Brincidofovir (AHFS DI)

Generic Name: Brincidofovir
Brand Information: Tembexa®

Boxed Warning:

> **Warning: Increased Risk For Mortality When Used For Longer Duration**
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> An increased incidence of mortality was seen in brincidofovir-treated subjects compared to placebo-treated subjects in a 24-week clinical trial when the drug was evaluated in another disease.[1]

Introduction
Brincidofovir is an orthopoxvirus nucleotide analog DNA polymerase inhibitor.[1]

Uses
Smallpox
Brincidofovir is indicated for the treatment of human smallpox disease in adult and pediatric patients, including neonates, and has been designated an orphan drug by FDA for the treatment of smallpox.[1,2]

Brincidofovir is not indicated for the treatment of diseases other than human smallpox disease.[1]

The manufacturer states that the effectiveness of brincidofovir for the treatment of smallpox disease has not been determined in humans because adequate and well-controlled field trials have not been feasible, and inducing smallpox disease in humans to study the drug's efficacy is not ethical.[1] Brincidofovir has been administered to healthy people and people with other viral infections, but has not been tested in sick people with smallpox.[72] Therefore, it is not known whether such therapy would be beneficial; however, the CDC states that use of the drug may be considered during a smallpox outbreak.[72]

Brincidofovir efficacy may be reduced in immunocompromised patients based on studies in immune deficient animals.[1]

Mpox
Brincidofovir has been used in the treatment of mpox infection (off-label).[71] In vitro and animal studies have demonstrated effectiveness of brincidofovir against orthopoxviruses; however, data are not available in treating mpox infections in humans.[71] Mpox is an orthopoxvirus closely related to the causative agent of smallpox.[50,71] No specific treatments are currently available for mpox infection.[71] For most patients who have an intact immune system and do not have a skin disease, supportive care and pain control are usually

sufficient.[71] However, additional therapy may be necessary in some patients (e.g., immunocompromised patients) with more severe manifestations.[71] The CDC has issued recommendations and clinical considerations for severe manifestations of mpox infection.[71] Drugs that have shown to be effective against other orthopoxviruses (e.g., cidofovir, tecovirimat, brincidofovir, vaccinia immune globulin intravenous [VIGIV]) have been used to treat severe mpox.[71] CDC guidelines state that tecovirimat is typically the first therapy that should be considered in patients with mpox who require more than supportive care.[71] Brincidofovir and VIGIV are additional therapeutics available from the Strategic National Stockpile (SNS) that can be considered in certain patients who need an additional or alternative treatment to tecovirimat; cidofovir can also be considered.[71] Treatment decisions should be individualized.[71] Healthcare providers may request a clinical consultation with CDC at poxvirus@cdc.gov or 770-488-7100.[71]

Brincidofovir is available from the SNS for treatment of mpox upon request through an FDA-authorized, single-patient, emergency use IND.[71] Consult CDC guidelines for criteria for use.[71] Nearly all patients who receive brincidofovir are severely immunocompromised and require brincidofovir in combination with tecovirimat.[71] Brincidofovir should not be used in combination with cidofovir.[71]

Dosage and Administration

General

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

1. Tablets: 100 mg[1]
2. Oral Suspension: 10 mg/mL[1]

Dosage

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

Dosage summary:

Administration

1. Before initiation and during treatment with brincidofovir perform hepatic laboratory testing.[1] Perform pregnancy testing before initiation of the drug in individuals of childbearing potential.[1]

2. Avoid direct contact with broken or crushed tablets or oral suspension.[1] If contact with skin or mucous membranes occurs, wash thoroughly with soap and water, and rinse eyes thoroughly with water.[1]

3. *Administration instructions for tablets*: Take on an empty stomach or with a low-fat meal (approximately 400 calories, with approximately 25% of calories from fat).[1] Swallow the tablets whole; do not crush or divide.[1]

4. *Administration instructions for oral suspension*: Take on an empty stomach.[1] Shake oral suspension before use.[1] Use an appropriate oral dosing syringe to correctly measure the total prescribed dose.[1] Discard unused portion after completion of 2 prescribed doses.[1] For patients who cannot swallow, the oral suspension can be administered by enteral tube (naso-gastric or gastrostomy tubes).[1]

5. See full prescribing information for additional details on administration and preparation of the drug.[1]

Adult and Pediatric Dosage

1. Adult and pediatric patients weighing 48 kg or above: 200 mg (two 100 mg tablets or 20 mL oral suspension for patients who cannot swallow tablets) once weekly for 2 doses (on Days 1 and 8).[1]

2. Adult and pediatric patients weighing 10 kg to less than 48 kg: 4 mg/kg oral suspension once weekly for 2 doses (on Days 1 and 8).[1]

3. Pediatric patients weighing less than 10 kg: 6 mg/kg oral suspension once weekly for 2 doses (on Days 1 and 8).[1]

Cautions

Contraindications

None.[1]

Warnings and Precautions

Increased Risk for Mortality when Used for Longer Duration

Brincidofovir is not indicated for use in diseases other than human smallpox.[1] An increase in mortality was observed in a randomized, placebo-controlled, Phase 3 trial when the drug was evaluated in another disease.[1] An increased risk in mortality is possible if brincidofovir is used for a duration longer than at the recommended dosage on Days 1 and 8.[1]

Study 301 (CMX001-301) evaluated brincidofovir versus placebo for the prevention of cytomegalovirus infection.1 A total of 303 subjects received brincidofovir (100 mg twice weekly) and 149 subjects received matching placebo for up to 14 weeks.[1] The primary endpoint was evaluated at Week 24.[1] All-cause mortality at Week 24 was 16% in the brincidofovir group compared to 10% in the placebo group.[1] Safety and effectiveness of brincidofovir have not been established for diseases other than human smallpox disease.[1]

Elevations in Hepatic Transaminases and Bilirubin

Elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and

total bilirubin have been observed, including cases of concurrent increases in ALT and bilirubin.[1] During the first 2 weeks of brincidofovir therapy in 392 subjects, ALT elevations >3x the upper limit of normal were reported in 7% of subjects and bilirubin elevations >2x the upper limit of normal were reported in 2% of subjects; these elevations in hepatic laboratory tests were generally reversible and did not require discontinuation of brincidofovir.[1] Severe hepatobiliary adverse events including hyperbilirubinemia, acute hepatitis, hepatic steatosis, and venoocclusive liver disease have been reported in less than 1% of subjects.[1]

Perform hepatic laboratory testing in all patients before starting brincidofovir and while receiving the drug, as clinically appropriate.[1] Monitor patients who develop abnormal hepatic laboratory tests during brincidofovir therapy for the development of more severe hepatic injury.[1] Consider discontinuing brincidofovir if ALT levels remain persistently >10x the upper limit of normal.[1] Do not give the second and final dose of brincidofovir on Day 8 if ALT elevation is accompanied by clinical signs and symptoms of liver inflammation or increasing direct bilirubin, alkaline phosphatase, or International Normalized Ratio (INR).[1]

Diarrhea and Other GI Adverse Events
During the first 2 weeks of brincidofovir therapy in 392 subjects, a composite term of diarrhea (all grade, all cause) occurred in 40% of brincidofovir-treated subjects compared with 25% of subjects in the placebo control group.[1] Treatment with brincidofovir was discontinued in 5% of subjects for diarrhea (composite term) compared with 1% in the placebo control group.[1] Additional GI adverse events included nausea, vomiting, and abdominal pain; some of these adverse events required discontinuation of brincidofovir.[1]

Monitor patients for GI adverse events including diarrhea and dehydration, provide supportive care, and if necessary, do not give the second and final dose of brincidofovir.[1]

Coadministration with Related Products
Brincidofovir should not be co-administered with IV cidofovir.[1] Brincidofovir, a lipid-linked derivative of cidofovir, is intracellularly converted to cidofovir.[1]

Embryo-fetal Toxicity
Based on findings from animal reproduction studies, brincidofovir may cause fetal harm when administered to pregnant individuals.[1] Brincidofovir administration to pregnant rats and rabbits resulted in embryotoxicity, decreased embryo-fetal survival and/or structural malformations.[1] These effects occurred in animals at systemic exposures less than the expected human exposure based on the recommended dose of brincidofovir.[1] Use an alternative therapy to treat smallpox during pregnancy, if feasible.[1] Perform pregnancy testing in individuals of childbearing potential before initiation of brincidofovir.[1] Advise individuals of childbearing potential to avoid

becoming pregnant and to use effective contraception during treatment with brincidofovir and for at least 2 months after the last dose.[1] Advise individuals of reproductive potential with partners of childbearing potential to use condoms during treatment with brincidofovir and for at least 4 months after the last dose.[1]

Carcinogenicity
Brincidofovir is considered a potential human carcinogen.[1] Mammary adenocarcinomas and squamous cell carcinomas occurred in rats at systemic exposures less than the expected human exposure based on the recommended dose of brincidofovir.[1] Do not crush or divide brincidofovir tablets.[1] Avoid direct contact with broken or crushed tablets or oral suspension.[1] If contact with skin or mucous membranes occurs, wash thoroughly with soap and water, and rinse eyes thoroughly with water.[1]

Male Infertility
Based on testicular toxicity in animal studies, brincidofovir may irreversibly impair fertility in individuals of reproductive potential.[1]

Specific Populations
Pregnancy
Based on findings from animal reproduction studies, brincidofovir may cause fetal harm when administered to pregnant individuals.[1] Use an alternative therapy to treat smallpox during pregnancy, if feasible.[1] There are no available data on the use of brincidofovir in pregnant individuals to evaluate for a drug-associated risk of major birth defects, miscarriage, and other adverse maternal and fetal outcomes.[1] In animal reproduction studies, oral administration of brincidofovir to pregnant rats and rabbits during the period of organogenesis resulted in embryotoxicity and structural malformations.[1] These effects occurred in animals at systemic exposures less than the expected human exposure based on the recommended dose of brincidofovir.[1]

The estimated background risk of major birth defects for the indicated population is unknown, and the estimated background risk of miscarriage for the indicated population is higher than the general population.[1] All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.[1] In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.[1]

Lactation
Because of the potential for variola virus transmission through direct contact with the breastfed infant, breastfeeding is not recommended in patients with smallpox.[1] There are no data on the presence of brincidofovir in human milk, the effects of the drug on the breastfed infant, or on milk production.[1] Brincidofovir is present in animal milk.[1]

Females and Males of Reproductive Potential

Based on animal data, brincidofovir may cause fetal harm.[1]

Perform pregnancy testing in individuals of childbearing potential before initiation of brincidofovir.[1]

Advise individuals of childbearing potential to use effective contraception during treatment and for at least 2 months after the last dose of brincidofovir.[1]

Advise sexually active individuals with partners of childbearing potential to use condoms during treatment and for at least 4 months after the last dose of brincidofovir.[1]

Based on testicular toxicity in animal studies, brincidofovir may irreversibly impair fertility in individuals of reproductive potential.[1]

Pediatric Use
As in adults, the effectiveness of brincidofovir in smallpox infected pediatric patients, including neonates, is based solely on efficacy studies in animal models of orthopoxvirus disease.[1] The recommended pediatric dosing regimen is expected to produce brincidofovir exposures that are comparable to those in adults based on a population pharmacokinetic modeling and simulation approach.[1] The dosage for pediatric patients is based on weight.[1]

There have been 23 pediatric subjects aged 7 months to 17 years who received brincidofovir in a randomized, placebo-controlled clinical trial.[1] The safety in adult and pediatric subjects treated with brincidofovir were similar.[1] An additional 166 pediatric subjects 3 months to 18 years of age received brincidofovir from uncontrolled studies and expanded access.[1] The dosage of brincidofovir in pediatric patients <3 months of age was based on modeling and simulations.[1]

Geriatric Use
Of the 392 subjects in the controlled clinical studies, 21% were ≥65 years of age and 1% were ≥75 years of age.[1] The nature and severity of adverse events was comparable between subjects older and younger than 65 years.[1] No alteration of dosing is recommended for patients ≥65 years of age.[1]

Renal Impairment
No dosage adjustment of brincidofovir is required for patients with mild, moderate, or severe renal impairment or patients with end stage renal disease (ESRD) receiving dialysis.[1]

Hepatic Impairment
Perform hepatic laboratory testing in all patients before starting brincidofovir and while receiving brincidofovir, as clinically appropriate.[1] No dosage adjustment is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C).[1]

Common Adverse Effects
Common adverse reactions (occurring in at least 2% of brincidofovir-treated subjects) were diarrhea, nausea, vomiting, and abdominal pain.[1]

Drug Interactions

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:
Concomitant use with organic anion transporting polypeptide (OATP) 1B1 and 1B3 inhibitors increases brincidofovir exposure, which may increase brincidofovir-associated adverse reactions.[1] Consider alternative medication that are not OATP1B1 or 1B3 inhibitors.[1] If concomitant use is necessary, increase monitoring for adverse reactions associated with brincidofovir and postpone the dosing of OATP1B1 or 1B3 inhibitors at least 3 hours after brincidofovir administration.[1]

No vaccine-drug interaction studies have been performed in human subjects.[1] Animal studies have indicated that coadministration of brincidofovir at the same time as live smallpox vaccine (vaccinia virus) may reduce the immune response to the vaccine.[1] It is also possible that brincidofovir may reduce the immune response to replication-defective smallpox vaccine (modified vaccinia virus Ankara).[1] The clinical impacts of these potential interactions on vaccine efficacy are unknown.[1]

Actions
Mechanism of Action
Brincidofovir is an antiviral drug against variola (smallpox) virus.[1]

Brincidofovir is a lipid conjugate of cidofovir, an acyclic nucleotide analog of deoxycytidine monophosphate.[1] The lipid conjugate is designed to mimic a natural lipid, lysophosphatidylcholine, and thereby use endogenous lipid uptake pathways.[1] Once inside cells, the lipid ester linkage of brincidofovir is cleaved to liberate cidofovir, which is then phosphorylated to produce the active antiviral, cidofovir diphosphate.[1] Based on biochemical and mechanistic studies using recombinant vaccinia virus E9L DNA polymerase, cidofovir diphosphate selectively inhibits orthopoxvirus DNA polymerase-mediated viral DNA synthesis.[1] Incorporation of cidofovir into the growing viral DNA chain results in reductions in the rate of viral DNA synthesis.[1]

Non-antagonistic antiviral activity of brincidofovir and tecovirimat has been demonstrated in cell culture and animal models.[1]

There are no known instances of naturally occurring brincidofovir resistant orthopoxviruses, although brincidofovir resistance may develop under drug selection.[1] Cell culture studies have shown that certain amino acid substitutions in the target viral DNA

polymerase protein can confer reductions in brincidofovir antiviral activity.[1] The possibility of resistance to brincidofovir should be considered in patients who either fail to respond to therapy or who develop recrudescence of disease after an initial period of responsiveness.[1]

Cross-resistance between brincidofovir and tecovirimat is not expected based on their distinct mechanisms of action.[1] Where tested, orthopoxvirus isolates resistant to tecovirimat have not been resistant to brincidofovir and/or cidofovir and vice versa.[1]

Advice to Patients

1. Advise the patient to read the FDA-approved patient labeling.[1]
2. Inform patients that the efficacy of brincidofovir is based solely on efficacy studies demonstrating a survival benefit in animals and that the effectiveness of brincidofovir has not been tested in humans with smallpox disease.[1]
3. Inform patients of the need for liver monitoring before treatment with brincidofovir and during treatment if signs or symptoms of liver injury occur.[1] Advise patients to report symptoms that may indicate liver injury, including right upper abdominal discomfort, dark urine, or jaundice.[1]
4. Inform patients of the risk of diarrhea and other GI adverse events (nausea, vomiting, and abdominal pain) while taking brincidofovir.[1] Advise patients to inform their healthcare provider if they develop severe diarrhea or other severe GI symptoms.[1]
5. Inform patients that brincidofovir may interact with some drugs.[1] If concomitant use of OATP1B1 and 1B3 inhibitors with brincidofovir is necessary, advise patients to postpone the dosing of these medicines for at least 3 hours after brincidofovir administration.[1]
6. Advise pregnant individuals and individuals of childbearing potential of the risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy.[1] Advise individuals of childbearing potential to use effective contraception during treatment with brincidofovir and for at least 2 months after the last dose.[1] Due to animal findings of testicular toxicity, advise individuals of reproductive potential with partners of childbearing potential to use condoms during treatment with brincidofovir and for at least 4 months after the last dose.[1]
7. Advise individuals of reproductive potential that treatment with brincidofovir may deplete sperm, resulting in infertility.[1]
8. Instruct individuals with smallpox not to breastfeed their infant because of the risk of passing variola virus to the breastfed infant.[1]
9. Instruct patients or caregivers to use an oral dosing syringe to correctly measure the prescribed amount of medication.[1] Oral dosing syringes may be obtained from the pharmacy.[1] Refer to instructions in the prescribing information for administration of brincidofovir oral suspension through enteral tubes.[1] Advise patients taking the oral suspension to discard any unused portion after completion of the 2 prescribed doses.[1]
10. Advise patients not to divide, break, or crush tablets.[1] Advise patients to avoid direct contact with broken or crushed tablets and oral suspension.[1] If contact with skin or mucous membranes occurs, inform patients to wash thoroughly with soap and water, and rinse eyes thoroughly with water.[1]

AHFSfirstRelease™. For additional information until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is essential that the manufacturer's labeling be consulted for more detailed information on usual uses, dosage and administration, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Restricted Distribution

Brincidofovir is stockpiled by the Assistant Secretary for Preparedness and Response (ASPR) Strategic National Stockpile.[71,72]

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

Brincidofovir

Suspension
10 mg/mL
Tembexa® ,
Emergent BioDefense Operations Lansing

Tablets, film-coated
100 mg
Tembexa® ,
Emergent BioDefense Operations Lansing

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