AMPHOTERICIN B CHOLESTERYL COMPLEX (Systemic)

Antifungal (systemic).

Indications

General considerations

Amphotericin B cholesteryl complex is active in vitro against Aspergillus and Candida species, as well as against other fungi 1.

Accepted

Aspergillosis (treatment)¾Amphotericin B cholesteryl complex is indicated in the treatment of invasive aspergillosis in patients who are refractory to or intolerant of amphotericin B deoxycholate therapy 1.

Mechanism of action/Effect:

Amphotericin B binds primarily to ergosterol in cell membranes of sensitive fungi, causing leakage of intracellular contents and cell death due to changes in membrane permeability 1.

Amphotericin B also binds to cholesterol in mammalian cell membranes; this action is believed to account for its toxicity in animals and humans 1.

Precautions to Consider

Carcinogenicity

Long-term studies in animals have not been done to evaluate the carcinogenic potential of amphotericin B cholesteryl complex 1.

Mutagenicity

No mutagenic effects were found in vitro in the Salmonella reverse mutation assay, the CHO cell chromosomal aberration assay, or the mouse lymphoma forward mutation assay, or in vivo in the mouse bone marrow micronucleus assay 1.

Pregnancy/Reproduction

Fertility¾Studies have not been done to evaluate the effects of amphotericin B cholesteryl complex on fertility 1.

However, doses of up to 0.4 and 0.5 times the recommended human dose given to dogs and rats, respectively, for up to 13 weeks did not affect ovarian or testicular histology 1.

Pregnancy¾Adequate and well-controlled studies in humans have not been done 1.

Studies at doses of up to 0.4 and 1.1 times the recommended human dose given to rats and rabbits, respectively, showed no evidence of fetal harm 1.

FDA Pregnancy Category B 1.

Breast-feeding

It is not known whether amphotericin B cholesteryl complex is distributed into breast milk. Because of the potential for serious adverse effects in nursing infants, a decision should be made to either stop breast-feeding or discontinue taking amphotericin B cholesteryl complex. 1

Pediatrics

Ninety-seven pediatric patients have been treated with amphotericin B cholesteryl complex at daily doses similar to those in adults (on a mg per kg of body weight basis), and no unexpected adverse events have been reported 1.

Geriatrics

Sixty-eight patients 65 years of age and older have been treated with amphotericin B cholesteryl complex, and no unexpected events have been reported 1.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
>> Antineoplastic agents 1

(concurrent use with amphotericin B cholesteryl complex may enhance the potential for bronchospasm, hypotension, and renal toxicity 1 ; caution is required if these medications are to be used concurrently 1)

Clotrimazole 1 or

Fluconazole 1 or

Ketoconazole 1 or

Miconazole 1 or

Other imidazoles 1

(in vitro and in vivo animal studies have reported antagonism between amphotericin B and imidazole derivatives, such as ketoconazole and miconazole, that inhibit ergosterol synthesis 1 ; the clinical significance of these findings has not been determined 1)

>> Corticosteroids 1 or

>> Corticotropin (ACTH) 1

(concurrent use with amphotericin B cholesteryl complex may potentiate hypokalemia, which may predispose the patient to cardiac dysfunction 1 ; cardiac function and serum electrolytes should be monitored 1)

Cyclosporine 1 or

Tacrolimus 1

(adult and pediatric patients receiving amphotericin B cholesteryl complex with cyclosporine or tacrolimus had a 31% incidence of renal toxicity [a doubling or an increase of 1 mg per dL or more from baseline serum creatinine, or ³ 50% decrease from baseline calculated creatinine clearance], compared with a 68% incidence of renal toxicity for patients receiving amphotericin B deoxycholate with cyclosporine or tacrolimus 1)

>> Digitalis glycosides 1

(concurrent use with amphotericin B cholesteryl complex may induce hypokalemia and may potentiate digitalis toxicity 1 ; serum potassium concentrations should be monitored closely 1)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Risk-benefit should be considered when the following medical problem exists

>> Hypersensitivity to amphotericin B cholesteryl complex 1

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
Complete blood count (CBC) 1

(counts should be monitored as medically indicated 1)

Electrolytes, serum 1

(concentrations should be monitored as medically indicated 1)

Hepatic function tests 1 and

Prothrombin time (PT) 1 and

Renal function tests 1

(values should be monitored as medically indicated 1)

Side/Adverse Effects

Note: Anaphylaxis has been reported with amphotericin B-containing medications 1.

Acute infusion-related reactions, including chills, fever, headache, hypotension, hypoxia, nausea, and tachypnea, usually occur 1 to 3 hours after intravenous infusion has been initiated 1.

These reactions are usually more severe or more frequent with initial doses of amphotericin B cholesteryl complex and usually diminish with subsequent doses 1.

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence more frequent

Infusion-related reaction 1 chills); fever); headache); hypoxia); nausea)
Incidence less frequent

Dyspnea 1 difficulty in breathing); hypertension 1; hypotension 1 dizziness or fainting); tachycardia 1 increased heartbeat); thrombocytopenia 1 (unusual bleeding or bruising)
Incidence rare

Anaphylactic reaction 1 (difficulty in breathing or swallowing; hives; itching, especially of feet or hands; reddening of skin, especially around ears; swelling of eyes, face, or inside of nose; unusual tiredness or weakness, sudden and severe)
Those indicating need for medical attention only if they continue or are bothersome

Incidence less frequent

Nausea 1; vomiting 1

Overdose

Amphotericin B deoxycholate overdose has been reported to result in cardiopulmonary arrest 1.

Amphotericin B cholesteryl complex is not dialyzable 1.

For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Treatment of overdose

Supportive care¾Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric consultation.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Amphotericin B Cholesteryl Complex (Systemic)¾Introductory Version .
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Sensitivity to amphotericin B cholesteryl complex
Other medications, especially antineoplastic agents, corticosteroids, corticotropin (ACTH), digitalis glycosides, nephrotoxic medications, or nondepolarizing neuromuscular blocking agents
Side/adverse effects

Signs of potential side effects, especially infusion-related reaction, dyspnea, hypertension, hypotension, tachycardia, thrombocytopenia, or anaphylactic reaction

General Dosing Information

Intravenous infusion should be administered at a rate of 1 mg per kg of body weight per hour 1.

A test dose immediately preceding the first dose is advisable when beginning all new courses of treatment 1.

A small amount of the medication (e.g., 10 mL of the final preparation containing 1.6 to 8.3 mg) should be infused over 15 to 30 minutes, and the patient carefully observed for the next 30 minutes 1.

The infusion time may be shortened to a minimum of 2 hours for patients who show no evidence of intolerance or infusion-related reactions 1.

If the patient experiences acute reactions or cannot tolerate the infusion volume, the infusion time may be extended 1.

used for reconstitution and dilution. 1