Brincidofovir (Lexi-Drugs)

ALERT: US Boxed Warning

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Increased risk for mortality when used for longer duration

An increased incidence of mortality was seen in brincidofovir-treated subjects compared to placebo-treated subjects in a 24-week clinical trial when brincidofovir was evaluated in another disease.

Pronunciation

(BRIN sye DOF oh vir)

Pharmacologic Category

Antiviral Agent; Antiviral Agent, Oral

Dosing: Adult

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Smallpox

Smallpox: Oral:

10 to <48 kg: 4 mg/kg once weekly for 2 doses (days 1 and 8).

≥48 kg: 200 mg once weekly for 2 doses (days 1 and 8).

Dosage adjustment for concomitant therapy: Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information.

Dosing: Older Adult

Refer to adult dosing.

Dosing: Altered Kidney Function: Adult

No dosage adjustment necessary.

Dosing: Hepatic Impairment: Adult

*Hepatic impairment **prior to** treatment:* Mild, moderate, or severe impairment (Child-Pugh class A, B, or C): No dosage adjustment necessary.

*Hepatic impairment **during** treatment:* Consider discontinuation if ALT levels remain persistently >10 × ULN. Do not administer second (final) dose on day 8 if ALT elevation is accompanied by clinical signs and symptoms of liver inflammation or increasing direct bilirubin, alkaline phosphatase, or INR.

Dosing: Adjustment for Toxicity: Adult

GI adverse effects: If severe GI adverse events occur, including diarrhea and dehydration, consider discontinuing therapy.

Dosing: Pediatric

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Smallpox

Smallpox (variola virus infection): Infants, Children, and Adolescents:

<10 kg: Oral suspension: Oral: 6 mg/kg once weekly for 2 doses (on day 1 and day 8).

10 to <48 kg: Oral suspension: Oral: 4 mg/kg once weekly for 2 doses (on day 1 and day 8).

≥48 kg: Oral suspension or tablet: Oral: 200 mg once weekly for 2 doses (on day 1 and day 8).

Dosage adjustment for concomitant therapy: Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information.

Dosing: Altered Kidney Function: Pediatric

Infants, Children, and Adolescents: Oral:

Altered kidney impairment: No dosage adjustment needed for any degree of renal impairment (including end-stage renal disease).

Hemodialysis: No dosage adjustment needed.

Dosing: Hepatic Impairment: Pediatric

Hepatic impairment prior to initiation (baseline): Infants, Children, and Adolescents: Oral:

Mild, moderate, or severe impairment: No dosage adjustment necessary.

Hepatotoxicity during treatment:

ALT persistently >10 × ULN: Consider not administering second dose.

ALT elevation with increased direct bilirubin, alkaline phosphatase, INR, or clinical signs of liver inflammation: Discontinue; do not administer second dose.

Use: Labeled Indications

Smallpox: Treatment of human smallpox disease caused by variola virus in adult and pediatric patients, including neonates.

Limitations of use: Not indicated for the treatment of diseases other than human smallpox disease. Effectiveness 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. Efficacy may be reduced in immunocompromised patients based on studies in immune deficient animals.

Administration: Oral

Note: Due to carcinogenic potential, avoid direct contact with broken or crushed tablets and oral suspension. If contact with skin or mucous membranes occurs, wash thoroughly with soap and water, and rinse eyes thoroughly with water.

Tablets: Administer on an empty stomach or with a low-fat meal. Swallow tablet whole; do not crush or divide.

Suspension: Administer on an empty stomach. Shake oral suspension before use.

Administration: Other

Note: Due to carcinogenic potential, avoid direct contact with broken or crushed tablets and oral suspension.

Enteral tube: Oral suspension can be administered by enteral tube (following administration, refill the catheter-tip syringe with 3 mL of water, shake, and administer contents via tube to ensure full dose is administered); flush tube with water before and after enteral administration.

Administration: Pediatric

Oral:

Note: Due to carcinogenic potential, avoid direct contact with broken or crushed tablets and oral suspension. If contact with skin or mucous membranes occur, wash thoroughly with soap and water, and rinse eyes thoroughly with water.

Tablets: Administer on empty stomach or with low-fat meal (~400 calories with ~25% calories from fat). Swallow tablets whole; do not crush or divide.

Suspension: Administer on empty stomach. Shake well. Use oral syringe to accurately measure prescribed dose. Discard unused portion after 2 doses.

Enteral feeding tube: Flush enteral feeding tube with water prior to administration; may administer via tube using a catheter tip syringe, then refill syringe with 3 mL of water, shake, and administer to ensure all drug administered. Flush with water again following administration.

Dietary Considerations

Tablet: Take on an empty stomach or with a low-fat meal (~400 calories, with ~25% of calories from fat).

Oral suspension: Take on an empty stomach.

Hazardous Drugs Handling Considerations

This medication is not on the NIOSH (2016) list; however, it may meet the criteria for a hazardous drug. Brincidofovir may cause carcinogenicity, reproductive toxicity, and has a structural and/or toxicity profile similar to existing hazardous agents.

Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. Follow NIOSH and USP 800 recommendations and institution-specific policies/procedures for appropriate containment strategy (NIOSH 2016; USP-NF 2020).

Note: Facilities may perform risk assessment of some hazardous drugs to determine if appropriate for alternative handling and containment strategies (USP-NF 2020). Refer to institution-specific handling policies/procedures.

Storage/Stability

Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F). Do not freeze oral suspension.

Medication Safety Issues

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Sound-alike/look-alike issues:

Brincidofovir may be confused with cidofovir.

Prescribing and Access Restrictions

Tembexa is not available for general public use. Supplies are owned by the US federal government. Additional information is available at https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/smallpox-preparedness-and-response-updates-fda.

Contraindications

There are no contraindications listed in the manufacturer's labeling.

Warnings/Precautions

Concurrent drug therapy issues:

• Cidofovir: Do not coadminister with IV cidofovir; brincidofovir is a lipid-linked derivative of cidofovir that is intracellularly converted to cidofovir.

Reproductive Considerations

Pregnancy testing is recommended prior to use in patients who may become pregnant.

Patients who may become pregnant should use effective contraception during therapy and for at least 2 months after the last brincidofovir dose. Patients with partners who may become pregnant should use condoms during therapy and for at least 4 months after the last dose of brincidofovir.

Pregnancy Considerations

Maternal toxicity and adverse pregnancy outcomes were observed in animal reproduction studies with doses less than the expected human exposure. Based on data from animal reproduction studies, in utero exposure to brincidofovir may cause fetal harm.

Smallpox infection during pregnancy is associated with adverse events. Contracting smallpox while pregnant increases the risk of severe maternal disease (including hemorrhagic smallpox) and death; the fatality rate in unvaccinated pregnant patients can be up to 70% (CDC [Petersen 2015]).

Alternative therapy to treat smallpox infection in pregnant patients should be used if available. Brincidofovir is not recommended as an alternative therapy to treat patients with monkeypox during the first trimester (CDC 2022).

Breastfeeding Considerations

It is not known if brincidofovir is present in breast milk.

Lactating patients with smallpox infection have the potential to transmit the virus via direct contact to a breastfed infant. Therefore, breastfeeding is not recommended. In addition, brincidofovir is not recommended as an alternative therapy to treat lactating patients with monkeypox (CDC 2022).

Adverse Reactions (Significant): Considerations

Expand All

GI effects

Hepatotoxicity

Adverse Reactions

The following adverse drug reactions and incidences are derived from product labeling unless otherwise specified.

1% to 10%:

Cardiovascular: Peripheral edema (<2%)

Dermatologic: Skin rash (<2%, including maculopapular rash and pruritic rash)

Gastrointestinal: Abdominal pain (3%) (See Table 1), decreased appetite (<2%), diarrhea (8%) (See Table 2), dysgeusia (<2%), nausea (5%), vomiting (4%) (See Table 3)

Hepatic: Increased serum alanine aminotransferase (grades 2/3: 2% to 7%) (See Table 4), increased serum aspartate aminotransferase (grades 2/3: 1% to 2%) (See Table 5), increased serum bilirubin (grades 2/3: 1% to 3%)

Nervous system: Myasthenia (<2%)

<1%:

Hepatic: Hepatic sinusoidal obstruction syndrome, hepatitis (acute), hyperbilirubinemia, liver steatosis

Renal: Increased serum creatinine

Frequency not defined: Gastrointestinal: Dyspepsia, enteritis

Metabolism/Transport Effects

Substrate of OATP1B1/1B3 (SLCO1B1/1B3); **Inhibits** MRP2

Drug Interactions Open Interactions

Cabozantinib: MRP2 Inhibitors may increase the serum concentration of Cabozantinib. *Risk C: Monitor therapy*

Cladribine: Agents that Undergo Intracellular Phosphorylation may diminish the therapeutic effect of Cladribine. *Risk X: Avoid combination*

Corticosteroids (Systemic): May diminish the therapeutic effect of Brincidofovir. *Risk C: Monitor therapy*

Immunosuppressants (Cytotoxic Chemotherapy): May diminish the therapeutic effect of Brincidofovir. *Risk C: Monitor therapy*

Immunosuppressants (Miscellaneous Oncologic Agents): May diminish the therapeutic effect of Brincidofovir. *Risk C: Monitor therapy*

Immunosuppressants (Therapeutic Immunosuppressant Agents): May diminish the therapeutic effect of Brincidofovir. *Risk C: Monitor therapy*

Methotrexate: May diminish the therapeutic effect of Brincidofovir. *Risk C: Monitor therapy*

OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors: May increase the serum concentration of Brincidofovir. Management: Consider alternatives to OATP1B/1B3 inhibitors in patients treated with brincidofovir. If coadministration is required, administer OATP1B1/1B3 inhibitors at least 3 hours after brincidofovir and increase monitoring for brincidofovir adverse reactions. *Risk D: Consider therapy modification*

Smallpox and Monkeypox Vaccine (Live): Brincidofovir may diminish the therapeutic effect of Smallpox and Monkeypox Vaccine (Live). *Risk C: Monitor therapy*

Smallpox Vaccine Live: Brincidofovir may diminish the therapeutic effect of Smallpox Vaccine Live. *Risk C: Monitor therapy*

Voclosporin: May increase the serum concentration of OATP1B1/1B3 (SLCO1B1/1B3) Substrates (Clinically Relevant with Inhibitors). *Risk C: Monitor therapy*

Food Interactions

Food decreases the brincidofovir oral tablet AUC and C_{max} by 31% and 49%, respectively. The effect of food on brincidofovir oral suspension has not been studied. Management: Take brincidofovir tablets on an empty stomach or with a low-fat meal. Take brincidofovir oral suspension on an empty stomach.

Monitoring Parameters

LFTs (at baseline and during therapy as clinically appropriate); GI adverse effects (eg, diarrhea, dehydration); pregnancy testing prior to initiation in individuals of childbearing potential.

Mechanism of Action

Brincidofovir is a lipid conjugate that is converted intracellularly to cidofovir, which is subsequently phosphorylated to an active metabolite, cidofovir diphosphate. Cidofovir diphosphate selectively inhibits orthopoxvirus DNA polymerase-mediated viral DNA synthesis. Incorporation of cidofovir into the growing viral DNA chain results in reductions in the rate of viral DNA synthesis

Pharmacokinetics

Absorption: Administration of oral tablet with a low-fat meal resulted in decreases in AUC (31%) and C_{max} (49%) relative to administration under fasted conditions. The effect of food on oral suspension absorption was not studied.

Distribution: V_d: 1,230 L.

Protein binding: >99.9 % bound to human plasma proteins.

Metabolism: Hydrolyzed to cidofovir, then phosphorylated to form cidofovir diphosphate (active metabolite).

Bioavailability: Tablet: 13.4%; oral suspension: 16.8%.

Half-life elimination: Brincidofovir: 19.3 hours; cidofovir diphosphate (active metabolite): 113 hours.

Time to peak: Brincidofovir: 3 hours (range: 2 to 8 hours); cidofovir diphosphate (active metabolite): 47 hours (range: 23 to 311 hours).

Excretion: Urine (51%, as metabolites); feces (40%, as metabolites).

Pharmacokinetics: Additional Considerations

Pediatric: Recommended pediatric dosing regimen is expected to result in similar exposures to adults, based on population pharmacokinetic modeling and simulation.

Dental: Local Anesthetic/Vasoconstrictor Precautions

No information available to require special precautions.

Dental: Effects on Dental Treatment

Key adverse event(s) related to dental treatment: Occurrence of altered sense of taste.

Dental: Effects on Bleeding

No information available to require special precautions.

Related Information

- Oral Medications That Should Not Be Crushed or Altered
- Safe Handling of Hazardous Drugs

Index Terms

CMX001; Tembexa

FDA Approval Date

June 04, 2021

References

<800> Hazardous Drugs—Handling in Healthcare Settings. *United States Pharmacopeia and National Formulary* (USP 43-NF 38). Rockville, MD: United States Pharmacopeia Convention; 2020:74-92.

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