FOR THE USE ONLY OF A REGISTERED MEDICAL PRACTITIONER OR A HOSPITAL OR A LABORATORY.

AMPHOTERICIN B FOR INJECTION U.S.P.

AMPHOTRET®

(Lyophilized)

DESCRIPTION:
AMPHOTRET® (Amphotericin B for Injection U.S.P) is a freeze dried preparation of Amphotericin B for intravenous injection. **AMPHOTRET®** (Amphotericin B for Injection U.S.P.) is a yellow coloured cake, on reconstitution, gives a clear yellow solution in 10 ml vial. **AMPHOTRET®** (Amphotericin B for Injection U.S.P.) is required to be reconstituted with Sterile Water for Injection before administration. Amphotericin B is a polyene macrolide antifungal antibiotic obtained from a strain of Streptomyces nodosus. Amphotericin B is insoluble in water at neutral pH and hence formulated as a colloidal dispersion using sodium deoxycholate as a solubiliser.

COMPOSITION:
Each vial contains:

Amphotericin B U.S.P.	50mg
Sodium Deoxycholate	q.s. (as solubiliser)
Sodium Phosphate (as buffer)	

CLINICAL PHARMACOLOGY:
Amphotericin B is fungistatic or fungicidal depending on the concentration obtained in body fluids and the susceptibility of the fungus. The drug acts by binding to sterols in the cell membrane of susceptible fungi with a resultant change in membrane permeability allowing leakage of intracellular components. Mammalian cell membranes also contain sterols and it has been suggested that the damage to human cells and fungal cells may share common mechanisms. Amphotericin B shows a high order of *in vitro* activity against many species of fungi. *Histoplasma capsulatum, Coccidioides immitis, Candida species, Blastomyces dermatitidis, Rhodotorula, Cryptococcus neoformans, Sporothrix schenckii, Mucor mucedo,* and *Aspergillus fumigatus* are all inhibited by concentrations of Amphotericin B ranging from 0.03 to 1.0 mcg/mL *in vitro*. While *Candida albicans* is generally quite susceptible to amphotericin B, non-albicans species may be less susceptible. *Pseudallescheria boydii* and *Fusarium sp.* are often resistant to amphotericin B. The antibiotic is without effect on bacteria, rickettsiae, and viruses.

PHARMACOKINETICS:
An initial intravenous infusion of 1 to 5mg of amphotericin per day, gradually increased to 0.65mg/kg daily, produces peak plasma concentrations of approximately 2 to 4mg/l which can persist between doses since the plasma half-life of amphotericin is about 24 hours. It has been reported that amphotericin is highly bound (more than 90%) to plasma proteins and is poorly dialyzable. The average plasma concentration tends to reach 500 nanograms/mL with maintenance doses.
Amphotericin B is reported to be highly bound to plasma proteins and is widely distributed, but passes into the CSF only in small quantities.
The plasma half-life has been reported to be about 24 hours, with long term administration, the terminal half-life increases to 15 days.
Unchanged Amphotericin B is excreted in small amounts slowly in the urine. Traces have been reported to be present in the serum and urine several weeks after completion of treatment.
Amphotericin B is not removed by haemodialysis.

INDICATIONS & USAGE:
AMPHOTRET® (Amphotericin B for Injection U.S.P.) Intravenous should be administered primarily to patients with progressive, potentially life-threatening fungal infections. This potent drug should not be used to treat noninvasive fungal infections, such as oral thrush, vaginal candidiasis and esophageal candidiasis in patients with normal neutrophil counts.
AMPHOTRET® (Amphotericin B for Injection U.S.P.) Intravenous is specifically intended to treat potentially life-threatening fungal infections : aspergillosis, cryptococcosis (torulosis), North American blastomycosis, systemic candidiasis, coccidioidomycosis, histoplasmosis, zygomycosis including mucormycosis due to susceptible species of the genera Absidia, Mucor and Rhizopus, and infections due to related susceptible species of Conidiobolus and Basidiobolus, and sporotrichosis.

CONTRAINDICATIONS:
AMPHOTRET® (Amphotericin B for Injection U.S.P.) is contraindicated in those patients who are hypersensitive to Amphotericin B or any of the component in the formulation.

WARNING:
Amphotericin B is frequently the only effective treatment available for potentially life-threatening fungal disease. In each case, its possible life-saving benefit must be balanced against its untoward and dangerous side effects.
General: Amphotericin B should be administered intravenously under close clinical observation by medically trained personnel. It should be reserved for treatment of patients with progressive, potentially life-threatening fungal infections due to susceptible organisms.
Acute reactions including fever, shaking chills, hypotension, anorexia, nausea, vomiting, headache, and tachypnea are common 1 to 3 hours after starting an intravenous infusion. These reactions are usually more severe with the first few doses of amphotericin B and usually diminish with subsequent doses.
Rapid intravenous infusion has been associated with hypotension, hypokalemia, arrhythmias, and shock and should, therefore, be avoided. Amphotericin B should be used with care in patients with reduced renal function; frequent monitoring of renal function is recommended. In some patients hydration and sodium repletion prior to Amphotericin B administration may reduce the risk of developing nephrotoxicity.
Supplemental alkali medication may decrease renal tubular acidosis complications. Since acute pulmonary reactions have been reported in patients given Amphotericin B during or shortly after leukocyte transfusions, it is advisable to temporarily separate these infusions as far as possible and to monitor pulmonary function. Leukoencephalopathy has been reported following use of Amphotericin B. Total body irradiation may be a predisposition. Whenever medication is interrupted for a period longer than seven days, therapy should be resumed by starting with the lowest dosage level, e.g., 0.25mg/kg of body weight, and increased gradually.

PEDIATRIC USE:
Safety and effectiveness in pediatric patients have not been established through adequate and well-controlled studies.

PREGNANCY AND LACTATION:
Safety for use in pregnancy has not been established; therefore it should be used during pregnancy only if the possible benefits to be derived outweigh the potential risks involved.

ADVERSE EFFECTS:
Although some patients may tolerate full intravenous doses of amphotericin B without difficulty, most will exhibit some intolerance, often at less than the full therapeutic dose. Tolerance may be improved by treatment with aspirin, antipyretics (e.g., acetaminophen), antihistamines, or antiemetics.
Meperidine (25 to 50mg IV) has been shown in some patients to decrease the duration of shaking chills and fever that may accompany the infusion of amphotericin B.

Size : L x H = 122 x 220 mm

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Paper : 40 gsm, ITC Print Paper
Outline & Cutting marks not to print
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Administration of Amphotericin B on alternate day may decrease anorexia and phlebitis. Intravenous administration of small doses of adrenal corticosteroids just prior to or during the Amphotericin B infusion may help decreased febrile reaction. Dosage and duration of such corticosteroid therapy should be kept to a minimum. Addition of heparin (1000 units per infusion), and the use of a pediatric scalp-vein needle may lessen the incidence of thrombophlebitis. Extravasation may cause chemical irritation. The adverse reactions most commonly observed are:
General (body as a whole): fever (sometimes accompanied by shaking chills usually occurring within 15 to 20 minutes after initiation of treatment); malaise; weight loss.

Cardiopulmonary : hypotension; tachypnea.
Gastrointestinal : anorexia; nausea; vomiting; diarrhea; dyspepsia; cramping epigastric pain.
Hematologic : normochromic, normocytic anemia.
Local : pain at the injection site with or without phlebitis or thrombophlebitis.
Musculoskeletal : generalized pain, including muscle and joint pains.
Neurologic : headache.
Renal : decreased renal function and renal function abnormalities including: azotemia, hypokalemia, hyposthenuria, renal tubular acidosis; and nephrocalcinosis.

DOSAGE & ADMINISTRATION:
DOSAGE:
CAUTION: Under no circumstances should a total daily dose of 1.5mg/kg be exceeded. Amphotericin B overdoses can result in cardio-respiratory arrest.
AMPHOTRET® (Amphotericin B for Injection U.S.P.) Intravenous should be administered by slow intravenous infusion. Intravenous infusion should be given over a period of approximately 2 to 6 hours (depending on the dose) observing the usual precautions for intravenous therapy. The recommended concentration for intravenous infusion is 0.1mg/mL (1mg/10mL). Since patient tolerance varies greatly, the dosage of amphotericin B must be individualized and adjusted according to the patient's clinical status (e.g., site and severity of infection, etiologic agent, cardio-renal function, etc). A single intravenous test dose (1mg in 20 mL of 5% dextrose solution) administered over 20-30 minutes may be preferred. The patient's temperature, pulse, respiration, and blood pressure should be recorded every 30 minutes for 2 to 4 hours. In patients with good cardio-renal function and a well tolerated test dose, therapy is usually initiated with a daily dose of 0.25mg/kg of body weight. However, in those patients having severe and rapidly progressive fungal infection, therapy may be initiated with a daily dose of 0.3mg/kg of body weight. In patients with impaired cardio-renal function or a severe reaction to the test dose, therapy should be initiated with smaller daily doses (i.e., 5 to 10mg). Depending on the patient's cardiorenal status, doses may gradually be increased by 5 to 10mg per day to final daily dosage of 0.5 to 0.7mg/kg. There are insufficient data presently available to define total dosage requirements and duration of treatment necessary for eradication of specific mycoses. The optimal dose is unknown. Total daily dosage may range up to 1.0mg/kg per day or up to 1.5mg/kg when given on alternate day.
Sporotrichosis: Therapy with intravenous amphotericin B for sporotrichosis has ranged up to nine months with a total dose up to 2.5 g.
Aspergillosis: Aspergillosis has been treated with amphotericin B intravenously for a period up to 11 months with a total dose up to 3.6 g.

ADMINISTRATION:
Reconstitute the content of **AMPHOTRET®** (Amphotericin B for Injection U.S.P.) adding 10 ml of Sterile Water for Injection B.P. into the vial, shaking the content till a visibly clear solution is obtained. The solution for infusion is prepared by diluting further with 5% Dextrose Injection B.P. (of pH above 4.2). Since **AMPHOTRET®** (Amphotericin B for Injection U.S.P.) contains no preservative or a bacteriostatic agent, aseptic techniques must strictly observed during handling and administration of **AMPHOTRET®** (Amphotericin B for Injection U.S.P.).
Discard the solution on reconstitution if the solution is not visibly clear or contains evidence of foreign particles. In-line microbial membrane filter with pore size 1µ or more may be used for intravenous administration of **AMPHOTRET®** (Amphotericin B for Injection U.S.P.) (See WARNING).

INCOMPATIBILITIES:
None known.

DRUG INTERACTION:
Amphotericin B is potentially nephrotoxic and hence close monitoring of the renal function is required in patients receiving concomitantly other nephrotoxic drugs like antibacterials, immunosuppressant, parenteral pentamidine. If possible, Amphotericin B should not be given to patients receiving anti-neoplastics. Diuretics should generally be avoided in patients taking Amphotericin B. If a diuretic has to be given, then volume and electrolyte depletion should be monitored carefully.
The potassium-depleting effect of Amphotericin B may enhance the effects of neuromuscular blocking drugs and may increase the toxicity of digitalis glycosides. Corticosteroids may enhance the depletion of potassium and their immunosuppressive effects may be detrimental in patients with severe fungal infections. Local anaesthetics such as Procaine hydrochloride and Lidocaine hydrochloride cause precipitation of Amphotericin B. Amphotericin B is also stated to be incompatible with Ranitidine hydrochloride. Amphotericin B is stated to be incompatible with anti-histamines and vitamins. Flucytosine: While a synergistic relationship with amphotericin B has been reported, concomitant use may increase the toxicity of flucytosine by possibly increasing its cellular uptake and/or impairing its renal excretion. Imidazoles (e.g., ketoconazole, miconazole, clotrimazole, fluconazole, etc.) : in vitro and animal studies with the combination of amphotericin B and imidazoles suggest that imidazoles may induce fungal resistance to amphotericin B. Combination therapy should be administered with caution, especially in immunocompromised patients. Skeletal muscle relaxants : amphotericin B-induced hypokalemia may enhance the curariform effect of skeletal muscle relaxants (e.g., tubocurarine). Serum potassium levels should be monitored and deficiencies corrected. Leukocyte transfusions : acute pulmonary toxicity has been reported in patients receiving intravenous amphotericin B and leukocyte transfusions.

OVERDOSAGE:
Amphotericin overdoses can result in cardio-respiratory arrest. If an overdose is suspected, discontinue therapy and monitor the patent's clinical status (e.g. cardiorespiratory, renal and liver function, haematologic status serum electrolytes) and administer supportive therapy as required. Amphotericin is not haemodialysable. Prior to reinstituting therapy, the patient's condition should be stabilised (including correction of electrolyte deficiencies, etc.).

STORAGE:
Store **AMPHOTRET®** (Amphotericin B for Injection U.S.P.) at a temperature not exceeding 8ºC preferably in a refrigerator. Protect **AMPHOTRET®** (Amphotericin B for Injection U.S.P.) vials from direct sunlight. Solution should be protected from light during administration. The reconstituted solution is stable upto 7 days when stored at 2ºC - 8ºC.

PRESENTATION:
AMPHOTRET® (Amphotericin B for Injection U.S.P.) is available as a Lyophilized product in a single dose USP Type I clear, colorless vial / box providing 50mg of Amphotericin B.

Keep out of reach of children.

Date of Revision: February 2024.

Manufactured by :
BHARAT SERUMS AND VACCINES LIMITED
Plot No. K-27, K-27 Part and K-27/1, Anand Nagar, Jambivili Village,
Additional MIDC, Ambernath (East), Thane 421506, Maharashtra State, India.

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