Dear Healthcare Provider:

To facilitate a therapeutic option for patients with orthopoxvirus infection in the United States, the Centers for Disease Control and Prevention (CDC) has an expanded access Investigational New Drug application (IND 116039) filed with FDA to allow access to and use of stockpiled tecovirimat for non-variola orthopoxvirus infections. Tecovirimat (available as oral capsules and injection) is FDA approved for treatment of smallpox but its use for other orthopoxvirus infections (e.g., monkeypox virus) is considered unapproved by FDA, requiring use under IND. On May 18, 2022, injection formulation of tecovirimat (brand name TPOXX) also received FDA-approval for smallpox treatment in adults and pediatric patients weighing at least 3 kg.

The CDC-sponsored IND 116039/Protocol #6401 is for treatment purposes only (i.e., non-research). To reduce the logistical and regulatory burden of individual hospitals or other sites from having to procure tecovirimat, develop an IND treatment protocol, obtain FDA permission, and comply with FDA's IND regulations, including IRB approval per 21 CFR parts 50 and 56, CDC holds an expanded access IND that is in effect with FDA, which permits distribution and use of tecovirimat for treatment of patients with orthopoxvirus infection in the United States.

Expiry dating:
Please note that the immediate container/packaging of tecovirimat does not have a printed expiry date. Your health department will include the lot# and corresponding expiration of oral tecovirimat that is provided to you.

Central IRB information:
CDC IRB serves as the central IRB for continuing review and approval of the tecovirimat IND protocol (CDC IRB Protocol #6402) to help reduce the administrative burden on local IRBs and allow timely access to tecovirimat treatment. Therefore, hospitals or other sites may elect to use CDC IRB's approval for this protocol in place of local IRB review per local hospital/institution policy with internal documentation, as applicable. CDC IRB determined that use of tecovirimat as described in Protocol #6402 does not constitute human subjects research as defined in 45 CFR 46.102(1) and therefore, does not need to be reviewed for compliance with 45 CFR 46. Each hospital/site that receives tecovirimat for treatment of orthopoxvirus infection under IND 116039 may elect to use the CDC IRB approval to meet FDA's regulatory requirements for IRB review (21 CFR Parts 50, 56, and 312). Due to the volume of hospitals that may be involved in administration of drugs for compassionate, treatment use under CDC-sponsored IND programs, CDC IRB will not be providing IRB authorization agreements for protocols solely for treatment (i.e., non-research) purposes. Hospitals that choose to perform their own local IRB review rather than utilizing the central IRB review should be aware that CDC is unable to accommodate requests for changes to Protocol #6402. Additionally, since this IND protocol for tecovirimat is solely for treatment use and determined as non-research, Federalwide Assurance is also not applicable.

Expanded Access IND requirements:
Informed consent must be obtained prior to tecovirimat treatment. In requesting, obtaining, and administering tecovirimat, the treating physician is serving as a site investigator and is required to comply with the requirements of the IND (per FDA regulations 21 CFR part 312, subpart D), which includes completing and returning to CDC all case report forms within the protocol. If serious adverse events occur, you must notify CDC within 24 hours by calling the CDC smallpox duty officer or the CDC Emergency Operations Center at 770-488-7100. **Your compliance with returning required information to CDC is appreciated and critical to CDC's ability to maintain the tecovirimat Expanded Access IND program and ensure a therapeutic option for orthopoxvirus in the United States.**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Centers for Disease Control
and Prevention (CDC)

Memorandum

Date September 17, 2021

From Felecia Peterson
IRB Analyst
Human Research Protection Office

Subject CDC IRB Approval of Continuation #8 of Protocol #6402 "Use of Tecovirimat for Treatment of Human Orthopoxvirus Infections" (Convened)

To Brett Petersen, MD, MPH
NCEZID/DHCPP

CDC's IRB S has reviewed and approved the request to continue protocol #6402, for the maximum allowable period of one year. CDC IRB approval will expire on **7/23/2022.** The continuation action was reviewed at a meeting of the convened IRB on September 17, 2021.

If other institutions involved in this protocol are being awarded CDC funds through the CDC Procurement and Grants Office (PGO), you are required to send a copy of this IRB approval to the CDC PGO award specialist handling the award. You are also required to verify with the award specialist that the awardee has provided PGO with the required documentation and has approval to begin or continue involving human subjects as described in this protocol.

As a reminder, the IRB must review and approve all treatment protocols at intervals appropriate to the degree of risk, but not less than once per year. There is no grace period beyond one year from the last IRB approval date. It is ultimately your responsibility to submit your protocol for continuation review and approval by the IRB. Please keep this approval in your protocol file as proof of IRB approval and as a reminder of the expiration date. **To avoid lapses in approval of your protocol and the possible suspension of subject enrollment and/or termination of the protocol, please submit your continuation request at least six weeks before the protocol's expiration date of 7/23/2022.**

Any problems of a serious nature should be brought to the immediate attention of the IRB, and any proposed changes to the protocol should be submitted as an amendment to the protocol for IRB approval before they are implemented.

If you have any questions, please contact your National Center Human Subjects Contact or the CDC Human Research Protection Office at (404) 639-7570 or by e-mail at huma@cdc.gov.

cc:
NCEZIDHumanStudies

Expanded Access IND Protocol: Use of Tecovirimat (TPOXX®) for Treatment of Human Orthopoxvirus Infections

IND No. 116,039

CDC IRB No. 6402

Version No. 5.1
May 20, 2022

Principal Investigator:
Brett Petersen, M.D., M.P.H.

Sponsored by:

Centers for Disease Control and Prevention

In Collaboration with:
Biomedical Advanced Research and Development Authority
Office of the Assistant Secretary for Preparedness and Response
Department of Health and Human Services

PROGRAM CONTACT INFORMATION

Clinical:
Principal Investigator
Brett Petersen, M.D., M.P.H.
Epidemiology Team Lead, Poxvirus and Rabies Branch
DHCPP, NCEZID, CDC
1600 Clifton Road NE, MS H24-12, Atlanta, GA 30333
Phone (404) 639-5464, Fax (404) 639-1060

Regulatory:
Yon Yu, Pharm.D.
Lead, Regulatory Affairs and Clinical Guidelines Team
Emergency Preparedness and Response Branch, Division of Preparedness and Emerging Infections, NCEZID, CDC
1600 Clifton Road NE, MS H24-11, Atlanta, GA 30333

TABLE OF CONTENTS

ATTACHMENTS

1.0 INTRODUCTION AND BACKGROUND

Orthopoxviruses belonging to the *Poxviridae* family that infect humans are *variola virus* (smallpox), *vaccinia virus*, *monkeypox virus*, *cowpox virus*, and newly discovered species *Akhmeta virus* and *Alaskapox virus*. Poxviruses are large (200–450 nm in size), brick- or ovoid-shaped double-stranded DNA viruses that are especially adapted to epidermal cells. Variola virus, the etiologic cause of smallpox, is the only one that affects humans exclusively, while the others are zoonotic infections. Poxvirus infections may be localized to the skin or disseminated. The initial site of infection may be the skin, a mucosal surface, or the respiratory tract. Variola virus then spreads through regional lymphatics to cause viremia and involvement of the reticuloendothelial system with secondary viremia.

Two different strains of variola virus, Variola major and Variola minor, caused clinically similar disease that was distinguished largely by case fatality rates. Epidemiologically, four general types of smallpox have been described: ordinary (accounted for over 85% of cases during the smallpox era, with prototypical maculopapular to vesicular pustular rash progression); modified (mild, sometimes with more atypical rash presentation, and occurred in previously vaccinated persons); flat; and hemorrhagic. Both of the latter two forms were rare and did not manifest typical vesiculopustular rash. Historically, Variola major had an overall fatality rate of about 30%; however, flat and hemorrhagic smallpox was usually fatal. Variola minor is a much less severe disease, with death rates historically of 1% or less.

In addition, other orthopoxviruses related to vaccinia virus, such as monkeypox, can also cause serious clinical illness including, but not limited to: encephalitis, severe inflammatory response syndrome, respiratory failure, painful head and neck lymph node swelling with or without associated airway and/or swallowing compromise, extensive dermal disruption during rash phase, and/or other septic syndromes.

In July 2018, the U.S. Food and Drug Administration (FDA) approved the oral formulation of tecovirimat (also referred to as ST-246 or its brand name TPOXX) for the treatment of human smallpox disease in adults and pediatric patients weighing at least 13 kg[1-3]. In May 2022, an intravenous (IV) formulation was FDA-approved for smallpox treatment in adults and children weighing at least 3 kg. Tecovirimat has shown effectiveness in animal and *in vitro* studies using related orthopoxviruses and variola as the infecting virus. It has been used in the treatment of severe adverse events to live vaccinia vaccination; however, there are limited efficacy data in humans. Efficacy of tecovirimat treatment has also been demonstrated within multiple animal model studies measuring survival in animals infected with either variola virus or other closely related orthopoxviruses.

1.1 Unmet Medical Need and Rationale for Use of Tecovirimat under Expanded Access IND

Although tecovirimat is FDA-approved for treatment of smallpox in adults and children, the approved indication is limited to smallpox. Therefore, this expanded access Investigational New Drug (IND) protocol provides for use of tecovirimat for treatment of non-variola orthopoxvirus infection in adults and children.

Tecovirimat shows broad-spectrum *in vitro* anti-orthopoxviral activity against multiple members of the orthopoxvirus genus, including vaccinia, monkeypox, camelpox, cowpox, rabbitpox,

ectromelia (mousepox), and variola viruses. Tecovirimat has been shown to be effective against various orthopoxviruses in multiple animal challenge models (mouse, rat, squirrel, prairie dog, rabbit, dog, and nonhuman primate).[4,5] The oral formulation is found to be orally bioavailable in humans and several animal species, and a similar PK profile has been observed for the IV formulation in humans and several animal species. Tecovirimat was approved under the FDA's Animal Rule, which allows efficacy findings from adequate and well-controlled animal studies to support an FDA approval when it is not feasible or ethical to conduct efficacy trials in humans. Based on available animal safety and efficacy and human safety data to date, it is reasonable to believe that tecovirimat may provide benefit in individuals with orthopoxvirus infections in the absence of adequate, FDA-approved treatment alternatives.

Oral administration of tecovirimat may be inadequate in circumstances when rapid, reliable drug at therapeutic levels is necessary for seriously ill patients. The oral bioavailability of tecovirimat is dependent on the fed state with adequate intake of a full, fatty meal to achieve therapeutic drug plasma levels. Critically ill patients may not be able to take the oral formulation under fed conditions. Additionally, disseminated orthopoxvirus infections have been reported to disrupt gastrointestinal tract functioning which may further inhibit absorption of the drug. The determining factors for treatment of patients with IV tecovirimat or oral capsules include inability to tolerate the oral form, severity of symptoms (e.g., systemic illness), comorbidities, underlying disease, and/or other factors that may alter oral drug absorption. Additionally, oral tecovirimat is provided as a 200 mg capsule, requiring additional dose preparation to yield doses of less than one capsule. In the absence of an oral suspension formulation or smaller oral dosage form that could provide more exact dosing, the option for IV administration of tecovirimat may provide for more exact dosing for children less than 13 kg based on clinical assessment of risk/benefit and if IV treatment is appropriate on an individual basis determined by the treating physician in consultation with CDC.

Patients may benefit from concomitant administration of other drugs. These may include products available in the SNS (vaccinia immune globulin intravenous [VIGIV], cidofovir) as well as non-stockpiled investigational products undergoing research and development and available only from the manufacturer (e.g., CMX-001). VIGIV is FDA-approved for complications due to vaccinia vaccination such as progressive vaccinia and eczema vaccinatum. Cidofovir is an FDA-approved drug but not approved for treatment of orthopoxvirus or complications from vaccinia vaccination. Combination therapy will be determined on a case-by-case basis depending on a patient's clinical and immune status as the safety profile of other products may limit their use (e.g., renal toxicity is a known side-effect of cidofovir).

Vaccination is the key modality for prevention of orthopoxvirus infections. However, vaccination must occur soon after exposure to be effective in preventing or reducing the seriousness of the disease caused by orthopoxvirus infections. There are two FDA-approved vaccines for prevention of smallpox: ACAM2000 (replication-competent, live vaccinia vaccine) and Jynneos (replication-deficient, Modified Vaccinia Ankara-Bavarian Nordic [MVA-BN]). Jynneos is also FDA-approved for prevention of monkeypox. There is one additional investigational smallpox vaccine currently in the Strategic National Stockpile (SNS): Aventis Pasteur Smallpox Vaccine (APSV) is intended to be utilized once ACAM2000 is depleted and will require usage under Emergency Use Authorization (EUA)[6]. The potential use of these

smallpox vaccines against other orthopoxvirus infections such as monkeypox will be provided under the appropriate regulatory mechanism(s) (e.g., IND, EUA, approved labeling). Effective treatment options for non-variola orthopoxvirus infections, including complications from vaccinia vaccination, is essential. Additionally, with widespread vaccination, vaccinia-vaccine related complications are anticipated and may necessitate treatment options in addition to the FDA-approved VIGIV, including tecovirimat.

2.0 PRODUCT DESCRIPTION

Tecovirimat (tecovirimat monohydrate) is an inhibitor of the orthopoxvirus VP37 envelope wrapping protein. Tecovirimat specifically targets and inhibits the activity of the VP37 orthopoxvirus protein 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[1] Depending upon the poxvirus species, its inhibitory activity is from 600- to several thousand-fold greater than that of cidofovir and other drugs used for treatment of orthopoxviruses. In cell culture assays, the effective concentrations of tecovirimat resulting in a 50% reduction in virus-induced cytopathic effect (EC50), were 0.016–0.067μM, 0.014–0.039 μM, 0.015 μM, and 0.009 μM for variola, monkeypox, rabbitpox, and vaccinia viruses, respectively. There is no structural resemblance of tecovirimat to any other compound currently used in human therapeutics; therefore, no comparison or correlation can be made to human experience for any other known drug.

2.1 Chemical Compound, Name, Formulation, and Storage

Tecovirimat has a molecular formula of $C_{19}H_{15}F_3N_2O_3 \cdot H_2O$ and a molecular weight of 394.35 g/mol. 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)benzamide monohydrate. Tecovirimat monohydrate is practically insoluble in water and across the pH range of 2.0–6.5 (<0.1 mg/ml).

2.1.1 Oral Formulation (Tecovirimat Capsules, 200 mg)

The oral formulation of tecovirimat is provided as oral capsules containing white to off-white powder in orange and black hard gelatin capsules. Each capsule contains 200 mg of tecovirimat active ingredient and comes in Unit of Use bottle containing 42 capsules. All inactive ingredients/excipients are generally recognized as safe and are United States Pharmacopeia /National Formulary grade. The capsules include the following ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The capsule shell is composed of gelatin, FD&C blue #1, FD&C red #3, FD&C yellow #6, and titanium dioxide.

Tecovirimat capsules should be stored at room temperature at 20–25°C (68–77°F). Excursions permitted to 15–30°C (59–86°F).

2.1.2 IV Formulation (Tecovirimat Injection 10 mg/mL)

IV tecovirimat is provided in a 30 ml vial consisting of tecovirimat 10 mg/mL in 20 mL of aqueous solution with rubber stopper and aluminum overseal. Each single-dose vial contains tecovirimat monohydrate (unmicronized) equivalent to 200 mg tecovirimat and the excipient hydroxypropyl betadex (8000 mg). Tecovirimat injection must be diluted with 2 parts 0.9%

normal saline or 5% dextrose solution prior to dosing. See **Section 4.2.1** for administration information.

IV tecovirimat should be stored at 2–8°C (36–46°F) and used as soon as possible after dilution (not to exceed 24 hours post-dilution). Do not freeze.

3.0 PROGRAM OBJECTIVE

The purpose of this expanded access IND treatment program is to provide tecovirimat for primary or early empiric treatment of confirmed or suspected (based on clinical signs and symptoms with known exposure while laboratory confirmation may be pending) non-variola orthopoxvirus infections (e.g., vaccinia, monkeypox, cowpox or other human virus infection identified as an orthopoxvirus) and secondary treatment of complications from replication-competent vaccinia vaccine in adults and children.

Clinical evaluation and patient monitoring information are also intended to be collected under this expanded access IND program regarding safety and patient outcomes (e.g., recovered or not recovered from orthopoxvirus infection, death) following administration of tecovirimat as well as relevant information about concomitant use of any other orthopoxvirus treatments (e.g., VIGIV, cidofovir, or CMX001). Other concomitant treatments are allowed under this IND treatment program for tecovirimat. To assess clinical resolution of infection, viral resistance, and safety, patients treated with tecovirimat will be followed until hospital discharge for inpatients and up to 30 days after treatment with the last dose of tecovirimat for outpatients. Please refer to **Section 7.3.2** "Patient Evaluation and Monitoring Parameters during Post-Tecovirimat Treatment Period." Pharmacokinetic (PK) sampling will be performed as therapeutic drug monitoring to ensure adequate dose exposure of individuals receiving tecovirimat treatment (see **Section 4.1**).

This program allows consideration of all patient populations, who meet eligibility criteria, to receive tecovirimat treatment under this IND program (e.g., children and all adults including pregnant and nursing women, and prisoners).

Clinical information generated from this program will be reported to FDA and IRB per regulations. Information reported to FDA will include annual and safety reporting requirements per 21 CFR 312.32 and 312.33 and as outlined in **Section 9.3** "CDC Reporting Requirements to FDA and CDC IRB." Any further analysis of data collected under this protocol that may contribute to generalizable knowledge will require further consideration by CDC IRB as applicable under 45 CFR part 46.

3.1 Population Size

Population size will depend on the number of eligible patients (e.g., children and all adults including pregnant and nursing women, and prisoners), from whom informed consent is obtained to receive tecovirimat treatment under this expanded access IND program.

3.2 Eligibility Criteria

Patient must meet the criteria for primary **OR** secondary treatment. See **Section 3.2.1** for details regarding considerations for IV tecovirimat.

Primary or early empiric treatment: Patients are eligible for primary or early empiric treatment with tecovirimat under this protocol if they have non-variola orthopoxvirus infection confirmed by laboratory diagnostic testing or have suspected infection based on known exposure(s) and/or clinical manifestations of disease, while laboratory confirmation may be pending.

Secondary treatment: Patients with complications of replication-competent vaccinia infection (e.g., serious inadvertent inoculation with vaccinia, eczema vaccinatum, severe generalized vaccinia, or progressive vaccinia) resulting from vaccination, secondary transmission, or other exposure are eligible for treatment with tecovirimat. Tecovirimat may be used after VIGIV treatment has been exhausted or in conjunction with VIGIV and/or other therapies based on the treating physician's clinical judgment.

3.2.1 Considerations for IV tecovirimat:
Adults and children who are unable to take oral therapy or for whom there is a concern that oral drug absorption may be altered should be considered for treatment with IV tecovirimat. This includes very ill patients hospitalized and unable to feed sufficiently by mouth, as oral tecovirimat absorption is expected to be lower in these patients. Evidence of gastrointestinal disfunction that may negatively impact drug absorption may also be considered for treatment with IV tecovirimat. IV tecovirimat should not be administered in patients with severe renal impairment (creatinine clearance <30 mL/min) and should be used with caution in patients with moderate (creatinine clearance 30-49 mL/min) or mild (creatinine clearance 50-80 mL/min) renal impairment. See **Section 6.4** for additional details.

Treating providers should discuss the appropriate route of administration with the CDC smallpox duty officer at the time tecovirimat is requested. The route of administration will be determined based on clinical consultation among the treating physician(s) and CDC (and FDA, when necessary). **Patients who receive IV tecovirimat should be switched to the oral formulation as soon as they are able to take oral medications and/or gastrointestinal disfunction impacting absorption has resolved.** The timing of transition to oral therapy should be made by the treating physician in consultation with CDC depending on the clinical progress of the patient.

3.2.2 Tecovirimat treatment while awaiting test results:
It is anticipated that tecovirimat treatment may be initiated based on epidemiologic evidence of exposure and clinical signs and symptoms while laboratory results are pending. For patients with an initial negative orthopoxvirus test but both epidemiologic and clinical evidence suggests disease (particularly if clinical progression is worsening), patients should be re-tested and in the meantime treated with tecovirimat. If results from re-testing confirm orthopoxvirus, patients should continue tecovirimat treatment. If results from re-testing are in agreement with initial test results indicating negative orthopoxvirus, tecovirimat will be suspended in those patients.

3.3 Exclusion Criteria

- Patient or legally authorized representative unwilling to sign an informed consent and refuse tecovirimat treatment
- Known allergy to tecovirimat and/or excipients of tecovirimat

- Upon negative laboratory results for orthopoxvirus in individuals whose tecovirimat treatment is initiated based on clinical manifestations of disease prior to laboratory results.
- For IV tecovirimat only: patients with severe renal impairment (creatinine clearance <30 mL/min)

4.0 DOSAGE AND ADMINISTRATION OF TECOVIRIMAT

The recommended dosage of oral and IV tecovirimat are described in **Section 4.1** and **4.2**, respectively. Modifications to the dose, frequency, and duration may be appropriate or necessary based on the individual patient's clinical condition, disease progression, therapeutic response, therapeutic drug monitoring, and/or clinical judgement. Clinical decisions on dosing adjustments will be based on clinical consultation among the treating physician(s), CDC and FDA when necessary. For additional information on dosing rationale for adults and pediatrics, refer to **Section 10.5**.

4.1 Oral Therapy for Adults and Children

4.1.1 The recommended dosage of oral tecovirimat for adult and pediatric patients is displayed in **Table 1**.

Table 1. Recommended Oral Dosage Instructions for 14 Days*

Weight (kg)**	Weight (lbs)	Recommended Dose (mg)*
< 6	<13	50 mg (¼ capsule) every 12 hours
6 to < 13	13 to < 28	100 mg (½ capsule) every 12 hours
13 to < 25	28 to < 55	200 mg (1 capsule) every 12 hours
25 to < 40	55 to < 88	400 mg (2 capsules) every 12 hours
40 to < 120	88 to < 264	600 mg (3 capsules) every 12 hours
120 and above	≥ 264	600 mg (3 capsules) every 8 hours

* Tecovirimat capsules should be taken within 30 minutes after a full meal containing moderate or high fat.
** Opening tecovirimat capsules and mixing with food for children weighing < 13 kg, which differs from the FDA-approved tecovirimat package insert, is still allowed under the IND.

4.1.2 Administration of Oral Therapy

Oral tecovirimat should be taken by mouth with a full glass of water within 30 minutes after eating a full meal of moderate or high fat (ideally about 600 calories and 25 grams of fat) in order to improve bioavailability. Treating physicians should dispense tecovirimat and provide outpatients with the appropriate dose and duration.

4.1.3 Duration of Oral Therapy

Total duration of tecovirimat treatment for patients of all ages is 14 days, but may be longer (not to exceed 90 days) depending on the progression of the disease and clinical condition of the patient. Dose adjustments may be required per individual clinical considerations and/or therapeutic drug monitoring during the course of tecovirimat treatment; see **Section 4.4.**

The adult dosing does not preclude pregnant and nursing women if careful clinical assessment of risk/benefit deems tecovirimat treatment appropriate (see **Section 6.0** for Special Populations). Please refer to **ATTACHMENT 3** for instructions on opening capsules and mixing with food for infants and children who require less than a 200 mg dose or who are unable to swallow capsules.

Dosing frequency for children may be once or twice a day depending on assessment of individual patient's clinical condition, disease progression, therapeutic response, therapeutic drug monitoring, and/or clinical judgement. Clinical decisions on dosing adjustments will be based on clinical consultation among the treating physician(s), CDC and FDA.

Pediatric dosing is derived from population PK simulation predicted to provide pediatric patients with exposures comparable to the observed exposure in healthy adult volunteers receiving 600 mg twice daily.

The amount of tecovirimat excreted as metabolites (<20%) in S9 fractions in mice indicates tecovirimat is metabolized and eliminated by glucuronidation. Children under 18–24 months of age have lower expression of glucuronidating enzymes. Therefore, tecovirimat exposure in children under 18–24 months of age may be higher at otherwise equivalent doses in adults. Future refinements in the model and availability of additional data may change this pediatric dosing recommendation.

For very ill patients hospitalized and unable to feed sufficiently by mouth, tecovirimat absorption via the oral route is expected to be lower in these patients and thus use of IV tecovirimat may be considered or if the IV formulation is unavailable, modifications to the oral dose, frequency, and duration may be considered, including an initial dose of > 600 mg of oral tecovirimat, based on clinical judgment of the treating physician in consultation with CDC and FDA when necessary. For inpatients (adults and children) unable to feed by mouth and no evidence of gastrointestinal disfunction, tecovirimat may be administered via a nasogastric tube per hospital protocol based on clinical judgment on an individual basis if IV tecovirimat is unavailable or occurrence of adverse events with IV administration.

4.2 IV Therapy for Adults and Children Who Weigh ≥ 3 kg

4.2.1 The recommended dosage of IV tecovirimat for adult and pediatric patients (≥ 3 kg) is displayed in **Table 2**.

Table 2. Recommended Pediatric and Adult Tecovirimat Injection for IV Infusion[a]

Weight (kg)	Weight (lbs)	Recommended Dose	Volume of IV Tecovirimat[b]	Volume of Diluent[c]
3 kg to <35 kg	7 to < 77 lbs	6 mg/kg every 12 hours by IV infusion over 6 hours	0.6 mL/kg	1.2 mL/kg
35 kg to <120 kg	77 to < 264 lbs	200 mg every 12 hours by IV infusion over 6 hours	20 mL	40 mL
120 kg and above[d]	≥ 264 lbs	300 mg every 12 hours by IV infusion over 6 hours	30 mL	60 mL

[a] Patients should be switched to tecovirimat oral capsules to complete the 14 day treatment course as soon as oral therapy can be tolerated.

[b] 10 mg/mL stock solution containing 40% hydroxypropyl betadex (8 g per vial) with water for injection.

[c] Diluent is either 0.9% (w/v) sodium chloride injection or 5% (w/v) dextrose injection solution.

[d] Depending on size of syringe available with syringe pump system, two separate syringes may be needed for each 6 hour administration

Pediatric dosing should be assessed on a case-by-case basis in consultation with the treating physicians, SIGA, CDC (and FDA, if necessary) based on the latest available data in this population. The doses presented here are derived from a population PK model developed by SIGA. Clinical studies in children have not been conducted.

4.2.1 Administration of IV Therapy

IV tecovirimat must be diluted with 2 equal parts 0.9% normal saline or 5% dextrose solution prior to dosing and should be administered via an IV infusion pump over a 6-hour period. Tecovirimat injection should be stored at 2-8°C (35-46°F) and used as soon as possible after dilution (not to exceed 24 hours post-dilution).

4.2.2 Duration of IV Therapy

The duration of IV tecovirimat for patients of all ages is 14 days if the patient's condition necessitates IV administration (e.g., inability to tolerate the oral form, severity of symptoms [e.g., systemic illness], comorbidities, underlying disease, and/or other factors that may alter oral drug absorption). IV tecovirimat should only be administered while patients are unable to take oral therapy or there is a concern that oral drug absorption may be altered. **Patients should be switched to the oral formulation as soon as they are able to take oral medications and/or gastrointestinal disfunction impacting absorption has resolved.** Treating physicians should consult with CDC regarding the timing of transition to oral therapy and additional monitoring that may need to ensure adequate oral drug absorption.

4.3 Outpatients who are Unable to Swallow Capsules

For outpatients (adults and children) unable to swallow capsules, treating physicians should provide instructions on how to open capsules and mix with food (**ATTACHMENT 3)**.

4.4 Therapeutic Drug Monitoring

For purposes of monitoring tecovirimat levels to ensure adequate drug exposure and possible dose adjustment, plasma samples (5 mL whole blood) will be collected according to the schedule flow charts in **Figure 1A** for outpatients and **Figure 1B** for inpatients. Collected PK samples will be assessed at a designated laboratory. Please refer to **ATTACHMENT 4** for further instructions on laboratory specimen preparation, handling, and shipping. Complete the applicable PK Sampling Record found in **ATTACHMENT 2B/2C**. *In certain instances, the sample collection schedule may be modified to synchronize sample collection related to other treatments (e.g., VIGIV) to minimize the number of blood draws and/or visits. The treating physician should consult with CDC regarding the sample collection schedule in these instances and receive approval in writing of a sample collection schedule modification.*

Outpatients

For ambulatory patients treated as outpatients (**Figure 1A**), plasma samples for PK analysis should be collected on at least 1 day early in the treatment course (e.g. Days 2–6) after at least two doses of tecovirimat have been taken in sequence, and on at least 1 day near the end of the treatment course (e.g. Days 10–14). To the extent possible, plasma samples should be drawn just prior (< 30 minutes) to a dose in order to obtain trough values due to the importance of C_{min} for assessing adequate dosing. If trough samples cannot be obtained, plasma collection can occur at 4 hours after a dose. If these time windows are missed, still collect a plasma sample. Plasma samples may be collected up to 48 hours after the last dose, if necessary. Record the exact time

the patient took the dose and exact time of all plasma collections. Dose adjustment will be considered on an individual patient basis upon clinical evaluation of disease progression and assessment of patients' plasma levels; additional plasma samples may be required. Example plasma sampling days and times are shown in **Figure 1A**.

Inpatients

To the extent possible, trough and post-dose plasma samples should be drawn early in the patient's treatment period (Day 2–6) and toward the end of the treatment period (Day 7–14). Patients who receive IV tecovirimat and then are switched to oral tecovirimat therapy should be monitored early at the initiation of IV therapy (day 2–6 of IV therapy) and again early at the initiation of oral therapy (day 2–6 of oral therapy). Those patients should have at least one additional sample drawn toward the end of the treatment period, regardless of the route of administration (Day 7-14). Example plasma sampling days and times are shown in **Figure 1B.**

Trough samples should be collected just prior (<30 minutes) to a dose due to the importance of obtaining C_{min} values. Post-dose samples should be collected 4 hours after a dose. If these time windows are missed, still collect a plasma sample. Plasma samples may be collected up to 48 hours after the last dose, if necessary. Record the exact time the patient took the dose and exact time of all plasma collections.

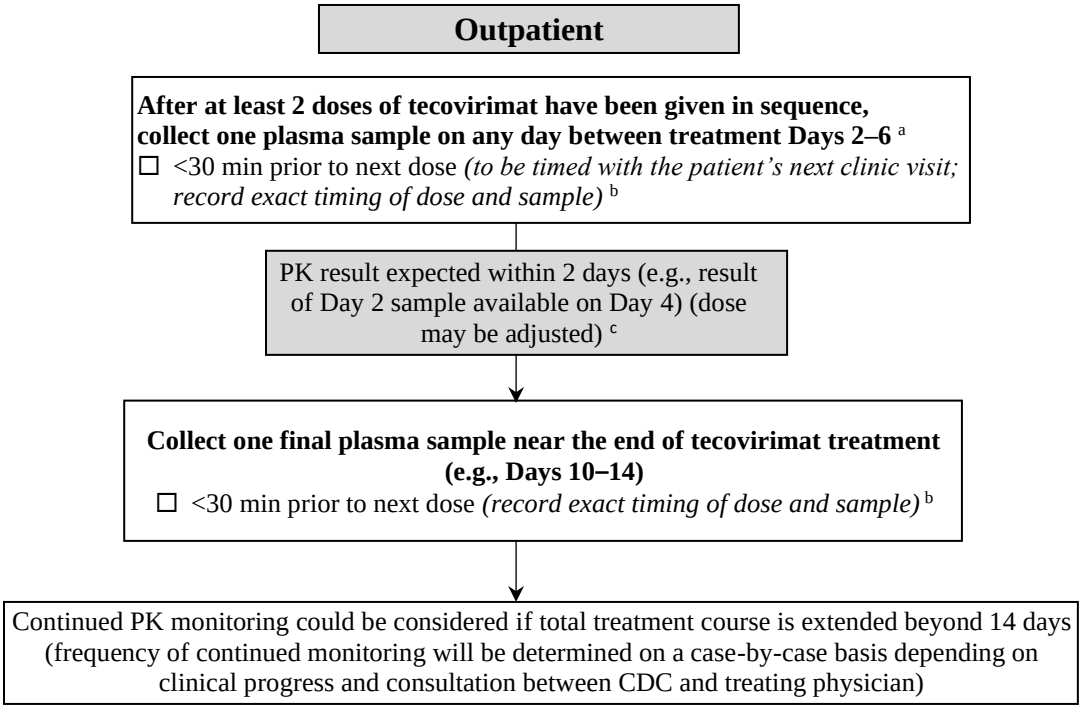
If feasible, plasma samples should be collected on Day 2, just prior (<30 minutes) to patient's receipt of the third dose and at 4 hours after the third dose. Additional plasma samples should be collected toward the end of the treatment course (e.g., Day 7–14), with one collection occurring prior to a dose and one collection occurring 4 hours after a dose. Dose adjustment will be considered on an individual patient basis upon clinical evaluation of disease progression and assessment of patient's plasma levels. Physicians treating patients with IV tecovirimat should consult CDC regarding PK monitoring.

Dose Assessment

Results from PK analysis of plasma samples will be available approximately 2 days after shipment. CDC will contact treating physicians upon availability of results. Consideration for any dose adjustment will be individualized based on clinical evaluation of treatment response in conjunction with the patient's measured plasma levels of tecovirimat. Dose assessment will be based on consultation among the treating physician, CDC, FDA, and SIGA, as necessary. Plasma samples will be collected for at least 1 day at the adjusted dose for further assessment.

For certain patients or populations, more frequent PK monitoring may be deemed necessary (e.g., pregnant women due to the increased intravascular volume and other physiological changes, children due to physiological differences/immaturity from adults) to establish therapeutic tecovirimat level. Specific PK monitoring and assessment, including frequency of PK sample collection, will be determined on a case-by-case basis in such patients/populations.

Figure 1A. Example Flow Chart of Tecovirimat Plasma Sampling Schedule for Pharmacokinetic Analysis and Dose Adjustment During Oral Therapy (Outpatients)

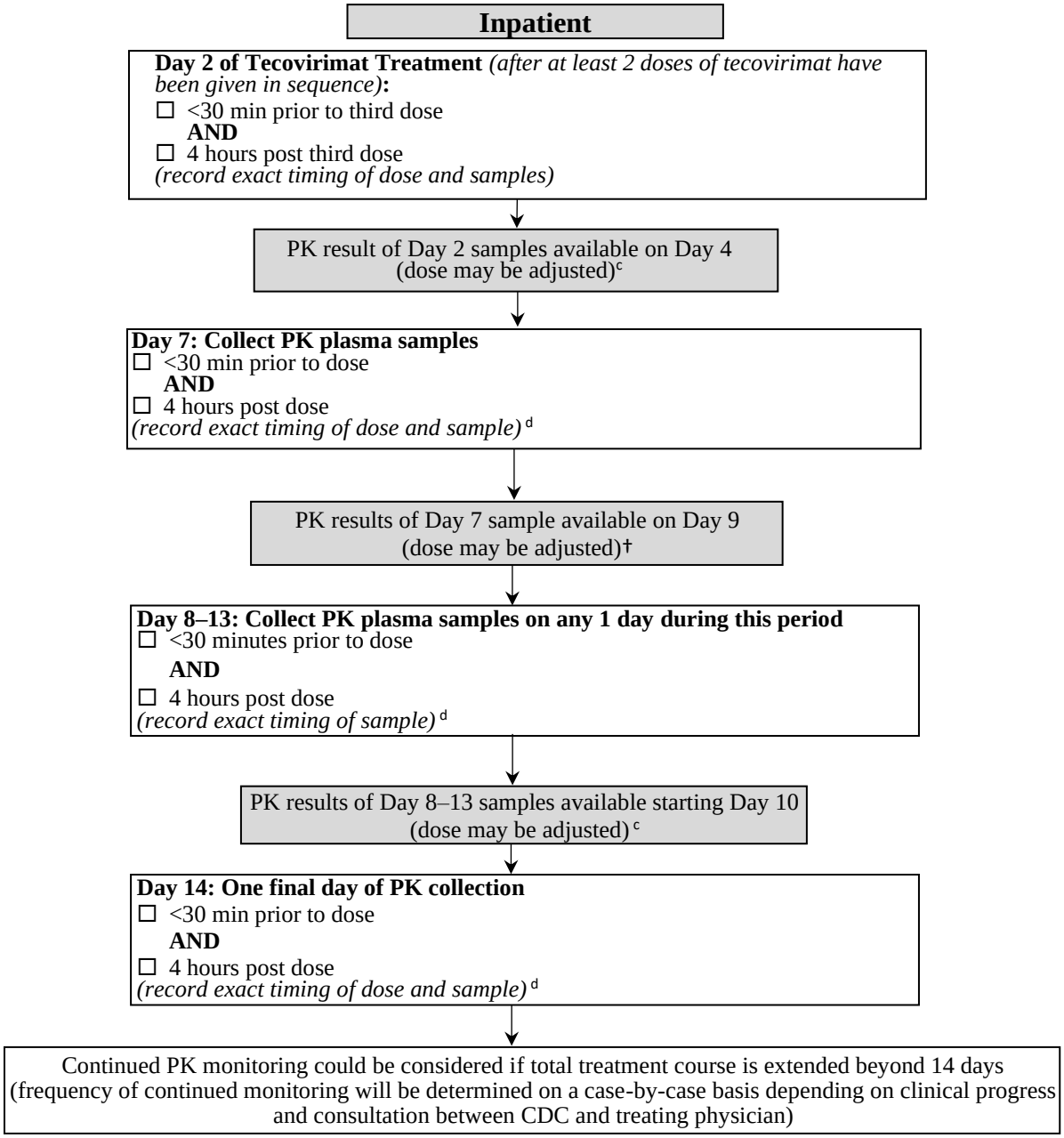


a To the extent feasible, collect a plasma sample for PK analysis on one of the days early in treatment course (any day between treatment Days 2−6) and a final plasma sample between Days 10−14. Plasma collection days may occur on days corresponding to patient follow-up visits for convenience.

b Where feasible, schedule patient's appointment for plasma collection before a dose (<30 min); if not feasible, then collect at 4 hours after a dose. If these time windows are missed, still collect post-dose plasma and record time patient took the dose and exact time of plasma collection. Timing of plasma sample should be approximately the same time relative to dose to allow for relevant comparison.

c Dose adjustment will be considered on an individual patient basis upon clinical evaluation of disease progression (e.g., symptom improvement) as well as assessment of patient's plasma levels.

Figure 1B. Example Flow Chart of Tecovirimat Plasma Sampling Schedule for Pharmacokinetic Analysis and Dose Adjustment (Inpatients)[a,b]



a Adjustment to frequency of plasma collection will be considered based on patient's clinical progress in consultation between treating physician and CDC.

b For patients who receive IV tecovirimat, CDC should be consulted regarding PK monitoring. If a patient is switched from IV to oral therapy, a PK sample should be obtained just prior (<30 minutes) to patient's receipt of the third **oral dose** and at 4 hours after the third **oral dose**. Additional monitoring thereafter can proceed per the above schedule according to the overall treatment day.

c Dose adjustment will be considered on an individual patient basis upon clinical evaluation of disease progression (e.g., symptom improvement) as well as assessment of patient's plasma levels.

d Timing of plasma sample collection should be approximately at the same time post-dose to allow for relevant comparison.

4.5 Discontinuation of Tecovirimat

Under certain circumstances, a patient may voluntarily discontinue or refuse tecovirimat treatment, treatment may terminate due to serious adverse events (SAEs) (such as anaphylaxis), or according to the clinical judgment of the treating physician and/or appropriate health authority.

These reasons include but are not limited to:

- Patients may refuse voluntarily from treatment at any time and for any reason.
- Patients may need to discontinue tecovirimat per clinical judgment of the treating physician and/or the appropriate health authority (i.e., CDC, FDA or their representatives).
    - There is a concern of immediate or imminent risk to the patient (i.e., intolerable or unacceptable SAEs such as anaphylaxis). If the patient discontinues tecovirimat due to an AE related to the treatment, he/she will be provided appropriate care under medical supervision until the symptoms of any AE resolve or the patient's condition becomes stable;
    - There are clinically significant abnormalities in their laboratory result (National Institutes of Health's reference ranges [http://cclnprod.cc.nih.gov/dlm/testguide.nsf/Index?OpenForm] may be used for determining significant laboratory abnormalities);
    - There is a need to take other medication(s) for which unknown but potential negative interaction with tecovirimat may be a risk.

4.6 Drug-Drug Interactions

Co-administration of tecovirimat with repaglinide may cause hypoglycemia. Monitor blood glucose and monitor for hypoglycemic symptoms during co-administration. Tecovirimat is a weak inducer of cytochrome P450 (CYP)3A 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 tecovirimat. See **Table 4** for clinical recommendations for select sensitive substrates. Based on a drug interaction study, no clinically significant drug interactions have been observed when tecovirimat is co-administered with bupropion, flurbiprofen, or omeprazole. **Table 4** provides a listing of established or significant drug interactions.

Table 4. Significant Drug Interactions

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

[a] ↓ = decrease, ↑ = increase

[b] These interactions have been studied in healthy adults

A complete list of concomitant medications and medication history should be documented and patients should be monitored for any AEs (**Section 9.0** for required AE reporting). Document all AEs in **ATTACHMENT 2, "Adverse Event Form."**

No vaccine-drug interaction studies have been performed in human subjects. Some animal studies, including non-human primate studies, have indicated that co-administration of tecovirimat at the same time as live smallpox vaccine (vaccinia virus) may reduce the immune response to the vaccine.[7] The clinical impact of this interaction on vaccine efficacy is unknown.

5.0 POSSIBLE RISKS OF TECOVIRIMAT TREATMENT

Co-administration with repaglinide may cause hypoglycemia. Monitor blood glucose and monitor for hypoglycemic symptoms during co-administration. Other risks associated with administration of tecovirimat to patients with orthopoxvirus infections are unknown.

5.1 Risks Associated with Oral Tecovirimat

Based on limited information from clinical safety studies in 359 healthy adult volunteers who received oral tecovirimat, the possible risks of tecovirimat include headache (12%), nausea (5%), abdominal pain (2%), and vomiting (2%). In safety study SIGA-246-001, which administered single doses of oral tecovirimat ranging from 500 mg to 2,000 mg, one subject in the 1,000 mg group developed neutropenia. Neutropenia did not occur in the 2,000 mg fasted group. Tecovirimat is associated with seizures in dogs at doses at or greater than 100 mg/kg. This finding has not been seen in the monkey model or in the four completed clinical studies.

5.2 Risks Associated with IV Tecovirimat

IV tecovirimat was shown to be safe and relatively well-tolerated in two phase I studies conducted in 82 healthy adults, 64 of whom received doses at or above the 200 mg IV adult dose. Twenty-six subjects participated in a multi-dose regimen (240 mg twice daily) for 7 days. No serious adverse events were reported in either study. Headache was the most commonly reported adverse reaction in the single-dose IV study (SIGA-246-IV-201) with no instances of nausea reported. No subjects discontinued due to an adverse reaction. In a multiple-dose IV study (SIGA-246-IV-202), the most commonly reported AEs included infusion site pain, infusion site swelling, infusion site erythema, infusion site extravasation, headache, and dizziness. Three subjects in the multi-dose treatment group had their treatment with IV tecovirimat discontinued due to an adverse event—two for infusion site extravasation (one mild and one moderate that both lasted four days and resolved without treatment) and one for mild infusion site swelling that lasted 16 days and resolved without treatment. See **Section 10.3** for additional details.

5.2.1 Contraindications, Warnings, and Precautions

Given the theoretical safety concern of renal toxicity related to hydroxypropyl betadex exposure, under this protocol, IV tecovirimat is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min). In patients with mild (defined as creatinine clearance 50-80 mL/min) and moderate (defined as creatinine clearance 30-49 mL/min) renal impairment, IV tecovirimat should be used with caution (i.e., case-by-case determination to treat with IV tecovirimat based on clinical judgment regarding the risk/benefit for the patient). Serum creatinine levels should be closely monitored and, if renal toxicity is suspected, consideration should be given to modifying the regimen to the oral formulation, if feasible. Because of the

potential risk of hydroxypropyl betadex accumulation, renal function and laboratory values should be monitored during the course of therapy for all patients who receive IV tecovirimat. See **Section 6.4** and **Section 10.1** for additional information.

Pediatric patients

In pediatric patients < 2 years of age, there are limited data regarding the use of hydroxypropyl-β-cyclodextrin. Given that renal tubular function rapidly matures over the first few years of life, clearance of hydroxypropyl-β-cyclodextrin may be reduced in young pediatric patients, resulting in higher exposure to hydroxypropyl-β-cyclodextrin. Tecovirimat Injection should be used with caution in this population given that animal studies have shown potential for nephrotoxicity at very high exposure levels of hydroxypropyl-β-cyclodextrin. Given the potential for drug accumulation due to renal immaturity in pediatric patients < 2 years of age, monitoring of renal function after treatment is recommended.

6.0 SPECIAL POPULATIONS

Tecovirimat treatment may be considered for patients in the following special populations based on careful clinical assessment of individual patient's clinical condition and weighing the serious risk of deadly orthopoxvirus infection and potential benefit of tecovirimat with the potential risks of this product. See **Section 4.0** for dosing recommendations.

6.1 Pregnancy

Tecovirimat has not been studied in pregnant women; however, reproductive development studies have been performed in mice and rabbits and no embryo-fetal abnormalities were recorded. Pregnant mice were administered tecovirimat orally at doses up to 1,000 mg/kg/day from gestation Days 6-15 (approximately 23 times higher than human exposure at the recommended human dose). Considering the deadly risks associated with orthopoxvirus infections (e.g., vaccinia [including complications from smallpox vaccine or secondary exposure to a smallpox-vaccinee], monkeypox, and cowpox), the potential benefits of treatment with oral or intravenous tecovirimat may outweigh the unknown pregnancy risks associated with tecovirimat.

6.2 Lactation

No studies of tecovirimat use in nursing women have been conducted. In lactating mice given oral tecovirimat 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 on lactation Day 10 or 11. Considering the deadly risks associated with orthopoxvirus infections (e.g., variola, vaccinia [including complications from smallpox vaccine or secondary exposure to a smallpox-vaccinee], monkeypox, and cowpox), the potential benefits of treatment with oral or intravenous tecovirimat may outweigh the unknown risks associated with tecovirimat.

6.3 Pediatric Population

No clinical studies have been performed in pediatric subjects. However, in March 2007, SIGA provided tecovirimat to support an E-IND (No. 74,773) sponsored by the CDC for the treatment of a 28-month-old child with eczema vaccinatum. His 14-day oral tecovirimat treatment started with an initial once-daily dose of 50 mg (5 mg/kg) for 2 days, increased to 75 mg (7.5 mg/kg) once-daily for 2 days, then final increase to 100 mg (10 mg/kg) once-daily for the remainder of

treatment duration. There were no AEs that could be attributed to tecovirimat. Tecovirimat also has been studied in male and female juvenile monkeys (2–2.5 years of age). In monkeys, daily oral administration of tecovirimat at dose levels of up to 300 mg/kg for 13 weeks did not result in any drug-related mortality or systemic toxicity. Considering the deadly risks associated with orthopoxvirus infections (e.g., vaccinia [including complications from smallpox vaccine or secondary exposure to a smallpox-vaccinee], monkeypox, and cowpox), the potential benefits of treatment with oral or intravenous tecovirimat may outweigh the unknown pediatric risks associated with tecovirimat.

There are limited data regarding the use of hydroxypropyl-β-cyclodextrin, an ingredient in IV tecovirimat, in pediatric patients < 2 years of age. Monitoring of renal function after treatment is recommended. See **Section 5.2** for more information.

6.4 Patients with Renal Impairment

IV tecovirimat is formulated with hydroxypropyl betadex as a solubilizing/complexing agent at a concentration of 400 mg/mL (200 mg dose of IV tecovirimat would contain 8000 mg of hydroxypropyl betadex). Hydroxypropyl betadex, when administered intravenously, is eliminated through glomerular filtration[8,9]. Given the theoretical safety concern of renal toxicity related to hydroxypropyl betadex exposure, under this protocol, IV tecovirimat is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min). In patients with mild (creatinine clearance 50-80 mL/min) and moderate (creatinine clearance 30-49 mL/min) renal impairment, IV tecovirimat should be used with caution (i.e., case-by-case determination to treat with IV tecovirimat based on clinical judgment regarding the risk/benefit for the patient). Serum creatinine levels should be closely monitored and, if renal toxicity is suspected, consideration should be given to modifying the regimen to the oral formulation, if feasible. Because of the potential risk of hydroxypropyl betadex accumulation, renal function and laboratory values should be monitored during the course of therapy for all patients receiving IV tecovirimat. See **Section 10.6** for additional pharmacokinetic information.

7.0 REQUIRED REPORTING OF CLINICAL EVALUATION AND MONITORING OF PATIENTS

Treating physicians will be responsible for performing and collecting the clinical evaluation and patient monitoring parameters as well as reporting the required information to CDC. Completed tecovirimat Case Report Forms (**ATTACHMENT 2**) must be returned to CDC, including the Product Accountability Form within 7 days of completion of tecovirimat treatment. For outpatients, treating physicians will provide a diary card for patients to complete at home daily. Patients will be instructed by their treating physician to complete and bring the diary card to each of their follow-up visits for review with the treating physician. Patients will turn in the completed diary card to their physician within 3–5 days of completion of tecovirimat treatment; physicians will send a copy to CDC.

7.1 Clinical Evaluation

A medical history will be collected, concomitant medications will be recorded, and a physical examination with vital signs (e.g., weight, blood pressure, pulse, respiratory rate, temperature, and height [only once]) will be completed.

Photographs of affected areas, should lesions develop, will be taken for establishing a baseline and may be requested weekly to follow lesion progression and healing during and after treatment. Photographs may be requested daily if regression is not seen after the first 3 days.

7.2 Laboratory Evaluation

Under this IND program, the following laboratory parameters will be collected to monitor the safety of tecovirimat treatment for investigational uses:

- Hematology: prothrombin time and partial thromboplastin time, platelet count, hemoglobin, hematocrit, red blood cell count, absolute white blood cell and differential count.
- Chemistry: calcium, magnesium, sodium, potassium, chloride, bicarbonate, phosphorus, urea, creatinine, calculated creatinine clearance, glucose, uric acid, albumin, total bilirubin, total protein, aspartate transaminase, alanine transaminase, and alkaline phosphatase.
- Urinalysis: protein, Hgb, glucose, microscopic analysis.
- Serum hCG for female patients of child-bearing age, as appropriate.
- Immunochemistry: Orthopoxvirus specific IgM, IgG, and neutralizing antibodies.
    - As necessary, serum and lesion sampling for virologic assessments (PCR, viral culture, and resistance) will be collected from all patients (quantification of viral load will be undertaken as soon as reasonably possible). Lesion sampling will be performed based on patient's clinical presentation and progression (e.g., based on evaluation of digital photos) by treating physician. Detailed instructions on procedures for collection of patient diagnostic specimens (blood/lesion/vesicular/scab samples) can be found here: http://www.cdc.gov/ncidod/monkeypox/diagspecimens.htm.

The approximate amount of extra blood volume required for PK testing for outpatients and inpatients is shown below **Table 5**). Please see **ATTACHMENT 4** for further instructions on laboratory specimen preparation, handling, and shipping.

Table 5. Approximate Amount of Extra Blood Volume Required for PK Testing

Weight (kg)	Amount of blood drawn for PK testing (mL) (Tablespoons)
Blood Volume for PK testing by Weight for Outpatients During 14-day Tecovirimat Treatment*	
> 20 kg	5 mL X 4 = 20 mL (2 Tablespoons)
11 – 20 kg	2.5 mL X 4 = 10 mL (1 Tablespoons)
≤ 10 kg	1.2 mL X 4 = 4.8 mL (1 Tablespoons)
Blood Volume for PK testing by Weight for Inpatients* During 14-day Tecovirimat Treatment*	
> 20 kg	5 mL X 13 = 65 mL (5 Tablespoons)
11 – 20 kg	2.5 mL X 13 = 32.5 mL (3 Tablespoons)
≤ 10 kg	1.2 mL X 13 = 15.6 mL (2 Tablespoons)

*Approximate blood volumes based on scenario of inpatients unable to feed by mouth, who may require frequent PK monitoring and therapeutic dose adjustment. Adjustment to frequency of plasma collection will be considered based on patient's clinical progress and if treatment duration is extended beyond 14 days, additional blood samples may be collected. Volume in tablespoons is approximate and rounded up to the nearest 1 tablespoon.

7.3 Clinical Evaluation and Monitoring Parameters

Table 6. Summary of Clinical Evaluation and Monitoring Parameters for Outpatients*

Days / Parameters	Pre Tecovirimat Treatment	Tecovirimat Treatment Period Day 1–14		Post Tecovirimat Treatment Period	
	Prior to first dose of Tecovirimat (≤ 24 hours)	Tecovirimat Diary for Outpatients	Treating Physician Assessment	7 Days After Last Dose	30 Days After Last Dose
Sign Informed Consent	x				
Inclusion/Exclusion Criteria	x				
Medical History	x				
Summary of Clinical Status/Progress	x	x	x	x	x
Physical Examination	x		x	x	x
Vital Signs[a]	x		x	x	x
Concomitant-Medications[b]	x	x	x		
Hematology[c]	x		x	x	x
Chemistry[d]	x		x	x	x
Serum hCG	x				
Immunochemistry[e]	x		x	x	x
Urinalysis[f]	x		x	x	x
Lesion and Blood Sampling[g]	x		x	x	x
Lesion Photos[h]	x	x	x	x	x
PK Samples[i]		(refer to Figure 1A)			
Adverse Events[j]		x	x	x	x

* For outpatients, treating physicians will provide a diary card for patients to complete at home daily. Lesion and blood samples will be collected by treating physician at time of patient's follow-up visit, during which time physician will also complete a physical assessment.

[a] Vital signs will include weight, height (only once), blood pressure, pulse, respiratory rate, and temperature.

[b] Concomitant medications will be recorded from 24 hours before the first dose of tecovirimat until the last dose of tecovirimat, if possible.

[c] Hematologic parameters will include PT and PTT, platelet count, Hgb, HCT, RBC, absolute WBC, and differential count.

[d] Chemistry parameters will include Ca, Mg, Na, K, Cl, HCO_3, P, urea, creatinine, calculated CrCl, glucose, uric acid, albumin, total bilirubin, total protein, ALT, AST, and ALP.

[e] Immunochemistry parameters will include orthopoxvirus specific immunoglobulins, IgM and IgG. Immunochemistry will be required 7 days and 30 days after the last dose of tecovirimat.

[f] Urinalysis parameters will include protein, Hgb, glucose, and microscopic analysis.

[g] Lesion sampling will be performed based on patient's clinical presentation and progression (e.g., based on evaluation of digital photos).

[h] Digital photos of lesions on a standardized part of the body will be taken by patient or during patient's follow-up doctor visits and if regression is not seen after the first 3 days.

[i] PK samples for patients should be drawn according to Figure 1A.

[j] SAEs should be recorded immediately and reported to CDC within 24 hours of occurrence.

Table 7. Summary of Clinical Evaluation and Monitoring Parameters for Inpatients

Days / Parameters	Pre-Tecovirimat	Tecovirimat Treatment Period					Post Tecovirimat Treatment Period
	Prior to first dose of Tecovirimat (≤ 24 hours)	1–6	7	8–13	14	Every 7 days Thereafter (if still on tecovirimat beyond 14 days)	Upon Discharge
Sign Informed Consent	x						
Inclusion/Exclusion Criteria	x						
Medical History	x						
Summary of Clinical Status/Progress	x		x		x	x	x
Physical Examination	x		x		x	x	x
Vital Signs[a]	x		x		x	x	x
Concomitant-Medications[b]	x	x		x		x	x
Hematology[c]	x		x		x	x	x
Chemistry[d]	x		x		x	x	x
Serum hCG	x						
Immunochemistry[e]	x		x		x	x	x
Urinalysis[f]	x		x		x	x	x
Lesion and Blood Sampling[g]	x		x		x	x	x
Lesion Photos[h]	x	x	x	x	x	x	x
PK Samples[i]		(refer to Figure1B)					
Adverse Events[j]		x	x	x	x	x	x

[a] Vital signs will include weight, height (only once), blood pressure, pulse, respiratory rate, and temperature.

[b] Concomitant medications will be recorded from 24 hours before the first dose of tecovirimat until the last dose of tecovirimat, if possible.

[c] Hematologic parameters will include PT and PTT, platelet count, Hgb, HCT, RBC, absolute WBC, and differential count.

[d] Chemistry parameters will include Ca, Mg, Na, K, Cl, HCO_3, P, urea, creatinine, calculated CrCl, glucose, uric acid, albumin, total bilirubin, total protein, ALT, AST, and ALP.

[e] Immunochemistry parameters will include orthopoxvirus specific immunoglobulins, IgM and IgG. Immunochemistry will be required until clinical signs and symptoms have either resolved or stabilized and upon hospital discharge.

[f] Urinalysis parameters will include protein, Hgb, glucose, and microscopic analysis.

[g] Lesion sampling will be performed based on patient's clinical presentation and progression (e.g., based on evaluation of digital photos).

[h] Digital photos of lesions on a standardized part of the body will be taken weekly or daily if regression is not seen after the first 3 days.

[i] PK samples for patients should be drawn according to Figures 1B.

[j] SAEs should be recorded immediately and reported within 24 hours of occurrence.

7.3.1 Baseline Patient Evaluation and Monitoring Parameters prior to Tecovirimat Treatment (≤ 24 hours prior to first dose of tecovirimat)

For both inpatients and outpatients:

- Perform a physical examination, including vital signs.
- Record concomitant medications and medical history.
- Collect blood and/or lesion samples, vesicular or scab material, to ascertain for orthopoxvirus disease.
- Collect blood samples to establish baseline lab values (e.g. immunochemistry, hematology, chemistry, and urinalysis).
- Take photographs of affected areas, should lesions develop, for establishing a baseline.

7.3.2 Patient Evaluation and Monitoring Parameters during Tecovirimat Treatment

For outpatients, the treating physician will provide a diary card during the initial visit (**ATTACHMENT 2**) to the patient. Treating physicians should review with the patient potential AEs that may occur with the tecovirimat and provide guidance on how to complete the diary card and how to assess AEs and timing and severity of AEs. Treating physicians should instruct that if the patient experiences any serious adverse events (e.g., difficulty breathing, hives), the patient should seek medical attention immediately. Patients will be instructed by their treating physician to complete and bring the diary card to each of their follow-up visits for review with the treating physician. Patients will turn in the completed diary card to their physician within 3–5 days of completion of tecovirimat treatment; physicians will send a copy to CDC.

Blood/lesion/vesicular/scab samples and photographs of lesions will be conducted by the treating physician and will coincide with patient's scheduled follow-up visits. Treating physician may also ask patients to take photographs of lesions at home and send them to their treating physician.

The following will be collected for inpatients:

Collect Daily during Tecovirimat Treatment Period

- Continue recording concomitant medications.
- Take digital photographs of lesions on Day 1. Take digital photographs daily if regression is not seen after the first 3 days.

Collect on Day 7 and Day 14 during Tecovirimat Treatment Period

- Perform physical examination with vital signs on days 7 and 14.
- Collect blood samples to obtain and record lab values (e.g. immunochemistry, hematology, chemistry, and urinalysis).
- Take digital photographs of lesions on days 7 and 14.
- Collect blood and/or lesion samples, vesicular or scab material, for orthopoxvirus testing on day 14.

Collect Every 7 Days if Tecovirimat Treatment Duration Continues Beyond 14 Days

If tecovirimat treatment duration continues beyond 14 days per clinical determination per treating physician and/or CDC, continued PK monitoring could be considered for continued therapeutic drug monitoring (Figures 1A, and 1B) and report the following evaluation and parameters to CDC every 7 days:

- Perform physical examination with vital signs.
- Collect blood samples to obtain and record lab values (e.g. immunochemistry, hematology, chemistry, and urinalysis).
- Record concomitant medications.
- Take digital photographs of lesions.
- Collect blood and/or lesion samples, vesicular or scab material, for orthopoxvirus testing.

During Tecovirimat Treatment Period

Collect PK samples throughout treatment duration following Figures 1A for outpatients and 1B for inpatients.

7.3.3 Patient Evaluation and Monitoring Parameters after Tecovirimat Treatment

Follow-up of patients will be required (including immunochemistry and photographs of lesions) until clinical signs and symptoms, laboratory abnormalities, and other AEs have either resolved or stabilized. Follow-up visits should be scheduled to coincide with clinical assessments, to the extent feasible. Patients who have abnormal physical examination findings or an ongoing AE/SAE seven days after receiving the last dose should return at 30 days (Treatment Day 44) after the last dose for a follow-up visit, if possible**.** The emergence 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.

All other outpatients and inpatients who are unable to return for a follow-up visit will have the 30-day post-dose visit conducted via telephone. The following treatment days assume a 14-day course of tecovirimat treatment; if treatment extends beyond 14 days, follow-up assessments should be scheduled accordingly to coincide with 7 days and 30 days after the last dose of tecovirimat.

For Outpatients:

- On Treatment Day 21 (+7 days, i.e., up to Treatment Day 28), an assessment of the patient's clinical status and any AEs should be recorded.
- On Treatment Day 44 ($\pm$2 days), a final assessment of the patient's clinical status and any AEs should be recorded to assess resolution of infection, viral resistance, and safety.

For Inpatients:

- Upon hospital discharge, a final assessment of the patient's clinical status and any AEs should be recorded to assess resolution of infection, viral resistance, and safety for inpatients.

- After discharge, follow-up visits should proceed according to Outpatient assessment schedule and patient treatment day, as applicable.

7.4 Final Product Accountability of Dispensed Tecovirimat

All dispensed medication will be accounted for and any unused medication must be appropriately disposed of per the Product Accountability Form (**ATTACHMENT 2**).

7.5 Early Termination of Tecovirimat Treatment

To the extent possible, the above-mentioned clinical evaluation and patient monitoring parameters should be followed for all patients who receive at least one dose of tecovirimat, even if the prescribed duration of treatment is not completed:

- If the patient discontinues tecovirimat due to an AE related to the product, he/she will be given appropriate care under medical supervision until the symptoms of any AE resolve or the patient's condition becomes stable.
- If a patient voluntarily discontinues tecovirimat for any reason, he/she will be asked to continue scheduled evaluations and complete a final evaluation.

8.0 SPECIMEN PREPARATION, HANDLING, AND SHIPPING

Please use the following instructions regarding preparing, handling, and shipping patient specimens for analysis at CDC and the analytical laboratory, Alturas Analytics, Inc. (**ATTACHMENT 4**).

8.1 Viral blood and lesion samples to CDC

As the transmission of orthopoxviruses can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this protocol, as currently recommended by CDC and the National Institutes of Health.

Viral lesion samples and anti-virus immunoglobulin samples and EDTA blood should be shipped refrigerated at 4°C (as per CDC guidelines) to:

Centers for Disease Control and Prevention Laboratory
Division of High Consequence Pathogens and Pathology
Poxvirus and Rabies Branch
Mailstop G-06
1600 Clifton Road
Atlanta, GA 30333

Additional instructions, including precautions when handling specimens and information on shipping, can be found on CDC's website: http://www.cdc.gov/ncidod/monkeypox/lab.htm and in **ATTACHMENT 4**.

8.2 Plasma Samples for PK analysis

Treating physicians must arrange for plasma samples to be collected for each patient and obtain a specimen collection kit from Alturas Analytics Inc. Samples should be collected following the instructions in **ATTACHMENT 4** and shipped to Alturas Analytics Inc.; 1324 Alturas Drive; Moscow, ID 83843.

8.3 Long-term Storage of Remaining Samples

Any remaining patient specimens for laboratory testing (including viral blood and lesion samples) may be stored for future orthopoxvirus-related investigation unless a patient requests that they be removed from storage. The consent form includes a section for patients to document their agreement with storage of their samples for future orthopoxvirus testing and contains information for patients to request removal of their specimens. Patient specimens in long-term storage will be anonymized after all testing for clinical care are completed. The consent form describes when specimens will be anonymized. Remaining specimens will be held in long-term storage at CDC's Poxvirus and Rabies Branch laboratory until it is determined that they are no longer needed. If a patient wishes for his/her specimens to be destroyed, they will be discarded if it is still possible to identify the samples and documentation of the patient's wishes will be maintained in the Poxvirus and Rabies Branch laboratory records and as part of the IND records for the patient.

9.0 RECORDING AND REPORTING ADVERSE EVENTS

9.1 Definitions (21 CFR 312.32)

An **ADVERSE EVENT** (AE) is any untoward medical occurrence associated with the use of tecovirimat in humans, whether or not considered related to tecovirimat. It can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of tecovirimat, without any judgment about causality.

A **SUSPECTED ADVERSE REACTION** is any AE for which there is a reasonable possibility that tecovirimat caused the AE. It is a subset of all AEs for which there is a reasonable possibility that tecovirimat caused the event. "Reasonable possibility" means there is evidence to suggest a causal relationship between tecovirimat and the AE. "Suspected adverse reaction" implies a lesser degree of certainty about causality than "adverse reaction."

An **ADVERSE REACTION** is any AE caused by tecovirimat. Adverse reactions are a subset of all suspected adverse reactions for which there is a reason to conclude that tecovirimat caused the event.

UNEXPECTED: An AE is considered "unexpected" if it is not listed in this protocol or Package Insert, or is not listed at the specificity or severity observed.

SERIOUS: An AE or suspected adverse reaction is considered "serious" if in the view of either the treating physician or CDC, it results in any of the following outcomes:

- death
- a life-threatening AE
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect

NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they

may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes previously listed.

LIFE-THREATENING: An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the treating physician or CDC, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused a death.

9.2 Treating Physician Reporting Requirements to CDC

All AEs must be reported on the Adverse Event Form (**ATTACHMENT 2**). These include all SAEs that the patient reports spontaneously, those the physician observes, and those the physician elicits in response to open-ended questions. All SAEs, whether or not the treating physician considers the event to be drug-related, must be reported to CDC within 24 hours of occurrence or as soon as possible by contacting the CDC smallpox duty officer. If this individual cannot be reached, then contact the CDC Emergency Operations Center at 770-488-7100 to be connected to the CDC smallpox duty officer on call.

9.3 CDC Reporting Requirements to FDA and CDC IRB

CDC will review all AEs and report serious, unexpected suspected adverse reactions to FDA within 15 calendar days of initial receipt or after determining that the information qualifies for reporting under 21 CFR 312.32(c)(1).

In cases of unexpected suspected adverse reactions that are fatal or life-threatening (serious), CDC will report to FDA as soon as possible, but no later than 7 calendar days after initial receipt of the information (21 CFR 312.32(c)(2)).

All three (3) of the definitions contained in the requirement must be met for expedited reporting to FDA:

1. Serious,
2. Unexpected, and
3. Suspected Adverse Reaction.

AEs that do not meet the requirements for expedited reporting will be reported to FDA in the IND Annual Report.

CDC will report all serious and unexpected suspected adverse reactions and incidents to CDC IRB according to CDC IRB's policy and procedures.

10.0 SUMMARY OF AVAILABLE SAFETY AND EFFICACY DATA OF TECOVIRIMAT

10.1 Tecovirimat Safety in Animals

The non-clinical safety of tecovirimat has been evaluated in acute and repeated dose oral and IV toxicity studies in multiple animal models, including non-human primates. The following lists significant conclusions of these studies.

10.1.1 Oral tecovirimat

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 at 100 mg/kg/dose (similar to the highest observed human exposure at the RHD based on C_{max}), although no convulsions or EEG findings were observed at this dose.

Reproductive Toxicity Studies

Reproductive studies were conducted in both mice and rabbits, in which no embryofetal developmental toxicity was observed during organogenesis. Decreased fertility due to testicular toxicity was observed in male mice (increased percent abnormal sperm and decreased sperm motility) was observed at 1,000 mg/kg/day (approximately 24 times the human exposure at the recommended human dose). Maternal toxicity was observed in the rabbit, only at the highest dose tested (100 mg/kg). There was no maternal toxicity noted in the mouse. Placental and milk transfer were observed but recovery was less than 1% of the delivered dose and did not accumulate in milk with time.

Genotoxicity Studies

Tecovirimat was not mutagenic in bacterial or mammalian cells.

- Tecovirimat did not cause chromosomal damage or bone marrow cell toxicity *in vivo*.

Special Toxicology Studies

- Tecovirimat is associated with behavioral and electroencephalogram (EEG) evidence of seizure in dogs. However, this finding has not been seen in the monkey model, even at significantly higher exposure levels and after repeated doses. The lack of central nervous system (CNS) effects consistent with altered seizure thresholds has been confirmed in the monkey model, using state-of-the-art EEG monitoring procedures, which adds credence to this negative finding.
- The greater sensitivity of dogs to tecovirimat-induced seizures relative to the monkey appears to represent possible species differences in susceptibility, differences in absolute levels of exposure to the CNS, as reflected in the plasma/cerebral spinal fluid (CSF) ratio, and possibly the use of non-naive dogs (i.e., dogs that had previously received a test pharmacological agent) in early studies.
- Old World monkeys, including cynomolgus, are the closest feasible model of CNS function to humans, and the findings in this species should be strongly considered in justifying and defining clinical studies. There is no evidence that tecovirimat causes seizures or pre-seizure changes in EEG in the monkey model at doses of 300 mg/kg (3,600 mg/m^2), which is 2.3- to 2.9-fold higher than the targeted doses of 250 mg total dose (154 mg/m^2) up to 2,000 mg total dose (1,250 mg/m2) in the completed and planned Phase I clinical trials.

10.1.2 IV tecovirimat

Single dose studies

- An IV study in monkeys using single doses of 20 and 30 mg/kg infused over 4 or 6 hours demonstrated that IV administration of tecovirimat was generally well-tolerated with the exception of transient tremors observed in animals dosed at 30 mg/kg over 4 hours.

Repeat dose studies

- The 14-day repeat IV dose NOEL in monkeys was 30 mg/kg. Overall, a 6 hour intravenous infusion of QD dosing at levels of 3, 10, or 30 mg/kg/day for 14 consecutive days was well-tolerated with no clinical, neurological, cardiovascular, respiratory, gross pathological, histological or histopathological drug-related findings in male and female monkeys. No changes in these endpoints were observed during a 2-week recovery period following the 14-day dosing phase in these animals.

Carcinogenicity Studies

Carcinogenicity studies have not been conducted with tecovirimat.

Hydroxypropyl betadex, the excipient used in IV tecovirimat has been 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 (lowest dose in rats is equivalent to approximately 1.7 times the exposure to humans of hydroxypropyl betadex at the recommended clinical dose of IV tecovirimat) [8,9]. The clinical relevance of these findings to treatment with IV tecovirimat is unknown.

10.2 Tecovirimat Efficacy in Animals

The effectiveness of tecovirimat 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 effectiveness of tecovirimat for treatment of smallpox disease 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.

Study Design

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.

Study Results

Treatment with oral 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 8** below).

Table 8. Survival Rates in Tecovirimat Treatment Studies in Cynomolgus Macaques and NZW Rabbits Exhibiting Clinical Signs of Orthopoxvirus Disease

Treatment Initiation[a]	Survival Percentage (# survived/n)		p-value[b]	Survival Rate Difference[c] (95% CI)[d]	
	Placebo	Tecovirimat			
Cynomolgus Macaques					
Study 1	Day 4	0% (0/7)	80% (4/5)	0.0038	80% (20.8%, 99.5%)
Study 2	Day 4	0% (0/6)	100% (6/6)	0.0002	100% (47.1%, 100%)
Study 3	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%)
NZW Rabbits					
Study 4	Day 4	0% (0/10)	90% (9/10)	<	90% (50.3%, 99.8%)
Study 5	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

10.3 Human Safety Data of Tecovirimat

Because clinical trials are conducted under widely varying 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 tecovirimat has not been studied in patients with smallpox disease.

Oral tecovirimat

The largest safety study of oral tecovirimat was 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 tecovirimat, 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 tecovirimat in a twice daily regimen for 14 days.

Most Frequently Reported Adverse Reactions to Oral Tecovirimat

The most frequently reported adverse reactions were headache and nausea. Adverse reactions that occurred in at least 2% of subjects in the tecovirimat treatment group are shown in **Table 9**.

Table 9. Adverse Reactions Reported in ≥ 2% of Healthy Adult Subjects Receiving at Least One Dose of Oral Tecovirimat 600 mg

	TPOXX 600 mg N =359 (%)	**Placebo N = 90 (%)**
Headache	12	8
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, and epigastric pain.

Adverse Reactions Leading to Discontinuation of Oral Tecovirimat

Six subjects (2%) had tecovirimat 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

Less Common Adverse Reactions to Oral Tecovirimat

Clinically significant adverse reactions that were reported in < 2% of subjects exposed to tecovirimat 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 and pruritis

Adverse Events to IV Tecovirimat

The most frequently reported AEs in a multiple-dose study of IV tecovirimat included infusion site pain, infusion site swelling, infusion site erythema, infusion site extravasation, and headache. Three of 49 subjects enrolled in the study (6.1%) had their treatment with IV tecovirimat discontinued due to an AE for the following reasons: infusion site extravasation (moderate); infusion site extravasation (mild); infusion site swelling and pain (mild). Adverse reactions that occurred in at least 4% of subjects in the tecovirimat treatment group are in **Table 10**. Adverse reactions that were reported in in < 4% of subjects exposed to tecovirimat and at rates higher than subjects who received placebo were: infusion site discomfort, infusion site edema, myalgia, arthritis, back pain, muscle tightness, diarrhea, photophobia, and pruritus generalized.

Table 10. Adverse Reactions Reported in ≥ 4% of Healthy Adult Subjects receiving IV Tecovirimat

	IV Tecovirimat 600 mg N =26	Placebo N = 6
Infusion Site Pain	73	67
Infusion Site Swelling	39	67
Infusion Site Erythema	23	67
Infusion Site Extravasation	19	50
Headache	15	0

10.4 Clinical Use of Tecovirimat in Diseased Patients to Date

No human efficacy data are currently available. However, oral tecovirimat has been used under an emergency IND in four cases in the United States, in two patients under this protocol, and in four cases outside the US. These treatment uses have been in a child as well as male and female adults.

E-IND No. 74,773: In March 2007, at the request of CDC, SIGA provided tecovirimat for the treatment of a 28-month old male child with eczema vaccinatum due to direct contact with a vaccinia vaccinee [10]. The patient's history included eczema and failure to thrive. The patient presented to the emergency room with high fever and severe eczema. Initially, the child was treated with Vaccinia Immune Globulin Intravenous (Human) (VIGIV) but his condition continued to worsen and on hospital Day 6 he exhibited progressive metabolic then respiratory acidosis, hypoalbuminemia, hypothermia, and hypotension through March 10, 2007. Tecovirimat was orally administered via a nasogastric tube for 14 days, beginning on March 11, 2007 (hospital Day 9). The dosing regimen of tecovirimat was:

50 mg (5 mg/kg) March 11–12
75 mg (7.5 mg/kg) March 13–14
100 mg (10 mg/kg) daily from March 19–24

Tecovirimat doses were adjusted to achieve a target peak level of 1,000 ng/ml, based on the efficacy NHP studies available to date at the time. Prior to initiation of tecovirimat, the child also received cidofovir (5 mg/kg) and repeated doses of VIGIV, with the last dose of VIGIV administered on March 27, 2007. Clinical signs of the child's improvement were observed within 1 week of the anti-viral intervention (tecovirimat and cidofovir) and VIGIV. The child was extubated on April 2, 2007, moved out of intensive care on April 8, 2007, and discharged to home on April 19, 2007 (hospital Day 48). There were no AEs that could be attributed to tecovirimat. (Vora et. al., 2008)

E-IND No. 104,793: On March 2, 2009, CDC received information of a possible progressive vaccinia (PV) case involving a 20-year-old male military smallpox vaccinee [11]. The patient's history included post-vaccination neutropenic fever which was diagnosed on January 28, 2009 as acute myelogenous leukemia M0 (AML M0). Approximately two weeks after a second round of induction chemotherapy, the patient's vaccination site deteriorated to a deep bulla, 4 cm in diameter, with a raised edge and central bleeding crust. Viral culture of a lesion swab and PCR viral analysis confirmed the presence of orthopoxvirus. Serum showed equivocal to absent anti-

orthopoxvirus IgG or IgM by an ELISA test. Based on the patient's history and test results, a diagnosis of PV was made. After receiving an initial dose of VIGIV, oral and topical tecovirimat was administered per the following dosing regimen:

400 mg once daily (oral) March 5–19, except March 8 (no dose administered)
800 mg once daily (oral) March 20–24
1200 mg once daily (oral) March 25–May 18
Topical 1%, 0.5 mL once daily March 6, April 21–May 12
1%, 0.5 mL twice daily March 7–April 20

Doses were adjusted to achieve a peak level of tecovirimat of 1500 ng/mL. The patient also received repeated doses of VIGIV, topical Imiquimod, and six oral doses of CMX001 (lipidated cidofovir). Early in treatment, the patient developed *Pseudomonas aeruginosa* sepsis, multiorgan failure, required stress dose steroids because of his prior induction regimens, required excessive vasopressor support ultimately later resulting in bilateral trans-tibial amputation. Also later during treatment, methicillin-resistant *Staphylococcus aureus* infection was detected in vaccination satellite lesions. Despite the patient's protracted clinical course with sepsis and superinfections, probably due to cellular immunodeficiencies, after more than 2 months of antiviral therapy, the patient was ultimately discharged in September 2009 after testing negative for vaccinia virus.

E-IND No. 106,338: On August 15, 2009, CDC notified SIGA to provide tecovirimat for the treatment of a 35-year-old female patient who developed vesiculopustular skin lesions on her arm and hand due to accidental exposure to recombinant-vaccinia-based rabies vaccine in a bait found by the patient's dog[12]. The patient had a history of Crohn's disease and was undergoing treatment with daily azathioprine and infliximab every 6 weeks. On August 22, 2009, after vaccinia-positive PCR results, the patient was given VIGIV and started on a daily oral dose of tecovirimat (400 mg) for 14 days. The lesions healed and the patient was discharged on August 29, 2009.

E-IND No. 112,324: In May 2011, tecovirimat was used to treat a 25-year-old healthy, immunocompetent female patient with a history of acne who was believed to have contracted a live vaccinia virus infection on her chin while changing a bandage covering the smallpox vaccination site of her boyfriend, a military contractor. The patient was treated with VIGIV and placed under house quarantine. A daily oral dose of tecovirimat (400 mg) was administered for 14 days. The patient responded well to treatment, with no apparent AEs. As of August, 2011, the patient was doing well and her lesions had completely healed with minimal scarring.

IND 116,039, CDC IRB #6402: In January 2016, a previously healthy 19-year-old male in the U.S. military sought treatment for complications that developed 1 day after receiving ACAM2000® (live vaccinia vaccination) inoculation[13]. Symptoms included malaise requiring bed rest, odynophagia, and retrosternal chest pain. Later the patient developed worsening erythema and deep pain in the area surrounding the inoculation site, a lesion on his right scalp, and a lesion on his left flank. PCR results of the lesion swabs confirmed the presence of orthopoxvirus. The patient was diagnosed with acute myeloid leukemia. Due to the need for the patient to receive chemotherapy and concern for immunosuppression that might lead to

progression of vaccinia infection, the patient received tecovirimat treatment under protocol CDC IRB #6402. The patient received oral tecovirimat 600 mg twice daily (BID) for a total duration of 62 days. No dose adjustments were made during his tecovirimat treatment course. The patient tolerated the course of tecovirimat well; there were no reports of adverse events. Throughout the patient's course, he received three doses of VIGIV and treatment for acute myeloid leukemia including chemotherapy.

IND 116,039, CDC IRB #6402: In January 2019, an unvaccinated healthy 26-year-old female laboratorian working with vaccinia virus developed a single vesicular lesion and swelling on her left index finger 10 days after a needle-stick injury[14]. Two days later, she developed fever, left axillary lymphadenopathy, malaise, pain, and worsening edema of her finger. The patient received tecovirimat treatment under protocol CDC IRB #6402. The patient received 600 mg orally BID for a total of 14 days. During the patient's course, she received a single dose of VIGIV and antibiotics (clindamycin and cephalexin) because of concern about possible secondary bacterial infection. Within 48 hours of treatment initiation, fever and lymphadenopathy resolved, and the local pain and edema decreased. During treatment with tecovirimat and antibiotics, the patient experienced mild adverse events (i.e., nausea, loss of appetite, fatigue, myalgia, and pruritus), and pain in her left finger and arm. Areas of necrotic tissue did not fully resolve until day 94.

IND 116,039, CDC IRB #6402: In July 2021, an early middle-aged male developed fever, cough, and fatigue, followed by onset of a diffuse rash within 1 week of traveling in Nigeria. The patient had extensive pustular rash on his face. His symptoms progressed to diarrhea, vomiting, cough, subjective fever, fatigue, and purulent rash. The patient was confirmed to have monkeypox virus infection and was treated with a 14-day course of tecovirimat, receiving 600 mg oral BID for the first 19 doses and 200 mg IV BID for the remaining 9 doses. The patient was reported not to have experienced any tecovirimat-related AEs and experienced resolution of monkeypox symptoms.

Tecovirimat use outside the US:

- In December 2009, the Division of Infectious Diseases at Helsinki University Central Hospital requested from SIGA tecovirimat for compassionate use in a 32-year-old female patient who was suffering from severe keratoconjunctivitis. The patient had been on various treatments since September 2009 and the Chief Physician reported the possibility of orthopoxvirus infection, as she tested PCR-positive for ocular cowpox virus. Plasma, serum and tear tecovirimat concentrations were monitored during treatment, and appeared adequate. There were no serious drug-related AEs reported. As of April 2010, the patient's corneal inflammation had improved. Orthopoxviral culture remained negative, but the PCR assay still tested positive.
- In August 2019, SIGA provided TPOXX capsules for treatment of a 32-year-old male patient with cowpox infection. The patient had a kidney transplant in 2006 and had taken immunosuppressive drugs (tacrolimus and mycophenolate mofetil). A total of 18 doses of TPOXX were administered. The patient was hospitalized for 15 days and was in intensive care for 5 days for the orthopoxvirus infection; however the patient did not recover from the infection. The patient's liver and kidney functions worsened over time. Additionally, he experienced severe worsening of oral mucosa [sic], obstruction of airways with acute respiratory failure and cardiopulmonary resuscitation (CPR), and septic shock. In September

2019, the patient died from multi-organ failure due to cowpox. The patient was reported to have tolerated the shorter than recommended course of TPOXX well. Information on adverse events with an onset after the initiation of TPOXX was not provided.

- In August 2019, SIGA provided TPOXX capsules for treatment of a 57-year-old white female with cowpox who had had a history of lung transplantation and renal impairment. The patient was treated with an extended course of TPOXX for one month, discontinued TPOXX, and then restarted TPOXX treatment again at the end of November until the patient succumbed to renal failure in March 2020. No adverse events attributed to TPOXX were reported.
- In November 2019, SIGA provided TPOXX capsules for treatment of a 35-year-old white female with a pre-existing condition of neorodermitis (atopic dermatitis) with no smallpox vaccination record and unknown exposure date. Her baseline physical assessment on November 2019 recorded 5 lesions assumed to be cowpox over <10% of her body (right hand). She received TPOXX capsules twice daily for a total of 7 days (14 doses). Note this is shorter than the 14-day courses recommended for treatment. The patient reported no adverse events during the treatment. The patient recovered from the infection.

Based on the outcomes of the human medical uses to date, it appears that tecovirimat may provide clinical benefit in the treatment of orthopoxvirus infections.

10.5 Dosage Rationale

Using survival as a primary endpoint, a minimum oral dose of 3 mg/kg/day (36 mg/m^2) for a period of 14 days starting at 3 days post infection in fed monkeys confers close to 100% (92.8%) protection from death, and significantly reduced viremia and lesion counts. This dose (3 mg/kg/day) defines the lower limit of protection in this NHP model. Use of the minimum efficacious dose cannot be justified if the therapeutic index allows for selection of a higher safe dose given the high rate of mortality and morbidity with orthopoxvirus infections. The NOAEL in monkeys in a 3-month safety study was 300 mg/kg/day (3600 mg/m^2), providing a 100-fold therapeutic index in this species. The 600 mg (360 mg/m^2) dose in the fed state provided plasma exposure levels five-fold below the 3 month NOAEL of 300 mg/kg/day (3600 mg/m^2) in NHPs. In addition, it is approximately 60% lower than the plasma drug exposure in humans administered tecovirimat at 800 mg (480 mg/m^2) for 21 days, which was well-tolerated. These results have been evaluated in population PK analyses that indicated that the mean predicted exposure after a 600 mg dose would be nearly three-fold above the 3 mg/kg dose, which appears to be the minimum efficacious dose in cynomolgus monkeys. Therefore, the human adult dose of 600 mg twice daily is anticipated to achieve or exceed comparable the PK/PD parameters of tecovirimat corresponding to the 10mg/kg dose in NHP challenge model, which has been selected as the efficacious dose in this model (**Table 9**). The adult dose of 200 mg administered IV is considered to be therapeutically-equivalent to 600 mg oral tecovirimat (see **Section 10.6** for information on pharmacokinetics).

<u>Effect of Food on Oral Tecovirimat Exposures</u>

SIGA-246-001 evaluated the effect of food on the exposure of oral tecovirimat. Healthy adult subjects administered tecovirimat in the fed state had approximately 60% higher exposure than those administered the compound in the fasted state. The results of that study were consistent with a previous NHP study demonstrating an approximate two-fold increase in exposure when a suspension of tecovirimat was administered in the fed versus the fasted state (50% versus 28%).

For very ill patients who cannot eat it may be acceptable to increase the tecovirimat dose to account for lower exposure (fed dose/0.6) to 1,200 mg.

Results from a comparison of tecovirimat exposures achieved in healthy human subjects to those observed in animal models of orthopoxvirus infection indicated that 600 mg BID provides for human exposures that achieve or exceed animal exposures and do not approach the levels associated with neurological signs of toxicity in dogs (lowest C_{max} associated with toxicity in dogs was reported as 3,825 ng/mL). A summary comparison of exposure parameters in NHPs (10 mg/kg QD) and in humans (600 mg QD and BID) is shown in **Table 11**.

Table 11. Comparison of PK Parameters for Oral Tecovirimat in Non-Human Primates and Healthy Adults

Dose Administered (Oral)	Infected NHP: 10 mg/kg QD	Human: 600 mg QD (fed)	Human: 600 mg BID (fed)	Human: 600 mg BID (fasted)
Day 1 (N*)	**6**	**44**	**16**	**16**
Mean C_{max} ng/mL (%CV)	749 (46)	1467 (626)**	1468 (35)	1203 (40)
Mean C_{min} ng/mL (%CV)	158 (93)	---	936 (31)	814 (42)
Mean C_{avg} ng/mL (%CV)	318 (40)	---	830 (35)	573 (46)
Mean AUC_{0-t} ng*hr/mL (%CV)	7629 (40)	12469 (5280)**	19918 (35)	13744 (46)
Day 14 (N*)	**6**	**42*****	**16**	**15**
Mean C_{max} ng/mL (%CV)	1403 (27)	1523 (607)	2322 (37)	1581 (42)
Mean C_{min} ng/mL (%CV)	146 (72)	201 (112)	623 (39)	353 (58)
Mean C_{avg} ng/mL (%CV)	569 (38)	616 (238)	1276 (36)	905 (42)
Mean AUC_{0-t} ng*hr/mL (%CV)	13650 (38)	19448 (9800)	30621 (36)	21709 (42)

Geometric mean and coefficient of variation values given in table, except where noted
*Number of subjects
**Arithmetic mean and standard deviation given
***C_{max} derived from 42 subjects, C_{min} from 41 subjects, and AUC and C_{avg} from 40 subjects

10.6 Pharmacokinetics Data

Overall, the PK profiles of tecovirimat and its metabolites following a single oral dose and single, 6-hour IV infusion were similar in animal and human studies.[15,16] For both oral and IV routes of administrations, accumulation is observed after repeated administration, and steady-state is achieved within 6 days. Refer to **Tables 12 and 13** for pharmacokinetic parameters of tecovirimat.

Oral tecovirimat

Completed clinical studies to date indicate that oral tecovirimat is slowly absorbed and reaches maximum plasma concentrations approximately 4 hours after administration (**Table 12**). The bioavailability is approximately 39% higher when the compound is administered to subjects in the fed state. The t½ appears to be independent of dose and is approximately 20-29 hours. Steady-state area under the curve (AUC) is achieved by Day 6. The steady-state exposure is approximately 20-25% higher than the single-dose exposure at 1 week and at 14 days.

IV tecovirimat

The PK and absolute bioavailability of a single IV dose of 200 mg tecovirimat infused over 6 hours was evaluated in study SIGA-246-IV-202. The geometric mean total exposures, estimated

as AUC0-t, AUC0-24, and AUC∞, of tecovirimat were 14677, 10911, and 15514 h*ng/mL, respectively, and the geometric mean peak exposure (Cmax) of tecovirimat was 1269 ng/mL. The median Tmax of tecovirimat was approximately 6 hours (at the end of infusion) and then the concentration declined in a biphasic manner with a mean t½ of 18.97 hours. The mean CL and Vz values were 13.35 L/h and 358.50 L, respectively (**Table 13**).

The PK of a 240 mg dose of tecovirimat infused over 6 hours, BID for 7 days was evaluated in study SIGA-246-IV-202. On Day 1, tecovirimat reached Cmax at the end of second dose infusion with median Tmax of approximately 18 hours. After 7 days of 240 mg IV TPOXX administration BID, the Tmax was in the range of 6 to 11 hours for tecovirimat.

Pharmacokinetic studies of IV tecovirimat were also conducted in 3 pilot studies in monkeys using single IV doses ranging from 1-30 mg/kg administered daily or twice daily (BID) over 4 or 6 hours as well as 1 pilot study in rabbits using repeat 4 mg/kg doses administered as a 6 hour infusion daily for 14 days. The NOAEL in monkeys was considered to be 30 mg/kg. The Cmax and AUC0-24 values at this NOEL were up to 6- and 2.7-fold, respectively, higher than those observed in human at 600 mg BID clinical dose for 14 days.

Table 12. Pharmacokinetic Parameters of Oral Tecovirimat

Absorption	
Tmax (h)[a]	4-6
Effect of food (relative to fasting)[b]	↑39%
Distribution	
% Bound to human plasma proteins	77-82
Blood-to-plasma ratio (drug or drug-related materials)	0.62-0.90
Volume of distribution (Vz/F, L)	1030
Metabolism	
Metabolic pathways[c]	Hydrolysis, UGT1A1[d], UGT1A4
Elimination	
Major route of elimination	Metabolism
Clearance (CL/F, L/hr)	31
$t_{1/2}$ (h)[e]	20
% of dose excreted in urine[f]	73, predominantly as metabolites
% of dose excreted in feces[f]	23, predominantly as tecovirimat

[a] Value reflects administration of drug with food.
[b] Value refers to mean systemic exposure (AUC24hr). Meal: ~ 600 kcal, ~ 25 g fat.
[c] 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)
[d] Uridine diphosphate (UDP)-glucuronosyl transferase (UGT) enzymes
[e] t1/2 value refers to mean terminal plasma half-life.
[f] Single dose administration of [^{14}C]-tecovirimat in mass balance study.

Table 13. Summary of Plasma Pharmacokinetic Parameters of IV Tecovirimat – Single IV Dose (SIGA-246-IV-202)

Treatment Statistic	Cmax (ng/mL)	DCmax (ng/mL/mg)	Tmax (h)	AUC0-t (h*ng/mL)	DAUC0-t (h*ng/mL/mg)	AUC0-24 (h*ng/mL)	DAUC0-24 (h*ng/mL/mg)	AUC0-∞ (h*ng/mL)
Tecovirimat IV 200 mg once								
n	32	32	32	32	32	32	32	32
Mean	1308	6.54	-	15218	76.09	11262	56.31	16063
SD	357.8	1.789	-	4255.6	21.278	3068.8	15.344	4391.5
CV	27.4	27.4	-	28.0	28.0	27.2	27.2	27.3
Geo. mean	1269	6.35	-	14677	73.39	10911	54.56	15514
Geo. CV	24.1	24.1	-	27.8	27.8	25.3	25.3	27.3
Median	1235	6.18	5.98	14702	73.51	10396	51.98	15273
Minimum	926	4.63	5.98	7028	35.14	7028	35.14	7502
Maximum	2490	12.45	6.52	25842	129.21	19460	97.30	27083
Treatment Statistic	**DAUC0-∞ (h*ng/mL/mg)**	**%AUCextrap (%)**	**t1/2 (h)**	**λz (1/h)**	**CL (L/h)**	**Vz (L)**	**Total MR,AUC0-24**	**Total MR,AUC0-t**
n	32	32	32	32	32	32	32	32
Mean	80.32	5.33	18.97	0.0399	13.35	358.50	0.18	0.14
SD	21.958	3.379	5.814	0.01271	3.700	130.348	0.029	0.030
CV	27.3	63.3	30.6	31.8	27.7	36.4	16.2	22.3
Geo. mean	77.57	-	-	-	-	-	0.18	0.13
Geo. CV	27.3	-	-	-	-	-	15.4	21.9
Median	76.36	4.49	17.45	0.0397	13.10	330.04	0.18	0.13
Minimum	37.51	0.99	8.33	0.0194	7.38	186.61	0.14	0.09
Maximum	135.41	15.88	35.75	0.0832	26.66	726.86	0.26	0.22

Abbreviations: CV, coefficient of variation; geo, geometric; IV, intravenous.
Source: Table 11–1 from the SIGA-246-IV-202 clinical study report.
Notes: Tecovirimat intravenous (IV) = tecovirimat injection administered by IV infusion over 6 hours using a syringe pump. Tecovirimat IV injection was supplied at a concentration of 10 mg/mL and was diluted with normal saline 1:2 for administration. Tecovirimat oral = 3 × 200 mg tecovirimat capsules taken orally within 30 minutes after a meal consisting of approximately 600 calories and 25 g fat. Subjects with predose concentrations greater than 5% of Cmax were excluded from pharmacokinetic summary statistical calculations. AUC0-∞ and DAUC0-∞ values were excluded where %AUCextrap was greater than 20%.

Specific Populations

No clinically significant differences in the pharmacokinetics of tecovirimat were observed based on age, sex, ethnicity. At the 600 mg twice-daily dosage, tecovirimat exposure was reduced in adult subjects weighing more than 120 kg compared to the exposures in adult subjects weighing less than 120 kg. Specifically, in 34 adult subjects weighing more than 120 kg who received 600 mg tecovirimat twice daily, the observed mean steady state values of $AUC_{0\text{-}24hr}$, C_{max}, and C_{trough} were 19500 hr•ng/mL (CV: 23%), 1300 ng/mL (CV: 29%), and 585 ng/mL (CV: 31%), respectively.

Pediatric Patients
Tecovirimat 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.

Renal impairment
Studies of oral tecovirimat in patients with varying degrees of renal impairment found that there was a small impact on the overall extent of tecovirimat exposure, and a modest effect of renal function impairment on the peak and overall extent of exposure to the metabolites of tecovirimat. Hemodialysis did not have a significant impact on tecovirimat. No dosage adjustment for oral tecovirimat is required for patients with mild, moderate or severe renal impairment or patients with end stage renal disease (ESRD) requiring hemodialysis.

IV tecovirimat is formulated with hydroxypropyl betadex as a solubilizing/complexing agent at a concentration of 400 mg/mL (200 mg dose of IV tecovirimat contains 8000 mg of hydroxypropyl betadex). In a pharmacokinetic study in patients with normal renal function who were treated with IV itraconazole at the same concentration of hydroxypropyl betadex per dose as IV tecovirimat (8000 mg of hydroxypropyl betadex per dose), the study found hydroxypropyl betadex had a short half-life of 1 to 2 hours, demonstrated no accumulation following successive daily doses, and the majority of the 8000 mg dose of hydroxypropyl betadex was eliminated in the urine[8]. In a study following a single IV dose of itraconazole containing 8000 mg dose of hydroxypropyl betadex, clearance of hydroxypropyl betadex was reduced in subjects with mild, moderate, and severe renal impairment, resulting in higher exposure to 8000 mg dose of hydroxypropyl betadex; in these subjects, half-life values were increased over normal values by approximately two-, four-, and six-fold, respectively[8]. In these patients, successive infusions may result in accumulation of hydroxypropyl betadex until steady state is reached. Hydroxypropyl betadex is removed by hemodialysis.

Under this protocol, IV tecovirimat <u>is contraindicated in patients with severe renal impairment</u> (creatinine clearance <30 mL/min). In patients with mild (defined as creatinine clearance 50-80 mL/min) and moderate (defined as creatinine clearance 30-49 mL/min) renal impairment, IV tecovirimat should be used with caution. See **Section 6.4** for more information on use of IV tecovirimat in patients with renal impairment.

Hepatic impairment
Studies of oral tecovirimat in patients with varying degrees of hepatic impairment found that there was a small impact on the overall extent of tecovirimat exposure, and a modest effect of hepatic function impairment on the peak and overall extent of exposure to the metabolites of tecovirimat. No dosage adjustment is required for patients with mild, moderate or severe hepatic impairment (Child Pugh Class A, B, or C).

<u>Drug Interaction Studies</u>

The effect of tecovirimat on the exposure of co-administered drugs are shown in **Table 14**.

Table 14. Drug Interactions – Changes in Pharmacokinetic Parameters for Co-Administered Drug in the Presence of Oral Tecovirimat[a]

Co-Administered Drug	Dose of Co-Administered Drug (mg)	N	Mean Ratio (90% CI) of Co-Administered Drug PK With/Without TPOXX No Effect = 1.00	
			C_{max}	AUC_{∞}
Flurbiprofen + omeprazole + midazolam[b]	omeprazole 20 single dose	24	1.87 (1.51, 2.31)	1.73 (1.36, 2.19)
	midazolam 2 single dose		0.61 (0.54, 0.68)	0.68 (0.63, 0.73)
Repaglinide	2 single dose	30	1.27 (1.12, 1.44)	1.29 (1.19, 1.40)
Bupropion	150 single dose	24	0.86 (0.79, 0.93)	0.84 (0.78, 0.89)

[a] All interaction studies conducted in healthy volunteers with tecovirimat 600 mg twice daily.
[b] Comparison based on exposures when administered as flurbiprofen + omeprazole + midazolam.

No pharmacokinetic changes were observed for flurbiprofen when co-administered with tecovirimat.

Cytochrome P450 (CYP) Enzymes: Tecovirimat is a weak inhibitor of CYP2C8 and CYP2C19, and a weak inducer of CYP3A4. Tecovirimat is not an inhibitor or an inducer of CYP2B6 or CYP2C9.

In Vitro Studies Where Drug Interaction Potential Was Not Further Evaluated Clinically

CYP Enzymes: Tecovirimat is not an inhibitor of CYP1A2, CYP2D6, CYP2E1 or CYP3A4, and is not an inducer of CYP1A2. Tecovirimat is not a substrate for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4.

UGT Enzymes: Tecovirimat is a substrate of UGT1A1 and UGT1A4.

Transporter Systems: Tecovirimat inhibited Breast Cancer Resistance Protein (BCRP) *in vitro*.

Tecovirimat is not an inhibitor of P-glycoprotein (P-gp), organic anion transporting polypeptides 1B1 and 1B3 (OATP1B1 and OATP1B3), organic anion transporter 1 (OAT1), OAT3, and organic cation transporter 2 (OCT2). Tecovirimat is not a substrate for P-gp, BCRP, OATP1B1, and OATP1B3.

10.7 Pharmacokinetic Sampling Rationale

Because the effectiveness of tecovirimat 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, Cmax, and Cmin) of tecovirimat following a twice daily dose of 600 mg when compared to the therapeutic exposures in these animal models.

Since tecovirimat has not been studied in humans with smallpox or orthopoxvirus infection and support for the dosage regimen is limited to animal efficacy studies, therapeutic drug monitoring in patients infected with smallpox or orthopoxvirus will ensure adequate drug exposure and inform possible dose adjustment (see **Section 4.1**).

11.0 PROGRAM MODIFICATIONS

Any change or modification to the program that affects purpose, procedures, or significant data or administrative aspects of the program will require a formal amendment. Such amendments

will be agreed upon and approved by the Principal Investigator and submitted to and approved by the CDC IRB prior to any implementation of said change or modification.

12.0 PROGRAM DEVIATIONS

Deviations are defined as isolated occurrences involving a procedure that did not adhere to the program. The treating physician is responsible for identifying any program deviations. Each deviation will be recorded and noted in the patient's case report form at the program site (i.e., hospital). Each deviation will promptly be reported by the Principal Investigator to the CDC IRB overseeing this protocol, and the report shall include the treating physician's assessment of the effect on the patient and proposed remedial action.

13.0 DATA MANAGEMENT

Recording Clinical Data

Case report forms, laboratory reports, hospital discharge summaries, medical records, etc., may be used as source documentation. All original case report forms and data collected under this expanded access IND program should be regarded and handled similarly to the information collected and records maintained routinely by healthcare personnel for clinical management of patients.

Data Handling

The information obtained through the case report forms of this IND protocol and additional supplemental information provided by treating physicians to CDC will be maintained by the CDC. Any analysis of data contents will be conducted without individual identifiers. The information gathered under this expanded access IND program and any analysis generated will be reported to the FDA as part of the annual report for this IND. Data from case report forms and other related information collected under this IND will also be provided to SIGA Technologies, Inc. and the Department of Health and Human Services/Biomedical Advanced Research and Development Authority (HHS/BARDA).

14.0 ETHICAL, LEGAL, AND ADMINISTRATIVE REQUIREMENTS

14.1 Good Clinical Practices

The procedures set forth in this program are designed to ensure that the Sponsor and all program personnel abide by the U.S. Code of Federal Regulations (CFR) and the International Conference of Harmonisation/Good Clinical Practice guidelines. The Principal Investigator and Site Investigator (i.e., treating physician) acknowledges this by signing the Form FDA 1572.

14.2 Informed Consent

Written informed consent in compliance with 21 CFR 50 will be obtained before any program-related procedures are initiated. Consent via the enclosed informed consent/permission form (**ATTACHMENT 1**) must be obtained from the patient before tecovirimat is administered. If the patient is unable to give consent, consent must be obtained from the next-of-kin or legal guardian/representative. The treating physician or designee will provide information on tecovirimat in lay terms to the patient. Questions about the nature of the program, the means by which the program is to be conducted, and the risks to the patient will be solicited.

A single consent form will be used to obtain informed consent from adults or parental permission for minors. Waiver of assent for children (7–11 years of age) under 21 CFR 50.55(c)(1) and for children (12–17 years of age) under 21 CFR 50.55(c)(2) was approved by the CDC IRB for all patients under this IND program. Parental permission will be sought in accordance with 21 CFR 50.55 for all minors aged 17 and younger (permission of only one parent is required). Please see **ATTACHMENT 1**. The ultimate responsibility for decision-making regarding treatment with tecovirimat in all minors should lie with the parent or guardian.

If a patient is unable to respond and make wishes known about tecovirimat treatment, and no next-of-kin or legal representative is available, and the patient's illness is life-threatening, per 21 CFR 50.23 "Exception from General Requirements", informed consent may be deemed not feasible and the treating physician can make the determination to administer tecovirimat. Per 21 CFR 50.23, the patient's treating physician, acting as site investigator, and a physician who is not otherwise participating in this expanded access IND treatment program, will document the following on the consent form and will return a copy of the consent form to CDC. CDC will also report to CDC IRB as required and according to CDC IRB's policy and procedures.

1. Patient is confronted by a life-threatening situation necessitating the use of tecovirimat.
2. Informed consent cannot be obtained from the patient because of an inability to communicate with, or obtain legally-effective consent from, the patient.
3. Time is not sufficient to obtain consent from the patient's legal representative.
4. There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the patient.

If immediate use of tecovirimat is, in the treating physician's opinion, required to preserve the life of the patient, and time is not sufficient to obtain the independent determination required above in advance of administering tecovirimat to the patient, the determinations of the treating physician shall be made, be reviewed and evaluated in writing by a physician who is not participating in this treatment protocol, and a copy of the informed consent form be returned to CDC within 3 working days after initiation of tecovirimat treatment.

15.0 FINANCIAL REMUNERATION AND INSURANCE

CDC is providing tecovirimat for this program at no cost. All other costs related to treatment of orthopoxvirus, including hospital and medical care costs, are the responsibility of the patient. Should a patient be injured as a direct result of participating in this program, he/she should be treated as indicated clinically. CDC is not responsible for payment for such treatment. The patient should understand that this does not constitute a waiver or release of legal rights. This issue is addressed in the informed consent/permission form (**ATTACHMENT 1**) and will be discussed with the patient by the treating physician.

16.0 REFERENCES

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Attachment 1
Informed Consent/Parental Permission Form

INFORMED CONSENT/ PARENTAL PERMISSION FORM FOR TECOVIRIMAT TREATMENT

Please read this consent form carefully and ask any questions you/your child may have. If you want to get tecovirimat under this treatment program, we will ask you to sign this consent form. You will get a copy of this form to keep. The use of "you" in this consent form may not apply for minors or people who, for other reasons (such as serious illness), cannot read and/or fully understand the contents. In those cases, the parents or other legal guardians must review the contents of the consent form and give permission for the person to be treated.

BACKGROUND

You are being offered tecovirimat because you:

- Have or may have been exposed to a pox virus (such as cowpox or monkeypox) and have developed or may be at risk of developing a serious or life-threatening infection.

OR

- Have or may have been exposed to vaccinia (the virus in one of the smallpox vaccines that contains live virus) through getting the vaccine, contact with another person who got the smallpox vaccine, or some other way, and have developed a serious reaction.

This program is sponsored by the Centers for Disease Control and Prevention (CDC). This form provides information you may want to know about tecovirimat before you decide to take it.

WHAT ARE POXVIRUSES?

Poxviruses are a family of viruses that can cause serious diseases such as smallpox, monkeypox and cowpox. Poxviruses also include vaccinia virus, which is most commonly caused by exposure to the smallpox vaccine. Poxviruses may cause the following symptoms:

- Severe rash, which can leave scars when healed
- High fever
- Chills
- Tiredness
- Severe headaches
- Backache and/or muscle aches
- Swollen glands in the armpits (lymph nodes)

Other symptoms may develop before the rash appears which may spread and become raised bumps and pus-filled blisters (called lesions). They usually crust, scab, and fall off after about 2-4 weeks, leaving a pitted scar.

Some people who get the smallpox vaccine or come in contact with a person who got the vaccine may develop serious reactions such as spread of the vaccinia virus to other parts of the body or serious reaction at the injection site known as eczema vaccinatum, severe generalized vaccinia, or progressive vaccinia. These conditions may require treatment with tecovirimat.

WHAT IS TECOVIRIMAT?

Tecovirimat (also known as TPOXX or ST-246) is a drug that may help to treat infections caused by pox viruses and reactions to the smallpox vaccine. Tecovirimat is approved by the Food and Drug Administration (FDA) to treat smallpox in adults and children. Tecovirimat is available as capsules (pills). It also comes in a liquid injection form that is given directly into a vein (bloodstream) on your arm or hand through a needle or tube (called an IV infusion). Your doctor will decide if you should be treated with tecovirimat pills or by IV infusion. FDA has reviewed information on tecovirimat and determined that tecovirimat may help to treat certain serious or life-threatening disease from poxviruses.

WHAT WILL HAPPEN IF YOU CHOOSE TO BE TREATED WITH TECOVIRIMAT?

- If you agree to tecovirimat treatment, you will need to sign this consent form to begin receiving tecovirimat.

- You will be asked about your health, any medicines that you are taking, and any allergies you may have.
- Your doctor will give you the right dose of tecovirimat and explain how to take it (such as taking 30 minutes after a meal and type of meal) and for how long. Tecovirimat is usually given for 14 days, but your treatment may be longer depending on how serious your infection is.
  - For most adults treated with tecovirimat capsules, the dose is 600 mg (three 200 mg capsules) two times a day. Patients who weigh 264 pounds (120 kg) or more should take three 200 mg capsules three times a day. Take tecovirimat by mouth with a full glass of water and within 30 minutes after eating a meal containing about 600 calories and 25 grams of fat. For adults and children unable to swallow capsules, follow the Instructions for Opening and Mixing Tecovirimat Capsules with Food.
  - For people who are hospitalized with serious illness and have trouble taking capsules or eating a full meal, tecovirimat may be given through a tube placed in your arm or hand, called an IV.
  - How you take tecovirimat, your dose, and how often you take it may change depending on your condition and treatment needs. Your doctor will tell you how tecovirimat will be given to you, how much to take, and how often.
- If you are being treated as an outpatient, your doctor will give you a diary card for you to fill out to track your illness progress. You will be asked to fill out this diary card and return it to your treating physician at each clinic visit and at the end of your tecovirimat treatment.
- Infection with a poxvirus is a serious illness, so you will have blood drawn regularly so that your doctor can check your medical condition and to see if the virus is still in your blood (this may involve you giving urine, including a pregnancy test, and blood samples throughout your treatment for routine hospital tests). To make sure that you are getting the right amount of drug, some extra amount of blood will be taken just before and/or after a few doses of tecovirimat during your treatment or more often as necessary. See below for the total amount of blood that may be collected for tecovirimat testing. You may be asked to give additional blood than the total below if your tecovirimat dose and/or duration need to change.
  - Adults and children who weigh over 44 pounds: 6 more blood draws and a total of 5 tablespoons of blood.
  - Children who weigh 44 pounds or less: 6 more blood draws and a total of 3 tablespoons of blood.
  - Infants who weigh 22 pounds or less: 6 more blood draws and a total of 2 tablespoons of blood.
- If you have any lesions, medical staff will take pictures of them throughout your treatment to see if they are getting better. If you are being treated as an outpatient, your doctor may also ask you to take pictures of your lesions to send to your doctor.
- Your doctor will follow up with you 30 days after the last dose or until you have gotten better.
- Any remainders of your or your child's samples used for orthopoxvirus testing at CDC will be stored for future orthopoxvirus-related investigations. After all testing required for your clinical care is completed, samples will be stored at CDC without your name or any other identifier that could link it to you or your child until they are no longer needed. If you do not wish for these specimens to be stored, then they will be destroyed. Whether or not you agree to store these leftover specimens, you will still be able to get tecovirimat. If at any time you would like for your specimens to stop being stored, then call Dr. Brett Petersen at 404-639-5464.

WHAT ARE THE BENEFITS OF TECOVIRIMAT?

We do not know for certain if you will benefit from tecovirimat. Based on what we know about tecovirimat, the drug may help to treat your infection or vaccine reaction and prevent it from getting worse. The potential benefit of tecovirimat is that it may help to cure your illness.

WHAT ARE THE RISKS OF TECOVIRIMAT?

The risks of tecovirimat in people with smallpox or other poxviruses are known. Tecovirimat has not been studied in people with weak immune systems, the elderly, or children. Tecovirimat capsules

were tested in 359 healthy adults, including 336 healthy adults who received tecovirimat capsules 600 mg twice a day for 14 days. Tecovirimat for injection was also tested in 82 healthy adults. No serious problems occurred in any of the participants in these studies. Tecovirimat capsules have also been given to 7 people with viral infections to date and no one had serious problems with tecovirimat. Still, tecovirimat may cause some adverse events. There also may be other adverse events that we cannot predict. The most common adverse events in people who have taken tecovirimat were:

- Headache
- Nausea
- Vomiting
- Stomach pain
- Dizziness (only with IV tecovirimat)
- Pain/swelling/redness at the injection site (only with IV tecovirimat)

Low blood sugar can happen when tecovirimat is taken with repaglinide, a medicine used to treat type 2 diabetes. If you are taking repaglinide, tell your healthcare provider if you get any of these symptoms of low blood sugar:

- Headache
- Hunger
- Dizziness
- Sweating
- Fast heartbeat
- Drowsiness
- Feeling jittery or shaky
- Confusion
- Weakness
- Irritability

As with any medication, there is a potential risk of an allergic reaction. An allergic reaction after receiving tecovirimat could include a rash, difficulty breathing, wheezing, sudden drop in blood pressure causing dizziness or fainting, swelling (around the mouth, throat, or eyes), fast pulse, and sweating.

During tecovirimat treatment, a small amount of your blood (5 mL or 1 teaspoon) may be taken regularly to do lab tests. The risks of taking blood are brief pain, bleeding, bruising of the skin where the needle enters, soreness and swelling at that spot, and possible infection at that spot. A trained person skilled in blood collection will collect your blood sample using a sterile technique. Please tell the doctor or nurse about any medical conditions or problems that you have.

ARE THERE RISKS RELATED TO PREGNANCY OR NURSING?

Tecovirimat has not been studied in pregnant women or nursing mothers. It is not known if giving tecovirimat to a pregnant woman could hurt her unborn child. Very high amounts of tecovirimat have been tested on pregnant mice and rabbits. There were no serious problems in the unborn animals. Smallpox or related viruses during pregnancy can cause serious harm to the mother and the unborn baby. Given that your illness is serious, the potential benefits of tecovirimat likely outweigh the risks.

WHAT OTHER CHOICES DO I HAVE?

Smallpox can be prevented with the smallpox vaccine, but the vaccine will not treat or get rid of existing smallpox or other poxvirus infections. There is no proven way to treat poxviruses, but research is ongoing. Also, you may benefit from supportive therapy (such as intravenous fluids, medicine to control fever or pain) and antibiotics for any bacterial infections that may occur. There may be other medications that your doctor may consider using to treat your infection. There may also be research studies looking at other new treatments for poxviruses. You should discuss any questions you have and other choices you may have with your doctor.

WHAT ARE MY COSTS?

CDC is providing tecovirimat for free. Other costs of the hospital and medical care will not be paid by CDC. Other costs will need to be paid by your insurer, Medicare, Medicaid, or you.

WHAT IF YOU REFUSE TECOVIRIMAT TREATMENT?
You have the right to refuse tecovirimat. Talk to the doctor if you do not want to get tecovirimat. He/she will explain how it may affect your health and will tell you about other treatments. You also have the right to stop tecovirimat at any time without penalty especially if you have any side effects that you cannot stand. It will not change your regular medical care if you decide not to take it.

WHAT HAPPENS IF YOU ARE HARMED?
You will get immediate medical care if you are harmed because of being in this program. But CDC will not give this care. CDC does not normally pay for harm done to you because of being in a program like this. Thus, you or your insurer (such as Medicare or Medicaid) will have to pay for any care that is needed. But, you are not giving up any of your rights by signing this consent form and agreeing to be treated with tecovirimat in this program.

WHAT ABOUT PRIVACY?
We will keep all facts about you private to the extent allowed by applicable law. People who work for CDC, FDA, U.S. Department of Health and Human Services, local/state health authorities, and SIGA Technologies Inc. (the company that makes tecovirimat) may look at your medical records, including your name and personal information, to ensure and monitor the appropriate and safe use of tecovirimat. If this information is shared with anyone else, your name and personal information will not be used or listed. If we share photos, we will only use those that will not reveal your identity. This includes reports or any publications such as articles in scientific journals. But, CDC is allowed to give your name to public health or medical people who, for example, need to find out how you got the infection and how to prevent other cases.

WHAT IF I HAVE PROBLEMS OR QUESTIONS?
If you have questions about this treatment program or feel that you or your child have been harmed as a result of participation in this program, please contact your treating physician. If you have questions about your rights as a participant in this program, please call CDC's Human Research Protection Office at 1 (800) 584-8814 and say that you are calling about CDC protocol #6402. Leave a brief message with your name and phone number. Someone will call you back as soon as possible.

WRITTEN INFORMED CONSENT FOR TREATMENT WITH TECOVIRIMAT
I have read the form or it has been read to me. I have been given a chance to ask questions and my questions have been answered. I agree to get (or have my child get) tecovirimat.

I also agree that any samples I/my child give can be stored for future orthopoxvirus-related testing:
☐ Yes ☐ No

Print Patient's Name:_____

Patient's/Parent's Signature: _____ Date:_____

Note: If patient or parent/guardian is unable to sign, a legally authorized representative may sign.
Legally Authorized Representative Signature: _____
Print Name: _____
Date: _____

TRANSLATOR DOCUMENTATION (if applicable)
Translator to document if patient gave informed consent through another language other than English
I have translated this form into the _____ language.
Print Name: _____

Translator's Signature:_____
Date:_____

IF OBTAINING INFORMED CONSENT IS NOT FEASIBLE

In the event that obtaining informed consent is not feasible because the patient is unable to respond and make wishes known about tecovirimat treatment *and* no legal guardian or next-of-kin is present the following provides for the treating physician to make a clinical determination to treat with tecovirimat provided that the treating physician and an independent physician certifies to the following within 3 working days of initiating treatment with tecovirimat:

1. Patient is confronted by a life-threatening situation necessitating the use of tecovirimat.
2. Informed consent cannot be obtained from the patient because of an inability to communicate with, or obtain legally-effective consent from, the patient.
3. Time is not sufficient to obtain consent from the patient's legal representative.
4. There is no available alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the patient.

☐ Document as such in the patient's medical record and ensure the patient or patient's legally authorized representative is made aware that tecovirimat was administered for uses for which it is not FDA-approved.

☐ Name & signature of treating physician who made the determination to administer tecovirimat to patient when informed consent could not be obtained:

_____	_____	_____
Name	Signature	Date

☐ Name & signature of second physician, who is not otherwise participating in this treatment protocol, reviewing and evaluating decision to administer tecovirimat to patient:

_____	_____	_____
Name	Signature	Date

☐ Return copy of this signed page to CDC within 3 working days of initiation of tecovirimat treatment

Attachment 2
Case Report Forms

- Attachment 2A:
  Case Report Forms for **inpatients and outpatients**
  1. FORM A: Patient Intake Form
  2. FORM B: Tecovirimat Product Accountability Form
  3. FORM C: Adverse Event Form

- Attachment 2B
  Case Report Forms for **outpatients only**
  1. FORM D: During Tecovirimat Treatment Period
  2. FORM E: Post Tecovirimat: Treatment Day 21 (7 Days After Last Dose)
  3. FORM F: Post Tecovirimat: Treatment Day 44 (30 Days After Last Dose)
  4. FORM G: Tecovirimat Diary for Outpatients

- Attachment 2C
  Case Report Forms for **inpatients only**
  1. FORM H: Daily Form (Days 1–6, 8–13)
  2. FORM I: Day 7 of Tecovirimat Treatment Form
  3. FORM J: Day 14 of Tecovirimat Treatment Form
  4. FORM K: Every 7 Days If Still Receiving Tecovirimat Beyond 14 Days
  5. FORM L: Post Tecovirimat: Upon Hospital Discharge

CASE REPORT FORMS

IND No.: **116,039**

Protocol No. and Title: **CDC IRB #6402 "Use of Tecovirimat for Treatment of Human Orthopoxvirus Infections"**

Protocol Version: **Version 5.1**

Sponsor: **Centers for Disease Control and Prevention**

Return Case Report Forms to CDC via Fax at 404-639-1060

Poxvirus and Rabies Branch
Division of High-Consequence Pathogens and Pathology (DHCPP)
National Center for Emerging and Zoonotic Infectious Diseases (NCEZID)
Centers for Disease Control and Prevention
1600 Clifton Road NE, MS H24-12, Atlanta, GA 30333
Phone number: 404-639-5464

Attachment 2A

Complete for Inpatients and Outpatients:

1. FORM A: Patient Intake Form (Prior to First Dose of Tecovirimat)
2. FORM B: Tecovirimat Product Accountability Form
3. FORM C: Adverse Event Form

FORM A: Patient Intake Form
To Be Completed by Treating Physician for Inpatients and Outpatients Prior to First Dose of Tecovirimat (≤ 24 hours) (Page 1 of 6)

Date (MM/DD/YY): _____/_____/_____

HOSPITAL INFORMATION

Treating Physician Name: _____

Telephone Number: _____ **Fax number:** _____

Email address: _____

Hospital/Medical Facility Name and Address:

_____

_____

_____

DEMOGRAPHICS

Patient Name: _____

Hospital-assigned Patient ID: _____

Date of Birth (MM/DD/YY): _____ **Age:** _____**years** _____**months**

Sex: ☐ Male ☐ Female

Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino

Race:
☐ African American/Black
☐ American Indian or Alaska Native
☐ Asian
☐ Native Hawaiian or Other Pacific Islander
☐ White
☐ Other

ELIGIBILITY CRITERIA for TECOVIRIMAT TREATMENT

1. Primary Treatment for Orthopoxvirus Infections

1. Does the patient have an orthopoxvirus infection that has been confirmed by laboratory diagnostic testing or is suspected based on known exposure(s) and/or clinical manifestations of disease, while laboratory confirmation may be pending?
   ☐ Yes ☐ No
   Indicate orthopoxvirus species:_____

OR

FORM A: Patient Intake Form (Page 2 of 6)

2. Secondary Treatment for Complications Resulting from Vaccinia Vaccination/Exposure

2a. Has the patient developed vaccine-related complications from being vaccinated with vaccinia vaccine?
☐ Yes ☐ No If Yes, Date of Vaccination: _____

OR

2b. Has the patient been exposed to vaccinia virus without vaccination and developed vaccinia-related complications? ☐ Yes ☐ No Date of Exposure: _____

- What is the complication? (check one below)
  - ☐ Severe generalized vaccinia (GV)
    Describe the extent of lesions and other systemic manifestations of GV:
    _____
    _____
  - ☐ Eczema vaccinatum
  - ☐ Progressive vaccinia (vaccinia necrosum)
  - ☐ Serious inadvertent inoculation: describe how assessed and systemic findings
    _____
    _____

3. Eligibility for IV Tecovirimat

1. Is patient unable to take oral therapy or is there a concern that oral drug absorption may be altered (e.g., by gastrointestinal disfunction)?
   ☐ Yes ☐ No
   If yes, provide details on patient's condition: _____
   _____
   _____

INELIGIBILITY/STOPPING CRITERIA for TECOVIRIMAT TREATMENT

(if any of the following is Yes, tecovirimat treatment cannot be initiated or continue)

1. Unwilling to sign informed consent.
   ☐ Yes ☐ No
2. Refuse tecovirimat treatment.
   ☐ Yes ☐ No
3. Known allergy to tecovirimat and/or excipients of tecovirimat?
   ☐ Yes ☐ No
4. Negative laboratory results for orthopoxvirus in individuals whose tecovirimat treatment is initiated based on clinical manifestations of disease prior to laboratory results.
   ☐ Yes ☐ No
5. For IV tecovirimat only: patients with severe renal impairment (creatinine clearance <30 mL/min)
   ☐ Yes ☐ No

FORM A: Patient Intake Form (Page 3 of 6)

MEDICAL HISTORY

Date of illness onset (MM/DD/YY): _____/_____/_____
Date and time of exposure (if known) (MM/DD/YY): _____/_____/_____ _____Time (24h)
Date and time of smallpox vaccination (if known) (MM/DD/YY): ____/____/_____ _____Time (24h)
☐ ACAM2000 ☐ MVA
If vaccinated with ACAM2000, was there a documented vaccine "take?"
☐ Yes ☐ No If Yes, Date:_____

Pre-existing conditions:

1. Immunocompromising condition (i.e.: HIV/AIDS, atopic dermatitis or other skin disease, congenital/acquired immune defects, autoimmune/connective tissue disorders, bone marrow/organ transplants, leukemia/lymphoma/other cancers)?
   ☐ Yes ☐ No Type of condition: _____
2. Treatment with a medication affecting immunocompetency?
   ☐ Yes ☐ No Medication name(s): _____
3. History of superinfection? ☐ Yes ☐ No
   (If yes, describe) _____
4. Other pre-existing conditions? ☐ Yes ☐ No
   If yes, list: _____

Therapeutic Intervention: List all medications such as VIGIV and/or other antivirals administered for the treatment of orthopoxvirus infection (*tecovirimat can be used in conjunction with VIGIV or other therapies based on treating physician's clinical judgment)*:

Medication	Date of administration	Dose	Route of administration	Outcome

Other Concomitant Medications:

Note: Co-administration with repaglinide may cause hypoglycemia. Monitor blood glucose and monitor for hypoglycemic symptoms during co-administration.

Medication:	Dosage/route of administration:
Medication:	Dosage/route of administration:
Medication:	Dosage/route of administration:
Medication:	Dosage/route of administration:
Medication:	Dosage/route of administration:

FORM A: Patient Intake Form (Page 4 of 6)

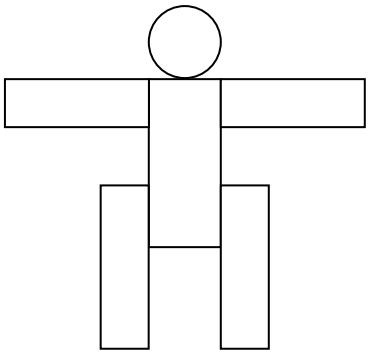
SIGNS/SYMPTOMS ON INITIAL PRESENTATION

Program & Baseline Physical Assessment:
Date and Time of Assessment: _____ (MM/DD/YY) _____ Time (24h)

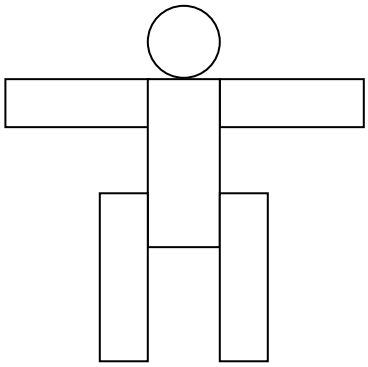
Presenting Signs/Symptoms:
Number of Lesions: ☐ < 10 lesions ☐ 10–100 lesions ☐ > 100 lesions
Size of Maximal Lesion: _____ mm
Percent of body affected: _____ %

Distribution of Lesions:

Ventral



Dorsal



LESION PHOTOS

Were lesion photos taken? ☐ Yes (Date taken: _____) If yes, send photos to CDC.
☐ No

VITAL SIGNS

Height: _____
Weight (kg): _____
Pulse (bpm): _____
Blood Pressure (sitting)
Systolic (mmHg): _____
Diastolic (mmHg): _____
Respiratory Rate (rpm): _____
Temperature (ºF): _____

FORM A: Patient Intake Form (Page 5 of 6)

Baseline Physical Assessment	
Body System	**Comment (if abnormal)**
General ☐ Normal ☐ Abnormal	
HEENT and Neck ☐ Normal ☐ Abnormal	
Lungs ☐ Normal ☐ Abnormal	
Cardiac ☐ Normal ☐ Abnormal	
Abdomen ☐ Normal ☐ Abnormal	
Extremities ☐ Normal ☐ Abnormal	
Neurological ☐ Normal ☐ Abnormal	
Other ☐ Normal ☐ Abnormal	

Clinical Narrative (please include site and circumstances of exposure and medical condition at time of program enrollment; may attach clinical narrative from medical chart):

FORM A: Patient Intake Form (Page 6 of 6)

CLINICAL LABORATORY RESULTS (may attach laboratory printouts or reports)

Laboratory Parameters		Date/time of sample	Value (indicate units)
HEMATOLOGY	Prothrombin time		
	Partial thromboplastin time		
	Platelet count		
	Hemoglobin		
	Hematocrit		
	RBC count		
	Absolute WBC		
	Differential count		
CHEMISTRY	Calcium		
	Magnesium		
	Sodium		
	Potassium		
	Chloride		
	Bicarbonate		
	Phosphorous		
	Urea		
	Creatinine		
	Calculated creatinine clearance		
	Glucose		
	Uric acid		
	Albumin		
	Total bilirubin		
	Total protein		
	Aspartate transaminase		
	Alanine transaminase		
	Alkaline phosphatase		
URINALYSIS	Human Chorionic Gonadotropin (hCG)		
	Protein		
	Hemoglobin		
	Glucose		
	Microscopic analysis		

SERUM IMMUNOCHEMISTRY AND SCAB/LESION* SAMPLING

Were samples collected & sent to CDC for immunochemistry, PCR, viral culture, and resistance testing? ☐ Yes ☐ No

Sample type	Date of sample collection	Date sample sent to CDC

*Lesion sampling will be based on the patient's clinical presentation and progression (e.g. based on evaluation of photos).

TECOVIRIMAT TREATMENT INITIATION

Was tecovirimat given to this patient? ☐ Yes ☐ No Route of Administration (at initiation) ☐ Oral ☐ IV

What dose was prescribed for this patient? _____ mg _____ times per day

What is the planned duration of treatment? _____days

On what date /time was the first dose? ____/_____/_____ (*MM/DD/YYYY*) _____:_____ (*hh:mm am/pm*)

Patient Name: _____ **Hospital-assigned Patient ID: _____**

FORM B: TECOVIRIMAT PRODUCT ACCOUNTABILITY FORM
(return to CDC within 7 days of completion of tecovirimat therapy)

Hospital/Medical Facility Name:	**Pharmacy Phone Number:**

Were Tecovirimat Capsules Received: ☐ **Yes** ☐ **No**

Number of Capsules Received:	
Date Received:	
Lot Number:	
Product storage temperature:	
Number of Capsules Used:	
Date(s) Used:	
Number of Capsules Remaining:	
Number of Capsules Returned:	
Date Returned:	
Number of Capsules Disposed of:	
Date of Disposal:	
Method of Disposal:	

Was IV Tecovirimat Received: ☐ **Yes** ☐ **No**

Number of Vials Received:	
Date Received:	
Lot Number:	
Product storage temperature:	
Number of Vials Used:	
Date(s) Used:	
Number of Vials Remaining:	
Number of Vials Returned:	
Date Returned:	
Number of Vials Disposed of:	
Date of Disposal:	
Method of Disposal:	

Name of Responsible Individual: _____

Signature of Responsible Individual: _____

FORM C: ADVERSE EVENT FORM

To be completed by the treating physician: Did the patient experience adverse event(s) related to tecovirimat? ☐ Yes ☐ No

If any adverse event(s) occurred, please indicate in table below.

Adverse Event	Date & Time Developed	Duration of AE	Severity	Relationship to Tecovirimat	Outcome	Specify AE Treatment (indicate date & time)	Description of AE
Anaphylaxis	____/____/____ _____:_____		☐ Mild ☐ Moderate ☐ Severe	☐ Definitely related ☐ Probably related ☐ Possibly related ☐ Unlikely related ☐ Not related	☐ Recovered without sequelae ☐ Recovered with sequelae Describe:_____		
Seizure	____/____/____ _____:_____		☐ Mild ☐ Moderate ☐ Severe	☐ Definitely related ☐ Probably related ☐ Possibly related ☐ Unlikely related ☐ Not related	☐ Recovered without sequelae ☐ Recovered with sequelae Describe:_____		
Neutropenia	____/____/____ _____:_____		☐ Mild ☐ Moderate ☐ Severe	☐ Definitely related ☐ Probably related ☐ Possibly related ☐ Unlikely related ☐ Not related	☐ Recovered without sequelae ☐ Recovered with sequelae Describe:_____		
Renal adverse event	____/____/____ _____:_____		☐ Mild ☐ Moderate ☐ Severe	☐ Definitely related ☐ Probably related ☐ Possibly related ☐ Unlikely related ☐ Not related	☐ Recovered without sequelae ☐ Recovered with sequelae Describe:_____		
Hepatic adverse event	____/____/____ _____:_____		☐ Mild ☐ Moderate ☐ Severe	☐ Definitely related ☐ Probably related ☐ Possibly related ☐ Unlikely related ☐ Not related	☐ Recovered without sequelae ☐ Recovered with sequelae Describe:_____		
QT prolongation	____/____/____ _____:_____		☐ Mild ☐ Moderate ☐ Severe	☐ Definitely related ☐ Probably related ☐ Possibly related ☐ Unlikely related ☐ Not related	☐ Recovered without sequelae ☐ Recovered with sequelae Describe:_____		
Headache	____/____/____ _____:_____		☐ Mild ☐ Moderate ☐ Severe	☐ Definitely related ☐ Probably related ☐ Possibly related ☐ Unlikely related ☐ Not related	☐ Recovered without sequelae ☐ Recovered with sequelae Describe:_____		
Fatigue	____/____/____ _____:_____		☐ Mild ☐ Moderate ☐ Severe	☐ Definitely related ☐ Probably related ☐ Possibly related ☐ Unlikely related ☐ Not related	☐ Recovered without sequelae ☐ Recovered with sequelae Describe:_____		
Back/neck pain	____/____/____ _____:_____		☐ Mild ☐ Moderate ☐ Severe	☐ Definitely related ☐ Probably related ☐ Possibly related ☐ Unlikely related ☐ Not related	☐ Recovered without sequelae ☐ Recovered with sequelae Describe:_____		
Death	____/____/____ _____:_____		☐ Mild ☐ Moderate ☐ Severe	☐ Definitely related ☐ Probably related ☐ Possibly related ☐ Unlikely related ☐ Not related	☐ Recovered without sequelae ☐ Recovered with sequelae Describe:_____		
Other (specify):	____/____/____ _____:_____		☐ Mild ☐ Moderate ☐ Severe	☐ Definitely related ☐ Probably related ☐ Possibly related ☐ Unlikely related ☐ Not related	☐ Recovered without sequelae ☐ Recovered with sequelae Describe:_____		
Comments:							

Attachment 2B: Outpatient Case Report Forms

To be completed by treating physician for outpatients:

1. FORM D: During Tecovirimat Treatment Period
2. FORM E: Post Tecovirimat: 7 Days After Last Dose
3. FORM F: Post Tecovirimat: 30 Days After Last Dose

To be given to outpatients by treating physician:

4. FORM G: Tecovirimat Diary for Outpatients

OUTPATIENT CASE REPORT FORMS
FORM D: During Tecovirimat Treatment Period (Page 1 of 3)
Complete at patient follow-up during tecovirimat treatment

Date and Time of Visit:_____(MM/DD/YY) _____ Time (24h)
Patient Name: _____

Evaluating Physician: _____

Tecovirimat Dose: _____ mg **Dose frequency: _____**

Did any serious adverse events occur? ☐ Yes ☐ No if yes, complete Adverse Event Form

Did patient consume a meal containing about 600 calories and 25 grams of fat when taking tecovirimat?
☐ Yes ☐ No

PHYSICAL ASSESSMENT

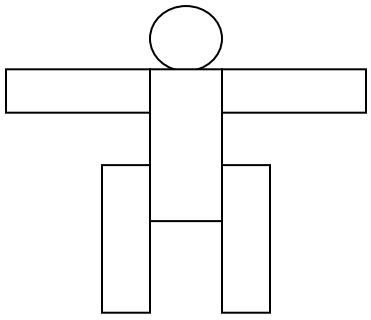
Evaluation of Lesions:
Number of Lesions: ☐ < 10 lesions ☐ 10–100 lesions ☐ > 100 lesions
Size of Maximal Lesion: _____ mm
Percent of body affected: _____ %

Has there been a change in the size or stage of healing of lesions (describe)?
_____
_____

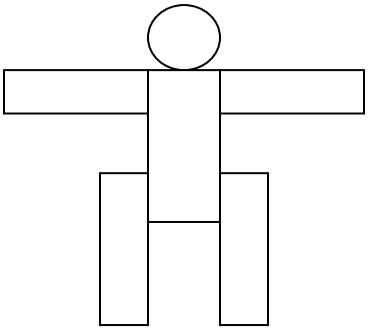
Has there been a change in other clinical signs/symptoms (describe)?
_____
_____
_____

Distribution of Lesions:

Ventral



Dorsal



LESION PHOTOS

Were lesion photos taken? ☐ Yes (Date taken:_____) If yes, send photos to CDC.
☐ No

VITAL SIGNS

Weight (kg): _____ Respiratory Rate (rpm): _____
Pulse (bpm): _____ Temperature (ºF): _____
Blood Pressure (sitting)
Systolic (mmHg): _____
Diastolic (mmHg): _____

OUTPATIENT CASE REPORT FORMS
FORM D: During Tecovirimat Treatment Period (Page 2 of 3)

CONCOMITANT MEDICATIONS:

Medication:	Dosage/route of administration:
Medication:	Dosage/route of administration:
Medication:	Dosage/route of administration:
Medication:	Dosage/route of administration:
Medication:	Dosage/route of administration:

Physical Assessment	
Body System	**Comment (if abnormal)**
General ☐ Normal ☐ Abnormal	
HEENT and Neck ☐ Normal ☐ Abnormal	
Lungs ☐ Normal ☐ Abnormal	
Cardiac ☐ Normal ☐ Abnormal	
Abdomen ☐ Normal ☐ Abnormal	
Extremities ☐ Normal ☐ Abnormal	
Neurological ☐ Normal ☐ Abnormal	
Other ☐ Normal ☐ Abnormal	

Clinical Narrative: _____

OUTPATIENT CASE REPORT FORMS

FORM D: During Tecovirimat Treatment Period (Page 3 of 3)

CLINICAL LABORATORY RESULTS (may attach laboratory printouts or reports)

Laboratory Parameters		Date/time of sample	Value (indicate units)
HEMATOLOGY	Prothrombin time		
	Partial thromboplastin time		
	Platelet count		
	Hemoglobin		
	Hematocrit		
	RBC count		
	Absolute WBC		
	Differential count		
CHEMISTRY	Calcium		
	Magnesium		
	Sodium		
	Potassium		
	Chloride		
	Bicarbonate		
	Phosphorous		
	Urea		
	Creatinine		
	Calculated creatinine clearance		
	Glucose		
	Uric acid		
	Albumin		
	Total bilirubin		
	Total protein		
	Aspartate transaminase		
	Alanine transaminase		
	Alkaline phosphatase		
URINALYSIS	Protein		
	Hemoglobin		
	Glucose		
	Microscopic analysis		

PLASMA PHARMACOKINETIC (PK) SAMPLING *(to the extent possible, after 2 doses have been given in sequence, collect plasma immediately prior to (<30 min) the next dose or 4 hours after the dose; if time window is missed or a modified schedule has been approved by CDC, still collect plasma sample and record time patient took the dose and exact time of plasma collection)* **PK samples should be sent to Alturas Analytics, Inc., and not to CDC. See Attachment 4.**

Date and Time of PK Sample Collection	Date and Time of Tecovirimat Dose	Tecovirimat Dose (mg) and frequency	Dose taken with meal?
____/_____/_____ ____:____	____/_____/_____ ____:____		☐ Yes ☐ No
____/_____/_____ ____:____	____/_____/_____ ____:____		☐ Yes ☐ No

SERUM IMMUNOCHEMISTY AND SCAB/LESION* SAMPLING

Were samples collected & sent to CDC for immunochemistry, PCR, viral culture, and resistance testing? ☐ Yes ☐ No

Sample type	Date of sample collection	Date sample sent to CDC

*Lesion sampling will be based on the patient's clinical presentation and progression (e.g. based on evaluation of photos).

Patient Name: _____ **Hospital-assigned Patient ID:** _____

OUTPATIENT CASE REPORT FORMS
FORM E: Post Tecovirimat: Treatment Day 21 (Page 1 of 3)

Date and Time of Assessment:_____(MM/DD/YY) _____ Time (24h)
Patient Name: _____

Date of last dose of tecovirimat: _____ Dose: _____ mg

Total tecovirimat treatment duration (# days): _____

Was the patient hospitalized? ☐ Yes ☐ No
If yes, how many days was the patient hospitalized? _____
If yes, how many days were in intensive care? _____

Did the patient develop any adverse events related to tecovirimat? ☐ Yes ☐ No
If yes, please complete the Adverse Event form

What was the outcome of the patient?
☐ Recovered from orthopoxvirus infection
☐ Not recovered from orthopoxvirus infection
☐ Death If patient died, when did patient die (date)? _____
What was the cause of death? _____

PHYSICAL ASSESSMENT

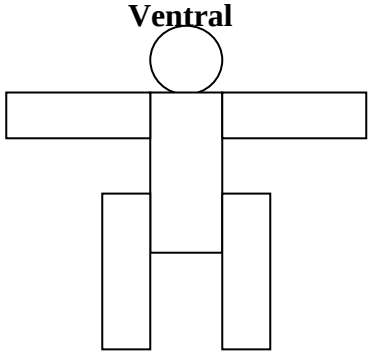
Evaluation of Lesions:
Number of Lesions: ☐ < 10 lesions ☐ 10–100 lesions ☐ > 100 lesions
Size of Maximal Lesion: _____ mm
Percent of body affected: _____ %

Has there been a change in the size or stage of healing of lesions (describe)?
_____
_____

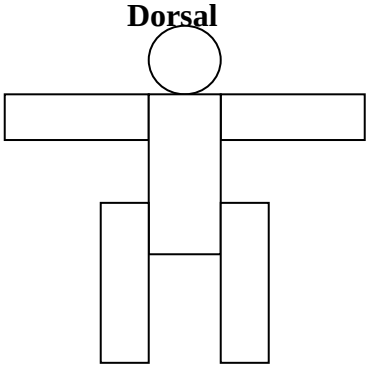
Has there been a change in other clinical signs/symptoms (describe)?
_____
_____
_____

Distribution of Lesions:

Ventral



Dorsal



LESION PHOTOS

Were lesion photos taken? ☐ Yes (Date taken:_____) If yes, send photos to CDC.
☐ No

OUTPATIENT CASE REPORT FORMS
FORM E: Post Tecovirimat: Treatment Day 21 (Page 2 of 3)

VITAL SIGNS

Weight (kg): _____ Respiratory Rate (rpm): _____
Pulse (bpm): _____ Temperature (°F): _____
Blood Pressure (sitting)
Systolic (mmHg): _____
Diastolic (mmHg): _____

Physical Assessment	
Body System	**Comment (if abnormal)**
General ☐ Normal ☐ Abnormal	
HEENT and Neck ☐ Normal ☐ Abnormal	
Lungs ☐ Normal ☐ Abnormal	
Cardiac ☐ Normal ☐ Abnormal	
Abdomen ☐ Normal ☐ Abnormal	
Extremities ☐ Normal ☐ Abnormal	
Neurological ☐ Normal ☐ Abnormal	
Other ☐ Normal ☐ Abnormal	

Clinical Narrative: _____

CLINICAL LABORATORY RESULTS (may attach laboratory printouts or reports)

Laboratory Parameters		**Date/time of sample**	**Value (indicate units)**
HEMATOLOGY	Prothrombin time		
	Partial thromboplastin time		
	Platelet count		
	Hemoglobin		
	Hematocrit		
	RBC count		
	Absolute WBC		
	Differential count		
CHEMISTRY	Calcium		
	Magnesium		
	Sodium		
	Potassium		
	Chloride		
	Bicarbonate		
	Phosphorous		
	Urea		
	Creatinine		
	Calculated creatinine clearance		
	Glucose		
	Uric acid		
	Albumin		
	Total bilirubin		
	Total protein		
	Aspartate transaminase		
	Alanine transaminase		
	Alkaline phosphatase		
URINALYSIS	Protein		
	Hemoglobin		
	Glucose		
	Microscopic analysis		

SERUM IMMUNOCHEMISTRY AND SCAB/LESION* SAMPLING

Were samples collected & sent to CDC for immunochemistry, PCR, viral culture, and resistance testing? ☐ Yes ☐ No

Sample type	**Date of sample collection**	**Date sample sent to CDC**

*Lesion sampling will be based on the patient's clinical presentation and progression (e.g. based on evaluation of photos).

FORM F: Post Tecovirimat: Treatment Day 44 (Page 1 of 3)

Date and Time of Assessment:_____(MM/DD/YY) _____ Time (24h)
Patient Name: _____

Date of last dose of tecovirimat: _____ Dose: _____ mg

Total tecovirimat treatment duration (# days): _____

Was the patient hospitalized? ☐ Yes ☐ No
If yes, how many days was the patient hospitalized? _____
If yes, how many days were in intensive care? _____

Did the patient develop any adverse events related to tecovirimat? ☐ Yes ☐ No
If yes, please complete the Adverse Event form

What was the outcome of the patient?
☐ Recovered from orthopoxvirus infection
☐ Not recovered from orthopoxvirus infection
☐ Death If patient died, when did patient die (date)? _____
What was the cause of death? _____

PHYSICAL ASSESSMENT

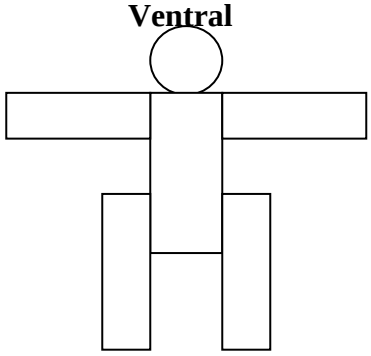
Evaluation of Lesions:
Number of Lesions: ☐ < 10 lesions ☐ 10–100 lesions ☐ > 100 lesions
Size of Maximal Lesion: _____ mm
Percent of body affected: _____ %

Has there been a change in the size or stage of healing of lesions (describe)?
_____
_____

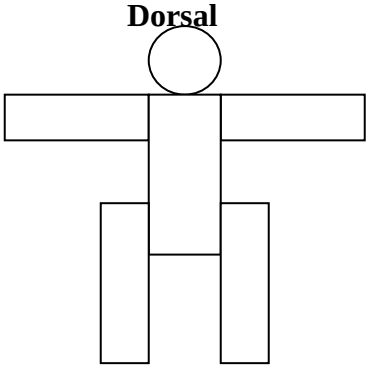
Has there been a change in other clinical signs/symptoms (describe)?
_____
_____
_____

Distribution of Lesions:

Ventral



Dorsal



LESION PHOTOS

Were lesion photos taken? ☐ Yes (Date taken:_____) If yes, send photos to CDC.
☐ No

FORM F: Post Tecovirimat: Treatment Day 44 (Page 2 of 3)

VITAL SIGNS

Weight (kg): _____ Respiratory Rate (rpm): _____
Pulse (bpm): _____ Temperature (ºF): _____
Blood Pressure (sitting)
Systolic (mmHg): _____
Diastolic (mmHg): _____

Physical Assessment	
Body System	**Comment (if abnormal)**
General ☐ Normal ☐ Abnormal	
HEENT and Neck ☐ Normal ☐ Abnormal	
Lungs ☐ Normal ☐ Abnormal	
Cardiac ☐ Normal ☐ Abnormal	
Abdomen ☐ Normal ☐ Abnormal	
Extremities ☐ Normal ☐ Abnormal	
Neurological ☐ Normal ☐ Abnormal	
Other ☐ Normal ☐ Abnormal	

Clinical Narrative: _____

OUTPATIENT CASE REPORT FORMS
FORM F: Post Tecovirimat: Treatment Day 44 (Page 3 of 3)

CLINICAL LABORATORY RESULTS (may attach laboratory printouts or reports)

Laboratory Parameters		**Date/time of sample**	**Value (indicate units)**
HEMATOLOGY	Prothrombin time		
	Partial thromboplastin time		
	Platelet count		
	Hemoglobin		
	Hematocrit		
	RBC count		
	Absolute WBC		
	Differential count		
CHEMISTRY	Calcium		
	Magnesium		
	Sodium		
	Potassium		
	Chloride		
	Bicarbonate		
	Phosphorous		
	Urea		
	Creatinine		
	Calculated creatinine clearance		
	Glucose		
	Uric acid		
	Albumin		
	Total bilirubin		
	Total protein		
	Aspartate transaminase		
	Alanine transaminase		
	Alkaline phosphatase		
URINALYSIS	Protein		
	Hemoglobin		
	Glucose		
	Microscopic analysis		

SERUM IMMUNOCHEMISTRY AND SCAB/LESION* SAMPLING

Were samples collected & sent to CDC for immunochemistry, PCR, viral culture, and resistance testing? ☐ Yes ☐ No

Sample type	**Date of sample collection**	**Date sample sent to CDC**

*Lesion sampling will be based on the patient's clinical presentation and progression (e.g. based on evaluation of photos).

FORM G: Tecovirimat Diary for Outpatients

Instructions for Patients: Remember to **take tecovirimat capsules with a full glass of water and after eating a full, fatty meal** (containing about 600 calories and 25 grams of fat). It is important to report any adverse events (symptoms you experience) with tecovirimat. Please use this Diary Card to report any adverse events (such as nausea, vomiting, headache etc.). Please bring this Diary Card to each clinic visit. When you have completed this Diary Card, return it in a timely manner (within 3–5 days) to your doctor where you were treated for your illness. **Do *NOT* delay in returning the Diary Card to your doctor at the end of your tecovirimat treatment.** If you experience a serious adverse event (such as difficulty breathing or hives) seek medical attention immediately.

Patient Last Name: _____	**First Name:_____**
Date of Birth (mm/dd/yyyy): _____/_____ /_____	**Date of First Tecovirimat Dose (mm/dd/yyyy): _____/_____/_____**
Treating Physician Name:	**Treating Physician Phone #:**

Adverse Events (check if any adverse events occur and using the scale below rate how severe each adverse event is in the appropriate box)

1: Mild (Does not interfere with routine activities) **2:** Moderate (Interferes with routine activities)

3: Severe (Unable to perform routine activities)

Record Every Day While Taking Tecovirimat

		Day1	Day2	Day3	Day4	Day5	Day6	Day7	Day8	Day9	Day10	Day11	Day12	Day13	Day14
Date/Time of Dose	**AM**														
	PM														
Nausea															
Vomiting															
Abdominal pain															
Fever (≥ 101ºF)															
Loss of appetite															
Headache															
Backache															
Muscle pain															
Joint pain															
Fatigue															
Itching on body															
Difficulty breathing															
Hives															
Other (specify):															

Patient Name: _____

Progress	**Daily While Taking Tecovirimat**													
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Number of lesions														
Are lesions improving? (Y/N)														
Compared to the previous day, are you generally feeling **1**: Much worse **2**: Worse **3**: About the same **4**: A little better **5**: Much better														

List all other medications you are taking:

Name of drug:	**Dose:**	**Dates taken:**

Other comments:

Attachment 2C: Inpatient Case Report Forms

To be completed by treating physician for inpatients:

1. FORM H: Daily Form (Days 1–6, 8–13)
2. FORM I: Day 7 of Tecovirimat Treatment Form
3. FORM J: Day 14 of Tecovirimat Treatment Form
4. FORM K: Every 7 Days If Still Receiving Tecovirimat Beyond 14 Days
5. FORM L: Post Tecovirimat: Upon Hospital Discharge

INPATIENT CASE REPORT FORMS

FORM H: Daily Form (Days 1–6, 8–13)

Patient Name: _____

Treat-ment Day	Date/Time of Tecovirimat Dose		Route of Tecovirimat Administra-tion	Tecovirimat Dosage (mg) and frequency	If oral, tecovirimat taken with meal or NG tube?	Concomitant Medications:			Lesion Photos*	Pharmacokinetic Sampling**
	AM	PM				Medication	Dosage/route of administration	Date initiated	Were lesion photos taken? (if yes, send photos to CDC)	Date/Time of PK Plasma Sample Collection
1	_____ _____:_____	_____ _____:_____	☐ Oral ☐ IV		☐ Yes ☐ No ☐ NG tube				☐ Yes (Date: _____) ☐ No	_____ _____:_____
2	_____ _____:_____	_____ _____:_____	☐ Oral ☐ IV		☐ Yes ☐ No ☐ NG tube				☐ Yes (Date: _____) ☐ No	_____ _____:_____
3	_____ _____:_____	_____ _____:_____	☐ Oral ☐ IV		☐ Yes ☐ No ☐ NG tube				☐ Yes (Date: _____) ☐ No	_____ _____:_____
4	_____ _____:_____	_____ _____:_____	☐ Oral ☐ IV		☐ Yes ☐ No ☐ NG tube				☐ Yes (Date: _____) ☐ No	_____ _____:_____
5	_____ _____:_____	_____ _____:_____	☐ Oral ☐ IV		☐ Yes ☐ No ☐ NG tube				☐ Yes (Date: _____) ☐ No	_____ _____:_____
6	_____ _____:_____	_____ _____:_____	☐ Oral ☐ IV		☐ Yes ☐ No ☐ NG tube				☐ Yes (Date: _____) ☐ No	_____ _____:_____
7		Please complete Day 7 form								

INPATIENT CASE REPORT FORMS

Treat-ment Day	Date/Time of Tecovirimat Dose		Route of Tecovirimat Administra-tion	Tecovirimat Dosage (mg) and frequency	If oral, tecovirimat taken with meal or NG tube?	Concomitant Medications:			Lesion Photos*	Pharmacokinetic Sampling**
	AM	PM				Medication	Dosage/route of administration	Date initiated	Were lesion photos taken? (if yes, send photos to CDC)	Date/Time of PK Plasma Sample Collection
8	_____ _____:_____	_____ _____:_____	☐ Oral ☐ IV		☐ Yes ☐ No ☐ NG tube				☐ Yes (Date: _____) ☐ No	_____ _____:_____
9	_____ _____:_____	_____ _____:_____	☐ Oral ☐ IV		☐ Yes ☐ No ☐ NG tube				☐ Yes (Date: _____) ☐ No	_____ _____:_____
10	_____ _____:_____	_____ _____:_____	☐ Oral ☐ IV		☐ Yes ☐ No ☐ NG tube				☐ Yes (Date: _____) ☐ No	_____ _____:_____
11	_____ _____:_____	_____ _____:_____	☐ Oral ☐ IV		☐ Yes ☐ No ☐ NG tube				☐ Yes (Date: _____) ☐ No	_____ _____:_____
12	_____ _____:_____	_____ _____:_____	☐ Oral ☐ IV		☐ Yes ☐ No ☐ NG tube				☐ Yes (Date: _____) ☐ No	_____ _____:_____
13	_____ _____:_____	_____ _____:_____	☐ Oral ☐ IV		☐ Yes ☐ No ☐ NG tube				☐ Yes (Date: _____) ☐ No	_____ _____:_____
14	Please complete Day 14 form									

***** Take digital photographs of lesions on Day 1. Take daily photographs of lesions unless regression is not seen after the first 3 days; take daily photos until regression is observed.

** To the extent possible, collect plasma immediately prior to (<30) and 4 hours after the day's dose; if time window is missed, still collect plasma samples and record time patient took the dose and exact time of plasma collection.

Patient Name: _____ **Hospital-assigned Patient ID: _____**

INPATIENT CASE REPORT FORMS
FORM I: Day 7 of Tecovirimat Treatment (Page 1 of 3)

Date and Time of Assessment:_____(MM/DD/YY) _____ Time (24h)

Patient Name: _____

Evaluating Physician: _____

Tecovirimat Dosage: _____ mg **Dose frequency:** _____ **Route of Administration:** ☐ Oral ☐ IV

Did any serious adverse events occur? ☐ Yes ☐ No if yes, complete Adverse Event Form

If tecovirimat route of administration was oral,

Did patient consume a meal containing about 600 calories and 25 grams of fat when taking tecovirimat? ☐ Yes ☐ No

Was tecovirimat given via nasogastric (NG) tube? ☐ Yes ☐ No

PHYSICAL ASSESSMENT

Evaluation of Lesions:

Number of Lesions: ☐ < 10 lesions ☐ 10–100 lesions ☐ > 100 lesions

Size of Maximal Lesion: _____ mm

Percent of body affected: _____ %

Has there been a change in the size or stage of healing of lesions (describe)?

_____

_____

Has there been a change in other clinical signs/symptoms (describe)?

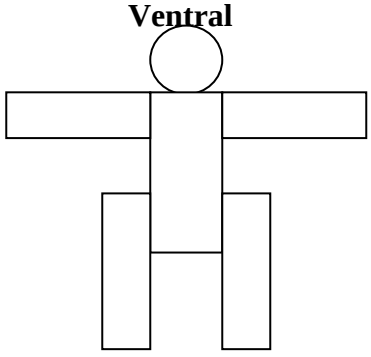
_____

_____

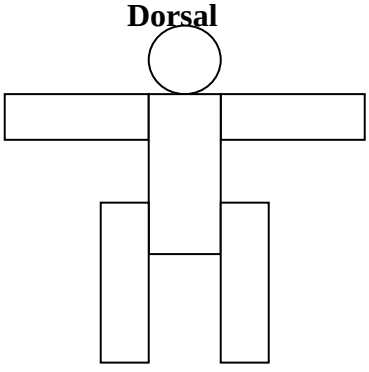
_____

Distribution of Lesions:

Ventral



Dorsal



LESION PHOTOS

Were lesion photos taken? ☐ Yes (Date taken:_____) If yes, send photos to CDC.

☐ No

VITAL SIGNS

Weight (kg): _____ Respiratory Rate (rpm): _____

Pulse (bpm): _____ Temperature (ºF): _____

Blood Pressure (sitting)

Systolic (mmHg): _____

Diastolic (mmHg): _____

INPATIENT CASE REPORT FORMS
FORM I: Day 7 of Tecovirimat Treatment (Page 2 of 3)

Physical Assessment	
Body System	**Comment (if abnormal)**
General ☐ Normal ☐ Abnormal	
HEENT and Neck ☐ Normal ☐ Abnormal	
Lungs ☐ Normal ☐ Abnormal	
Cardiac ☐ Normal ☐ Abnormal	
Abdomen ☐ Normal ☐ Abnormal	
Extremities ☐ Normal ☐ Abnormal	
Neurological ☐ Normal ☐ Abnormal	
Other ☐ Normal ☐ Abnormal	

Clinical Narrative: _____

Patient Name: _____ **Hospital-assigned Patient ID:** _____

INPATIENT CASE REPORT FORMS

FORM I: Day 7 of Tecovirimat Treatment (Page 3 of 3)

CLINICAL LABORATORY RESULTS (may attach laboratory printouts or reports)

Laboratory Parameters		Date/time of sample	Value (indicate units)
HEMATOLOGY	Prothrombin time		
	Partial thromboplastin time		
	Platelet count		
	Hemoglobin		
	Hematocrit		
	RBC count		
	Absolute WBC		
	Differential count		
CHEMISTRY	Calcium		
	Magnesium		
	Sodium		
	Potassium		
	Chloride		
	Bicarbonate		
	Phosphorous		
	Urea		
	Creatinine		
	Calculated creatinine clearance		
	Glucose		
	Uric acid		
	Albumin		
	Total bilirubin		
	Total protein		
	Aspartate transaminase		
	Alanine transaminase		
	Alkaline phosphatase		
URINALYSIS	Protein		
	Hemoglobin		
	Glucose		
	Microscopic analysis		

PLASMA PHARMACOKINETIC (PK) SAMPLING *(to the extent possible, collect plasma immediately prior to (<30 min) and 4 hours after the day's dose; if time window is missed or a modified schedule has been approved by CDC, still collect plasma samples and record time patient took the dose and exact time of plasma collection)* **PK samples should be sent to Alturas Analytics, Inc., and not to CDC.** See **Attachment 4** for details.

Date and Time of PK Sample Collection	Date and Time of Tecovirimat Dose	Tecovirimat Dose (mg) and frequency	Dose taken with meal?
____/_____/_____ ____:____	____/_____/_____ ____:____		☐Yes ☐No ☐NG Tube
____/_____/_____ ____:____	____/_____/_____ ____:____		☐Yes ☐No ☐NG Tube

PLASMA IMMUNOGENICITY AND SCAB/LESION* SAMPLING

Were samples collected & sent to CDC for immunochemistry, PCR, viral culture, and resistance testing? ☐Yes ☐ No

Sample type	Date of sample collection	Date sample sent to CDC

*Lesion sampling will be based on the patient's clinical presentation and progression (e.g. based on evaluation of photos).

Patient Name: _____ **Hospital-assigned Patient ID:** _____

INPATIENT CASE REPORT FORMS
FORM J: Day 14 of Tecovirimat Treatment (Page 1 of 3)

Date and Time of Assessment:_____(MM/DD/YY) _____ Time (24h)

Patient Name: _____

Evaluating Physician: _____

Tecovirimat Dose: _____ mg **Dose frequency: _____** **Route of Administration:** ☐ Oral ☐ IV

Did any serious adverse events occur? ☐ Yes ☐ No if yes, complete Adverse Event Form

If tecovirimat route of administration was oral,

Did patient consume a meal containing about 600 calories and 25 grams of fat when taking tecovirimat? ☐ Yes ☐ No

Was tecovirimat given via nasogastric (NG) tube? ☐ Yes ☐ No

PHYSICAL ASSESSMENT

Evaluation of Lesions:

Number of Lesions: ☐ < 10 lesions ☐ 10–100 lesions ☐ > 100 lesions
Size of Maximal Lesion: _____ mm
Percent of body affected: _____ %

Has there been a change in the size or stage of healing of lesions (describe)?

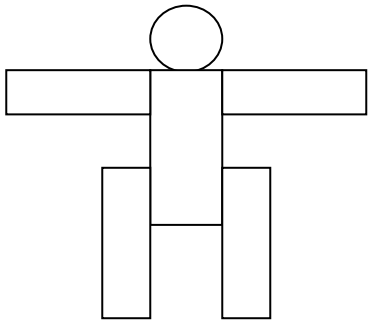
_____
_____

Has there been a change in other clinical signs/symptoms (describe)?

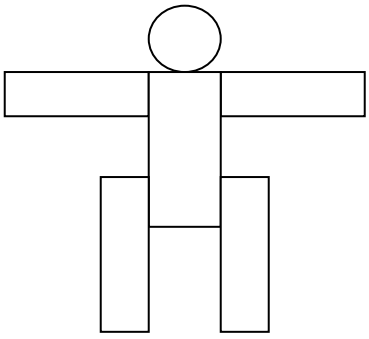
_____
_____
_____

Distribution of Lesions:

Ventral



Dorsal



LESION PHOTOS

Were lesion photos taken? ☐ Yes (Date taken:_____) If yes, send photos to CDC.
☐ No

VITAL SIGNS

Weight (kg): _____ Respiratory Rate (rpm): _____
Pulse (bpm): _____ Temperature (ºF): _____
Blood Pressure (sitting)
Systolic (mmHg): _____Diastolic (mmHg): _____

INPATIENT CASE REPORT FORMS
FORM J: Day 14 of Tecovirimat Treatment (Page 2 of 3)

Physical Assessment	
Body System	**Comment (if abnormal)**
General ☐ Normal ☐ Abnormal	
HEENT and Neck ☐ Normal ☐ Abnormal	
Lungs ☐ Normal ☐ Abnormal	
Cardiac ☐ Normal ☐ Abnormal	
Abdomen ☐ Normal ☐ Abnormal	
Extremities ☐ Normal ☐ Abnormal	
Neurological ☐ Normal ☐ Abnormal	
Other ☐ Normal ☐ Abnormal	

Clinical Narrative: _____

Patient Name: _____ **Hospital-assigned Patient ID:** _____

INPATIENT CASE REPORT FORMS

FORM J: Day 14 of Tecovirimat Treatment (Page 3 of 3)

CLINICAL LABORATORY RESULTS (may attach laboratory printouts or reports)

Laboratory Parameters		Date/time of sample	Value (indicate units)
HEMATOLOGY	Prothrombin time		
	Partial thromboplastin time		
	Platelet count		
	Hemoglobin		
	Hematocrit		
	RBC count		
	Absolute WBC		
	Differential count		
CHEMISTRY	Calcium		
	Magnesium		
	Sodium		
	Potassium		
	Chloride		
	Bicarbonate		
	Phosphorous		
	Urea		
	Creatinine		
	Calculated creatinine clearance		
	Glucose		
	Uric acid		
	Albumin		
	Total bilirubin		
	Total protein		
	Aspartate transaminase		
	Alanine transaminase		
	Alkaline phosphatase		
URINALYSIS	Protein		
	Hemoglobin		
	Glucose		
	Microscopic analysis		

PLASMA PHARMACOKINETIC (PK) SAMPLING

(to the extent possible, collect plasma immediately prior to (<30 min) and 4 hours after the day's dose; if time window is missed or a modified schedule has been approved by CDC, still collect plasma samples and record time patient took the dose and exact time of plasma collection)

PK samples should be sent to Alturas Analytics, Inc., and not to CDC. See **Attachment 4** for details.

Date and Time of PK Sample Collection	Date and Time of Tecovirimat Dose	Tecovirimat Dose (mg) and frequency	Dose taken with meal?
____/_____/_____ ____:____	____/_____/_____ ____:____		☐Yes ☐No ☐NG Tube
____/_____/_____ ____:____	____/_____/_____ ____:____		☐Yes ☐No ☐NG Tube

SERUM IMMUNOCHEMISTRY AND SCAB/LESION* SAMPLING

Were samples collected & sent to CDC for immunochemistry, PCR, viral culture, and resistance testing? ☐Yes ☐ No

Sample type	Date of sample collection	Date sample sent to CDC

*Lesion sampling will be based on the patient's clinical presentation and progression (e.g. based on evaluation of photos).

Patient Name: _____ **Hospital-assigned Patient ID:** _____

INPATIENT CASE REPORT FORMS

FORM K: Every 7 Days If Still Receiving Tecovirimat beyond 14 Days (Page 1 of 4)

Date and Time of Assessment: _____(MM/DD/YY) _____ Time (24h)

Patient Name: _____

Evaluating Physician: _____

Tecovirimat Dose: _____ mg **Dose frequency:** _____

Did any serious adverse events occur? ☐ Yes ☐ No if yes, complete Adverse Event Form

If tecovirimat route of administration was oral,

Did patient consume a meal containing about 600 calories and 25 grams of fat when taking tecovirimat? ☐ Yes ☐ No

Was tecovirimat given via nasogastric (NG) tube? ☐ Yes ☐ No

PHYSICAL ASSESSMENT

Evaluation of Lesions:

Number of Lesions: ☐ < 10 lesions ☐ 10–100 lesions ☐ > 100 lesions
Size of Maximal Lesion: _____ mm
Percent of body affected: _____ %

Has there been a change in the size or stage of healing of lesions (describe)?

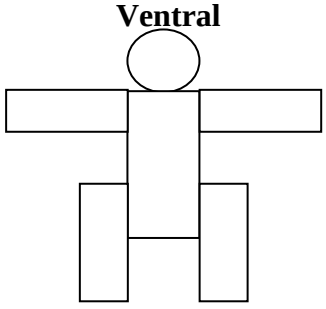
_____
_____

Has there been a change in other clinical signs/symptoms (describe)?

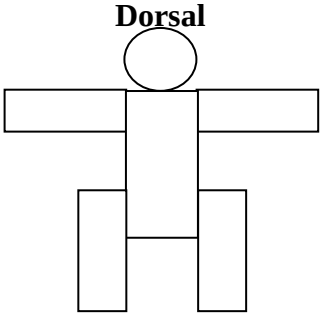
_____
_____
_____

Distribution of Lesions:

Ventral



Dorsal



LESION PHOTOS

Were lesion photos taken? ☐ Yes (Date taken:_____) If yes, send photos to CDC.
☐ No

VITAL SIGNS

Weight (kg): _____ Respiratory Rate (rpm): _____
Pulse (bpm): _____ Temperature (ºF): _____
Blood Pressure (sitting)
Systolic (mmHg): _____ Diastolic (mmHg): _____

INPATIENT CASE REPORT FORMS

FORM K: Every 7 Days If Still Receiving Tecovirimat beyond 14 Days (Page 2 of 4)

Physical Assessment	
Body System	**Comment (if abnormal)**
General ☐ Normal ☐ Abnormal	
HEENT and Neck ☐ Normal ☐ Abnormal	
Lungs ☐ Normal ☐ Abnormal	
Cardiac ☐ Normal ☐ Abnormal	
Abdomen ☐ Normal ☐ Abnormal	
Extremities ☐ Normal ☐ Abnormal	
Neurological ☐ Normal ☐ Abnormal	
Other ☐ Normal ☐ Abnormal	

Clinical Narrative: _____

INPATIENT CASE REPORT FORMS

FORM K: Every 7 Days If Still Receiving Tecovirimat beyond 14 Days (Page 3 of 4)

CLINICAL LABORATORY RESULTS (may attach laboratory printouts or reports)

Laboratory Parameters		**Date/time of sample**	**Value (indicate units)**
HEMATOLOGY	Prothrombin time		
	Partial thromboplastin time		
	Platelet count		
	Hemoglobin		
	Hematocrit		
	RBC count		
	Absolute WBC		
	Differential count		
CHEMISTRY	Calcium		
	Magnesium		
	Sodium		
	Potassium		
	Chloride		
	Bicarbonate		
	Phosphorous		
	Urea		
	Creatinine		
	Calculated creatinine clearance		
	Glucose		
	Uric acid		
	Albumin		
	Total bilirubin		
	Total protein		
	Aspartate transaminase		
	Alanine transaminase		
	Alkaline phosphatase		
URINALYSIS	Protein		
	Hemoglobin		
	Glucose		
	Microscopic analysis		

INPATIENT CASE REPORT FORMS

FORM K: Every 7 Days If Still Receiving Tecovirimat beyond 14 Days (Page 4 of 4)

CONCOMITANT MEDICATIONS:

Medication	Dosage/route of administration	Date initiated

PLASMA PHARMACOKINETIC (PK) SAMPLING

(to the extent possible, collect plasma immediately prior to (<30 min) and 4 hours after the day's dose; if time window is missed, still collect plasma samples and record time patient took the dose and exact time of plasma collection) **PK samples should be sent to Alturas Analytics, Inc., and not to CDC. See Attachment 4.**

Date and Time of PK Sample Collection	Date and Time of Tecovirimat Dose	Tecovirimat Dose (mg) and frequency	Dose taken with meal?
____/_____/_____ ____:____	____/_____/_____ ____:____		☐Yes ☐No ☐NG Tube
____/_____/_____ ____:____	____/_____/_____ ____:____		☐Yes ☐No ☐NG Tube

SERUM IMMUNOCHEMISTRY AND SCAB/LESION* SAMPLING

Were samples collected & sent to CDC for immunochemistry, PCR, viral culture, and resistance testing? ☐Yes ☐ No

Sample type	Date of sample collection	Date sample sent to CDC

*Lesion sampling will be based on the patient's clinical presentation and progression (e.g. based on evaluation of photos).

INPATIENT CASE REPORT FORMS

FORM L: Post Tecovirimat: Upon Hospital Discharge (Page 1 of 4)

Date and Time of Assessment: _____(MM/DD/YY) _____ Time (24h)

Patient Name: _____

Date of last tecovirimat dose: _____ Dose: ____ mg **Frequency**: _____ **Route:** ☐ Oral ☐ IV

Total tecovirimat treatment duration (# days both routes of admin combined): _____

- **Number of days of IV tecovirimat treatment: _____**
- **Number of days of oral tecovirimat treatment: _____**

How many days was the patient hospitalized? _____

How many days was the patient in intensive care? _____

Did the patient develop any adverse events related to tecovirimat? ☐ Yes ☐ No
If yes, please complete the Adverse Event form

What was the outcome of the patient?
☐ Recovered from orthopoxvirus infection
☐ Not recovered from orthopoxvirus infection
☐ Death If patient died, when did patient die (date)? _____
What was the cause of death? _____

PHYSICAL ASSESSMENT

Evaluation of Lesions:

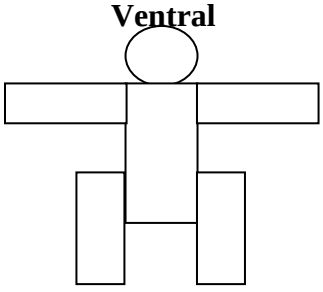
Number of Lesions: ☐ < 10 lesions ☐ 10–100 lesions ☐ > 100 lesions
Size of Maximal Lesion: _____ mm
Percent of body affected: _____ %

Has there been a change in the size or stage of healing of lesions (describe)?
_____
_____

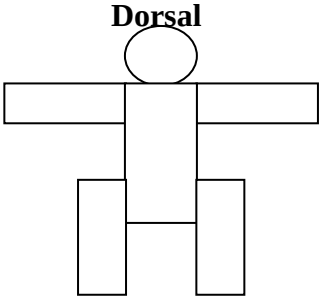
Has there been a change in other clinical signs/symptoms (describe)?
_____
_____
_____

Distribution of Lesions:

Ventral



Dorsal



LESION PHOTOS

Were lesion photos taken? ☐ Yes (Date taken:_____) If yes, send photos to CDC.
☐ No

INPATIENT CASE REPORT FORMS

FORM L: Post Tecovirimat: Upon Hospital Discharge (Page 2 of 4)

VITAL SIGNS

Weight (kg): _____ Respiratory Rate (rpm): _____
Pulse (bpm): _____ Temperature (ºF): _____
Blood Pressure (sitting)
Systolic (mmHg): _____
Diastolic (mmHg): _____

Physical Assessment	
Body System	**Comment (if abnormal)**
General ☐ Normal ☐ Abnormal	
HEENT and Neck ☐ Normal ☐ Abnormal	
Lungs ☐ Normal ☐ Abnormal	
Cardiac ☐ Normal ☐ Abnormal	
Abdomen ☐ Normal ☐ Abnormal	
Extremities ☐ Normal ☐ Abnormal	
Neurological ☐ Normal ☐ Abnormal	
Other ☐ Normal ☐ Abnormal	

Clinical Narrative: _____

INPATIENT CASE REPORT FORMS
FORM L: Post Tecovirimat: Upon Hospital Discharge (Page 3 of 4)

CLINICAL LABORATORY RESULTS (may attach laboratory printouts or reports)

Laboratory Parameters		**Date/time of sample**	**Value (indicate units)**
HEMATOLOGY	Prothrombin time		
	Partial thromboplastin time		
	Platelet count		
	Hemoglobin		
	Hematocrit		
	RBC count		
	Absolute WBC		
	Differential count		
CHEMISTRY	Calcium		
	Magnesium		
	Sodium		
	Potassium		
	Chloride		
	Bicarbonate		
	Phosphorous		
	Urea		
	Creatinine		
	Calculated creatinine clearance		
	Glucose		
	Uric acid		
	Albumin		
	Total bilirubin		
	Total protein		
	Aspartate transaminase		
	Alanine transaminase		
	Alkaline phosphatase		
URINALYSIS	Protein		
	Hemoglobin		
	Glucose		
	Microscopic analysis		

INPATIENT CASE REPORT FORMS
FORM L: Post Tecovirimat: Upon Hospital Discharge (Page 4 of 4)

CONCOMITANT MEDICATIONS:

Medication	Dosage/route of administration	Date initiated

SERUM IMMUNOCHEMISTRY AND SCAB/LESION* SAMPLING

Were samples collected & sent to CDC for immunochemistry, PCR, viral culture, and resistance testing? ☐ Yes ☐ No

Sample type	Date of sample collection	Date sample sent to CDC

*Lesion sampling will be based on the patient's clinical presentation and progression (e.g. based on evaluation of photos).

Patient Name: _____ **Hospital-assigned Patient ID: _____**

Attachment 3
Instructions for Opening and Mixing Tecovirimat Capsules with Food for Those Who Cannot Swallow Pills, Especially Infants and Children

Instructions for Opening and Mixing Tecovirimat Capsules with Food for Those Who Cannot Swallow Pills, Especially Infants and Children

INTRODUCTION

If your doctor prescribes tecovirimat for your child and your child cannot swallow capsules, the capsules may be opened to mix the contents with food to give a drug-food mixture. This sheet explains how to open the capsules and mix with infant formula or food for infants and children. Each capsule of tecovirimat (also known as TPOXX®) gives 200 mg of drug. Your child's dose is based on weight. Infants who weigh less than 13 pounds should receive one-quarter (¼) of a capsule (50 mg). For infants who weigh 13 to less than 28 pounds, the dose is half (½) of a capsule (100 mg). For infants who weigh 28 pounds or more, and older children, the dose will be in whole capsule(s). See the table below to locate the dose for your child and follow the corresponding instructions. Children who weigh 88 pounds or more receive the adult daily dose. Adults who are unable to swallow capsules may also use these instructions to open capsules and mix with food.

YOU WILL NEED

- 1, 2, or 3 tecovirimat capsules depending on weight (1 capsule = 200 mg of drug)
- 1 Tablespoon or an oral syringe that measures in milliliters (mL). If you have a small infant, a teaspoon is helpful.
- 1 small bowl and 1 baby bottle (if infant formula or breast milk is used)
- Small amount of water (only for infants who cannot eat semisolid foods)
- One of these foods (any one of the following is recommended):
  - For Infants : Infant formula or breast milk
  - For Infants on semisolid foods and older children: Baby food or applesauce, yogurt, pudding, or chocolate syrup

DIRECTIONS FOR MAKING THE DRUG-FOOD MIXTURE

Step 1: Find your child's weight in column **A** using the table on the next page. Use the information from the **row** with your child's weight for the rest of the directions.

Step 2: Column **B** is information on the dose of drug you will be giving to your child. In order to prepare this dose, use column **C** to find the number of capsules you will need to prepare the dose and remove that number from the tecovirimat pill bottle.

Step 3: Hold the tecovirimat capsule with your fingers over a small bowl. Carefully pull the capsule open and pour out the contents (white powder) completely into the bowl. Look inside the capsule to make sure no powder is left inside the capsule. Repeat for additional capsules, if applicable.

Step 4: Add 2 tablespoons (30 mL) of food or water into the bowl containing the drug powder (water should be used if your child cannot eat solid foods). Mix the powder with food or water very well with a spoon. This makes the drug-food (or water) mixture.

Step 5: Follow the directions in column **E** to measure out the amount of the drug-food mixture to create the correct dose. For infants, add that amount to 1 tablespoon of infant formula or milk in a baby bottle.

Step 6: Give the amount as directed in column **E**. For infants, be sure to give the entire amount of the mixed formula in the baby bottle in one sitting. If you have any questions, check with your healthcare provider for how much and how often to give tecovirimat to your child.

AMOUNT OF THE FINAL DRUG-FOOD MIXTURE TO GIVE EACH DAY

Use the table below to find how much of the drug-food mixture to give to your child 2 times a day for 14 days, unless your doctor tells you otherwise.

A	B	C	D	E
Child's weight in pounds*	**Dose**	**Number of tecovirimat capsules needed to prepare the dose**	**Amount of water or food to add**	**How much of the drug-food mixture to give your child (give this amount 2 times each day)**
<13 pounds	¼ capsule (50 mg)	1 	2 tablespoons (30 mL) of water	After mixing the capsule contents and water, measure out ½ tablespoon (equal to 1.5 TEAspoons or 7.5 mL) of the drug-water mixture and add to 1 tablespoon of breast milk or prepared formula in a baby bottle. Mix well. Give all the liquid in the bottle in one sitting. Throw out the unused drug-water mixture.
13 to <28 pounds	½ capsule (100 mg)	1 	2 tablespoons (30 mL) of water	After mixing the capsule contents and water, measure out 1 tablespoon (equal to 3 TEAspoons or 15 mL) of the drug-water mixture and add to 1 tablespoon of breast milk or prepared formula in a baby bottle. Mix well. Give all the liquid in the bottle in one sitting. Throw out the unused drug-water mixture.
28 to < 55 pounds	1 capsule (200 mg)	1 	2 tablespoons (30 mL) of food or liquid	Give all of the drug-food mixture
55 to < 88 pounds	2 capsules (400 mg)	2 	2 tablespoons (30 mL) of food or liquid	Give all of the drug-food mixture
88 pounds or more	3 capsules (600 mg)	3 	2 tablespoons (30 mL) of food or liquid	Give all of the drug-food mixture

***Adult dose** is 3 capsules (600 mg). Follow the same instructions for opening 3 capsules and mixing with food. Individuals who weigh 264 pounds or more should take 3 capsules (600 mg) 3 times a day.

Storing or Leftover Final Drug-Food Mixture

- Use the final drug-food mixture within 30 minutes of preparation.
- Throw out any unused final drug-food mixture (make a new final drug-food mixture each day).

Attachment 4
Laboratory Specimen Preparation, Handling, and Shipping

Laboratory Specimen Preparation, Handling, and Shipping*

I. VIRAL BLOOD AND LESION SAMPLES TO CDC:

Collect blood and/or lesion samples, vesicular or scab material, for orthopoxvirus testing on the following days:

- Within 24 hours prior to first dose of tecovirimat
- During tecovirimat treatment, lesion sampling will be performed based on patient's clinical progression
- Day 14 of tecovirimat treatment
- Every 7 days thereafter if tecovirimat treatment continues beyond 14 days
- Upon discharge (for inpatients); 7 and 30 days after last dose of tecovirimat (for outpatients)

Target volume of whole blood per time point:

- Patients ≤ 10 kg: 1.2 mL of whole blood
- Patients 11–20 kg: 2.5 mL of whole blood
- Patients > 20 kg: 5 mL of whole blood

As the transmission of orthopoxviruses can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this protocol, as currently recommended by CDC and the National Institutes of Health.

Viral lesion samples should be collected according to CDC guidelines (https://www.cdc.gov/smallpox/lab-personnel/specimen-collection/specimen-collection-procedures.html) and anti-virus immunoglobulin samples and EDTA blood should be shipped refrigerated (with cold packs) at 4°C (as per CDC guidelines) to:

Centers for Disease Control and Prevention
Attn: STAT Lab / Poxvirus Program
1600 Clifton Road NE, MS G-12
Atlanta, GA 30333
Phone: 404.639.4129

Additional instructions/guidelines, including precautions when handling specimens and information on shipping, can be found on CDC's website: https://www.cdc.gov/smallpox/lab-personnel/specimen-collection/pack-transport.htmltm.

II. PLASMA SAMPLES FOR PHARMACOKINETIC ANALYSIS:

Clinicians must arrange for plasma samples to be collected for each patient. A sample collection kit will be provided by Alturas Analytics, Inc. and should be returned to Alturas per the following instructions.

Sample Collection and Preparation Instructions:

1. Collect blood sample for each patient at each time point. Target volume of whole blood per time point:
   - Patients ≤ 10 kg: 1.2 mL of whole blood
   - Patients 11–20 kg: 2.5 mL of whole blood
   - Patients > 20 kg: 5 mL of whole blood
2. Anticoagulant: K_3EDTA tubes should be chilled (on wet ice) immediately following blood collection.
3. Whole blood samples should be centrifuged within 40 minutes of collection.
4. Samples should be processed to plasma by centrifugation at a speed of 2000–2200g for 10–15 minutes.
5. All plasma samples should be immediately pipetted into labeled tubes and **frozen either by placing on dry ice or put into a -20ºC (standard) freezer**.
6. Plasma samples must be stored in a standard freezer (-20ºC) within 2 hours after collection.
7. Be sure to label samples with the following minimum information:
   - Patient ID
   - Tecovirimat Dose (mg) and frequency
   - Tecovirimat Treatment Day Number (Dose Number)
   - Date & Time of Tecovirimat Dose (exact date & military time)
   - Date & Time of Plasma Collection (exact date & military time)
8. The plasma samples should be shipped **frozen on dry ice** after requested samples are collected along with the shipping log on the next page to the following laboratory:

   Jennifer Zimmer, Ph.D.
   Alturas Analytics Inc.
   1324 Alturas Drive
   Moscow, ID 83843
   Phone: (208) 883-3400 (extension 204)
   Send email notification to the following prior to shipment:
   jzimmer@alturasanalytics.com; rwoods@alturasanalytics.com; samplecustodian@alturasanalytics.com

   Note: If VIGIV is being administered concurrently, additional samples may be required. Discuss sample collection schedule with CDC.

Shipping Log: Patient Plasma Sample Collection for Tecovirimat PK Analysis

Complete and send this shipping log for each patient and shipment

Patient ID: _____

Treating Physician Name: _____

Hospital Name/Address: _____

Anticoagulant used *(K_3EDTA is preferred)*: _____

Tecovirimat Dose (mg) and frequency	**Tecovirimat Treatment Day Number**	**Date & Time of Tecovirimat Dose (exact date & military time)**	**Date & Time of Plasma Collection (exact date & military time)**
		_____/_____/_____ ____:____	_____/_____/_____ ____:____
		_____/_____/_____ ____:____	_____/_____/_____ ____:____
		_____/_____/_____ ____:____	_____/_____/_____ ____:____
		_____/_____/_____ ____:____	_____/_____/_____ ____:____

Name of Person Preparing Shipment (please print): _____

Contact Information for Shipment Preparer: _____

PLEASE INCLUDE A COPY OF THIS PAPERWORK WITH THE SHIPMENT

Ship to: Jennifer Zimmer, Ph.D.
1324 Alturas Dr.
Alturas Technology Park
Alturas Analytics, Inc.
Moscow, Idaho 83843
Phone: (208) 883-3400 (extension 204)

Please send confirmation of shipment to:

jzimmer@alturasanalytics.com

rwoods@alturasanalytics.com

samplecustodian@alturasanalytics.com

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TPOXX® safely and effectively. See full prescribing information for TPOXX.

TPOXX (tecovirimat) capsules, for oral use
TPOXX (tecovirimat) injection, for intravenous use
Initial U.S. Approval: 2018

RECENT MAJOR CHANGES

Indications and Usage (1.1)	5/2022
Dosage and Administration (2.1, 2.2, 2.3, 2.4, 2.5)	5/2022
Contraindications (4)	5/2022
Warnings and Precautions (5.2)	5/2022

INDICATIONS AND USAGE

TPOXX is an inhibitor of the orthopoxvirus VP37 envelope wrapping protein and is indicated for the treatment of human smallpox disease in adults and pediatric patients weighing at least 3 kg. (1.1)

Limitations of Use:

- The effectiveness 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. (1.2)
- TPOXX efficacy may be reduced in immunocompromised patients based on studies demonstrating reduced efficacy in immunocompromised animal models. (1.2)

DOSAGE AND ADMINISTRATION

- Pediatric and Adult Patients weighing 40 kg or more (2.3) (Oral Dosing):
  - 40 kg to less than 120 kg: 600 mg of TPOXX every 12 hours for 14 days
  - 120 kg or more: 600 mg of TPOXX every 8 hours for 14 days
- Pediatrics and adult patients weighing 13 kg or more and those who cannot swallow capsules (2.3) (Oral Dosing): TPOXX Capsules can be administered by carefully opening the number of capsule noted below and mixing and administering the entire contents in 30 mL of liquid (e.g., milk, chocolate milk) or soft food (e.g., apple sauce, yogurt):
  - 13 kg to less than 25 kg: 200 mg (1 Capsule) of TPOXX every 12 hours for 14 days
  - 25 kg to less than 40 kg: 400 mg (2 Capsules) of TPOXX every 12 hours for 14 days
  - 40 kg to less than 120 kg: 600 mg (3 Capsules) of TPOXX every 12 hours for 14 days.
  - 120 kg or more: 600 mg (3 capsules) every 8 hours for 14 days
- Patients weighing 3 kg and above (2.5) (Intravenous Dosing):
  - 3 kg to less than 35 kg: 6 mg/kg every 12 hours by intravenous infusion over 6 hours for up to 14 days
  - 35 kg to less than 120 kg: 200 mg every 12 hours by intravenous infusion over 6 hours for up to 14 days
  - 120 kg and above: 300 mg every 12 hours by intravenous infusion over 6 hours for up to 14 days.
- Pediatric patients weighing 13 kg or more should be switched to TPOXX Capsules to complete the 14-day treatment course as soon as oral therapy can be tolerated.
- Administration Instruction for TPOXX Capsules: Take within 30 minutes after a full meal containing moderate or high fat. (2.1, 2.3)
- Administration Instructions for TPOXX Injection: Infuse over 6 hours via infusion pump. (2.5)
- See Full Prescribing Information for additional information on the administration and preparation of TPOXX Capsules and Injection. (2)

DOSAGE FORMS AND STRENGTHS

Capsules
- 200 mg of tecovirimat (2.4)

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

CONTRAINDICATIONS

- TPOXX capsules: None
- TPOXX injection: TPOXX Injection is contraindicated in patients with severe renal impairment (defined as creatinine clearance below 30 mL/min) (4, 5.2)

WARNINGS AND PRECAUTIONS

Hypoglycemia: Co administration with repaglinide may cause hypoglycemia. Monitor blood glucose and monitor for hypoglycemic symptoms during co-administration. (5.1)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact SIGA Technologies Inc. at 1-888-899-3472 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

Consult the full prescribing information prior to and during treatment for potential drug interactions. (5.1, 7, 12.3)

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: 05/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

1.1. Treatment of Human Smallpox Disease

TPOXX® is indicated for the treatment of human smallpox disease caused by variola virus in adults and pediatric patients weighing at least 3 kg.

1.2. Limitations of Use

The effectiveness 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 *[see Clinical Studies (14)]*.

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

2. DOSAGE AND ADMINISTRATION

2.1. Important Dosing Instructions

It is recommended that patients 13 kg and above initiate oral treatment with TPOXX capsules if possible. If patients are unable to take oral TPOXX capsules or Drug-Food Preparation, treatment may be initiated with TPOXX injection as a 6 hour intravenous (IV) infusion. If IV treatment is necessary, conversion from IV to oral TPOXX is recommended as soon as oral treatment can be tolerated *[see Dosage and Administration (2.3)]*. In patients receiving an IV infusion, the first dose of oral treatment should be given at the time of and in place of the next scheduled IV dosing.

In patients receiving an oral treatment who subsequently require IV treatment, the first dose of IV infusion should be given at the time of and in place of the next scheduled oral dosing.

TPOXX capsules

Take TPOXX capsules within 30 minutes after a full meal containing moderate or high fat.

Missed Dose

If a dose of oral TPOXX is missed, the patient should take the dose as soon as possible and anytime up to 8 hours prior to the next scheduled dose. If less than 8 hours remain before the next scheduled dose, do not take the missed dose, and resume dosing at the next scheduled dose.

TPOXX injection

Administer TPOXX injection by IV infusion over 6 hours via an infusion pump. Must dilute TPOXX Injection prior to use *[see Dosage and Administration (2.5)]*.

2.2. Testing Before Initiating and During Treatment with TPOXX Injection

Determine creatinine clearance in all patients before starting TPOXX injection and monitor while receiving TPOXX injection as clinically appropriate [*see Dosage and Administration (2.4), Contraindications (4), Warnings and Precautions (5.2) and Use in Specific Populations (8.4, 8.6)*].

2.3. TPOXX Oral Dosage for Pediatric Patients Weighing at Least 13 kg and Adults

The recommended dosage of TPOXX capsules in pediatric patients weighing at least 13 kg and adults is displayed in Table 1 below.

Table 1: Recommended Dosage and Preparation Instructions for TPOXX Capsules in Pediatric Patients Weighing at Least 13 kg and Adults

Body Weight	**Oral Dosage for 14 Days[a]**	
	Dosage (Number of Capsules)	**Drug Food Preparation for Patients Who Cannot Swallow Capsules**
13 kg to less than 25 kg	200 mg (1 capsule) every 12 hours	Carefully open the required number of capsules and mix contents of capsule(s) of TPOXX with 30 mL of liquid (e.g., milk, chocolate milk) or soft food (e.g., apple sauce, yogurt). The entire mixture should be administered within 30 minutes of its preparation.
25 kg to less than 40 kg	400 mg (2 capsules) every 12 hours	
40 kg to less than 120 kg	600 mg (3 capsules) every 12 hours	
120 kg and above	600 mg (3 capsules) every 8 hours	

[a]TPOXX capsules should be taken within 30 minutes after a full meal containing moderate or high fat *[see Clinical Pharmacology (12.3)]*

2.4. Renal Impairment

TPOXX injection is contraindicated in patients with creatinine clearance below 30 mL per minute *[see Contraindications (4)]*.

2.5. Dosage and Administration of TPOXX Injection for Intravenous Infusion

The recommended dosage of TPOXX injection in pediatric patients weighing at least 3 kg and adults is displayed in Table 2 below.

TPOXX injection is supplied in a single-dose clear glass vial containing 200 mg/20 mL (10 mg/mL). Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. To administer:

- Use aseptic technique when preparing TPOXX injection.
- Withdraw the quantity of TPOXX injection (Table 2), add this volume to the syringe then dilute with two equal parts of either 0.9% (w/v) sodium chloride injection (normal saline) or 5% (w/v) dextrose injection in a syringe of suitable size. Injection with diluents other than 0.9% sodium chloride or 5% dextrose solution has not been studied. **NOT FOR IV BOLUS INJECTION. Do not use prefilled infusion bags for product preparation and administration.**
- The diluted TPOXX injection may be stored refrigerated (2°C - 8°C) for up to 24 hours or at room temperature (15°C - 25°C) for up to 4 hours.
- Gently swirl the syringe of in-use solution prior to inserting into the syringe pump and infuse over 6 hours every 12 hours for 14 days.
- Do not re-use the single-dose vial once it has been punctured.

Table 2: Recommended Pediatric and Adult Dosage and Preparation Instructions TPOXX Injection for IV Infusion[a]

Body Weight	Dosage for up to 14 days	Volume of TPOXX Injection[b]	Volume of Diluent[c]
3 kg to less than 35 kg	6 mg/kg every 12 hours by intravenous infusion over 6 hours[a]	0.6 mL/kg	1.2 mL/kg
35 kg to less than 120 kg	200 mg every 12 hours by intravenous infusion over 6 hours	20 mL	40 mL
120 kg and above[d]	300 mg every 12 hours by intravenous infusion over 6 hours	30 mL	60 mL

[a]Patients weighing at least 13 kg should be switched to TPOXX Capsules to complete the 14 day treatment course as soon as oral therapy can be tolerated.
[b]10 mg/mL TPOXX solution containing 40% hydroxypropyl betadex (8 g per vial) with water for injection *[see Dosage Forms and Strengths (3)]*.
[c]Diluent is either 0.9% (w/v) sodium chloride injection or 5% (w/v) dextrose injection solution.
[d]Depending on size of syringe available with syringe pump system, two separate syringes may be needed for each 6 hour administration.

3. DOSAGE FORMS AND STRENGTHS

TPOXX Capsules

TPOXX capsules are hard gelatin with an opaque orange body imprinted in white ink with "SIGA" followed by the SIGA logo followed by "®", and an opaque black cap imprinted in white ink with "ST-246®", containing white to off-white powder. Each capsule contains 200 mg of tecovirimat.

TPOXX Injection

TPOXX injection: 200 mg/20 mL (10 mg/mL) of tecovirimat as a clear, colorless to pale yellow solution in a single-dose vial for further dilution.

4. CONTRAINDICATIONS

TPOXX Capsules:

None.

TPOXX Injection:

The excipient hydroxypropyl-β-cyclodextrin is eliminated through glomerular filtration. Therefore, TPOXX Injection is contraindicated in patients with severe renal impairment (defined as creatinine clearance below 30 mL/min). *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]*

5. WARNINGS AND PRECAUTIONS

5.1. Hypoglycemia When Co-Administered with Repaglinide

Co-administration of repaglinide and tecovirimat may cause mild to moderate hypoglycemia. Monitor blood glucose and monitor for hypoglycemic symptoms when administering TPOXX with repaglinide *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

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 capsules. Symptoms resolved in all subjects after intake of food and/or oral glucose.

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

Patients with renal insufficiency

TPOXX Injection: In healthy patients and in patients with mild to severe renal insufficiency, the majority of an 8 g dose of hydroxypropyl-β-cyclodextrin (per 200 mg tecovirimat/20 mL solution) is eliminated in the urine. It is known that clearance of hydroxypropyl-β-cyclodextrin is reduced in patients with mild, moderate, and severe renal impairment, resulting in higher exposure to hydroxypropyl-β-cyclodextrin; in these patients, half-life values are increased over normal values by approximately two-, four-, and six-fold, respectively. In these patients, successive infusions may result in accumulation of hydroxypropyl-β-cyclodextrin until steady state is reached.

In patients with mild (defined as creatinine clearance 60-89 mL/min) and moderate (defined as creatinine clearance 30-59 mL/min) renal impairment, TPOXX Injection should be used with caution. Creatinine clearance should be closely monitored and, if renal toxicity is suspected, consideration should be given to administering TPOXX orally if possible or to using an alternative medication. TPOXX Injection is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min) *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

Pediatric patients

TPOXX Injection: In pediatric patients less than 2 years of age, there are limited data regarding the use of hydroxypropyl-β-cyclodextrin. Given that renal tubular function rapidly matures over the first few years of life, clearance of hydroxypropyl-β-cyclodextrin may be reduced in young pediatric patients, resulting in higher exposure to hydroxypropyl-β-cyclodextrin. TPOXX Injection should be used with caution in this population given that animal studies have shown potential for nephrotoxicity at very high exposure levels of hydroxypropyl-β-cyclodextrin. Given the potential for drug accumulation due to renal immaturity in pediatric patients less than 2 years, monitoring of renal function after treatment is recommended *[see Use in Specific Populations (8.4) and Clinical Pharmacology (12.3)]*.

6. ADVERSE REACTIONS

6.1. Clinical Trials Experience

Because clinical trials are conducted under widely varying 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.

TPOXX Clinical Trial (Oral Administration)

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 (every 12 hours) 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 2% of subjects in the TPOXX treatment group are shown in Table 3.

Table 3: Treatment-Related Adverse Reactions Reported in ≥ 2% of Healthy Adult Subjects Receiving at Least One Dose of TPOXX Capsules 600 mg

Adverse Reaction	**TPOXX 600 mg N = 359 (%)**	**Placebo N = 90 (%)**
Headache	12	8
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

Less Common Adverse Reactions

Clinically significant adverse reactions that were reported in < 2% 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

TPOXX Clinical Trial (Intravenous Administration)

The safety of multiple doses of 240 mg of TPOXX injection for IV infusion was evaluated in 26 healthy adult subjects ages 23-62 years, inclusive. An additional 6 subjects received placebo. TPOXX injection was administered over a 6 hour period via infusion pump twice daily (every 12 hours) for 7 days. Of the 26 subjects administered TPOXX, 42% were female, 69% were White, 23% were Black/African American, and 42% were Hispanic or Latino.

Most Frequently Reported Adverse Reactions

The most frequently reported adverse reactions included infusion site pain, infusion site swelling, infusion site erythema, infusion site extravasation, and headache. Adverse reactions that occurred in at least 4% of subjects in the TPOXX treatment group are shown in Table 4.

Table 4: Treatment-Related Adverse Reactions Reported in ≥ 4% of Healthy Adult Subjects Receiving at Least One Dose of TPOXX Injection 240 mg

	TPOXX 240 mg N =26 (%)	**Placebo N = 6 (%)**
Infusion Site Pain	73	67
Infusion Site Swelling	39	67
Infusion Site Erythema	23	67
Infusion Site Extravasation	19	50
Headache	15	0

Adverse Reactions Leading to Discontinuation of TPOXX Injection

Three subjects (12%) had their treatment with TPOXX injection discontinued due to adverse reactions. One subject had two adverse reactions. Each of these subject's adverse reactions (with severity) are listed below:

- Moderate Infusion site extravasation
- Mild Infusion site extravasation
- Mild Infusion site swelling and mild infusion site pain

Less Common Adverse Reactions

Clinically significant adverse reactions that were reported in < 4% of subjects exposed to TPOXX injection and at rates higher than subjects who received placebo are listed below:

- General and administration site: infusion site discomfort, infusion site edema
- Musculoskeletal and connective tissue: myalgia, arthritis, back pain, muscle tightness
- Gastrointestinal: diarrhea
- Eye: photophobia
- Skin and Subcutaneous Tissue: pruritus generalized

7. DRUG INTERACTIONS

7.1. Effect of TPOXX on Other Drugs

Tecovirimat is a weak inducer of cytochrome P450 (CYP)3A 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. See Table 5 for clinical recommendations for select sensitive substrates.

7.2. Established Drug Interactions

Table 5 provides a listing of established or significant drug interactions *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

Table 5: Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[a]	Clinical Effect/Recommendation
Blood Glucose-Lowering Agent:		
Repaglinide[b]	↑ repaglinide	Monitor blood glucose and monitor for hypoglycemic symptoms in patients when TPOXX is co-administered with repaglinide *[see Warnings and Precautions (5.1)]*.
CNS Depressant:		
Midazolam[b]	↓ midazolam	Monitor for effectiveness of midazolam.

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

7.3. Drugs Without Clinically Significant Interactions With TPOXX

Based on a drug interaction study, no clinically significant drug interactions have been observed when TPOXX is co-administered with bupropion, flurbiprofen, or omeprazole *[see Clinical Pharmacology (12.3)]*.

7.4. Vaccine Interactions

No vaccine-drug interaction studies have been performed in human subjects. Some 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 interaction on vaccine efficacy is unknown.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

There are no available data on the use of tecovirimat in pregnant individuals to evaluate for a drug-associated risk of major birth defects, miscarriage, and other adverse maternal and fetal outcomes.

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, and the estimated background risk of miscarriage for the indicated population is higher than the general population. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. 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 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

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 was present in animal milk *(see Data)*. When a drug is present in animal milk, it is likely to be present in human milk.

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

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)]*.

8.4. Pediatric Use

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 orally twice daily (every 12 hours) or 200 mg intravenously twice daily (every 12 hours). The dosage for pediatric patients is based on weight *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

TPOXX Injection:

There are limited data regarding the use of hydroxypropyl-β-cyclodextrin, an ingredient in TPOXX injection, in pediatric patients less than 2 years of age. Given the potential for drug accumulation due to renal immaturity in pediatric patients less than 2 years, monitoring of renal function after treatment is recommended *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

8.5. Geriatric Use

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 clinical study of oral TPOXX, 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 *[see Clinical Pharmacology (12.3)]*.

8.6. Renal Impairment

TPOXX Capsules:

No dosage adjustment is required for patients with mild, moderate or severe renal impairment or patients with end stage renal disease (ESRD) requiring hemodialysis *[see Clinical Pharmacology (12.3)]*.

TPOXX Injection:

Hydroxypropyl-β-cyclodextrin, an ingredient in TPOXX injection, when administered intravenously, is eliminated through glomerular filtration. No dosage adjustment is required for patients with mild (creatinine clearance 60-89 mL/min) or moderate (creatinine clearance 30-59 mL/min) renal impairment. TPOXX Injection is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min) *[see Contraindications (4)]*.

8.7. Hepatic Impairment

No dosage adjustment is required for patients with mild, moderate or severe hepatic impairment (Child Pugh Class A, B, or C) *[see Clinical Pharmacology (12.3)]*.

10. 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.

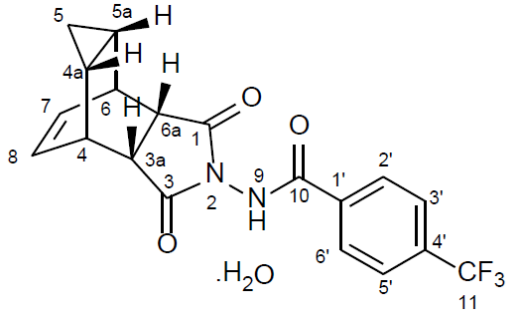
11. DESCRIPTION

TPOXX capsules and TPOXX injection contains tecovirimat, an inhibitor of the orthopoxvirus VP37 envelope wrapping protein.

TPOXX (tecovirimat) capsules, for oral use are immediate release capsules containing tecovirimat monohydrate equivalent to 200 mg of tecovirimat for oral administration. The capsules include the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The capsule shell is composed of gelatin, FD&C blue #1, FD&C red #3, FD&C yellow #6, and titanium dioxide.

TPOXX (tecovirimat) injection, for intravenous use is a sterile, colorless to pale yellow solution free of visible particles that is intended for intravenous use following dilution. Tecovirimat injection is available in a single-dose vial containing 200 mg/20 mL (10 mg/mL) of tecovirimat and 8,000 mg (400 mg/mL) of Hydroxypropyl Betadex, NF (hydroxypropyl β-cyclodextrin) and Water for Injection, USP/NF.

Tecovirimat monohydrate is a white to off-white crystalline solid with the chemical name Benzamide, N-[(3a*R*,4*R*,4a*R*,5a*S*,6*S*,6a*S*)-3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6 ethenocycloprop[f]isoindol-2(1H)-yl]-4-(trifluoromethyl), rel-(monohydrate). The chemical formula is $C_{19}H_{15}F_3N_2O_3 \cdot H_2O$ representing a molecular weight of 394.35 g/mol. The molecular structure is as follows:



Tecovirimat monohydrate is practically insoluble in water and across the pH range of 2.0-6.5 (< 0.1 mg/mL).

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

Tecovirimat is an antiviral drug against variola (smallpox) virus *[see Microbiology (12.4)]*.

12.2. Pharmacodynamics

Cardiac Electrophysiology

TPOXX does not prolong the QT interval to any clinically relevant extent at the anticipated therapeutic exposure.

12.3. Pharmacokinetics

At the recommended oral dosage of 600 mg every 12 hours administered in healthy adults weighing less than 120 kg, the mean steady-state values of tecovirimat $AUC_{0\text{-}24hr}$, C_{max}, and $C_{tau/trough}$ are 29816 hr·ng/mL (n, CV: 43, 34%), 2159 ng/mL (n, CV: 46, 32%), and 845 ng/mL (n, CV: 45, 47%), respectively. At the recommended intravenous dosage of 200 mg every 12 hours administered by IV infusion over 6 hours in healthy adults, the mean steady-state values of tecovirimat $AUC_{0\text{-}24hr}$, C_{max}, and C_{min} are 39405 hr.ng/mL (n, CV: 22, 23%), 2630 ng/mL (n, CV: 22, 22%), and 747 ng/mL (n, CV: 22, 29%). Refer to Table 6 for pharmacokinetic parameters of tecovirimat. Tecovirimat steady-state is achieved by Day 4-6.

Table 6: Pharmacokinetic Properties of Tecovirimat

Absorption	**200 mg intravenous**	**600 mg oral**
Median T_{max} (h) (Range)	6 (6-6.5)	6 (2-24)[a]
Effect of food (relative to fasting)	NA	↑39% [b]
Distribution		
% Bound to human plasma proteins	77-82	
Blood-to-plasma ratio (drug or drug-related materials)	0.62-0.90	
Volume of distribution (Vz or Vz/F, L) (CV%)	383 (46%)	1030
Metabolism		
Metabolic pathways[c]	Hydrolysis, UGT1A1[d], UGT1A4	
Elimination		
Major route of elimination	Metabolism	
Clearance (CL or CL/F, L/hr) (CV%)	13 (23%)	31
$t_{½}$ (h)[e] (CV%)	21 (45%)	19(29%)
% of dose excreted in urine[f]	NA	73, predominantly as metabolites
% of dose excreted in feces[f]	NA	23, predominantly as tecovirimat

[a]Value reflects administration of drug with food.
[b]Value refers to mean systemic exposure (AUC_{24hr}). Meal: ~ 600 kcal, ~ 25 g fat.
[c]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)
[d]Uridine diphosphate (UDP)-glucuronosyl transferase (UGT) enzymes
[e]$t_{½}$ value refers to mean terminal plasma half-life.
[f]Single dose administration of [^{14}C]-tecovirimat in mass balance study.
KEY: NA = Not Applicable or Not Available

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 every 12 hours for treatment of smallpox disease in humans. Humans achieve greater systemic exposure (AUC, C_{max}, and C_{min}) of tecovirimat following a dose of 600 mg every 12 hours when compared to the therapeutic exposures in these animal models.

Specific Populations

No clinically significant differences in the pharmacokinetics of tecovirimat were observed based on age, sex, ethnicity, renal impairment (based on estimated GFR), or hepatic impairment (Child Pugh Scores A, B or C). At the 600 mg twice-daily oral dosage, tecovirimat exposure was reduced in adult subjects weighing more than 120 kg compared to the exposures in adult subjects weighing less than 120 kg. Specifically, in 34 adult subjects weighing more than 120 kg who received 600 mg TPOXX orally every 12 hours, the observed mean steady state values of $AUC_{0\text{-}24hr}$, C_{max}, and C_{trough} were 19500 hr•ng/mL (CV: 23%), 1300 ng/mL (CV: 29%), and 585 ng/mL (CV: 31%), respectively.

Pediatric Patients

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 *[see Dosage and Administration (2.2) and Use in Specific Populations (8.4)]*.

Hydroxypropyl-β-cyclodextrin, when administered intravenously, is eliminated through glomerular filtration which may be reduced in pediatric patients with renal immaturity *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.4)]*.

Drug Interaction Studies

The effect of tecovirimat on the exposure of co-administered drugs are shown in Table 7.

Table 7: Drug Interactions – Changes in Pharmacokinetic Parameters for Co Administered Drug in the Presence of TPOXX[a]

Co-Administered Drug	Dose of Co-Administered Drug (mg)	N	Mean Ratio (90% CI) of Co-Administered Drug PK With/Without TPOXX No Effect = 1.00	
			C_{max}	AUC_{∞}
Flurbiprofen + omeprazole + midazolam[b]	omeprazole 20 single dose	24	1.87 (1.51, 2.31)	1.73 (1.36, 2.19)
	midazolam 2 single dose		0.61 (0.54, 0.68)	0.68 (0.63, 0.73)
Repaglinide	2 single dose	30	1.27 (1.12, 1.44)	1.29 (1.19, 1.40)
Bupropion	150 single dose	24	0.86 (0.79, 0.93)	0.84 (0.78, 0.89)

[a]All interaction studies conducted in healthy volunteers with tecovirimat 600 mg twice daily (every 12 hours).
[b]Comparison based on exposures when administered as flurbiprofen + omeprazole + midazolam.

No pharmacokinetic changes were observed for the following drug when co-administered with tecovirimat: flurbiprofen.

Cytochrome P450 (CYP) Enzymes: Tecovirimat is a weak inhibitor of CYP2C8 and CYP2C19, and a weak inducer of CYP3A4. Tecovirimat is not an inhibitor or an inducer of CYP2B6 or CYP2C9.

In Vitro Studies Where Drug Interaction Potential Was Not Further Evaluated Clinically

CYP Enzymes: Tecovirimat is not an inhibitor of CYP1A2, CYP2D6, CYP2E1 or CYP3A4, and is not an inducer of CYP1A2. Tecovirimat is not a substrate for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4.

UGT Enzymes: Tecovirimat is a substrate of UGT1A1 and UGT1A4.

Transporter Systems: Tecovirimat inhibited Breast Cancer Resistance Protein (BCRP) *in vitro*.

Tecovirimat is not an inhibitor of P-glycoprotein (P-gp), organic anion transporting polypeptides 1B1 and 1B3 (OATP1B1 and OATP1B3), organic anion transporter 1 (OAT1), OAT3, and organic cation transporter 2 (OCT2). Tecovirimat is not a substrate for P-gp, BCRP, OATP1B1, and OATP1B3.

12.4. 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.

Non-antagonistic antiviral activity of tecovirimat and brincidofovir against orthopoxviruses has been demonstrated in cell culture and animal models.

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

Cross-resistance between tecovirimat and brincidofovir is not expected based on their distinct mechanisms of action. Where tested, orthopoxvirus isolates resistant to cidofovir (the active metabolite of brincidofovir) have not been resistant to tecovirimat. Likewise, orthopoxvirus isolates resistant to tecovirimat retain their sensitivity to cidofovir.

13. NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

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$^{\pm}$ 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).

13.2. Animal Toxicology and/or Pharmacology

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 at 100 mg/kg/dose (similar to the highest observed human exposure at the RHD based on C_{max}), although no convulsions or EEG findings were observed at this dose.

14. CLINICAL STUDIES

Overview

The effectiveness 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 effectiveness of TPOXX for treatment of smallpox disease 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.

Study Design

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 x 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.

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 8).

Table 8: 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					
Study 1	Day 4	0% (0/7)	80% (4/5)	0.0038	80% (20.8%, 99.5%)
Study 2	Day 4	0% (0/6)	100% (6/6)	0.0002	100% (47.1%, 100%)
Study 3	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%)
NZW Rabbits					
Study 4	Day 4	0% (0/10)	90% (9/10)	< 0.0001	90% (50.3%, 99.8%)
Study 5	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

16. HOW SUPPLIED/STORAGE AND HANDLING

TPOXX Capsule

How Supplied

Each TPOXX capsule contains 200 mg of tecovirimat. TPOXX capsules are hard gelatin with an opaque orange body imprinted in white ink with "SIGA" followed by the SIGA logo followed by "®", and an opaque black cap imprinted in white ink with "ST-246®", containing white to off-white powder. Each bottle contains 42 capsules (NDC 50072-200-42) with an induction seal and child-resistant cap.

Storage and Handling

Store capsules in the original bottle at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

TPOXX Injection

How Supplied

TPOXX injection is supplied in a 30 mL single-dose vial as a clear, colorless to pale yellow solution for intravenous administration containing 200 mg/20 mL (10 mg/mL) of tecovirimat (NDC 50072-010-30). This solution is intended for dilution with either 0.9% (w/v) sodium chloride injection or 5% (w/v) dextrose injection solution. The vial stopper is not made with natural rubber latex. The vials are packed in cartons of seven vials. Short-term (up to 24 hours) storage and handling at an ambient temperature is acceptable.

Storage and Handling

Store TPOXX injection in a refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze.

The diluted solution(s) of TPOXX injection with either 0.9% (w/v) sodium chloride (normal saline) or 5% (w/v) dextrose solution should be used within 4 hours of preparation if stored at room temperature or within 24 hours of preparation if stored at 2°C to 8°C *[see Dosage and Administration (2.5)]*.

17. PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Efficacy Based on Animal Models Alone

Inform patients that the efficacy of TPOXX is based solely on efficacy studies demonstrating a survival benefit in animals and that the effectiveness of TPOXX has not been tested in humans with smallpox disease *[see Clinical Studies (14)]*.

Important Dosage and Administration Information

Advise patients to take TPOXX capsules as directed within 30 minutes of eating a full meal containing moderate or high fat with 6-8 oz. of water *[see Clinical Pharmacology (12.3)]*. Inform patients to take TPOXX for the entire duration without missing or skipping a dose *[see Dosage and Administration (2)]*.

Inform patients who cannot swallow capsules to refer to the Instructions for Use *[see Dosage and Administration (2)]*.

Drug Interactions

Inform patients that TPOXX may interact with other drugs. Advise patients to report to their healthcare provider the use of other prescription drugs. Co-administration of TPOXX with repaglinide may cause hypoglycemia *[see Warnings and Precautions (5.1) and Drug Interactions (7.2)]*.

TPOXX injection: Hydroxypropyl-β-cyclodextrin, a required component of TPOXX injection, is eliminated through glomerular filtration. Therefore, in patients with severe renal impairment (defined as creatinine clearance below 30 mL/min), the use of TPOXX injection is contraindicated. *[see Contraindications (4)]*. In patients with mild (defined as creatinine clearance 60-89 mL/min) and moderate (defined as creatinine clearance 30-59 mL/min) renal impairment, TPOXX injection should be used with caution *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]*.

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)]*.

TPOXX capsules manufactured by:

Catalent Pharma Solutions, LLC

1100 Enterprise Drive

Winchester, KY 40391

TPOXX injection manufactured by:
Patheon Manufacturing Services LLC
5900 Martin Luther King Jr. Highway
Greenville, NC 27834

Distributed by:
SIGA Technologies, Inc.
4575 SW Research Way, Suite 110
Corvallis, OR 97333

PATIENT INFORMATION

TPOXX® (Tē-Pox or Tee-pahx) **(tecovirimat)** **capsules, for oral use**	**TPOXX® (Tē-Pox or Tee-pahx)** **(tecovirimat)** **injection, for intravenous use**

What is TPOXX?

TPOXX is a prescription medicine used to treat smallpox disease caused by a type of virus called variola virus in adults and children who weigh at least 7 pounds (3 kg).

- The effectiveness of TPOXX has been studied only in animals with orthopoxvirus diseases. There have been no human studies in people who have smallpox disease.
- The safety of TPOXX was studied in adults. There have been no studies of TPOXX in children 17 years of age and younger.
- TPOXX may not work well in people who have a weakened immune system (immunocompromised).

Who should not receive TPOXX injection?

Do not receive TPOXX injection if you or your child have severe kidney problems TPOXX injection contains an ingredient called hydroxypropyl β-cyclodextrin which is cleared from your body through the kidneys. Tell your healthcare provider if you or your child have kidney problems because receiving TPOXX injection may not be right for you or your child.

Before taking or receiving TPOXX, tell your healthcare provider about all of your or your child's medical conditions, including if you or your child:

- have diabetes.
- have kidney problems.
- are pregnant or plan to become pregnant. It is not known if TPOXX can harm the unborn baby. Tell your healthcare provider if you or your child become pregnant during treatment with TPOXX.
- are breastfeeding or plan to breastfeed. It is not known if TPOXX passes into your breast milk. **You should not breastfeed during treatment with TPOXX.**
    - You should not breastfeed if you have smallpox because of the risk of passing variola virus to the breastfed infant.
    - Talk to your healthcare provider about the best way to feed the baby during treatment with TPOXX.

Tell your healthcare provider about all of the medicines you or your child take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Using TPOXX with certain other medicines may affect each other causing possible serious side effects. You can ask your healthcare provider or pharmacist for a list of medications that interact with TPOXX.

Especially tell your healthcare provider if you take a medicine used to treat type 2 diabetes called repaglinide.

Know the medicines you or your child take. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine. Do not start taking a new medicine without telling your healthcare provider. Your healthcare provider can tell you if it is safe to take TPOXX with other medicines.

How should I take TPOXX?

- **Stay under the care of your healthcare provider during treatment with TPOXX.**

TPOXX capsules:

- Take TPOXX capsules exactly as your healthcare provider tells you. Do not change the dose or stop taking TPOXX without talking to your healthcare provider.
- **For adults and children who weigh at least 40 kg and less than 120 kg**, take 3 capsules of TPOXX 2 times a day (every 12 hours) by mouth for 14 days.
- **For adults and children who weigh at least 120 kg**, take 3 capsules of TPOXX 3 times a day (every 8 hours) by mouth for 14 days.
- TPOXX should be taken within 30 minutes after eating a full meal of moderate or high fat (approximately 600 calories and 25 grams of fat). Swallow capsules whole with 6 to 8 ounces of water. Talk to your healthcare provider about examples of foods that you can eat that contain about 25 grams of fat. **Always take TPOXX with food.**
- See the "Instructions for Use" that comes with your TPOXX capsules for instructions on how to prepare and take a dose of TPOXX if:

- your child weighs less than 88 pounds (40 kg), **or**
- you or your child have trouble swallowing TPOXX capsules.

- It is important to take TPOXX for the full 14 day course of treatment. Do not miss or skip a dose of TPOXX.
- If you miss an oral dose of TPOXX, you should take the dose as soon as possible and anytime up to 8 hours before the next scheduled dose. If less than 8 hours remain before the next scheduled dose, do not take the missed dose, and take your next dose as scheduled.
- If you take too much TPOXX, call your healthcare provider or go to the nearest hospital emergency room right away.

TPOXX Injection for Intravenous Infusion (IV)

TPOXX injection is given to you or your child by intravenous (IV) infusion into a vein slowly over 6 hours using an infusion pump by a health care provider.

What are the possible side effects of TPOXX?

TPOXX may cause serious side effects, including:

- **Low blood sugar (hypoglycemia).** Low blood sugar can happen when TPOXX is taken or received with repaglinide, a medicine used to treat type 2 diabetes. Tell your healthcare provider if you get any of the following symptoms of low blood sugar:
  - headache
  - drowsiness
  - hunger
  - feeling jittery or shaky
  - dizziness
  - confusion
  - sweating
  - weakness
  - fast heartbeat
  - irritability

The most common side effects of TPOXX capsules include:

- headache
- nausea
- stomach pain
- vomiting

The most common side effects of TPOXX injection include:

- reactions at the site of your IV infusion

These are not all the possible side effects of TPOXX.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088

How should I store TPOXX capsules?

- Store TPOXX at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep TPOXX in its original container.

Keep TPOXX and all other medicines out of the reach of children.

General information about the safe and effective use of TPOXX.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use TPOXX for a condition for which it was not prescribed. Do not give TPOXX to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about TPOXX that is written for health professionals.

What are the ingredients in TPOXX?

TPOXX capsules: 200 mg

Active ingredient: tecovirimat

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The capsule shell is made of gelatin, FD&C blue No.1, FD&C red No.3, FD&C yellow No.6, and titanium dioxide.

TPOXX injection: 200 mg in each 20 mL vial

Active ingredient: tecovirimat

Inactive ingredients: hydroxypropyl β-cyclodextrin and water for injection.

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For more information, go to www.SIGA.com or call 1-888-899-3472.

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 05/2022

INSTRUCTIONS FOR USE
TPOXX® (Tē-Pox or Tee-pahx)
(tecovirimat)
capsules, for oral use

This Instructions for Use contains information on how to prepare and give a dose of TPOXX capsules to children who weigh 28 pounds (13 kg) to less than 88 pounds (40 kg) or adults or children who have trouble swallowing TPOXX capsules whole.

Read this Instructions for Use before taking TPOXX capsules. There may be new information. This Instructions for Use does not take the place of talking to your healthcare provider about your medicinal condition or treatment.

Step 1: Gather the supplies you need to prepare a dose of TPOXX:

- 1 bottle of TPOXX (1 capsule = 200 mg of medicine)
- 1 tablespoon
- 1 small bowl or cup
- Your choice of liquid or soft food:
  - Liquid such as milk, chocolate milk or infant formula
  - Soft food such as applesauce or yogurt

Step 2: Find the weight of the person taking the medicine on the TPOXX Dosing Table (see **Figure A**).

Step 3: Find the prescribed dose in the same row as the weight of the person taking the medicine on the TPOXX Dosing Table (See **Figure A**).

Step 4:

- Get a small bowl or cup and place it on a flat surface.
- Add 2 tablespoons (30 mL) of liquid or soft food to the bowl or cup.

Step 5: Find the number of TPOXX capsules needed in the same row as the weight of the person taking the medicine on the TPOXX Dosing Table (see **Figure A**).

- Take out the correct number of TPOXX capsules from the bottle.

Step 6: Hold the TPOXX capsule in a sideways (horizontal) position directly over the bowl or cup to make sure none of the medicine is lost.

- Hold the ends of the TPOXX capsule between the thumb and index (pointer) finger of both hands.
- Gently and slowly twist the ends of the capsule and pull it apart. Empty the contents of the capsule into the bowl or cup. Repeat this for each capsule that is needed for the total prescribed dose.
- Throw away the empty capsule shells.

Step 7: Use the tablespoon to mix together the capsule contents and the liquid or soft food.

- The powder may not completely dissolve.
- The TPOXX medicine mixture is now ready to take.

Step 8: Swallow the TPOXX medicine mixture.

All the TPOXX medicine mixture should be swallowed to make sure the entire dose it taken.

- The TPOXX mixture must be taken within 30 minutes after a meal containing approximately 25 grams of fat **and** within 30 minutes after mixing it.
- **For people weighing 28 pounds (13 kg) to less than 264 pounds (120 kg), TPOXX medicine mixture should be given 2 times a day (every 12 hours), by mouth, for 14 days.**
- **For people weighing 264 pounds (120 kg) and above, TPOXX medicine mixture should be given 3 times a day (every 8 hours), by mouth, for 14 days.**

TPOXX Dosing Table (Figure A)

Body Weight	Prescribed Dose	Amount of Liquid or Soft Food	Number of Capsules	Food and Medicine Mixture Instructions
28 pounds (13 kg) to less than 55 pounds (25 kg)[a]	200 mg (1 capsule) Every 12 hours	2 tablespoons	1 TPOXX capsule	Mix entire contents of 1 TPOXX capsule with 2 tablespoons of liquid or soft food.
55 pounds (25 kg) to less than 88 pounds (40 kg)[a]	400 mg (2 capsules) Every 12 hours	2 tablespoons	2 TPOXX capsules	Mix entire contents of 2 TPOXX capsules with 2 tablespoons of liquid or soft food.
88 pounds (40 kg) to less than 265 pounds (120 kg)[a]	600 mg (3 capsules) Every 12 hours	2 tablespoons	3 TPOXX capsules	Mix entire contents of 3 TPOXX capsules with 2 tablespoons of liquid or soft food.
265 pounds (120 kg) and above[b]	600 mg (3 capsules) Every 8 hours	2 tablespoons	3 TPOXX capsules	Mix entire contents of 3 TPOXX capsules with 2 tablespoons of liquid or soft food.

[a]Given twice daily every 12 hours, by mouth, for 14 days.

[b]Given three times a day every 8 hours, by mouth, for 14 days.

How should I store TPOXX Capsules?

- Store TPOXX at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep TPOXX in its original container

Keep TPOXX and all medicines out of the reach of children.

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