****Obtain informed consent prior to tecovirimat initiation****

Expanded Access IND Protocol: Use of Tecovirimat (TPOXX®) for Treatment of Human Non-Variola Orthopoxvirus Infections in Adults and Children

IND No. 116,039

CDC IRB No. 6402

Version 6.0
July 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

Coordinating Program:
Poxvirus and Rabies Branch
Division of High-Consequence Pathogens and Pathology (DHCPP)
National Center for Emerging and Zoonotic Infectious Diseases (NCEZID)
1600 Clifton Road, MS H24-12, Atlanta, GA 30329
Phone: (404) 639-4129
Email: Poxvirus@cdc.gov

Clinical:
Sponsor 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
Email: poxvirus@cdc.gov

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
Email: regaffairs@cdc.gov

CDC Emergency Operation Center: (770) 488-7100

TABLE OF CONTENTS

ATTACHMENTS

Attachments are posted on Information for Healthcare Providers on Obtaining and Using TPOXX (Tecovirimat) for Treatment of Monkeypox | Monkeypox | Poxvirus | CDC

1.0 INTRODUCTION AND BACKGROUND

Orthopoxviruses (OPXVs) belonging to the *Poxviridae* family that infect humans are *variola virus* (smallpox), *vaccinia virus* (the virus in smallpox vaccine ACAM2000 and smallpox/monkeypox vaccine Jynneos), *monkeypox virus*, *cowpox virus*, *Akhmeta virus* and *Alaskapox virus*. Variola virus, the etiologic cause of smallpox, is the only one that affects humans exclusively, while the others are zoonotic infections that can also be transmitted person-to-person. 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. Orthopoxviruses, 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.

Since the worldwide eradication of smallpox, the other orthopoxviruses or non-variola orthopoxvirus (NV-OPXV) infections are emerging as a growing public health concern given the potential for spread through international travel, especially among populations that have not been previously vaccinated, and delayed recognition of NV-OPXV infections by healthcare professional who may be less familiar with these infections. Recent cases of human monkeypox (MPX) in countries outside of west and central Africa underscore the risk of spread of MPX from beyond its normal endemic region and the potential for sustained local transmission.

In 2003, a MPX outbreak occurred in the United States (U.S.) through direct or indirect contact with MPXV-infected prairie dogs, where 47 confirmed or probable cases of human monkeypox were identified: 37% of cases were hospitalized, although illness severity was usually mild. Two patients were hospitalized with severe disease; there were no deaths reported. To prevent transmission of MPX, a replication-competent smallpox vaccine (Dryvax®, which is no longer available) was administered to 30 individuals (pre-exposure to 7 and post-exposure to 23) with no reported serious adverse events following smallpox vaccination [1, 2].

During September 2018–May 2021, seven unrelated persons traveling from Nigeria received diagnoses of monkeypox in non-African countries: five in the United Kingdom and one each in Israel and Singapore [3-5]. Response to the cases in United Kingdom included offering vaccination with Imvanex (marketed as Jynneos® in the U.S.) as post-exposure prophylaxis (PEP) and antiviral treatment in 3 MPX-infected individuals (1 received tecovirimat; 2 received brincidofovir). In July and November 2021, two independent cases of MPX in travelers from Nigeria were diagnosed in Texas and Maryland and one patient was treated with tecovirimat[6, 7]. Emerging cases of MPX reported in European countries and the U.S. in May 2022 with ongoing transmissions highlight the need for prevention and treatment measures. Refer to https://www.cdc.gov/poxvirus/monkeypox/outbreak/us-outbreaks.html for summary of U.S. monkeypox cases.

Vaccination is the key modality for prevention of orthopoxvirus infections. There are two FDA-approved vaccines, ACAM2000 (replication-competent, live vaccinia vaccine approved for smallpox for adults and children) and Jynneos (replication-deficient, Modified Vaccinia Ankara-Bavarian Nordic [MVA-BN] approved for smallpox and monkeypox in adults 18 years and older). However, vaccination must occur soon after exposure to be effective in preventing or reducing the seriousness of the disease caused by orthopoxvirus infections. During an outbreak, effective therapeutic options also are necessary. Additionally, with widespread vaccination, vaccinia vaccine-related complications may occur that necessitate treatment options.

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

Currently, there is no treatment approved by the Food and Drug Administration (FDA) for non-variola orthopoxvirus, including MPX. Although tecovirimat is FDA-approved for treatment of smallpox in adults and children, the approved indication is limited to smallpox. Therefore, this intermediate-size

patient population expanded access Investigational New Drug (IND), sponsored by the Centers for Disease Control and Prevention (CDC) and authorized by FDA, is to allow access to and use of stockpiled tecovirimat for treatment of non-variola orthopoxvirus (NV-OPXV) infection in adults and children.

While the effectiveness of tecovirimat in treating human non-variola orthopoxvirus infections, including monkeypox, has not been evaluated, it may be reasonable to anticipate potential treatment benefit based on animal efficacy data that supported FDA-approval for smallpox treatment and limited clinical uses of tecovirimat in the treatment of NV-OPXV infected individuals to date.

Tecovirimat has been shown to be effective against various orthopoxviruses in multiple animal challenge models [8-10]. Tecovirimat was approved for smallpox 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.

2.0 PROGRAM OBJECTIVE

The purpose of this expanded access IND (compassionate use) program is to provide stockpiled tecovirimat for treatment or prevention of 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.

To monitor clinical use of tecovirimat, including any occurrence of serious adverse events, patient monitoring and outcomes information are also intended to be collected under this expanded access IND program **to the extent feasible** (e.g., baseline clinical conditions, progression/improvement during treatment, recovered or not recovered from orthopoxvirus infection). Please refer to **Section 7.0** Clinical Assessment and Monitoring of Patients.

2.1 Tecovirimat Eligibility

All patient populations, who meet eligibility criteria, can receive tecovirimat treatment under this IND program (e.g., children and all adults including pregnant and nursing individuals, and prisoners). Other concomitant treatments and vaccination (e.g., ACAM2000, Jynneos) are allowed under this IND program for tecovirimat.

2.1.1 Primary or early empiric treatment

Tecovirimat treatment may be initiated for patients with laboratory confirmed non-variola orthopoxvirus infection or suspected infection based on known exposure(s) and/or clinical manifestations of disease. Patients with an initial negative OPXV test, but for whom both epidemiologic and clinical evidence suggests OPXV disease (particularly if clinical progression is worsening), should be re-tested but be treated with tecovirimat while results are pending. If results from re-testing confirm orthopoxvirus, patients should continue tecovirimat treatment. If results from re-testing are in agreement with the initial negative orthopoxvirus results, tecovirimat should be suspended in those patients.

2.1.2 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 if a patient is ineligible for Vaccinia Immune Globulin Intravenous (VIGIV) treatment, or after VIGIV treatment has been exhausted, or in conjunction with VIGIV and/or other therapies based on the treating clinician's clinical judgment. For more information, see https://www.cdc.gov/smallpox/clinicians/vaccine-adverse-events5.html

2.1.3 Post-exposure prophylaxis (PEP)

Tecovirimat may be considered for post-exposure prophylaxis on an **individual case-by-case basis** in consultation with CDC (Emergency Operations Center [EOC] (770) 488-7100; poxvirus@cdc.gov)

depending on the known high-risk exposure to a confirmed or probable case of NV-OPXV infection (as defined on https://www.cdc.gov/poxvirus) and clinical conditions that necessitate an alternative or complementary option to PEP vaccination based on clinical judgment, including taking into account exposure risk level and clinical status of the exposed individual (e.g., allergic to vaccine components, immunocompromising conditions).

2.1.4 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. These include critically ill patients hospitalized and unable to feed sufficiently by mouth, as oral tecovirimat absorption is expected to be lower in these patients since bioavailability of oral tecovirimat is dependent on adequate intake of a full, fatty meal. Patients with gastric bypass or evidence of gastrointestinal disfunction that may negatively impact drug absorption may also be considered for treatment with IV tecovirimat. In the absence of an oral tecovirimat suspension formulation, IV tecovirimat may be considered for children weighing less than 13 kg based on clinical assessment of risk/benefit and if determined appropriate by the treating clinician in consultation with CDC.

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 is based on the clinical judgement of the treating clinician depending on the clinical progress of the patient.

2.2 Tecovirimat Ineligibility

- Patient or legally authorized representative unwilling to sign an informed consent and refuse tecovirimat treatment
- Known allergy to tecovirimat and/or inactive ingredients in tecovirimat
- For IV tecovirimat only: patients with severe renal impairment (creatinine clearance <30 mL/min). Oral tecovirimat is an option for patients with severe renal impairment.

3.0 PRODUCT DESCRIPTION

Tecovirimat (tecovirimat monohydrate) is an inhibitor of the orthopoxvirus VP37 envelope wrapping protein, which prevents the formation of egress-competent enveloped virions necessary for cell-to-cell and long-range dissemination of virus [10]. 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. Refer to tecovirimat Package Insert for additional details.

3.1 Tecovirimat Formulations

Tecovirimat is available as oral capsules and injection vials. 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.

Tecovirimat injection (200 mg/20 mL) single-dose vial contains tecovirimat monohydrate (unmicronized) equivalent to 200 mg tecovirimat and the excipient hydroxypropyl betadex (8000 mg) (hydroxypropyl-β-

cyclodextrin). The vial stopper is not made with natural rubber latex. Tecovirimat injection must be diluted with 2 parts 0.9% normal saline or 5% dextrose solution prior to infusion.

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

Tecovirimat injection vials should be stored at 2–8°C (36–46°F). Do not freeze. Short-term storage of maximum 24 hours at ambient temperature is acceptable. The immediate container/packaging of tecovirimat does not have a printed expiry date. To determine the expiration date, find the lot number on the product label and refer to the table on the following website to locate the corresponding expiration date: https://aspr.hhs.gov/SNS/Pages/Monkeypox.aspx.

4.0 DOSAGE AND ADMINISTRATION OF TECOVIRIMAT

Tecovirimat dosing for adults and children are as shown in Table 1 (oral) and Table 2 (IV) for 14 days of therapy. In certain clinical situations, modifications to the dose, frequency, and duration may be appropriate or necessary depending on the individual patient's clinical condition, disease progression, therapeutic response, and/or clinical judgement. For clinical decisions regarding dosing adjustments, contact the CDC (EOC (770) 488-7100; poxvirus@cdc.gov) for clinical consultation among the treating clinician(s), CDC, and FDA, if necessary.

4.1 Oral Therapy for Adults and Children

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. Treatment duration is 14 days but may be longer (not to exceed 90 days) or shorter depending on the progression of the disease and clinical condition of the patient. Data on duration other than 14 days are limited.
** 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. Opening tecovirimat capsules and mixing with food for children weighing < 13 kg, which **differs** from the FDA-approved tecovirimat package insert, is **allowed** under this IND protocol.

The adult dosing does not preclude pregnant or nursing individuals if careful clinical assessment of risk/benefit deems tecovirimat treatment appropriate per the treating clinician's clinical judgement (see **Section 6.0** for Special Populations).
PK information is not available for pediatrics. The pediatric doses are solely based on predicted exposures from population PK simulation predicted to provide pediatric patients with exposures comparable to the observed exposure in healthy adult volunteers receiving oral 600 mg doses twice daily. Oral doses less than 200 mg require careful preparation by a caregiver (e.g., opening a capsule and mixing portion of capsule contents with a food/liquid vehicle) and has the potential for inaccurate dosing. Suboptimal dosing increases the potential for development of resistance. Tecovirimat absorption may likely be decreased and result in potential suboptimal exposure in ill children, particularly young children, who are unable or unwilling to take a full meal prior to tecovirimat administration. **The potential for inaccurate dosing when opening capsules for doses below 200 mg may be higher in the outpatient setting**.

For inpatients (adults and children) unable to feed by mouth and have 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 IV infusion is not feasible (e.g., lack of syringe pumps).

4.1.1 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.

4.1.2 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) or shorter depending on the progression of the disease and clinical condition of the patient. Dose adjustments may be required per individual clinical considerations during the course of tecovirimat treatment.

4.1.3 Outpatients who are Unable to Swallow Capsules

For outpatients (adults and children) who require less than a 200 mg dose or who are unable to swallow capsules, treating clinicians should provide instructions on how to open capsules and mix with food (**Attachment 3)**. The dosing instructions for using less than 1 capsule (200 mg) have not been formally evaluated but are included to provide dosing options for younger age children, especially if IV tecovirimat is not available or feasible for administration.

4.2 IV Therapy for Adults and Children

IV tecovirimat is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min).

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]	Total Volume for Infusion
<35 kg[d]	< 77 lbs	6 mg/kg every 12 hours by IV infusion over 6 hours	0.6 mL/kg	1.2 mL/kg	Varies by weight
35 kg to <120 kg	77 to < 264 lbs	200 mg every 12 hours by IV infusion over 6 hours	20 mL	40 mL	60 mL
120 kg and above[f]	≥ 264 lbs	300 mg every 12 hours by IV infusion over 6 hours	30 mL	60 mL	90 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. Treatment duration may be longer (not to exceed 90 days) or shorter depending on the progression of the disease and clinical condition of the patient.

[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] IV tecovirimat dose of 6 mg/kg for children <3 kg is **allowed** under this IND protocol, which **differs** from the FDA-approved tecovirimat package insert. Individualized dosing may need to be considered depending on the neonate or infant weight and any underlying conditions. Pediatric doses are solely based on predicted exposures from population PK simulation based on observed exposure in healthy adult subjects receiving 600 mg oral doses twice daily.

[e] For children under 2 years of age: monitor renal function during the treatment course given the potential for drug accumulation due to renal immaturity of pediatric patients less than 2 years.

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

Based on currently available information, the infusion should be administered over 6 hours via syringe pump. The 6-hour duration of infusion is based on how the IV formulation was evaluated, observed transient ataxia in nonhuman primates dosed over 4 hours at 30 mg/kg, and to target optimal antiviral effect. The administration via syringe pump is based on available compatibility data for the formulation. Cyclodextrin in tecovirimat formulation has an elevated risk for potential leaching of impurities from

administration equipment into the solution during dosing. This has been mitigated through appropriate studies for syringe pumps. However, the risk has not been evaluated for IV bags.

4.2.1 Administration of IV Therapy

See the Package Insert for preparation and administration instructions. The volume of IV tecovirimat for the needed dose (Table 2) must be diluted with 2 equal parts 0.9% normal saline or 5% dextrose solution in prior to dosing in a syringe and should be administered via a syringe 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 clinicians should consult with CDC regarding the timing of transition to oral therapy and additional monitoring that may be needed to ensure adequate oral drug absorption.

4.4 Discontinuation of Tecovirimat

At any time during treatment, a patient may voluntarily discontinue or refuse tecovirimat treatment for any reason, treatment may be terminated due to serious adverse events (SAEs) or clinically significant abnormalities in laboratory values, or according to the clinical judgment of the treating clinician and/or appropriate health authority.

4.5 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 3** 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 3** provides a listing of established or significant drug interactions.

Table 3. 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
Central Nervous System 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 8.0** for required AE reporting). Document all AEs in the Adverse Event Form (**Attachment 2, Form B)**.

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 [11]. 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. See **Section 10.1** for more information on human safety, including adverse events to oral and IV tecovirimat.

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** for additional information.

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 orthopoxvirus infection and potential benefit of tecovirimat with the potential risks of this product.

6.1 Pregnancy

Tecovirimat has not been studied in pregnant individuals; 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 serious, and potentially 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 individuals have been conducted. Considering the serious, and potentially deadly, risks associated with orthopoxvirus infections (e.g., variola, vaccinia [including complications from smallpox vaccine or secondary exposure to a replication-competent smallpox-vaccinee], monkeypox, and cowpox), the potential benefits of treatment with oral or intravenous tecovirimat may outweigh the unknown risks associated with tecovirimat use during lactation. Because of the potential for virus transmission through direct contact with the breastfed infant, breastfeeding is not recommended while the nursing individual has active lesions. A lactating individual may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment.

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.

6.3 Pediatric Population

As in adults, the effectiveness of tecovirimat in pediatric patients is based solely on efficacy studies in animal models of orthopoxvirus disease. As exposure of healthy pediatric subjects to tecovirimat with no

potential for direct clinical benefit is not ethical, PK simulation was used to derive dosing regimens that are predicted to provide pediatric patients with exposures comparable to the observed exposure in adults receiving 600 mg twice daily. The dosage for pediatric patients is based on weight. In March 2007, SIGA provided tecovirimat to support an emergency investigational new drug application (E-IND) (No. 74,773) sponsored by the CDC for the treatment of a 28-month-old child with eczema vaccinatum. See **Section 10.2** for more information. Considering the serious, and potentially 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.

IV tecovirimat
There are limited data regarding the use of hydroxypropyl-β-cyclodextrin, an ingredient in IV tecovirimat, in pediatric patients < 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 during the treatment course is recommended.

6.4 Patients with Renal Impairment

Tecovirimat 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)].

IV tecovirimat:
IV tecovirimat is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min). 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.

7.0 CLINICAL ASSESSMENT AND MONITORING OF PATIENTS

Upon presentation, the patient should be thoroughly assessed per clinician's judgement to evaluate the potential need for tecovirimat. This may include a medical history, review of concomitant medications, and a physical examination with vital signs (e.g., weight, blood pressure, pulse, respiratory rate, temperature, and height). Clinical assessment and monitoring can be conducted in person or by **telemedicine**, whichever is feasible.

Treating clinicians or their designees will be responsible for patient follow-up, monitoring, and reporting collected information to CDC. The following report forms are required to be completed, retained, and/or returned to CDC:

- Obtain Informed Consent – **prior** to initiating tecovirimat treatment; provide a copy to the patient and retain a copy at the treating facility/institution. A copy does NOT need to be returned to CDC. *Only if* the signed informed consent forms cannot be maintained at the treating facility/institution, then they can be sent to CDC within 3 working days of tecovirimat initiation.
- Complete Form FDA 1572 and return to CDC within 3 working days of tecovirimat initiation.
- Patient Intake Form (**Attachment 2 – Form A**). Please return to CDC within 3 working days of tecovirimat initiation. The form includes fields for:
    - Medical history, baseline signs/symptoms, vital signs, concomitant medications
    - Clinical laboratory parameters, *if* performed per treating clinician's clinical judgment depending on patient's underlying condition, then attach a copy of clinical laboratory results (e.g., hematology, chemistry, urinalysis).
- Clinical Outcome Form (**Attachment 2 – Form B**). Please return to CDC within 3 working days of last patient follow-up. The form includes fields for:

- Progress of tecovirimat therapy and clinical outcomes, clinical labs (*if* performed based on clinical judgment depending on patient's underlying condition), and lesion/scab and serum samples (*if* collected).
- Occurrence of SAEs – if yes, reported by completing a fillable-PDF MedWatch Form (**Attachment 6**) and returning to CDC via email (regaffairs@cdc.gov) within 72 hours of awareness or sooner if possible. A fillable-PDF MedWatch Form can also be downloaded from MedWatch Forms for FDA Safety Reporting | FDA.

Optional lesion photos: If feasible, take lesion photos at baseline prior to tecovirimat treatment, and post-treatment to follow lesion progression and healing during treatment. When submitting photos, please indicate date the photo was taken, the corresponding tecovirimat treatment day, patient name or MRN, and treating facility.

Methods of returning the above information are:

- Secure Share File for lesion photos and large file sizes (please zip multiple files and use filenames with patient identifier, hospital name, and date): https://centersfordiseasecontrol.sharefile.com/r-r3941801ebcbd4002b4dfe98e314ec697
- Encrypted email: regaffairs@cdc.gov (personally identifiable information should not be emailed without encryption)
- Fax: 404-902-5921

For outpatients: If feasible, treating clinicians may provide a diary form (**Attachment 2 – Form C**) for patients to complete at home daily and voluntarily return it directly to CDC.

Optional Laboratory Testing

Under this IND program, the following laboratory testing are **not required** and optional per treating clinician's decision:

- Perform clinical laboratory testing (e.g., hematology, chemistry, urinalysis) per treating clinician's clinical judgment depending on the underlying clinical conditions to monitor the safety of tecovirimat treatment (e.g., baseline, during, or post treatment) as appropriate.
- Ideally, obtain a sample from at least 1 lesion prior to tecovirimat treatment but **only if** baseline diagnostic testing wasn't already performed. Ideally, obtain samples from **any new lesions** that develop during tecovirimat treatment or after completion of tecovirimat treatment for development of antiviral resistance mutations. Submit samples to CDC with CDC Form 50.34 and indicate Poxvirus Molecular Detection (CDC-10515) as the test order (code).
  See **Attachment 4** (Optional Lesion Samples to CDC for Resistance Testing) for collection and shipping instructions on information. The resistance testing at CDC is available if there is clinical suspicion of lower effectiveness (not resolving lesion, new lesions). Results will not be made available to guide individual patient management, but will be used for public health purpose of monitoring potential emergence of antiviral resistance.

  Serology testing at CDC is available if requested by the treating clinicians. Testing may be considered if there are concerns that the patient may not develop a normal immune response. Samples collected at baseline may be important for later interpretation.
- If feasible to participate in plasma pharmacokinetic sample(s) collection for testing at a designated laboratory (Alturas Analytics) to help inform drug exposure, see **Attachment 5** for instructions. Clinicians may consider prioritizing collection of PK samples from certain patients (e.g., pediatric or critically ill patients) whose drug exposure levels may need to be monitored. Results may not be

available in time for directly informing individual patient management, but would inform drug exposure levels of patients with orthopoxvirus infections.

Table 4. Summary of Clinical Assessment and Monitoring Parameters

Parameters \ Days	Pre-Tecovirimat Treatment [a]	During Tecovirimat Treatment [a]	Post Completion of Tecovirimat Treatment [a]
	Patient Intake Form (Attachment 2 -A)	Clinical Outcome Form (Attachment 2 -B)	
	Prior to first dose of Tecovirimat (≤ 24 hours)	Day 1-14	Outpatients: 7-10 Days after treatment completion Inpatients: Upon Discharge
Sign Informed Consent	x		
Inclusion/Exclusion Criteria	x		
Baseline clinical assessment[b]; Give patient the Diary form[c]	x		
Clinical progress	N/A	x	x
Serious Adverse Events[d]	N/A	x	x
Lesion Photos[b]	Optional	Optional (between days 7-14)	
Hematology, chemistry, urinalysis	Optional	Optional	Optional
Lesion samples	Optional	Optional (for any new lesions)	Optional (for any new lesions post-treatment)
PK samples		Optional	

[a] For outpatients, assessment may be conducted via **telemedicine**.

[b] Optional digital photos of lesions at baseline and during therapy (between days 7–14), if feasible.

[c] Give Patient Diary form (**Attachment 2C**) to the patient for completing and returning directly to CDC by the patient.

[d] SAEs must be reported by emailing a completed fillable-PDF MedWatch Form (**Attachment 6**) to CDC (regaffairs@cdc.gov) within 72 hours of awareness or sooner if possible.

8.0 RECORDING AND REPORTING ADVERSE EVENTS

8.1 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 clinician 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 clinician 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.

8.2 Treating Clinician Reporting Requirements to CDC

All SAEs must be reported. These include all SAEs that the patient reports spontaneously, those the clinician observes, and those the clinician elicits in response to open-ended questions. All SAEs, whether or not the treating clinician considers the event to be drug-related, must be reported by emailing a completed fillable-PDF MedWatch Form (**Attachment 6**) to CDC (regaffairs@cdc.gov) within 72 hours of awareness or sooner if possible.

8.3 CDC Reporting Requirements to FDA and CDC Institutional Review Board (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 312.32I(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.

9.0 REGULATORY AND ADMINISTRATIVE REQUIREMENTS

CDC, the sponsor of the IND, and all licensed healthcare providers who request and receive tecovirimat under this IND protocol will abide by the Code of Federal Regulations (in particular, 21 CFR Parts 50, 56, and 312). The IND protocol is subject to FDA's review and authorization as well as review and approval by an Institutional Review Board (IRB). CDC IRB serves as the central IRB for review and approval and of tecovirimat IND protocol, and has determined it non-research (i.e., does not constitute human subjects research per 45 CFR 46.102(l)). Therefore, participating sites may use CDC IRB's approval of this protocol that meets FDA's requirements regarding IRB review per 21 CFR Parts 50 and 56.

Any change or modification to the IND protocol that affects purpose, procedures, or significant data or administrative aspects of the program will require a formal amendment. Such amendments will be submitted to FDA for review and approved by the CDC IRB prior to implementation. Revised IND protocol and/or procedural modifications will be communicated by CDC to the clinicians and medical facilities participating in the tecovirimat treatment.

Data Management and Handling

IND case report forms (**Attachment 2**), laboratory results, visit summaries, hospital discharge summaries, medical records, etc., may be used as source documents. The information obtained through the case report forms of this IND protocol and additional supplemental information provided by treating clinicians 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 may also be provided to SIGA Technologies, Inc. and the Department of Health and Human Services/Biomedical Advanced Research and Development Authority (HHS/BARDA). Information about specific treating clinicians (i.e., names, CVs, or Form FDA 1572) and/or hospitals/sites may be shared with FDA, and local public health jurisdictions, and the manufacturer. Any information pertaining to treating clinicians and/or participating sites that are provided to the manufacturer is limited to use in the manufacturer's discussions with health authorities concerning this CDC-sponsored IND program.

Informed Consent

Informed consent in compliance with 21 CFR 50 must be obtained via the enclosed informed consent/permission form (**Attachment 1**) from the patient before tecovirimat is administered. If the patient is unable to give consent, consent can be obtained from the next-of-kin or legal guardian/representative.

A single consent form (**Attachment 1)** will be used to obtain informed consent/parental permission. 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 children aged 12–17 years (permission of only one parent is required). The ultimate responsibility for decision-making regarding treatment with tecovirimat in 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 clinician can make the determination to administer tecovirimat. The patient's treating clinician and a clinicians who is not otherwise participating in this expanded access IND program, will document on the

last page of the informed consent form (**Attachment 1**). Notify CDC via email (regaffairs@cdc.gov) within 3 working days of tecovirimat initiation when the treatment determination was made based on the mentioned certification by the treating and an independent clinician.

10.0 SUMMARY OF AVAILABLE SAFETY AND EFFICACY DATA OF TECOVIRIMAT

10.1 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 or non-variola orthopoxvirus 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.

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 5**.

Table 5. 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:

- Electroencephalogram 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 subjects (12%) 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 6**. 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 6. Adverse Reactions Reported in ≥ 4% of Healthy Adult Subjects receiving IV Tecovirimat At Least One Dose of IV Tecovirimat 240 mg

	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

10.2 Clinical Use of Tecovirimat in NV-OPXV-infected Patients (2007–2021)

No human efficacy data are currently available. However, prior to the 2022 monkeypox outbreak, oral tecovirimat was used under expanded access IND (EA-IND) to treat 7 cases in the United States (including one pediatric patient) and in at least 5 cases outside the United States. Three of the U.S. patients were treated under this protocol. The outcomes of the clinician uses described below suggest tecovirimat may provide clinical benefit in the treatment of orthopoxvirus infections.

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 [12]. 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 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 [13]. 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 [14]. 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 [15]. 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 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 [16]. Two days later, she developed fever, left axillary lymphadenopathy, malaise, pain, and worsening edema of her finger. 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 neurodermitis (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.
- In 2021, a patient who was part of a cluster of cases with monkeypox in the UK associated with travel from Nigeria was treated with a 2-week course of oral tecovirimat (600 mg twice daily) after

developing malaise, headache, pharyngitis, and vesicles on her thorax that were PCR positive for monkeypox [4]. The patient's blood and upper respiratory tract samples became PCR negative 48 hours after initiation of tecovirimat and remained negative at 72 hours. The patient did not develop new lesions 24 hours of tecovirimat therapy and reported no adverse effects after 2 weeks of tecovirimat treatment.

10.3 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.

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. Treatment with oral tecovirimat given at Day 4 and 5 post-challenge 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. See the Package Insert for more information.

10.4 Pharmacokinetics Data

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. 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 [10, 17]. For both oral and IV routes of administrations, accumulation is observed after repeated administration, and steady-state is achieved within 6 days. Refer to the Package Insert for PK parameters of tecovirimat.

11.0 REFERENCES

1. Reynolds, M.G., et al., *Clinical Manifestations of Human Monkeypox Influenced by Route of Infection.* The Journal of Infectious Diseases, 2006. **194**(6): p. 773-780.
2. Centers for Disease Control and Prevention, *Update: Multistate Outbreak of Monkeypox—Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin, 2003.* JAMA, 2003. **290**(3): p. 325-327.
3. Hobson, G., et al., *Family cluster of three cases of monkeypox imported from Nigeria to the United Kingdom, May 2021.* Euro Surveill, 2021. **26**(32).
4. Adler, H., et al., *Clinical features and management of human monkeypox: a retrospective observational study in the UK.* Lancet Infect Dis, 2022.
5. Vaughan, A., et al., *Two cases of monkeypox imported to the United Kingdom, September 2018.* Euro Surveill, 2018. **23**(38).
6. Rao, A.K., et al., *Monkeypox in a Traveler Returning from Nigeria - Dallas, Texas, July 2021.* MMWR Morb Mortal Wkly Rep, 2022. **71**(14): p. 509-516.
7. Costello, V., et al., *Imported Monkeypox from International Traveler, Maryland, USA, 2021.* Emerg Infect Dis, 2022. **28**(5): p. 1002-1005.
8. Smith, S.K., et al., *Effective antiviral treatment of systemic orthopoxvirus disease: ST-246 treatment of prairie dogs infected with monkeypox virus.* J Virol, 2011. **85**(17): p. 9176-87.
9. Sbrana, E., et al., *Efficacy of the antipoxvirus compound ST-246 for treatment of severe orthopoxvirus infection.* Am J Trop Med Hyg, 2007. **76**(4): p. 768-73.
10. SIGA Technologies, Inc. TPOXX Prescribing Information. Accessed 19 July 2022]; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208627s007lbl.pdf

11. Russo, A.T., et al., *Co-administration of tecovirimat and ACAM2000 in non-human primates: Effect of tecovirimat treatment on ACAM2000 immunogenicity and efficacy versus lethal monkeypox virus challenge.* Vaccine, 2020. **38**(3): p. 644-654.
12. Vora, S., et al., *Severe eczema vaccinatum in a household contact of a smallpox vaccinee.* Clin Infect Dis, 2008. **46**(10): p. 1555-61.
13. Lederman, E.R., et al., *Progressive Vaccinia: Case Description and Laboratory-Guided Therapy With Vaccinia Immune Globulin, ST-246, and CMX001.* J Infect Dis, 2012. **206**(9): p. 1372-85.
14. Centers for Disease, C. and Prevention, *Human vaccinia infection after contact with a raccoon rabies vaccine bait - Pennsylvania, 2009.* MMWR Morb Mortal Wkly Rep, 2009. **58**(43): p. 1204-7.
15. Lindholm, D.A., et al., *Preemptive Tecovirimat Use in an Active Duty Service Member Who Presented With Acute Myeloid Leukemia After Smallpox Vaccination.* Clin Infect Dis, 2019. **69**(12): p. 2205-2207.
16. Whitehouse, E.R., et al., *Novel Treatment of a Vaccinia Virus Infection from an Occupational Needlestick - San Diego, California, 2019.* MMWR Morb Mortal Wkly Rep, 2019. **68**(42): p. 943-946.
17. Chen, Y., et al., *Comparison of the safety and pharmacokinetics of ST-246(R) after i.v. infusion or oral administration in mice, rabbits and monkeys.* PLoS One, 2011. **6**(8): p. e23237.