****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 116,039

CDC IRB #6402

Version 6.4

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[Changes from the prior version (v6.3 dated December 19, 2023) to the current protocol (v6.4 dated June 5, 2024) include Section 2.0 on updated eligibility criteria for tecovirimat treatment for mpox; Section 10.2 revised to reflect the updated clinical use experience information on tecovirimat; Informed Consent, Patient Intake and Clinical Outcome Forms updated to reflect relevant changes to the protocol]

Sponsored by:

Centers for Disease Control and Prevention

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ATTACHMENTS

Report serious adverse events and **selected adverse events of interest** by completing a fillable-PDF MedWatch Form and returning to CDC via email (regaffairs@cdc.gov) within 72 hours of occurrence or sooner (See Section 7.0).

1.0 INTRODUCTION AND BACKGROUND

Orthopoxviruses (OPXVs) belonging to the *Poxviridae* family that infect humans are variola virus, vaccinia virus (the virus in smallpox vaccine ACAM2000 and smallpox/mpox vaccine Jynneos), monkeypox virus (MPXV), cowpox virus, Akhmeta virus and Borealpox virus (formerly referred to as 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 mpox (previously known 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 (NVOPXV) 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 NVOPXV infections by a healthcare professional who may be less familiar with these infections. There are two genetic clades of MPXV: Clade I and Clade II, which have been historically found in central and west Africa, respectively, with only Cameroon reporting both clades [1]. An increased number of mpox cases have been reported in the Democratic Republic of Congo (DRC) since January 2023 where clade 1 MPXV has been confirmed among the cases tested [2].

The 2022 global mpox (Clade IIb) outbreak that emerged with sudden, simultaneous cases of human mpox in countries without historical transmission or prior reports of mpox underscored the risk of spread of MPXV beyond its normal endemic region and the potential for sustained local transmission. Over 94,000 mpox cases had been reported from 117 countries as of February 2024 [3].
Prior to this unprecedented multinational mpox outbreak, reported mpox cases in nonendemic areas had been limited; traveler-associated cases infected in the endemic country that were diagnosed in non-African countries (United Kingdom, Israel, Singapore) during 2018-2021, and 47 confirmed or probable cases from exposure to MPXV-infected, imported prairie dogs in the United States (U.S.) in 2003 [4-9].

During the 2022 mpox outbreak response in the U.S., there were over 32,000 cases with low mortality (<0.2%) [10]. The majority of reported cases were men who identify as gay, bisexual or men who have sex with other men while anyone, regardless of sexual orientation or gender identity, who has been in close contact with someone with mpox is at risk [11]. To contain the transmission, vaccine campaigns have been ongoing as it is the key modality for prevention of OPXV infections. There are 2 vaccines approved by the Food and Drug Administration (FDA) for OPXV infections: 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 and commercially available for smallpox and mpox in adults 18 years and older). Vaccination, however, must occur either before or soon after exposure to be effective in preventing or reducing the seriousness of the disease caused by OPXV infections. During an outbreak, effective therapeutic options are also necessary for treatment of mpox and potential complications from replication-competent vaccinia vaccine.

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

Currently, there is no treatment approved by the FDA for NVOPXV infections, including MPXV. Tecovirimat is FDA-approved only for treatment of smallpox in adults and children based on 2 lethal animal models that showed survival benefit over placebo and human safety data in healthy adults.

Although the effectiveness of tecovirimat in treating humans with NVOPXV infections, including mpox, has not yet been established, there are ongoing clinical trials to evaluate the efficacy of tecovirimat in

human mpox. Tecovirimat has been shown to be effective against various orthopoxviruses in multiple animal challenge models [13, 14]. While there are uncertainties with whether and how the animal efficacy may translate into humans, it may be reasonable to anticipate potential treatment benefit.

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 NVOPXV infection in adults and children.

2.0 PROGRAM OBJECTIVE

Since tecovirimat use for any indication other than treatment of smallpox is unapproved (investigational), this expanded access IND (compassionate use) program is to provide stockpiled tecovirimat for treatment of NVOPXV infections, caused by mpox, vaccinia (including complications from replication-competent vaccinia virus vaccine), or other human viruses identified as NVOPXV, in persons who meet eligibility for tecovirimat treatment under the IND.

To monitor clinical use of tecovirimat under this expanded access IND (EA-IND) program, baseline patient characteristics, clinical progression, and occurrence of serious adverse events and/or selected adverse events of interest, are intended to be collected through the treating provider's completion of required Patient Intake and Clinical Outcome forms and reporting of SAEs. Please refer to **Section 7.0** Clinical Assessment and Monitoring of Patients.

2.1 Tecovirimat Eligibility

2.1.1 Treatment of Mpox

Oral tecovirimat is also available through a clinical trial called Study of Tecovirimat for Mpox (STOMP), sponsored by the National Institutes of Health. It is actively recruiting and enrolling patients with mpox to evaluate the efficacy and safety of tecovirimat for mpox. Providers **should** inform patients about STOMP for their consideration of voluntary enrollment in this study. **Most non-pregnant or non-lactating adults without severe immunocompromised conditions** or **active skin conditions** (as defined below) **are not eligible** to receive tecovirimat for treatment of mpox under this EA-IND protocol; tecovirimat for these patients is available via enrollment in the randomized arm of STOMP where two-thirds receive tecovirimat.

Use of tecovirimat under this EA-IND protocol is for patients with laboratory-confirmed or suspected* mpox **who meet the eligibility criteria as described below.**

1. Patients with severely immunocompromised condition(s) defined as:
    - HIV with CD4 < 200 cells/mm^3
    - Leukemia or lymphoma
    - Generalized malignancy
    - Solid organ transplantation
    - Therapy with alkylating agents within 180 days prior to mpox illness onset
    - Antimetabolites within 180 days prior to mpox illness onset
    - Radiation therapy within 180 days prior to mpox illness onset
    - Tumor necrosis factor inhibitors within 180 days prior to mpox illness onset
    - High-dose corticosteroids (equivalent of 20 mg or greater of prednisone for at least 14 days) within 90 days prior to mpox illness onset
    - Being a recipient with hematopoietic stem cell transplant < 24 months post-transplant or ≥ 24 months but with graft-versus-host disease or disease relapse, or having autoimmune disease with immunodeficiency as a clinical component
    - Other comparable severe immunocompromising condition

* Meets one of the epidemiologic criteria and has a high clinical suspicion for mpox per CDC Case Definitions for Use in the 2022 Mpox Response

Persons with severe immunocompromise are known to be at high risk for protracted or life-threatening manifestations of mpox regardless of disease severity at presentation.

2. Patients in the following categories:
   a) Persons with active skin conditions placing the person at higher risk for disseminated infection defined as: atopic dermatitis; active exfoliative skin condition(s) such as eczema, burns, impetigo, active varicella zoster virus infection, psoriasis, or Darier disease (keratosis follicularis)
   b) Pregnant or lactating individuals, regardless of illness severity or underlying comorbidities at presentation
   c) Children (< 18 years), regardless of illness severity or underlying comorbidities at presentation

   These patients might be at high risk for protracted or life-threatening manifestations of mpox based on prior experience from other orthopoxvirus infections in humans.

3. Patients with protracted or life-threatening manifestations of mpox at presentation as defined by one of the following:
   - Lesions affecting ≥ 25% of body surface that may be confluent, necrotic, and/or hemorrhagic in appearance or cause sepsis
   - Disease resulting in airway compromise or affecting the nervous system
   - Cardiac (e.g., myocarditis) and/or neurologic disease (e.g., encephalitis) which might occur in a small number of patients with mpox
   - Ocular or periorbital infection, regardless of the time since infection onset

   Because the full scope of protracted or life-threatening mpxv infections is not known at this time, tecovirimat may also be considered on a **case-by-case basis** for an unusual situation wherein CDC consult team and/or CDC Principal Investigator in discussion with the treating clinician deem treatment under the EA-IND may potentially be beneficial; such consideration is expected to be rare and intended for unusual situations associated with disease that could result in clear long-term sequelae (e.g., urethral stricture).

Patients with mpox who meet the above-mentioned EA-IND eligibility for tecovirimat treatment may also be eligible for oral tecovirimat through the open-label tecovirimat arm of NIH's STOMP study. The EA-IND eligibility criteria are closely aligned with the STOMP open-label arm's eligibility criteria regarding those with severe immunocompromise, pregnant or lactating persons, and children. However, the prolonged or life-threatening manifestations of mpox listed above for tecovirimat treatment under the EA-IND protocol are narrower than STOMP's definition of severe disease for enrollment in their open-label tecovirimat arm.

Each patient receiving tecovirimat must be laboratory-confirmed. Patients with an initial negative test result, but for whom both epidemiologic and clinical evidence suggests mpox, should be re-tested; tecovirimat can continue while results are pending. If results from re-testing confirm OPXV/MPXV, patients should complete tecovirimat treatment. If the re-testing is consistent with the initial OPXV/MPXV-negative result, tecovirimat should be suspended in those patients.

The earliest optimization of immune function is critical to clearing MPXV from infected cells (e.g., initiating effective HIV antiretroviral therapy, delaying immunosuppressive therapies). For patients with protracted or life-threatening manifestations or at high risk for protracted or life-threatening manifestations of mpox due to severe immunocompromising conditions, tecovirimat treatment should be administered early in the course of illness along with supportive care and pain control. It may also be

reasonable to consider initiating tecovirimat treatment in these patients in combination with either IV cidofovir or oral brincidofovir (the prodrug of cidofovir) and/or Vaccinia Immune Globulin (VIGIV). While brincidofovir and IV cidofovir should not be used concurrently, a one-week drug holiday is not necessary when transitioning between IV cidofovir or brincidofovir.[§] IV cidofovir is commercially available; USG stockpiled brincidofovir and VIGIV are available upon request for patients with protracted or life-threatening manifestations of mpox or severe immunocompromising conditions. For brincidofovir, clinicians can submit an e-IND request to FDA for individual patients. To request VIGIV, contact the CDC Clinical Consultation Team by email (poxvirus@cdc.gov) during business hours or CDC Emergency Operations Center (770) 488-7100.

In immunocompromised patients, antiviral effect may be reduced as animal studies showed reduced efficacy of tecovirimat or brincidofovir alone in immunocompromised animal models. While limited, one animal study suggests concomitant tecovirimat and brincidofovir treatment might have synergistic effect [15]. VIGIV provides passive immunoglobulin G antibodies against vaccinia virus that might provide some cross-protection to severely immunocompromised, hospitalized patients with mpox.

2.1.2 Treatment of NVOPXV Infections Other than Mpox

- Patients with other laboratory-confirmed NVOPXV infections such as vaccinia, cowpox, Akhmeta or Borealpox (formerly Alaskapox) virus or suspected infection based on known exposure(s) and clinical manifestations of disease while laboratory confirmation is pending. Each patient receiving tecovirimat must be laboratory-confirmed. Patients with an initial OPXV-negative result, but for whom both epidemiologic and clinical evidence suggests OPXV disease, should be re-tested; tecovirimat can continue while results are pending. If results from re-testing confirm OPXV, patients should complete tecovirimat treatment. If the re-testing is consistent with the initial OPXV-negative result, tecovirimat should be suspended in those patients.

- Patients with complications from replication-competent vaccinia virus vaccination with ACAM2000 (e.g., serious inadvertent inoculation with vaccinia, eczema vaccinatum, severe generalized vaccinia, or progressive vaccinia), or secondary transmission from close contact with the vaccinee are eligible for treatment with tecovirimat. Tecovirimat may be used if a patient is ineligible for Vaccinia Immune Globulin Intravenous (VIGIV) treatment, after VIGIV treatment has been exhausted, or in conjunction with VIGIV and/or other therapies depending on the severity of the disease or risk of severe disease based on the treating clinician's clinical judgment in consultation with CDC. For information on smallpox vaccine adverse events, see https://www.cdc.gov/smallpox/clinicians/vaccine-adverse-events5.html

2.1.3 Post-exposure prophylaxis (PEP) for NVOPXV Infection

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) depending on the known high-risk exposure to NVOPXV (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 (e.g., severe allergic reaction to vaccine or vaccine components, immunocompromising conditions).

2.1.4 Considerations for IV tecovirimat

IV tecovirimat should be considered for adult and pediatric patients who meet EA-IND eligibility for treatment and are unable to take oral therapy or for whom there is a concern that oral drug absorption may be altered. 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

[§] Based on available information on the concentrations of plasma cidofovir and its relevance to the toxicity of concern (nephrotoxicity)

of gastrointestinal dysfunction that may negatively impact drug absorption may also be considered for IV tecovirimat. For patients with severe renal impairment (creatine clearance [CrCl] < 30 mL/min), IV tecovirimat is contraindicated due to potential accumulation of hydroxypropyl-β-cyclodextrin (HP-β-CD), an excipient in the IV tecovirimat formulation which is eliminated through glomerular filtration. Therefore, enteral administration of oral tecovirimat should be exhausted in renally impaired patients, and IV tecovirimat should not be administered in patients with CrCl < 30 mL/min. Exceptions may be considered ***only*** if drug absorption via enteral administration is not anticipated to be dependable or feasible, and based on individual patient risk-benefit assessment by the treating clinician to determine IV tecovirimat as clinically necessary in consultation with CDC. In these instances, IV tecovirimat use must be with caution and close continuous monitoring of renal function. See **Section 2.2** Tecovirimat Ineligibility.

In the absence of an oral tecovirimat suspension formulation, IV tecovirimat may be considered for pediatric patients weighing less than 13 kg based on clinical assessment of risk-benefit and if determined appropriate by the treating clinician in consultation with CDC. Opening the capsule and mixing the entire capsule contents with 20 mL of water to measure the right amount of drug-water mixture to give is an alternative option for younger children weighing less than 13 kg (see **Table 4.1**), which is allowed under the IND. However, oral doses less than a full capsule content (200 mg) require careful preparation by a caregiver and have the inherent potential for inaccurate dosing. Refer to Instructions for Opening and Mixing Tecovirimat Capsules with Water or Food for Those Who Cannot Swallow Pills, Especially Infants and Children (Attachment 3) for detailed preparation instructions.

Patients who receive IV tecovirimat should be switched to the oral tecovirimat capsules as soon as they are able to take oral medications and/or gastrointestinal dysfunction 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 is unwilling to sign an informed consent and/or refuses tecovirimat treatment.
- Known allergy to tecovirimat and/or inactive ingredients in tecovirimat.
- For IV tecovirimat only: patients with severe renal impairment (CrCl <30 mL/min)*. Oral tecovirimat is an option for patients with severe renal impairment.

Note**: IV tecovirimat has a labeled contraindication in patients with CrCl < 30 mL/min. Exceptions may be considered ***only if drug absorption via enteral administration is not anticipated to be dependable or feasible, and based on individual patient risk-benefit assessment by the treating clinician to determine IV tecovirimat as clinically necessary in consultation with CDC. In these instances, IV tecovirimat use must be with caution and close continuous monitoring of renal function.

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 [16]. 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, mpox, 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 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 (200 mg/20 mL) single-dose vial contains tecovirimat monohydrate (unmicronized) equivalent to 200 mg tecovirimat and the excipient HP-β-CD 8000 mg. The vial stopper is not made with natural rubber latex and there are typically 7 vials packaged per carton. Tecovirimat injection must be diluted with 2 parts 0.9% normal saline or 5% dextrose solution prior to infusion. 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** as expiry extensions may occur. 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/mpox.aspx. Refer to this website to check the expiry dates for both oral and IV tecovirimat by lot #s.

4.0 DOSAGE AND ADMINISTRATION OF TECOVIRIMAT

The specific recommended dose and dosing interval (i.e., number of doses that should be administered each day) are described for adults and children in Table 1 and Table 2 respectively. The standard duration of tecovirimat treatment is 14 days.

In certain clinical situations involving patients with severe immunocompromise who have ongoing onset of new lesions or worsening lesions, extending the duration of tecovirimat beyond the standard 14-day course at the standard dose and dosing interval per Tables 1 and 2 may potentially be necessary. Treating providers should only consider extending the duration at the standard tecovirimat dose and dosing interval on a case-by-case basis and after a careful consideration of the risks and benefits. The safety and efficacy data for treatment courses beyond 14 days are limited; however, patients with severe immunocompromise may benefit from extended courses when new or progressively worsening lesions occur despite a 14-day tecovirimat course.

Extending the duration of tecovirimat courses beyond 14 days is permissible based on the treating provider's clinical judgement of the potential benefits and harms and should be reported to CDC by completing the Clinical Outcome form. In contrast, **no changes can be made to the standard dose and/or dosing interval without prior CDC approval**; CDC must **be consulted before such changes are permitted**. Administration of a non-standard tecovirimat dose and/or dosing interval is a protocol deviation. If this inadvertently occurs without obtaining prior-approval from CDC, it must be reported to CDC immediately. For consultations about a modified dose and/or dosing interval (i.e., one that is different from the standard dosing regimen outlined in Tables 1 and 2 in Sections 4.1 and 4.2 below), contact the CDC mpox consultant 24 hours a day / 7 days a week at (770) 488-7100.

4.1 Oral Therapy for Adults and Children

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.

Table 1. Recommended Oral Dosage Instructions for 14 Days[a,b]

Weight (kg)	Weight (lbs)	Recommended Dose (mg)	Drug-Water or Drug-Food Preparation for Patients Who Cannot Swallow Capsules (see Attachment 3)[c,d]
< 3 kg	< 7 lbs	33.3 mg every 12 hours	Carefully open 1 capsule and empty the entire contents into a dosing cup of suitable size. Add 20 mL of water to the dosing cup and **thoroughly mix by swirling the cup for at least 30 seconds until there are no clumps**. **Do not use a spoon or any other utensil to mix**. Immediately after mixing, use an oral syringe to draw up and **administer 3.3 mL of the water and drug mixture**. Discard the remaining mixture. Give this amount 2 times each day, making a new mixture for each dose. Note: Dosing should be followed by a feeding.
3 kg to < 6 kg	7 lbs to < 13 lbs	50 mg every 12 hours	Carefully open 1 capsule and empty the entire contents into a dosing cup of suitable size. Add 20 mL of water to the dosing cup and **thoroughly mix by swirling the cup for at least 30 seconds until there are no clumps. Do not use a spoon or any other utensil to mix**. Immediately after mixing, use an oral syringe to draw up and **administer 5 mL of the water and drug mixture**. Discard the remaining mixture. Give this amount 2 times each day, making a new mixture for each dose. Note: Dosing should be followed by a feeding.
6 kg to < 13 kg	13 lbs to < 28 lbs	100 mg every 12 hours	Carefully open 1 capsule and empty the entire contents into a dosing cup of suitable size. Add 20 mL of water to the dosing cup and **thoroughly mix by swirling the cup for at least 30 seconds until there are no clumps. Do not use a spoon or any other utensil to mix**. Immediately after mixing, use an oral syringe to draw up and **administer 10 mL of the water and drug mixture**, either directly or mixed in a small amount of soft food (e.g., apple sauce, yogurt). Discard the remaining mixture. Give this amount 2 times each day, making a new mixture for each dose. Note: Dosing should be followed by a feeding.
13 kg to < 25 kg	28 lbs to < 55 lbs	200 mg (1 capsule) every 12 hours	Carefully open the required number of capsules and mix contents of capsule(s) with 30 mL of liquid (e.g., milk, chocolate milk, water) or soft

Weight (kg)	Weight (lbs)	Recommended Dose (mg)	Drug-Water or Drug-Food Preparation for Patients Who Cannot Swallow Capsules (see Attachment 3)[c,d]
			food (e.g., apple sauce, yogurt). Administer the entire mixture within 30 minutes of preparation.
25 kg to < 40 kg	55 lbs to < 88 lbs	400 mg (2 capsules) every 12 hours	Carefully open the required number of capsules and mix contents of capsule(s) with 30 mL of liquid (e.g., milk, chocolate milk, water) or soft food (e.g., apple sauce, yogurt). Administer the entire mixture within 30 minutes of preparation.
40 kg to < 120 kg	88 lbs to < 264 lbs	600 mg (3 capsules) every 12 hours	Carefully open the required number of capsules and mix contents of capsule(s) with 30 mL of liquid (e.g., milk, chocolate milk, water) or soft food (e.g., apple sauce, yogurt). Administer the entire mixture within 30 minutes of preparation.
120 kg and above	≥ 264 lbs	600 mg (3 capsules) every 8 hours	Carefully open the required number of capsules and mix contents of capsule(s) with 30 mL of liquid (e.g., milk, chocolate milk, water) or soft food (e.g., apple sauce, yogurt). Administer the entire mixture within 30 minutes of preparation.

[a] For patients weighing ≥ 13 kg, tecovirimat capsules should be taken within 30 minutes after a full meal containing moderate or high fat. For pediatric patients weighing < 13 kg, tecovirimat dose should be followed by a feeding. **The standard treatment duration is 14 days**. Based on the risk-benefit assessment of individual patients and depending on the disease progression, tecovirimat treatment may be extended beyond 14 days or shortened due to lack of virologic or clinical response, or occurrence of adverse events. Data on duration other than 14 days are limited.

[b] **No changes can be made to the standard dose and/or dosing interval without prior CDC approval**. CDC must **be consulted before such changes are permitted**. Administration of a non-standard tecovirimat dose and/or dosing interval is a protocol deviation that must be reported immediately to CDC should it inadvertently occur without obtaining prior-approval from CDC.

[c] Opening tecovirimat capsules and mixing in water for children weighing < 13 kg, which **differs** from the FDA-approved tecovirimat package insert, is **allowed** under this IND protocol.

[d] Use of water for oral dose preparation and administration is not in the FDA-approved labeling but 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 the capsule contents in water, then administering a portion of the drug-water preparation) and has the inherent 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**.

4.1.1 Duration of Oral Therapy

The standard duration of tecovirimat treatment for patients of all ages is 14 days. Data on duration other than 14 days are limited. Potential adjustments to duration of tecovirimat treatment may be necessary per individual clinical considerations. Based on the risk-benefit assessment of individual patients and

depending on the disease progression, oral tecovirimat treatment may be extended beyond 14 days or shortened due to lack of virologic or clinical response and/or occurrence of adverse events. Tecovirimat treatment beyond the standard 14-day course may be considered at short increments of extension (e.g., an additional 3–7 days) at a time while monitoring for clinical improvement or lack of response and adverse events to reassess continuing or stopping tecovirimat treatment accordingly. Tecovirimat resistance has been detected in a small number of patients with advanced HIV who received tecovirimat for durations of weeks to months [16-23]. In the 3-month general toxicology studies with oral (gavage) tecovirimat in mice and monkeys, no adverse, drug-related findings were observed [24].

4.1.2 Patients who are Unable to Swallow Capsules

For children who require less than a 200 mg dose or adults who are unable to swallow capsules being treated as outpatients, treating clinicians should provide instructions on how to open capsules and mix in water or 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.

For pediatric and adult inpatients unable to feed by mouth and with no evidence of gastrointestinal dysfunction, tecovirimat may be administered via a nasogastric tube (NGT) per hospital protocol based on clinical judgment of individual patients if IV tecovirimat is unavailable or IV infusion is not feasible (e.g., renally impaired patient, lack of syringe pumps). Although NGT administration is allowed under the IND to provide an alternative option in case of limited supply of IV tecovirimat or if infusion is not feasible, compatibility studies on enteral administration of tecovirimat have not been conducted.

4.2 IV Therapy for Adults and Children

Due to potential accumulation of HP-β-CD, an excipient in the IV tecovirimat formulation which is eliminated through glomerular filtration, FDA-approved package insert contraindicates IV tecovirimat in patients with CrCl <30 mL/min. Oral tecovirimat option should be exhausted, including enteral administration via NG tube. See **Section 2.2** Tecovirimat Ineligibility.

Tecovirimat injection vials should be stored at 2-8˚C (35-46˚F). IV tecovirimat must be diluted prior to administration. See the package insert for additional details.

- Withdraw the volume of tecovirimat injection solution corresponding to the dose in Table 2. Add this volume to a suitable size syringe. Then dilute by adding 2 equal parts of either 0.9% normal saline or 5% dextrose solution to the syringe containing tecovirimat solution.
- Gently swirly the syringe of in-use solution prior to inserting into the syringe pump and infuse over 6 hours.
- The diluted IV tecovirimat should be administered immediately upon preparation and must be used within 24 hours of preparation if stored at 2-8˚C (35-46˚F).

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

Weight (kg)	Weight (lbs)	Recommended Dose	Volume of IV Tecovirimat[c]	Volume of Diluent[d]	Total Volume for Infusion
< 35 kg[e,f]	< 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[g]	≥ 264 lbs	300 mg every 12 hours by IV infusion over 6 hours	30 mL	60 mL	90 mL

[a] FDA-approval of IV tecovirimat is for a 14-day treatment course of a life-threatening indication of smallpox.

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

[b] **No changes can be made to the standard dose and/or dosing interval without prior CDC consultation**. CDC must **be consulted before such changes are permitted**. Administration of a non-standard tecovirimat dose and/or dosing interval is a protocol deviation that must be reported immediately to CDC should it inadvertently occur without obtaining prior-approval from CDC.

[c] 10 mg/mL stock solution containing 40% hydroxypropyl-β-cyclodextrin (8 g per vial) with water for injection.

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

[e] 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.

[f] 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.

[g] 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. Due to the high content of the inactive ingredient hydroxypropyl-β-cyclodextrin in IV tecovirimat formulation (8 gm HP-β-CD per 200 mg tecovirimat injection vial), there is an elevated risk for potential leaching of impurities into the solution during preparation and administration when equipment other than syringes/syringe pumps are used. This has been mitigated through appropriate studies for syringe pumps. Therefore, the use of empty or prefilled infusion bags are not recommended for use with IV tecovirimat. The manufacturer recommends against the use of glass IV bottles for preparation and administration of IV tecovirimat (see SIGA's Dear Healthcare Provider letter at https://www.siga.com/wp-content/uploads/2022/08/NDA_Final.pdf).

4.2.1 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 dysfunction 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, and any 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, or treatment may be stopped or paused due to serious adverse events (SAEs), clinically significant abnormalities in laboratory values, or per the clinical judgment of the treating clinician and/or appropriate health authority.

4.5 Drug-Drug Interactions

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**

3a for clinical recommendations for select sensitive substrates. Co-administration of tecovirimat with repaglinide may cause hypoglycemia. Monitor blood glucose and monitor for hypoglycemic symptoms during co-administration.

Table 3a. 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.

Based on a drug interaction study, no clinically significant drug interactions have been observed when tecovirimat is co-administered with bupropion, flurbiprofen, or omeprazole.

While no clinical drug-drug interaction studies have been conducted between antiretroviral drugs and tecovirimat, based on FDA assessment of drug interaction study results with other drugs, no dose adjustments are needed when tecovirimat is co-administered with rilpivirine, doravirine, or maraviroc. However, Cabenuva (long-acting cabotegravir and rilpivirine kit) should not be initiated during tecovirimat treatment and for 2 weeks after completion of tecovirimat treatment (**Table 3b**). For more information, see: https://www.cdc.gov/mmwr/volumes/71/wr/mm7132e4.htm?s_cid=mm7132e4.

Table 3b. Antiretroviral Drug Interactions

Concomitant Drug Name	Clinical Effect/Recommendation
Cabenuva (long-acting cabotegravir and rilpivirine kit)	Avoid initiation of Cabenuva during tecovirimat treatment and within 2 weeks post tecovirimat treatment
Rilpivirine	No dose adjustment needed
Doravirine	No dose adjustment needed
Maraviroc	No dose adjustment needed

A complete list of concomitant medications and medication history should be reviewed when starting a patient on tecovirimat treatment, and clinicians should monitor for potential drug-drug interactions accordingly. Any SAEs that occur must be reported by returning a completed MedWatch form to CDC (see **Section 8.0** for required SAE reporting and definitions of AEs).

No vaccine-drug interaction studies have been performed in human subjects. Studies in mice and non-human primates have indicated that tecovirimat co-administered with live smallpox vaccine (vaccinia virus) may reduce the immune response to the vaccine [16, 25]. 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 HP-β-CD exposure, IV tecovirimat has a labeled contraindication in patients with severe renal impairment (CrCl <30 mL/min). IV tecovirimat in

patients with decreased renal function, including severe, moderate (defined as CrCl 30-49 mL/min) and mild (defined as CrCl 50-80 mL/min), should be used with caution, monitoring of renal function, and considered on a case-by-case determination by the treating clinician based on clinical judgment of the risk/benefit for the patient. Serum creatinine levels should be closely monitored and, if renal toxicity is suspected, consideration should be given to switching to oral tecovirimat as soon as feasible. 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], mpox, 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], mpox, 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. 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], mpox, 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 HP-β-CD, 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 has a labeled contraindication in patients with severe renal impairment (CrCl <30 mL/min) because of the potential risk of HP-β-CD accumulation, which is removed by glomerular filtration. Renal function and laboratory values should be monitored during IV tecovirimat treatment, especially in patients with decreased renal function.

7.0 CLINICAL ASSESSMENT AND MONITORING OF PATIENTS

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

Tecovirimat (TPOXX) IND Registry and Access to the Secure Electronic Patient Intake and Clinical Outcome Forms

- All providers must register as participating providers under the CDC-held EA-IND protocol by completing the Tecovirimat (TPOXX) IND Online Registry for Providers/Facilities. The registry includes an online Form FDA 1572. Providers should register **prior to** providing tecovirimat treatment to the extent feasible and **no later** than 7 calendar days of first prescribing or administering tecovirimat. A TPOXX IND registry factsheet was also posted that provides step-by-step instructions on completing the Tecovirimat (TPOXX) IND Online Registry for Providers/Facilities.
- The required **Patient Intake** and **Clinical Outcome forms** are available electronically for completion and submission to CDC for each patient treated with tecovirimat through the Tecovirimat (TPOXX) IND Online Registry for Providers/Facilities. Because these forms involve providing personally identifiable information, they are not publicly posted. Rather, access to the secure externally facing electronic forms will be sent v**ia email to registered providers.** Please be informed that system-generated emails containing a **tokenized link** for each electronic form (e.g., Patient Intake Form and Clinical Outcome Form) will be sent to registered **provider's email address from** "CDC TPOXX IND <noreply dcipher@cdc.gov>."

Treating clinicians or their designees will be responsible for patient assessment, monitoring, and reporting information to CDC. The following 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 and there are no other suitable means to store/retain the documents, then they may be sent to CDC within 7 calendar days of tecovirimat initiation.
- Register online (required for new providers only) – All new providers must register as participating providers by completing the Tecovirimat (TPOXX) IND Online Registry for Providers/Facilities prior

to providing tecovirimat treatment to the extent feasible and **no later** than 7 calendar days of first prescribing or administering tecovirimat.

- **Complete** the electronic **Patient Intake form:** For each patient who is prescribed and treated with tecovirimat, complete the electronic Patient Intake form as soon as feasible and **no later** than 7 calendar days of prescribing or initiating therapy. For patients who are being re-initiated on tecovirimat treatment after completing a prior tecovirimat treatment course (e.g., relapse of infection, recrudescence), a new Patient Intake form should be completed and returned to CDC. The relevant information may include:
    - Medical history, baseline signs/symptoms, vital signs, concomitant medications
    - Relevant clinical laboratory results if performed per treating clinician's clinical judgment depending on patient's underlying condition
- **Complete** the electronic **Clinical Outcome Form**: For each patient treated with tecovirimat, a follow-up should be conducted within 3–7 calendar days of completing tecovirimat treatment and complete the electronic Clinical Outcome form. The relevant information may include:
    - Tecovirimat treatment information, patient's progress, lesion status, and relevant clinical laboratory information if performed per treating clinician's clinical judgement on patient's condition

  During an outbreak response, the Clinical Outcome Form may be made optional to lessen the reporting burden on providers depending on specific circumstances, extent, and size of the outbreak. If the Clinical Outcome Form is made optional during an outbreak, CDC will communicate this accordingly on its website and through webinars and listserv notifications.

- **Adverse Event Reporting** – Report serious or life-threatening AEs (e.g., anaphylaxis, hospitalization/prolonged hospitalization, death; see below the definition of SAE), selected AEs of interest (see below the list) and/or medication errors associated with tecovirimat to CDC. Report SAEs and/or selected AEs of interest (defined below) by:
    - Completing a fillable-PDF MedWatch Form 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
    - SAE is defined as death, life-threatening AE, inpatient hospitalization, or prolongation of existing hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, congenital anomaly/birth defect, an important medical event that based on appropriate medical judgement may jeopardize the patient and may require medical or surgical intervention to prevent one of the aforementioned outcomes
    - Selected AEs of interest include seizure, tremor and/or tingling sensation, purpura, renal function abnormalities, or hepatic function abnormalities

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.
- Optional lesion specimens may be sent to CDC for tecovirimat-treated patients with persistent lesions during tecovirimat treatment and/or when any new lesions develop after ≥ 7 days of tecovirimat treatment to assess for development of antiviral resistance mutations. The resistance testing at CDC is available if there is lack of clinical and/or virologic response to tecovirimat

(clinical worsening, not resolving lesion, new lesions), giving clinical suspicion for potential resistance to tecovirimat.

- See **Attachment 4** (Optional Lesion Specimens to CDC for Resistance Testing) for collection and shipping instructions. The resistance testing at CDC is available if there is clinical suspicion of lower effectiveness (clinical worsening, not resolving lesion, new lesions).
- Please be informed that patient-specific results cannot be reported back to providers or patients to guide individual patient management as these tests are not certified under the Clinical Laboratory Improvement Amendments (CLIA) regulations. However, treating clinicians are encouraged to send specimens to CDC when clinical suspicions for resistance are present for public health surveillance purpose. This is important for continued monitoring for potential emergence of antiviral resistant MPXV as tecovirimat has a relatively low resistance barrier [16]. Tecovirimat resistance has been detected in 46 tecovirimat-treated mpox patients and in 11 tecovirimat-naïve mpox patients [17-23].

- 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 optional plasma pharmacokinetic sample(s) collection for testing at a designated laboratory (Alturas Analytics) to help inform drug exposure, see **Attachment 5** for instructions. Please ensure notifying CDC (regaffairs@cdc.gov) by email if PK samples are sent to Alturas to help match the patient information submitted to CDC under the IND with the patient PK samples sent to Alturas. Clinicians may consider prioritizing PK sample collection from certain patients (e.g., critically ill patients, those with concerns for altered drug absorption, pediatric, pregnant) whose oral tecovirimat drug exposure levels may be subtherapeutic. Patient-specific results cannot be reported back to the providers or patients for directly informing individual patient management as the PK test is not CLIA-certified. However, aggregated results when accumulated and available would inform drug exposure levels of patients with orthopoxvirus infections, especially given the lack of tecovirimat PK data in patients with poxvirus disease.

Table 4. Summary of Clinical Assessment and Monitoring Parameters

Parameters	Pre-Tecovirimat Treatment [a] Patient Intake Form (Attachment 2-A) Prior to first dose of Tecovirimat (≤ 24 hours)	Post Completion of Tecovirimat Treatment [a] Clinical Outcome Form (Attachment 2-B) Outpatients: 3–7 Days after treatment completion
Sign Informed Consent	x	N/A
Inclusion/Exclusion Criteria	x	N/A
Baseline clinical assessment	x	N/A
Clinical progress	N/A	x
Serious Adverse Events[b]	N/A	Report if SAEs, select AEs of interest, and/or medication errors occur
Hematology, chemistry, urinalysis	Optional	Optional
Lesion samples	Optional	Optional (for any new lesions post-treatment)
PK samples	Optional	Optional

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

[b] SAEs must be reported to CDC within 72 hours of awareness or sooner if possible.

8.0 RECORDING AND REPORTING SERIOUS 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 and selected AEs of interest must be reported. These include all SAEs and selected AEs of interest that the patient reports spontaneously, those the clinician observes, and those the clinician elicits in response to open-ended questions. All SAEs and selected AEs of interest, whether or not the treating clinician considers the event to be drug-related, must be reported to CDC within 72 hours of awareness or sooner if possible (see Section 7.0).

8.3 CDC Reporting Requirements to FDA and CDC Institutional Review Board (IRB)

CDC will review all SAEs 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.

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

AEs that are voluntarily reported by providers to CDC that do not meet the requirements for expedited reporting to FDA will be submitted under the IND in Annual Reports.

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 of this 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, including adolescents, deemed as mature or emancipated minors by state and/or local law who can consent for themselves, before tecovirimat is administered. If the patient is unable to give consent, consent can be obtained from a legally authorized representative (LAR).

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) with exceptions for adolescents, deemed as mature or emancipated minors by state and/or local law who can consent for themselves for medical care. The ultimate responsibility for decision-making regarding treatment with tecovirimat in minors should lie with the parent or guardian, or by the adolescents, deemed as mature or emancipated minors by state and/or local law who can consent for themselves for medical care.

For patients with limited English proficiency, if a version of the informed consent form is not available in the patient's (LAR's) language, the form must be translated orally by a certified interpreter. If a certified interpreter is not available, another adult who is fluent in both English and the language needed may interpret, provided the patient (parent/LAR) is comfortable sharing medical information (i.e., the reason treatment is being offered) with that person. If a facility wishes to create a written translation of the informed consent form, the CDC IRB-approved informed consent form must be translated by a certified translator and the translation must be submitted to and approved by the CDC IRB prior to use. A short form for obtaining informed consent from patients with limited English proficiency, along with a written summary of the information in the informed consent form (**Attachment 1**) for use with the short form are available online on CDC's website. The same requirements for interpretation or translation additionally apply to the short form.

In the rare situation that a patient is unable to respond and make wishes known about tecovirimat treatment, no next-of-kin or legal representative is available, and the patient's illness is life-threatening, obtaining informed consent may be deemed not feasible per 21 CFR 50.23 "Exception from general requirements." In such situations that necessitate tecovirimat treatment, the patient's treating clinician and a clinician who is not otherwise participating in this expanded access IND program will document the clinical determination on the last page of the informed consent form (**Attachment 1**). The information in the consent form should be provided to the patient or LAR at the first available opportunity. 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

Most Frequently Reported Adverse Reactions to Oral Tecovirimat

Based on a safety study of oral tecovirimat in 359 healthy adult subjects ages 18–79 years in a phase 3 clinical trial, 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 < 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 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

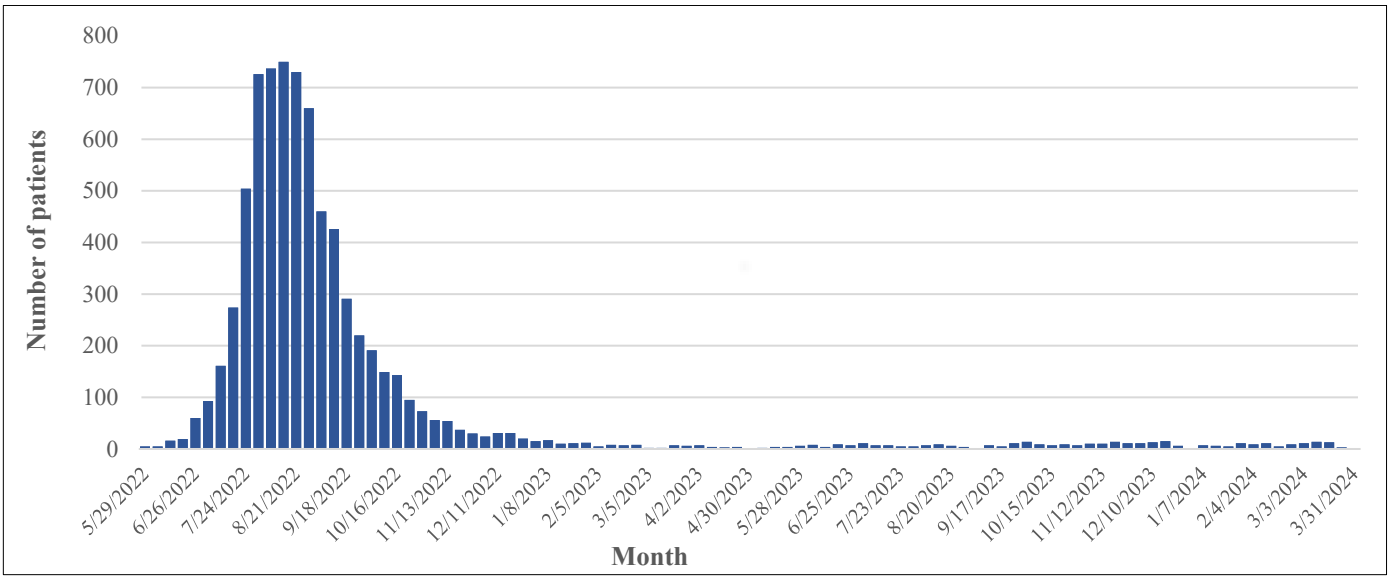
NVOPXV-infected Patients (2007-2021)

While tecovirimat has not been studied in human orthopoxvirus disease, tecovirimat treatment was provided under EA-IND to 7 patients in the U.S. (including one pediatric patient); at least 5 patients outside the U.S. also received tecovirimat treatment prior to the 2022 mpox outbreak. Infections were caused by vaccinia virus (n=6), cowpox virus (4), and mpox (n=2). All 6 patients with vaccinia virus infection had also received VIGIV and recovered from their infection [26-30]. In addition to oral tecovirimat and VIGIV, a 28-month old child with eczema vaccinatum was also treated with cidofovir and a 20-year-old patient with progressive vaccinia was also treated with brincidofovir and topical imiquimod [26, 28]. Two patients with mpox recovered from their illness [5, 7] while two of four patients with cowpox, who both had a history of organ transplant, resulted in death from their illness. Tecovirimat was generally well tolerated with one patient who experienced mild AEs (nausea, loss of appetite, fatigue, myalgia, and pruritus).

2022 U.S. Mpox Outbreak

During the 2022 mpox outbreak response in the U.S., stockpiled tecovirimat was made available under EA-IND for the treatment of mpox[31]. From May 29, 2022, through April 4, 2024, there were 7,571 patients who were prescribed or treated with tecovirimat under the EA-IND based on the returned IND Patient Intake forms (Figure 1). This likely underrepresents the total number of patients treated with tecovirimat given that the receipt of Patient Intake forms is dependent on compliance with the requirement to complete and submit the forms to CDC. Figure 2 summarizes the age and gender of patients who were prescribed tecovirimat.

Figure 1. Patients who were prescribed tecovirimat as of April 4, 2024, by month* (N=7,571)



* Number of patients based on date of assessment at start of tecovirimat treatment or date of prescription/administration of tecovirimat

Figure 2: Cumulative number of patients who were prescribed tecovirimat as of April 4, 2024: Age and Gender

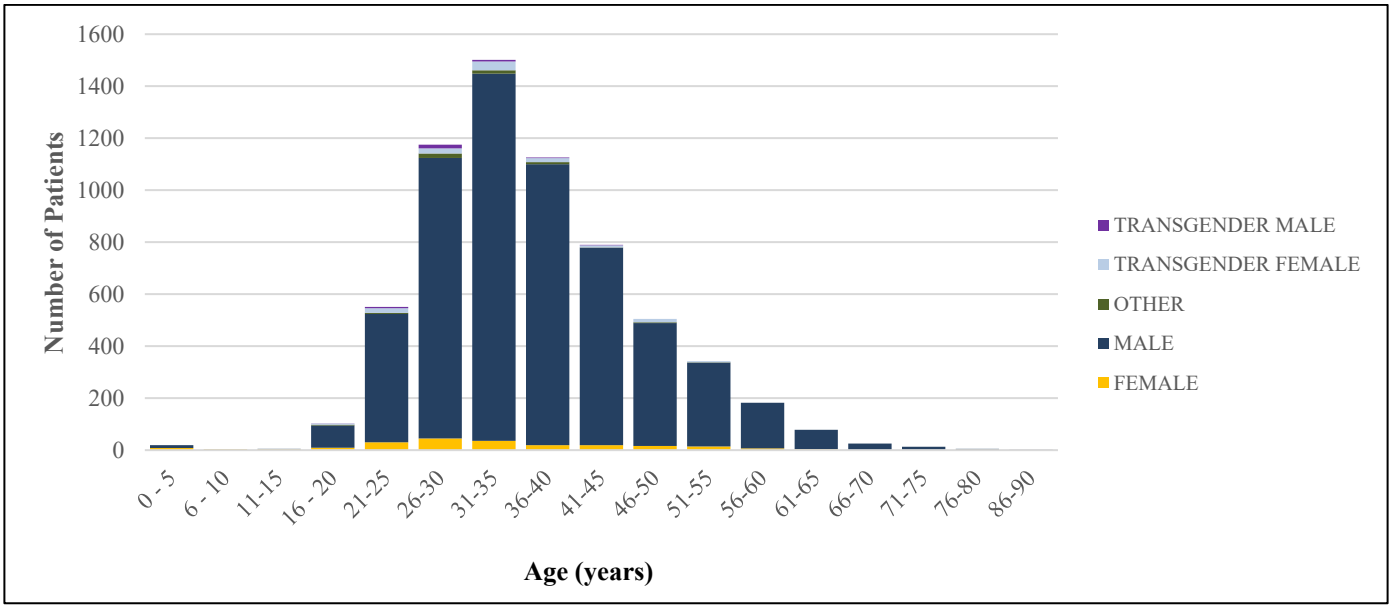
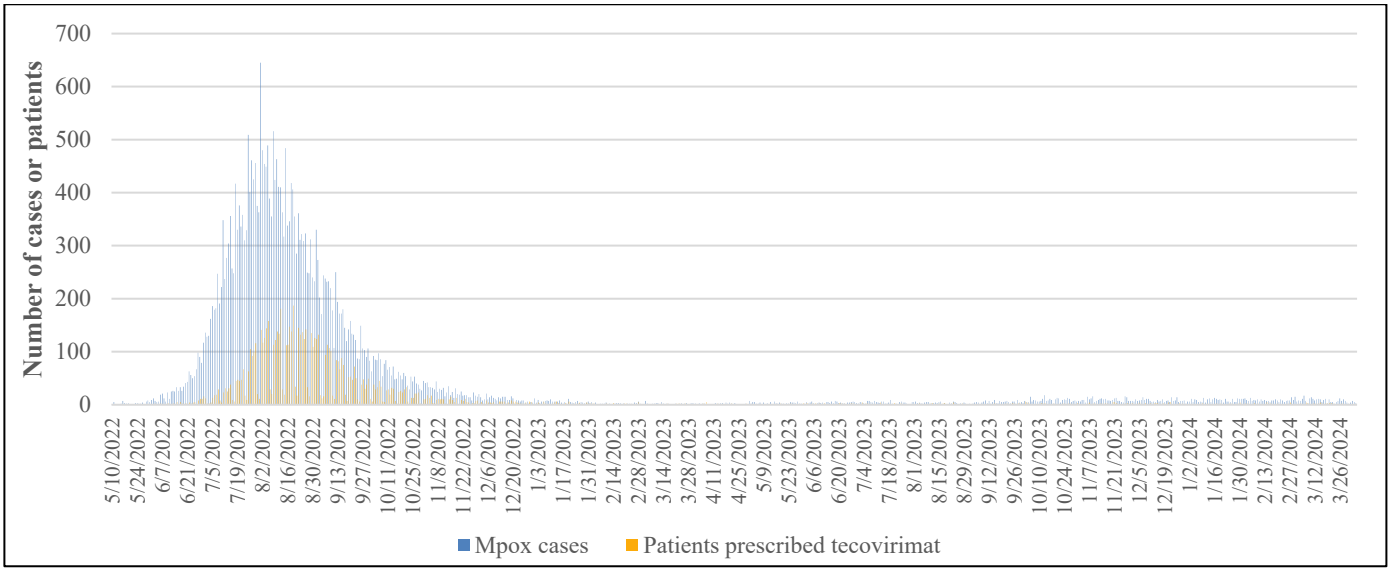


Figure 3: Number of mpox cases reported (n=32,562) and patients who were prescribed tecovirimat (n=7,571), May 29, 2022, through April 4, 2024.



The majority of the patients were prescribed oral tecovirimat and treated as outpatients. The age ranged from 5 days to 80 years with a median reported of 35 years and were predominantly male (both sex assigned at birth and gender they identify by). Approximately half of the patients prescribed tecovirimat were HIV-positive. The most frequently reported reasons for prescribing or initiating tecovirimat treatment included lesions in sensitive anatomical areas, pain, and risk of severe disease due to immunosuppression or other condition.

Adverse Events (AEs) in Patients Treated with Tecovirimat

There have been 148 adverse events reported in 82 patients and 44 deaths reported to the CDC under the EA-IND through the end of January 2024. With passively reported AEs from an uncertain size of drug-exposed population, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Reported AEs included: elevated liver enzymes, headache, pruritis, urticaria, fatigue, fever, acute renal dysfunction, tremor, seizure, hallucination, nightmares, paresthesia, dizziness, headache, fatigue, fever, edema, anaphylaxis, edema, and thrombocytopenia. The 44 deaths reported in patients who received tecovirimat were all adults (age range: 21 to 69 years), and all but 5 were HIV-positive (CD4 count range: 0 to 600). None of the deaths were assessed to be attributable to tecovirimat administration, but mpox-associated, including complications from severe disease compounded by presence of one or more severely immunocompromising conditions (e.g., advanced HIV/AIDS, lymphoma, leukemia, solid organ transplantation, cancer, common variable immunodeficiency), co-infections, and/or other clinically relevant conditions, played a role in their expiry.

Tecovirimat may cause other adverse events, including serious adverse events, that have not been observed yet. Tremors and seizures were observed in a toxicology study in beagle dogs that received high doses of tecovirimat (4 times higher than the highest drug level in human studies). Safety studies in monkeys to evaluate neurological and neuropsychiatric signals did not observe similar neurological or neuropsychiatric AEs. No such neurologic AEs were observed in a safety study involving 359 healthy adults who received the standard 600 mg oral tecovirimat dosing at the recommended dosing interval; however, the potential risk of neurological (e.g., tremor, seizure) or neuropsychiatric (e.g., hallucination) AEs may exist, particularly if higher than recommended doses are administered. There is also a potential for other adverse events if tecovirimat is taken in a way that is inconsistent with the recommended dosing

and/or dosing interval. It is important to take the tecovirimat at the standard doses and interval and to monitor for AEs and SAEs.

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 NVOPXV. 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 mpox 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

A comparison of tecovirimat exposures achieved in healthy human subjects to those observed in animal models of orthopoxvirus infection (non-human primates and rabbits infected with mpox virus and rabbitpox virus, respectively) in therapeutic efficacy studies 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 [16, 24]. 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. McCollum AM, Shelus V, Hill A, et al. Epidemiology of Human Mpox - Worldwide, 2018-2021. MMWR Morb Mortal Wkly Rep 2023; 72(3): 68-72.
2. World Health Organization. Mpox (monkeypox)-Democratic Republic of the Congo. Available at Mpox (monkeypox) - Democratic Republic of the Congo (who.int). Accessed April 22, 2024.
3. World Health Organization. 2022-2023 Mpox (Monkeypox) Outbreak: Global Trends. Available at: https://worldhealthorg.shinyapps.io/mpx_global/. Accessed April 18, 2024.
4. Hobson G, Adamson J, Adler H, et al. Family cluster of three cases of monkeypox imported from Nigeria to the United Kingdom, May 2021. Euro Surveill **2021**; 26(32).
5. Adler H, Gould S, Hine P, et al. Clinical features and management of human monkeypox: a retrospective observational study in the UK. Lancet Infect Dis **2022**.
6. Vaughan A, Aarons E, Astbury J, et al. Two cases of monkeypox imported to the United Kingdom, September 2018. Euro Surveill **2018**; 23(38).
7. Rao AK, Schulte J, Chen TH, et al. Monkeypox in a Traveler Returning from Nigeria - Dallas, Texas, July 2021. MMWR Morb Mortal Wkly Rep **2022**; 71(14): 509-16.
8. Costello V, Sowash M, Gaur A, et al. Imported Monkeypox from International Traveler, Maryland, USA, 2021. Emerg Infect Dis **2022**; 28(5): 1002-5.
9. Centers for Disease Control and Prevention. Multistate outbreak of monkeypox—Illinois, Indiana, and Wisconsin, 2003. MMWR Morb Mortal Wkly Rep 2003;52:537–40.
10. Centers for Disease Control and Prevention. 2022 Outbreak Cases and Data. Available at: https://www.cdc.gov/poxvirus/mpox/response/2022/index.html. Accessed April 1, 2024.
11. Philpott D, Hughes CM, Alroy KA, et al. Epidemiologic and Clinical Characteristics of Monkeypox Cases - United States, May 17-July 22, 2022. MMWR Morb Mortal Wkly Rep **2022**; 71(32): 1018-22.
12. Demographics of Patients Receiving TPOXX for Treatment of Mpox. Available at: https://www.cdc.gov/poxvirus/mpox/response/2022/demographics-TPOXX.html Accessed March 21, 2023.
13. SIGA Technologies, Inc TPOXX Investigator Brochure Version No 150, September 2020.
14. Smith SK, Olson VA, Karem KL, Jordan R, Hruby DE, Damon IK. In vitro efficacy of ST246 against smallpox and monkeypox. Antimicrobial agents and chemotherapy **2009**; 53(3): 1007-12.
15. Quenelle DC, Prichard MN, Keith KA, et al. Synergistic efficacy of the combination of ST-246 with CMX001 against orthopoxviruses. Antimicrob Agents Chemother 2007;51:4118–24.
16. SIGA Technologies Inc. TPOXX Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208627s007lbl.pdf. Accessed Mach 19, 2023.
17. Alarcon J, Kim M, Terashita D, et al. An Mpox-Related Death in the United States. N Engl J Med **2023**.
18. Centers for Disease Control and Prevention. Health Alert Network: Update on Managing Monkeypox in Patients Receiving Therapeutics. Available at: https://emergency.cdc.gov/han/2022/han00481.asp. Accessed March 19, 2023
19. Smith TG, Gigante CM, Wynn NT, et al. Tecovirimat Resistance in Mpox Patients, United States, 2022–2023. Emerging Infectious Diseases. 2023;29(12):2426-2432
20. Garrigues JM, Hemarajata P, Karan A, et al. Identification of Tecovirimat Resistance-Associated Mutations in Human Monkeypox Virus - Los Angeles County. Antimicrob Agents Chemother. 2023;67(7):e0056823.
21. Garrigues JM, Hemarajata P, Espinosa A, et al. Community spread of a human monkeypox virus variant with a tecovirimat resistance associated mutation. Antimicrob Agents Chemother. 2023;67(11):e0097223. Mitja O, Alemany A, Marks M, et al. Mpox in people with advanced HIV infection: a global case series. Lancet 2023; 401(10380): 939-49.

22. Mitja O, Alemany A, Marks M, et al. Mpox in people with advanced HIV infection: a global case series. Lancet **2023**; 401(10380): 939-49.
23. Rao AK, Schrodt CA, Minhaj FS, et al. Interim Clinical Treatment Considerations for Severe Manifestations of Mpox - United States, February 2023. MMWR Morb Mortal Wkly Rep **2023**; 72(9): 232-43.
24. Chen Y, Amantana A, Tyavanagimatt SR, 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): e23237.
25. Russo AT, Berhanu A, Bigger CB, 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): 644-54.
26. Lederman ER, Davidson W, Groff HL, et al. Progressive Vaccinia: Case Description and Laboratory-Guided Therapy With Vaccinia Immune Globulin, ST-246, and CMX001. J Infect Dis **2012**; 206(9): 1372-85.
27. Lindholm DA, Fisher RD, Montgomery JR, et al. Preemptive Tecovirimat Use in an Active Duty Service Member Who Presented With Acute Myeloid Leukemia After Smallpox Vaccination. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2019**; 69(12): 2205-7.
28. Vora S, Damon I, Fulginiti V, et al. Severe eczema vaccinatum in a household contact of a smallpox vaccinee. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2008**; 46(10): 1555-61.
29. Whitehouse ER, Rao AK, Yu YC, 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): 943-6.
30. Centers for Disease C, Prevention. Human vaccinia infection after contact with a raccoon rabies vaccine bait - Pennsylvania, 2009. MMWR Morb Mortal Wkly Rep **2009**; 58(43): 1204-7.
31. O'Laughlin K, Tobolowsky FA, Elmor R, et al. Clinical Use of Tecovirimat (Tpoxx) for Treatment of Monkeypox Under an Investigational New Drug Protocol - United States, May-August 2022. MMWR Morb Mortal Wkly Rep **2022**; 71(37): 1190-5.