SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AMPHOTRET [Amphotericin B for Injection USP 50 mg (Lyophilized)]

2. QUALITATIVE AND QUANTITATIVE COMPOSITIONS

Each vial contains :
Amphotericin B U.S.P. 50 mg.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilized powder for Injection
Product Appearance: AMPHOTRET is a yellow-colored cake which is required to be reconstituted with Sterile Water for Injection before administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Amphotret (Amphotericin B for Injection U.S.P.) should be administered primarily to patients with progressive, potentially life-threatening fungal infections. Amphotret (Amphotericin B for Injection U.S.P.) should not be administered to treat non-invasive fungal infections such as oral thrush, vaginal candidiasis and oesophageal candidiasis in patients having normal neutrophil counts. Amphotret (Amphotericin B for Injection U.S.P.) is specifically indicated in the treatment of fungal infections susceptible to Amphotericin B such as the one caused by Candida spp., Aspergillus spp., Crytococcus neoformans, Mucor spp., Rhodotorula spp., Absidia spp., Blastomyces dermatitidis.

4.2 Posology and method of administration and Dosage:

Dosage:
The determination of Amphotericin B doses is largely empirical and is influenced by therapeutic response data, nephrotoxicity and patient tolerance. The usual daily maintenance dose of Amphotret (Amphotericin B for Injection U.S.P.) is equivalent to 0.5 to 1mg/kg of Amphotericin B; the administration of higher daily dosage has been documented. at any given time of administration, a total dose of 1.5mg/kg should never be exceeded.
Amphotericin B overdoses can result in cardio respiratory arrest. Most susceptible fungi are inhibited in vitro by less than 2µg of Amphotericin B / ml and this drug concentration can be achieved with the administration of a dose equivalent to 50 to 70mg of Amphotericin B. Poor correlation exists between therapeutic outcome and in vitro susceptibility.
Amphotret (Amphotericin B for Injection U.S.P.) can be administered daily or on alternate days. Alternate day administration of twice daily dose of Amphotericin B will provide a predictably higher peak plasma concentration.
Tolerance is improved with alternate day therapy because of less frequent administration and consequently less frequent infusion

related adverse events.

Test Dose:
A test dose will identify patients who are prone to hyper pyretic reactions or exaggerated rigor and chills. A volume of the initial dose that will deliver 1mg of Amphotericin B may be infused over 10 - 30 minutes without administration of premedication. The patient should then be observed for possible severe adverse effects upto 3 hours. Therapy should not be delayed in patients who are acutely ill or immunocompromised.

Initiation with Partial or Full Dose:
Therapy with Amphotret (Amphotericin B for Injection U.S.P.) is normally initiated with gradual, incremental increases in the Amphotericin B dose until the desired maintenance dose is achieved. The rational is to improve patient's tolerance with respect to infusion related adverse events. This approach may actually be detrimental if it delays the administration of therapeutic doses of Amphotericin B for upto several days after the decision to start Amphotret (Amphotericin B for Injection U.S.P.) therapy. Except in very debilitated patients, these adverse events should not cause severe sequelae. A therapeutic dosage of Amphotericin B (0.25 to 0.3mg/kg/day) should not be delayed in an attempt to avoid infusion related adverse events. Also maintenance doses of Amphotret (Amphotericin B for Injection U.S.P.) should not be delayed in patients with immune suppression or acute illness.

Infusion Time:
In a randomised controlled trial to study the effects of rate of administration of Amphotericin B deoxycholate over a period of 4 hrs and 24 hrs, it was observed that slow infusion (over 24 hrs) of Amphotericin B deoxycholate reduced overall mortality, side effects and nephrotoxicity when compared to rapid infusion (over 4 hrs)7. Slow intravenous infusion of Amphotericin B is indicated in anuric patients and individuals with impaired potassium excretion.
The co-administration of 500 to 1000 ml of diluent 5% Dextrose Injection B.P. every 24 to 48 hours is recommended when Amphotret (Amphotericin B for Injection U.S.P.) is diluted to a concentration of Amphotericin B not exceeding 0.1mg/ml.
Administration:
Reconstitute the content of Amphotret (Amphotericin B for Injection U.S.P.) adding 10ml of Sterile Water for Injection B.P. into the vial, shaking the contents 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 be 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.).

4.3 Contra-indications

Amphotret (Amphotericin B for Injection U.S.P.) is contraindicated in those patients who are hypersensitive to Amphotericin B or any of the components in the formulation.

4.4 Special warning and precautions for use Anaphylactic reactions:

Amphotret (Amphotericin B for Injection U.S.P.) therapy is required to be initiated under close clinical observation by a qualified medical personnel.

Acute reactions which are common include fever, chills, headache, nausea and vomiting. A variety of ancillary medications, most often including acetaminophen, nonsteroidal anti-inflammatory drugs, antihistamines, antiemetics, meperidine, corticosteroids, and heparin are used for the prophylaxis and treatment of adverse effects associated with administration of Amphotret (Amphotericin B for Injection U.S.P.). Patients who experience a pronounced reaction to a test dose of Amphotret (Amphotericin B for Injection U.S.P.) should receive premedication before subsequent doses; otherwise the use of ancillary medications should be reserved for the treatment of symptoms.

4.5 Interaction with other drugs, other forms of interactions

Amphotericin B is potentially nephrotoxic and hence close monitoring of the renal function is required in patients receiving concomitantly other nephrotoxic drugs like anti-bacterials, immunosuppressants, parenteral pentamidine.

If possible, Amphotericin B should not be given to patients receiving antineoplastics. 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.

4.6 Pregnancy and lactation

A review of the use of anti-fungal drugs in pregnancy concluded that parenteral Amphotericin B was the drug of first choice in the treatment of serious fungal infections in pregnancy.

Amphotericin B for Injection has been used successfully to treat systemic fungal infections in pregnant women with no obvious effects on the foetus, but only a small number of cases have been studied.

Reproductive toxicity studies of Amphotericin B in rats and rabbits have been reported to show no evidence of embryotoxicity, foetoxicity or teratogenicity.

It is not known whether Amphotericin B is found in milk of nursing mothers. It is prudent to advise a nursing mother to discontinue nursing.

4.7 Effects on ability to drive and operate machine

The patient is hospitalized, the administration of amphotericin B is

intravenous therefore patient is not allowed to drive or operate the machines.

4.8 Undesirable effects

The adverse effects related to the intravenous administration of Amphotericin B include nephrotoxicity, anemia, infusion related adverse events and phlebitis. Nephrotoxicity is major dose limiting organ toxicity. One manifestation is tubular.

necrosis. Signs of nephrotoxicity include elevated serum creatinine and blood urea nitrogen, hypokalemia and hypomagnesemia.
Amphotericin B nephrotoxicity tends to be reversible, although there is evidence that doses exceeding 4 to 5gm place patients at risk for irreversible changes in renal function.

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdoses

Amphotret (Amphotericin B for Injection U.S.P.) overdoses may result in cardio respiratory arrest. Discontinue the therapy; monitor the patient providing supportive therapy as required.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacological classification: Antifungals, ATC code: J02AA01.
Clinical activity of Amphotericin B has been shown against Candida species. Cryptococcus neoformans, Blastomyces dermatitidis, Histoplasma capsulatum, Torulopsis glabrata, Coccidioides immitis, Paracoccidioides braziliensis, Aspergillus species and species causing mucomycosis.
Amphotericin B remains the antifungal of choice for progressive and potentially fatal infections with susceptible organisms. Depending on the concentration achieved in the body fluids and the susceptibility of the fungus, Amphotericin B acts as either fungicidal or fungistatic.

5.2 Pharmacokinetic properties

When administered intravenously, peak plasma concentrations of 0.5 to 4 micrograms/mL, have been reported.
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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Sodium Deoxycholate
- Phosphoric Acid
- Sodium Hydroxide
- Water for Injection

6.2 Incompatibilities:

Do not mix with other IV medications

6.3 Shelf-life:

36 months from the date of manufacturing.

6.4 Special precaution for storage

Store at 2°C – 8°C. Protect from light. Solution should be protected from light during administration.

6.5 Nature and contents of container:

The product is packed in 10 ml vial in a carton along with one pack insert

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES

MAH address:
Bharat Serums & Vaccines Ltd.
3rd Floor, Liberty Tower, Plot No. K-10,
Behind Reliable Plaza, Kalwa Industrial
Estate, Airoli, Navi Mumbai 400708

Manufactured by:
Bharat Serums and Vaccines
Limited. Plot No. K-27, K-27 PART
and K-27/1
Jambivili Village, Anand Nagar, Additional MIDC,
Ambernath (East), Thane 421506,
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8. MARKETING AUTHORIZATION NUMBER

H2005/15867/155

9. DATE OF FIRST AUTHORIZATION OR RENEWAL

1st July 2010.

10. DATE OF REVISION OF THE TEXT

17th March 2025.