:* In a dedicated study in subjects with renal insufficiency (based on estimated GFR), no clinically significant differences in the pharmacokinetics of tecovirimat were observed. No dosage adjustments are required for patients with mild, moderate, or severe renal impairment or patients with end-stage renal disease requiring hemodialysis.

Obesity*:* No studies have been conducted in individuals with obesity.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15-25°C).

This medicine should not be used after the expiry date shown on the bottle.

12 SPECIAL HANDLING INSTRUCTIONS

Disposal of Unused/Expired Medicines

The release of pharmaceuticals into the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

13. PHARMACEUTICAL INFORMATION

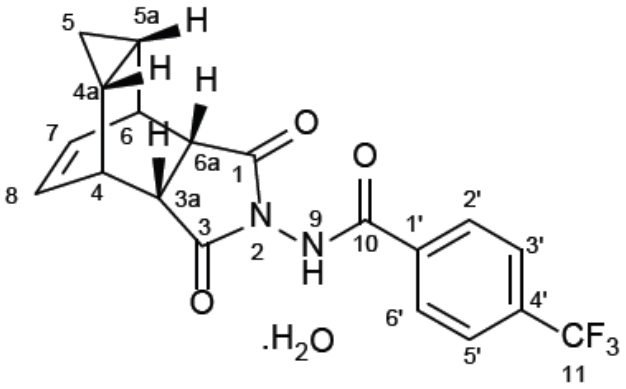
Drug Substance

Proper/Common name: Tecovirimat monohydrate

Chemical name: Benzamide, N-[(3aR,4R,4aR,5aS,6S,6aS)-3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl]-4-(trifluoromethyl), rel-(monohydrate)

Molecular formula and molecular mass: $C_{19}H_{15}F_3N_2O_3 \cdot H_2O$ (394.35 g/mol)

Structural formula:



Physicochemical properties: Tecovirimat monohydrate is a white to off-white solid substance, with a pK_a of 7.77. Tecovirimat monohydrate has a solubility of 1.6 – 4 µg/mL in aqueous buffers (pH 1.2-6.8) at 37°C and has a classification of BCS Class II in regards to solubility.

14 CLINICAL TRIALS

The efficacy of TPOXX for treatment of smallpox disease has not been determined in humans because adequate and well-controlled field trials have not been feasible, and inducing smallpox disease in humans to study the drug's efficacy is not ethical. Therefore, the efficacy of TPOXX for treatment of smallpox was established based on results of adequate and well-controlled animal efficacy studies of non-human primates and rabbits infected with non-variola orthopoxviruses. Survival rates observed in the animal studies may not be predictive of survival rates in clinical practice.

14.1 Trial Design and Study Demographics

Efficacy studies were conducted in cynomolgus macaques infected with monkeypox virus, and New Zealand White (NZW) rabbits infected with rabbitpox virus. The primary efficacy endpoint for these studies was survival. In non-human primate studies, cynomolgus macaques were lethally challenged intravenously with 5×10^7 plaque-forming units of monkeypox virus; tecovirimat was administered orally once daily at a dose level of 10 mg/kg for 14 days, starting at Day 4, 5 or 6 post-challenge. In rabbit studies, NZW rabbits were lethally challenged intradermally with 1,000 plaque-forming units of rabbitpox virus; tecovirimat was administered orally once daily for 14 days at a dose level of 40 mg/kg, starting at Day 4 post-challenge. The timing of tecovirimat dosing in these studies was intended to assess efficacy when treatment is initiated after animals have developed clinical signs of disease, specifically dermal pox lesions in cynomolgus macaques, and fever in rabbits. Clinical signs of disease were evident in some animals at Day 2-3 post-challenge but were evident in all animals by Day 4 post-challenge. Survival was monitored for 3-6 times the mean time to death for untreated animals in each model.

Table 6: Summary of Nonclinical Trials in Treatment of Orthopox Infections (Efficacy Studies)

Study No.	Species	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex (M/F)
FY10-087	Cynomolgus monkey (*Macaca fascicularis*)	Randomized, placebo-controlled, repeat-dose, unblinded in non-human primates following lethal monkeypox virus challenge	0, 3, 10, 20 mg/kg, oral tecovirimat, 14 days	n=6 per dose group	3-4 years	50% male / 50% female
AP-09-026G	Cynomolgus monkey (*Macaca fascicularis*)	Double-blinded, randomized, placebo-controlled, repeat-dose in non-human primates	0, 0.3, 1, 3, and 10 mg/kg, oral tecovirimat, 14 days	N=5 per dose group, N=7 in 0 mg/kg dose group	2.5-4 years	100% male
SR10-037F	Cynomolgus monkey (*Macaca fascicularis*)	Double-blinded, randomized, placebo-controlled, treatment delay, repeat-dose in non-human primates	0, 10 mg/kg, oral tecovirimat, 14 days	N=3 in 0 mg/kg dose group N=6 for 10 mg/kg dosing groups (days 4, 5, and 6 post-MPXV inoculation)	3.27-3.50 years	67% male/ 33% female (placebo) 50% male / 50% female (10 mg/kg groups)
SR10-038F	Cynomolgus monkey (*Macaca fascicularis*)	Double-blinded, placebo-controlled treatment duration, repeat-dose in non-human primates	0, 10 mg/kg, oral tecovirimat, for 3, 5, 7, or 10 days	N=4 in 0 mg/kg dose group N=4 for 10 mg/kg dosing group (3 doses post- MPXV inoculation) N=6 for 10 mg/kg dosing groups (5, 7, 10 doses post-MPXV inoculation	3.81-5.05 years	50% male / 50% female (0, 10 mg/kg, 3, 5, 7 doses post-inoculation) 40% male/60% female (10 mg/kg, 10 doses post- MPXV post inoculation)
SR14-008F	New Zealand White rabbits (*Oryctolagus cuniculus*)	Double-blinded, randomized, placebo-controlled, repeat-dose in New Zealand white rabbits	0, 20, 40, 80, 120 mg/kg, oral tecovirimat, 14 days	N=10 per dose group	14 weeks	50% male / 50% female
SR13-025F	New Zealand White rabbits (*Oryctolagus cuniculus*)	Double-blinded, randomized, repeat-dose study in New Zealand white rabbits	40, 80, 120 mg/kg, oral tecovirimat, 14 days	N=8 per dose group	13-14 weeks	50% male / 50% female

14.2 Study Results

Treatment with tecovirimat for 14 days resulted in statistically significant improvement in survival relative to placebo, except when given to cynomolgus macaques starting at Day 6 post-challenge (Table 7).

Table 7: Survival Rates in Tecovirimat Treatment Studies in Cynomolgus Macaques and NZW Rabbits Exhibiting Clinical Signs of Orthopoxvirus Disease

	Treatment Initiation[a]	Survival Percentage (No. survived/n)		p-value[b]	Survival Rate Difference[c] (95% CI)[d]
		Placebo	Tecovirimat		
Cynomolgus Macaques					
AP-09-026G	Day 4	0% (0/7)	80% (4/5)	0.0038	80% (20.8%, 99.5%)
FY10-087	Day 4	0% (0/6)	100% (6/6)	0.0002	100% (47.1%, 100%)
SR10-037F	Day 4	0% (0/3)	83% (5/6)	0.0151	83% (7.5%, 99.6%)
	Day 5		83% (5/6)	0.0151	83% (7.5%, 99.6%)
	Day 6		50% (3/6)	0.1231	50% (-28.3%, 90.2%)
SR10-038F	Day 4 (3 doses)	25% (1/4)	50% (2/4)	0.3643	25% (-51.0%, 83.0%)
	Day 4 (5 doses)		100% (6/6)	0.0141	75% (8.1%, 99.4%)
	Day 4 (7 doses)		100% (6/6/)	0.0141	75% (8.1%, 99.4%)
	Day 4 (10 doses)		80% (4/5)	0.0972	55% (-20.9%, 93.7%)
NZW Rabbits					
SR14-008F	Day 4	0% (0/10)	90% (9/10)	< 0.0001	90% (50.3%, 99.8%)
SR13-025F	Day 4	NA[e]	88% (7/8)	NA	NA

[a]Day post-challenge tecovirimat treatment was initiated.
[b]p-value is from 1-sided Boschloo Test (with Berger-Boos modification of gamma = 0.000001) compared to placebo.
[c]Survival percentage in tecovirimat treated animals minus survival percentage in placebo treated animals.
[d]Exact 95% confidence interval based on the score statistic of difference in survival rates.
[e]A placebo control group was not included in this study.
KEY: NA = Not Applicable

15 MICROBIOLOGY

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.

Activity in Cell Culture

In cell culture assays, the effective concentrations of tecovirimat resulting in a 50% reduction in virus-induced cytopathic effect (EC_{50}), were 0.016-0.067 µM, 0.014-0.039 µM, 0.015 µM, and 0.009 µM, for variola, monkeypox, rabbitpox, and vaccinia viruses, respectively. Ranges given for variola and monkeypox viruses are reflective of results from multiple strains assayed.

Resistance

There are no known instances of naturally occurring tecovirimat resistant orthopoxviruses, although tecovirimat resistance may develop under drug selection. Tecovirimat has a relatively low resistance barrier, and certain amino acid substitutions in the target VP37 protein can confer large reductions in tecovirimat antiviral activity. The possibility of resistance to tecovirimat should be considered in patients who either fail to respond to therapy or who develop recrudescence of disease after an initial period of responsiveness.

Cross Resistance: There are no other antiviral drugs approved for the treatment of orthopoxvirus infections.

16 NON-CLINICAL TOXICOLOGY

In a repeat-dose toxicology study in dogs, convulsions (tonic and clonic) were observed in one animal within 6 hours of a single dose of 300 mg/kg (approximately 4 times higher than the highest observed human exposure at the RHD based on C_{max}). Electroencephalography (EEG) findings in this animal were consistent with seizure activity during the observed convulsions. Tremors, which were considered non-adverse, were observed in 2 out of 3 animals and 1 out of 2 animals at 100 mg/kg/dose (similar to the highest observed human exposure at the RHD based on C_{max}), in two separate studies. No EEG findings were noted at 100 mg/kg/dose; however, convulsions were observed in 2 out of 3 animals in one study and were not observed in 2 animals administered this dose in another study. These findings were specific to dogs and not observed in other species.

Carcinogenicity

Carcinogenicity studies have not been conducted with tecovirimat.

Genotoxicity

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$^{\pm}$ cells, and in an *in vivo* mouse micronucleus study.

Reproductive and Developmental Toxicology

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).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

TPOXX®

Tecovirimat Capsules, 200 mg

Read this carefully before you start taking TPOXX and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about TPOXX.

"HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS EXTRAORDINARY USE NEW DRUG FOR TREATMENT OF HUMAN SMALLPOX DISEASE IN ADULTS AND PEDIATRIC PATIENTS WEIGHING AT LEAST 13KG BASED ON LIMITED CLINICAL TESTING IN HUMANS."

What is TPOXX used for?

TPOXX is used to treat smallpox disease in adults and in children and adolescents who weigh at least 13 kilograms (kg).

How does TPOXX work?

TPOXX stops the virus that causes smallpox disease from spreading from cell to cell within the body. This prevents the virus from spreading through your body. Your own body can then build up protection against the virus until you are better.

What are the ingredients in TPOXX?

Medicinal ingredients: Tecovirimat monohydrate

Non-medicinal ingredients: ammonium hydroxide, colloidal silicon dioxide, crocarmellose sodium, FD&C Blue No. 1, FD&C Red No. 3, FD&C Yellow No. 6, gelatin hydroxypropyl methylcellulose, isopropyl alcohol, lactose monohydrate, magnesium stearate microcrystalline cellulose, n-butyl alcohol, propylene glycol, shellac, simethicone, sodium lauryl sulfate, and titanium dioxide.

TPOXX comes in the following dosage forms:

As capsules containing 200 mg tecovirimat (as tecovirimat monohydrate).

Do not use TPOXX if:

- You are allergic to tecovirimat.
- You are allergic to any of the other ingredients in TPOXX or a component of the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TPOXX. Talk about any health conditions or problems you may have, including if you:

- Have a weakened immune system. TPOXX may not work as well for you.
- Plan to receive a live smallpox vaccine. Taking TPOXX at the same time may make the vaccine less effective.
- Are taking the medicine repaglinide, used to treat diabetes. Taking TPOXX along with repaglinide may make your blood sugar too low.
- Are taking the medicine midazolam, used to treat seizures, anxiety and sleep problems. TPOXX may make midazolam less effective.
- Are pregnant, think you might be pregnant or are planning to become pregnant.
- Are breastfeeding.

Other warnings you should know about:

Talk to your doctor or pharmacist before taking TPOXX.

TPOXX has only been studied in adults. It has not been studied in children and adolescents 17 years of age and younger. The effectiveness of TPOXX has only been studied in animals. It has not been studied in people with smallpox disease.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following drugs may interact with TPOXX:

- Repaglinide, used to treat diabetes.
- Midazolam, used to treat seizures, anxiety and sleep problems.

How to take TPOXX:

- Always take TPOXX exactly as your healthcare professional has told you.
- Check with your healthcare professional if you are not sure.
- Always take TPOXX with food.
- TPOXX must be taken no more than 30 minutes after eating a full meal of moderate or high fat. This is to make sure that TPOXX is absorbed by your body properly. A meal of moderate to high fat contains about 25 grams of fat. Talk to

your healthcare professional if you are not sure what kind of meal you should eat with TPOXX.

- Do not stop taking this medicine without consulting your healthcare professional first.
- You must take TPOXX for the full 14-day treatment period for it to work properly. Do not miss or skip a dose.
- **If you find swallowing capsules difficult, your healthcare professional may recommend opening the capsules and mixing with food. Follow these instructions:**
  - Wash and dry your hands before and after preparation.
  - Carefully open the capsule so that the contents do not spill or escape into the air.
  - Hold the capsule with the cap facing up and pull the cap away from the body of the capsule.
  - Empty the capsule contents into a small container for mixing.
  - Mix the entire contents of the capsule with 30 mL of liquid such as milk or chocolate milk or soft food such as yogurt or applesauce.
  - The mixture should be taken within 30 minutes after mixing and within 30 minutes of eating a meal.
  - Swallow the entire mixture to make sure the entire dose is taken.
  - Throw away the empty capsule shell.
  - Refer to the dosing information under “Usual dose” for the contents of how many capsules you should be taking. This differs for adults, children and adolescents.

Usual dose:

Adults:

Three capsules every 12 hours for 14 days. TPOXX must be taken no more than 30 minutes after a full meal that contains moderate or high fat.

Children and Adolescents who weight at least 13 kg:

The amount of TPOXX that children and adolescents should take depends on their weight in kilograms (kg). See table below for details. **This medicine is not recommended for use in children who weigh less than 13 kg.** TPOXX must be taken no more than 30 minutes after a full meal that contains moderate or high fat.

Recommended Doses for Children and Adolescents

Body Weight	TPOXX Dose
13 kg to less than 25 kg	One capsule every 12 hours for 14 days
25 kg to less than 40 kg	Two capsules every 12 hours for 14 days
40 kg and above	Three capsules every 12 hours for 14 days

Overdose:

If you think you have taken too much TPOXX, contact your healthcare professional, hospital emergency department or regional poison control center immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of TPOXX, take it as soon as you remember. Take you next dose at the regularly scheduled time.

What are possible side effects from using TPOXX?

These are not all the possible side effects you may feel when taking TPOXX. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Dizziness
- Nausea or vomiting
- Diarrhea
- Dry mouth
- Feeling tired or sleeping
- Being unable to concentrate or having a low attention span
- Experiencing taste disturbances
- Constipation
- Indigestion or upset stomach
- Abdominal pain or discomfort
- Chapped lips
- Belching or burping

- Joint pain or stiffness
- Fever
- Chills
- Generally feeling unwell (malaise)
- Feeling thirsty

Serious Side effects and what to do about them			
Symptom/ effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Headache	✓		
COMMON			
Abdominal Pain	✓		
RARE			
Red or purple spots on the skin that do not turn white when applying pressure		✓	
Mouth pain		✓	
Facial swelling, redness or itchiness		✓	
Feeling uneasy or dissatisfied	✓		
Depression or anxiety		✓	
Irritability	✓		
Panic attack: feeling of loss of control or danger, shortness of breath, shaking		✓	
Tingling or numbness in the hands, feet, or mouth		✓	
Itching, rash, or hives			✓
Pain	✓		
Abnormal scan of electrical activity of the brain called an electrocephalogram		✓	
Blood test result that shows you have lower numbers of red blood cells than usual		✓	
Increased heart rate		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

- You can report any suspected side effects associated with the use of health products to Health Canada by:
- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
  Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store TPOXX at room temperature (15°C to 25°C).

Do not use this medicine after the expiry date shown on the bottle.

Keep out of reach and sight of children.

If you want more information about TPOXX:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.siga.com or by calling 1-888-899-3472.

This leaflet was prepared by SIGA Technologies, Inc.

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