Tecovirimat

Tecovirimat is an inhibitor of the orthopoxvirus VP37 envelope wrapping protein.

Class: 8:18.92 • Antivirals, Miscellaneous (AHFS primary)

Brands: TPOXX®

Uses

Smallpox

Tecovirimat has the following uses:

Tecovirimat is indicated for the treatment of human smallpox disease in adults and pediatric patients weighing at least 3 kg.

Tecovirimat has the following limitations of use:

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.

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

Other Uses

- Use of tecovirimat for other orthopoxvirus infections including monkeypox is not approved by the FDA. However, the CDC holds a non-research expanded access Investigational New Drug (EA-IND) protocol that allows for the use of tecovirimat for primary or early empiric treatment of non-variola orthopoxvirus infections, including monkeypox†, in adults and children of all ages. For additional information, see the CDC website at https://www.cdc.gov/poxvirus/monkeypox/clinicians/Tecovirimat.html
- CDC states that tecovirimat may be considered for treatment of the following individuals infected with monkeypox: **people with severe disease** (e.g., hemorrhagic disease, confluent lesions, sepsis, encephalitis, or other conditions requiring hospitalization), **people who are at high risk of severe disease** including individuals with immunocompromising conditions (e.g., human immunodeficiency virus/acquired immune deficiency syndrome infection, leukemia, lymphoma, generalized malignancy, solid organ transplantation; therapy with alkylating agents, antimetabolites, radiation, tumor necrosis factor inhibitors, high-dose corticosteroids; 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), pediatric populations particularly patients younger than 8 years of age, people with a history or presence of atopic dermatitis, persons with other active exfoliative skin conditions (e.g., eczema, burns, impetigo, varicella zoster virus infection, herpes simplex virus infection, severe acne, severe diaper dermatitis with extensive areas of denuded skin, psoriasis, or Darier disease [keratosis follicularis]), pregnant or breastfeeding women, and people with one or more complications (e.g., secondary bacterial skin infection; gastroenteritis with severe nausea/vomiting, diarrhea, or dehydration; bronchopneumonia; concurrent disease or other comorbidities), and **people with aberrant infections** that include accidental implantation in eyes, mouth, or other anatomical areas where monkeypox virus infection might constitute a special hazard (e.g., the genitals or anus).

Dosage and Administration

General

Tecovirimat is available in the following dosage form(s) and strength(s):

Capsule: 200 mg (of anhydrous tecovirimat).

Injection: Single-use 30 mL vials containing 200 mg/20 mL of tecovirimat.

For patients who cannot swallow capsules, the capsules may be opened and the contents mixed with 30 mL of liquid (e.g., milk, chocolate milk) or soft food (e.g., applesauce, yogurt). The entire mixture should be administered within 30 minutes of preparation.

It is recommended that patients weighing 13 kg and above initiate oral treatment with tecovirimat capsules if possible. If patients are unable to take oral tecovirimat capsules (or the capsules opened and prepared in food), treatment may be initiated with tecovirimat injection. If IV treatment is necessary, conversion from IV to oral tecovirimat is recommended as soon as oral treatment can be tolerated. In patients receiving an IV infusion, the first dose of oral treatment should be given at the time of and in place of the next scheduled IV dosing. In patients receiving oral treatment who subsequently require IV treatment, the first dose of IV infusion should be given at the time of and in place of the next scheduled oral dosing.

Determine creatinine clearance in all patients before starting tecovirimat injection and monitor while receiving tecovirimat injection as clinically appropriate.

Dosage

It is *essential* that the manufacturer's labeling be consulted for more detailed information on dosage and administration of this drug. Dosage summary:

Dosage of the capsules containing tecovirimat monohydrate is expressed in terms of anhydrous tecovirimat.

Tecovirimat capsules should be taken within 30 minutes after a full meal of moderate or high fat.

Tecovirimat injection is administered by IV infusion over 6 hours using an infusion pump; do not administer by IV bolus injection. Depending on the size of syringe available with the syringe pump system, two separate syringes may be needed for each 6 hour administration.

Tecovirimat injection must be diluted prior to administration. The appropriate quantity of tecovirimat injection should be withdrawn into a syringe of suitable size and then diluted with 2 equal parts of either 0.9% sodium chloride injection or 5% dextrose injection; do not use prefilled infusion bags for product preparation and administration (see Table 1).

Table 1: Recommended Preparation Instructions for Tecovirimat Injection for IV Infusion in Pediatric Patients and Adults

Body Weight	Volume of Tecovirimat Injection[a]	Volume of Diluent[b]
3 kg to less than 35 kg	0.6 mL/kg	1.2 mL/kg
35 kg to less than 120 kg	20 mL	40 mL
120 kg and above	30 mL	60 mL

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

[b] Diluent is either 0.9% sodium chloride injection or 5% dextrose injection solution.

The diluted tecovirimat solution may be stored in the refrigerator (2–8°C) for up to 24 hours or at room temperature (15–25°C) for up to 4 hours.

Pediatric Patients

Smallpox

Oral: **Patients weighing 13 kg to less than 25 kg:** 200 mg taken every 12 hours orally for 14 days.

Patients weighing 25 kg to less than 40 kg: 400 mg (two 200-mg capsules) taken every 12 hours orally for 14 days.

Patients weighing 40 kg to less than 120 kg: 600 mg (three 200-mg capsules) taken every 12 hours orally for 14 days.

Patients weighing 120 kg or more: 600 mg (three 200-mg capsules) taken every 8 hours orally for 14 days.

IV: **Patients weighing 3 kg to less than 35 kg**: 6 mg/kg every 12 hours by IV infusion over 6 hours for up to 14 days.

Patients weighing 35 kg to less than 120 kg: 200 mg every 12 hours by IV infusion over 6 hours for up to 14 days.

Patients weighing 120 kg or more: 300 mg every 12 hours by IV infusion over 6 hours for up to 14 days.

Patients weighing at least 13 kg should be switched to tecovirimat capsules to complete the 14 day treatment course as soon as oral therapy can be tolerated.

Adults

Smallpox

Oral: **Patients weighing 13 kg to less than 25 kg:** 200 mg taken every 12 hours orally for 14 days.

Patients weighing 40 kg to less than 120 kg: 600 mg taken every 12 hours orally for 14 days.

Patients weighing 120 kg or more: 600 mg taken every 8 hours orally for 14 days.

IV: **Patients weighing 3 kg to less than 35 kg**: 6 mg/kg every 12 hours by IV infusion over 6 hours for up to 14 days.

Patients weighing 35 kg to less than 120 kg: 200 mg every 12 hours by IV infusion over 6 hours for up to 14 days.

Patients weighing 120 kg or more: 300 mg every 12 hours by IV infusion over 6 hours for up to 14 days.

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

Cautions

Contraindications

- Tecovirimat capsules: None
- Tecovirimat injection: Contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/minute) as it contains the excipient hydroxypropyl-β-cyclodextrin that is eliminated through glomerular filtration.

Warnings/Precautions

Hypoglycemia When Co-administered with Repaglinide

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

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

Risks of Hydroxypropyl-β-Cyclodextrin Excipient in Tecovirimat Injection for Patients with Renal Insufficiency and Pediatric Patients <2 Years of Age

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

In patients with mild (defined as creatinine clearance 60-89 mL/min) and moderate (defined as creatinine clearance 30-59 mL/min) renal impairment, tecovirimat injection should be used with caution. Creatinine clearance should be closely monitored and, if renal toxicity is suspected, consideration should be given to administering tecovirimat orally if possible or to using an alternative medication. Tecovirimat injection is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min).

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

Specific Populations

Pregnancy

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

In animal reproduction studies, no embryofetal developmental toxicity was observed in mice during the period of organogenesis at tecovirimat exposures (area under the curve [AUC]) up to 23 times higher than human exposure at the recommended human dose (RHD). In rabbits, no embryofetal developmental toxicity was observed during organogenesis at tecovirimat exposures (AUC) less than human exposures at the RHD. In a mouse pre-/post-natal development study, no toxicities were observed at maternal tecovirimat exposures up to 24 times higher than human exposure at the RHD.

The background risk of major birth defects and miscarriage for the indicated population is unknown, and the estimated background risk of miscarriage for the indicated population is higher than the general population. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Animal Data: Tecovirimat was administered orally to pregnant mice at doses up to 1000 mg/kg/day from gestation Days 6-15. No embryofetal toxicities were observed at doses up to 1000 mg/kg/day (approximately 23 times higher than human exposure at the RHD).

Tecovirimat was administered orally to pregnant rabbits at doses up to 100 mg/kg/day from gestation Days 6-19. No embryofetal toxicities were observed at doses up to 100 mg/kg/day (0.4 times the human exposure at the RHD).

In the pre-/post-natal development study, tecovirimat was administered orally to pregnant mice at doses up to 1000 mg/kg/day from gestation Day 6 to post-natal Day 20. No toxicities were observed at doses up to 1000 mg/kg/day (approximately 24 times higher than human exposure at the RHD).

Lactation

Risk Summary: Because of the potential for variola virus transmission through direct contact with the breastfed infant, breastfeeding is not recommended in patients with smallpox. There are no data on the presence of tecovirimat in human milk, the effects of the drug on the breastfed infant, or on milk production. Tecovirimat has been found to be present in animal milk. When a drug is present in animal milk, it is likely to be present in human milk.

Data: In a lactation study at doses up to 1000 mg/kg/day, mean tecovirimat milk to plasma ratios up to approximately 0.8 were observed at 6 and 24 hours post-dose when administered orally to mice on lactation Day 10 or 11.

Females and Males of Reproductive Potential

There are no data on the effect of tecovirimat on human fertility. Decreased fertility due to testicular toxicity was observed in male mice.

Pediatric Use

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, pharmacokinetic simulation was used to derive dosing regimens that are predicted to provide pediatric patients with exposures comparable to the observed exposure in adults receiving 600 mg orally twice daily (every 12 hours) or 200 mg intravenously twice daily (every 12 hours). The dosage for pediatric patients is based on weight.

Tecovirimat Injection: There are limited data regarding the use of hydroxypropyl-β-cyclodextrin, an ingredient in tecovirimat injection, in pediatric patients <2 years of age. Given the potential for drug accumulation due to renal immaturity in pediatric patients <2 years, monitoring of renal function after treatment is recommended.

Geriatric Use

Clinical studies of tecovirimat did not include sufficient numbers of subjects aged 65 and over to determine whether the safety profile of tecovirimat is different in this population compared to younger subjects. Of the 359 subjects in the clinical study of oral tecovirimat, 10% (36/359) were ≥65 years of age, and 1% (4/359) were ≥75 years of age. No alteration of dosing is needed for patients ≥65 years of age.

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.

Tecovirimat injection: Hydroxypropyl-β-cyclodextrin, an ingredient in tecovirimat injection, when administered intravenously, is eliminated through glomerular filtration. No dosage adjustment is required for patients with mild (creatinine clearance 60-89 mL/min) or moderate (creatinine clearance 30-59 mL/min) renal impairment. Tecovirimat injection is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min).

Hepatic Impairment

No dosage adjustment is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B, or C).

Common Adverse Effects

With oral therapy, common adverse reactions (≥2%) were headache, nausea, abdominal pain, and vomiting.

With IV therapy, common adverse reactions (≥4%) were administration site reactions and headache.

Interactions

Specific Drugs

It is *essential* that the manufacturer's labeling be consulted for more detailed information on interactions with this drug, including possible dosage adjustments. Interaction highlights:

Consult the full prescribing information prior to and during treatment for potential drug interactions.

Actions

Mechanism of Action

- Tecovirimat is an antiviral agent active against variola (smallpox) virus. Tecovirimat targets and inhibits the activity of the orthopoxvirus VP37 protein (encoded by and highly conserved in all members of the orthopoxvirus genus) and blocks its interaction with cellular Rab9 GTPase and TIP47, which prevents the formation of egress-competent enveloped virions necessary for cell-to-cell and long-range dissemination of virus.

Spectrum

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

Resistance

- There are no known instances of naturally occurring tecovirimat-resistant orthopoxviruses, although tecovirimat resistance may develop under drug selection. Tecovirimat has a relatively low resistance barrier, and certain amino acid substitutions in the target VP37

protein can confer large reductions in tecovirimat antiviral activity. The possibility of resistance to tecovirimat should be considered in patients who either fail to respond to therapy or who develop recrudescence of disease after an initial period of responsiveness.

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

Advice to Patients

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Inform patients that the efficacy of tecovirimat is based solely on efficacy studies demonstrating a survival benefit in animals and that the effectiveness of tecovirimat has not been tested in humans with smallpox disease.
- Advise patients to take tecovirimat capsules as directed within 30 minutes of eating a full meal of moderate or high fat with 6-8 oz. of water. Inform patients to take tecovirimat for the entire duration without missing or skipping a dose. Inform patients who cannot swallow capsules to refer to the manufacturer's Instructions for Use to mix the contents of the capsule with soft food or liquid.
- Inform patients that tecovirimat may interact with other drugs. Advise patients to report to their healthcare provider the use of other prescription drugs. Co-administration of tecovirimat with repaglinide may cause hypoglycemia.
- Advise patients that if a dose of oral tecovirimat is missed, to take the missed dose as soon as possible, up to 8 hours prior to the next dose. If less than 8 hours remain before the next scheduled dose, do not take the missed dose and resume dosing with the next scheduled dose.
- Inform patients with smallpox not to breastfeed their infant because of the risk of passing variola virus to the breastfed infant.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Tecovirimat is stored in the US Strategic National Stockpile (SNS) and is not commercially available in the US. The SNS ensures that certain drugs and medical supplies are readily available to prevent or treat specific diseases, including during public health emergencies, and is managed by the US Department of Health and Human Services (HHS) Office of the Assistant Secretary for Preparedness and Response (ASPR). To request a drug from the SNS, state health departments can contact the US Centers for Disease Control and Prevention (CDC) Emergency Operations Center at 770-488-7100 or the HHS Secretary's Operations Center at 202-619-7800.

Tecovirimat		
Oral		
Capsule		
	200 mg (of anhydrous tecovirimat)	**TPOXX®**, SIGA Technologies Inc.
Injection, for IV infusion		
	200mg/20 mL	**TPOXX®**, SIGA Technologies Inc.

† Use is not currently included in the labeling approved by the US Food and Drug Administration.