PRODUCT MONOGRAPH

[Pr]AMPHOTERICIN B FOR INJECTION, USP

Amphotericin B for Injection, USP
50 mg of Amphotericin B per vial

For intravenous infusion

Antifungal Agent

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PRODUCT MONOGRAPH
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THERAPEUTIC CLASSIFICATION

Antifungal Agent

ACTION AND CLINICAL PHARMACOLOGY

Amphotericin B is fungistatic or fungicidal depending on the concentration obtained in body fluids and the susceptibility of the fungus. It has been shown to exhibit a high order of *in vitro* activity against a broad spectrum of yeast and fungi.

The drug probably acts by binding to sterols present in the membrane of sensitive fungi, with the resultant change in permeability allowing leakage of a variety of small molecules. Since mammalian cell membranes also contain sterols, it has been suggested that the damage to human cells and fungal cells may share common mechanisms.

Following intravenous infusion, the antibiotic is slowly excreted by the kidneys, and demonstrable blood levels persist for at least 18 hours after the infusion is discontinued.

INDICATIONS AND CLINICAL USE

Amphotericin B for Injection, USP is specifically intended for the treatment of disseminated mycotic infections, including coccidioidomycosis; cryptococcosis (torulosis); disseminated candidiasis, histoplasmosis, South American leishmaniasis, North and South American blastomycosis; mucormycosis (phycomycosis) caused by species of the genera Mucor, Rhizopus, Absidia, Entomophthora, and Basidiobolus, sporotrichosis (*Sporotrichum schenckii*), and aspergillosis (*Aspergillus fumigatus*).

Other Clinical Uses

Limited studies have shown that amphotericin B powder for injection may be useful when administered by routes other than intravenous for the treatment of certain types of fungal infections.

1. Administration by Bladder Irrigation

The effective use of amphotericin B for fungal infections of the bladder has been reported in the literature.

The basic method used for bladder irrigation is as follows: 15 mg Amphotericin B for Injection, USP powder is dissolved in 100 to 400 mL of sterile water and injected via catheter after complete emptying of the bladder. The patient is then asked to retain the solution for as long as possible. An alkalizing mixture should be given every four hours. The treatment may be repeated until the culture is negative and the symptoms have disappeared.

2. Administration by Aerosol

Amphotericin B has also been administered by aerosol (nebulizer) for the treatment of pulmonary fungal infections.

A preparation suitable for administration by aerosol is prepared as follows: Dissolve a 50 mg vial of Amphotericin B for Injection, USP in a bottle of Alevaire or in 10 mL of distilled or sterile water. Administer 1-2 mL of this solution (5-10 mg amphotericin B) 3 to 4 times daily for a period of 1 to 2 weeks.

3. Administration for Eye Infections

Several studies have been done using topical administration of amphotericin B for fungal infections of the eye.

Such use has shown a low degree of efficacy after prolonged therapy and is not recommended unless there is no other alternative. It is unlikely to be of value except in superficial infections.

Reconstitute a 50 mg vial of Amphotericin B for Injection, USP by adding 10 mL of sterile water, giving a concentration of 5 mg/mL. Shake until the solution is clear. Further dilution of 1 mL of this solution to a concentration of 1 mg/mL using sterile water provides a solution suitable for use in the eye. Dosage varies from 2 drops every hour to 1 drop every 4 or 6 hours. Intervals between administration may be lengthened as improvement occurs. Amphotericin B has been reported in some instances to be toxic to the eye when applied locally and may cause local irritation and discomfort.

Solutions of 1.5 mg/mL up to 4.0 mg/mL have also been used. Normal (isotonic) saline is not recommended for dilution since it may cause precipitation of amphotericin B.

Higher concentrations can lead to serious damage to the eye and must not be used.

4. Administration for Ear Infections

There is little evidence to support the efficacy of such use.

CONTRAINDICATION

Amphotericin B for Injection, USP is contraindicated in those patients who have shown hypersensitivity to amphotericin B or any other component in the formulation, unless, in the opinion of the physician, the condition requiring therapy is life-threatening and amenable only to amphotericin B therapy.

WARNINGS

Serious Warnings and Precautions

Exercise caution to prevent inadvertent Amphotericin B for Injection, USP overdose. Verify the product name and dosage pre-administration, especially if dose exceeds 1.5 mg/kg.

Amphotericin B for Injection, USP should be administered primarily to patients with progressive, potentially fatal infections and should not be used to treat non-serious fungal infections.

In the treatment of potentially fatal fungal diseases, the possible life-saving benefit of Amphotericin B must be balanced against its untoward and dangerous side effects.

PRECAUTIONS

General

Prolonged therapy with amphotericin B is usually necessary. Adverse reactions are quite common when the drug is given parenterally at therapeutic dosage levels. Some of these reactions are potentially dangerous. Hence, Amphotericin B for Injection, USP should be used only in hospitalized patients or those under close clinical observation by medically trained personnel, and should be reserved for those patients in whom a diagnosis of the progressive potentially fatal forms of susceptible mycotic infections has been firmly established, preferably by positive culture or histologic study.

EXERCISE CAUTION to prevent inadvertent Amphotericin B for Injection, USP overdose, which can result in potentially fatal cardiac or cardiorespiratory arrest. **Verify the product name and dosage if dose prescribed exceeds 1.5 mg/kg** (see DOSAGE AND ADMINISTRATION and SYMPTOMS AND TREATMENT OF OVERDOSAGE).

Acute reactions including fever, shaking chills, hypotension, anorexia, nausea, vomiting, headache, and tachypnea are common 1 to 3 hours after starting an intravenous infusion.

Rapid intravenous infusion, over less than one hour, particularly in patients with renal insufficiency, has been associated with hyperkalemia and arrhythmias, and should, therefore, be avoided (see DOSAGE AND ADMINISTRATION).

Leukoencephalopathy has been reported following use of amphotericin B in patients who received total body irradiation.

Laboratory Tests

Renal function should be monitored frequently during amphotericin B therapy. Serum creatinine should be monitored on a regular basis and discontinuation or marked dose reduction of amphotericin B should be considered if a significant increase from baseline value of serum creatinine occurs.

It is also advisable to monitor on a regular basis liver function, serum electrolytes (particularly magnesium and potassium), blood counts, and hemoglobin concentrations. Low serum magnesium levels have been noted during treatment with amphotericin B. Laboratory test results should be used as a guide to subsequent dosage adjustments.

Whenever medication is interrupted for a period of longer than 7 days, therapy should be resumed by starting with the lowest dosage level, e.g., 0.25 mg/kg/day of body weight, and increased gradually to an optimum level as outlined under DOSAGE AND ADMINISTRATION.

DRUG INTERACTIONS

Antineoplastic agents: may enhance the potential for renal toxicity, bronchospasm and hypotension. Antineoplastic agents (e.g., nitrogen mustard, etc.) should be given concomitantly only with great caution.

Corticosteroids and Corticotropin (ACTH): may potentiate amphotericin B-induced hypokalemia and should not be administered concomitantly unless they are necessary to control drug reactions. Since deep fungal infections sometimes emerge in patients undergoing therapy with antibiotics and antineoplastic agents such as nitrogen mustard, they should not be given concomitantly with amphotericin B, if

avoidable. Other nephrotoxic agents (e.g., cisplatin, pentamidine, aminoglycosides and cyclosporine) may enhance the potential for renal toxicity and should not be given concomitantly except with great caution.

Digitalis glycosides: amphotericin B-induced hypokalemia may potentiate digitalis toxicity. Serum potassium levels and cardiac function should be closely monitored and any deficit promptly corrected.

Flucytosine: Concomitant administration may increase the toxicity of flucytosine possibly by 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.

Other nephrotoxic medications: agents such as aminoglycosides, cyclosporine, and pentamidine may enhance the potential for drug-induced renal toxicity, and should be used concomitantly only with great caution. Intensive monitoring of renal function is recommended in patients requiring any combination of nephrotoxic medications (see PRECAUTIONS, Laboratory Tests).

Leukocyte transfusions: Though not observed in all studies, acute pulmonary reactions have been observed in patients given amphotericin B during or shortly after leukocyte transfusions, thus it is advisable to separate these infusions as far as possible and to monitor pulmonary function.

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.

Caution should be observed when agents whose effects or toxicity may be increased by hypokalemia (eg, digitalis glycosides, skeletal muscle relaxants and antiarrhythmic agents) are administered concomitantly.

Pregnancy

Reproduction studies in animals have revealed no evidence of harm to the fetus due to Amphotericin B for injection. Systemic fungal infections have been successfully treated in pregnant women with Amphotericin B for injection without obvious effects to the fetus, but the number of cases reported has been small. Because animal reproduction studies are not always predictive of human response, and adequate and well-controlled studies have not been conducted in pregnant women, this drug should be administered during pregnancy with caution and only if the potential benefit to the mother outweighs the potential risk to the fetus.

Nursing Mothers

It is not known whether amphotericin B is excreted in human milk. Likewise, data are in conflict as to the extent of oral absorption, if any. Because many drugs are excreted in human milk and considering the potential toxicity of amphotericin B, it is prudent to advise a nursing mother to discontinue nursing.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established through adequate and well-controlled studies. Systemic fungal infections have been treated in pediatric patients without reports of unusual side effects.

ADVERSE REACTIONS

While a few patients may tolerate full intravenous doses of amphotericin B without difficulty, most will exhibit some intolerance often at less than the full therapeutic dosage. The adverse reactions most commonly observed are:

General (body as a whole): fever (sometimes accompanied by shaking chills occurring within 15 to 20 minutes after initiation of treatment) malaise and weight loss.

Digestive: anorexia, nausea, vomiting, diarrhea, dyspepsia and cramping epigastric pain.

Hematologic: normochromic and normocytic anemia.

Local: local venous 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 hyposthenuria, renal tubular acidosis and nephrocalcinosis, an increase in the serum creatinine level, a decrease in the serum creatinine clearance rate or a decrease in the phenolsulfonphthalein (PSP) excretion is commonly observed. Hypokalemia with or without concomitant impairment of renal function has often been observed. Potassium replacement may be considered by oral or parenteral route. Concomitant diuretic therapy may be a predisposition for renal impairment whereas sodium repletion or supplementation may reduce the occurrence of nephrotoxicity.

Renal damage is often accompanied by the appearance of granular and hyaline casts, and sometimes by microhematuria. Renal dysfunction is usually reversible on discontinuance of therapy, but serious and permanent renal damage has been reported in patients given large doses for prolonged periods, especially in those receiving a total dosage exceeding 5 g.

The following adverse reactions have also been reported:

General (body as a whole): flushing.

Allergic: anaphlactoid and other allergic reactions.

Cardiovascular: cardiac arrest, cardiovascular toxicity including arrhythmias, ventricular fibrillation, cardiac failure, hypertension, hypotension and shock.

Dermatologic: maculopapular rash and pruritus (without rash). Skin exfoliation, toxic epidermal necrolysis, and reports of Stevens-Johnson syndrome have been received during postmarketing surveillance.

Digestive: acute liver failure, jaundice, liver function test abnormalities, melena or hemorrhagic gastroenteritis and hepatotoxicity.

Hematologic: coagulation defects, thrombocytopenia, leukopenia, agranulocytosis, eosinophilia, leukocytosis.

Neurologic: hearing loss, tinnitus, transient vertigo, blurred vision or diplopia, peripheral neuropathy, encephalopathy, convulsions and other neurologic symptoms.

Pulmonary: dyspnea, bronchospasm, non-cardiac pulmonary edema and hypersensitivity pneumonitis.

Renal: hypomagnesemia, hyperkalemia, acute renal failure, anuria and oliguria. Nephrogenic diabetes insipidus has been reported during postmarketing surveillance.

Fever, nausea, vomiting, headache and malaise sometimes subside with continued administration. Reactions to amphotericin B may be made less severe by administration of an antipyretic, e.g., acetylsalicylic acid, an antihistaminic and/or an antiemetic prior to and concurrently with amphotericin B, or by modifying the rate of infusion. Meperidine (25 to 50 mg IV) has been shown in some patients to decrease the duration of shaking chills and fever that may accompany the infusion of amphotericin B. Addition of a small amount of heparin, rotation of the injection site, the use of a pediatric scalp-vein needle and alternate day therapy may lessen the incidence of thrombophlebitis and anorexia. Supplemental alkali medication may decrease renal tubular acidosis complications. Extravasation may cause chemical irritation.

Intravenous or intramuscular administration of small doses of adrenal corticosteroids just prior to, or during the amphotericin B infusion may decrease febrile reactions. The dosage and duration of such corticosteroid therapy should be kept to a minimum (see PRECAUTIONS).

If a severe reaction occurs during the course of an infusion, therapy should be interrupted for about 15 minutes to allow the patient to recover. If the reaction recurs, therapy should be resumed at a lower dosage the next day. Blood transfusions may be required when reversible normocytic, normochromic anemia occurs during prolonged therapy.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to:** **Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

Amphotericin B overdoses can result in potentially fatal cardiac or cardio-respiratory arrest. If an overdose is suspected, discontinue therapy and monitor the patients' clinical status (eg., cardio-respiratory, renal, and liver function, hematologic status, serum electrolytes) and administer supportive therapy as required. Amphotericin B is not hemodialyzable. Prior to reinstituting therapy, the patients' condition should be stabilized (including correction of electrolyte deficiencies, etc.).

DOSAGE AND ADMINISTRATION

Caution: Under no circumstances should a total daily dose of 1.5 mg/kg be exceeded. Amphotericin B overdoses can result in potentially fatal cardiac or cardio-respiratory arrest (see WARNINGS AND PRECAUTIONS and SYMPTOMS AND TREATMENT OF OVERDOSAGE). Large total doses may cause significant and permanent renal impairment. Consideration must be given to the potential risk versus the expected benefit.

Amphotericin B for Injection, USP 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 (see PRECAUTIONS, General). The recommended concentration for intravenous infusion in 5 % Dextrose is 0.1 mg/mL (1 mg/10 mL) (see Preparation of Solutions).

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 intensity of infection, etiologic agent, cardio-renal function, etc.).

Though not proven to be a reliable predictor of intolerance, a single intravenous test dose (1 mg 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 0.25 mg/kg of body weight but, in those patients having severe and rapidly progressive fungal infection, therapy may be initiated with a daily dose of 0.3 mg/kg of body weight. However, the need for more aggressive therapy, which may include the need to attain full therapeutic dose within 24 hours, depends on the disease entity being treated, the etoiologic agent involved, the patient's immune status as well as the patient's ability to tolerate the drug. It should be noted that Amphotericin B does not penetrate well into certain tissues/fluids, such as CSF.

Depending on the patient's cardio-renal status (see, PRECAUTIONS, General), doses may gradually be increased by 5 to 10 mg per day to final daily dosage of 0.5 to 1.0 mg / kg. 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 10 mg).

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. Dosage may range up to 1.0 mg/kg per day when administered daily or up to 1.5 mg/kg body weight when given on alternate days.

Duration of therapy depends on such factors as the etiologic agent, anatomic locations of the lesions, stage and severity of the infection, ability of the patient to tolerate amphotericin B and the patient's response to therapy. Several months of therapy may be required; a shorter period of therapy may produce an inadequate response and lead to a relapse.

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 administered intravenously for a period up to 11 months. Doses of 0.5 to 1 mg/kg/day or more, and cumulative doses of 2 to 4 g in adults may be required for serious infections (e.g., pneumonia or fungemia).

Rhinocerebral phycomycosis: This fulminating disease, generally occurs in association with diabetic ketoacidosis. Therefore, it is imperative that rapid restoration of diabetic control be instituted in order to accomplish successful treatment with Amphotericin B for Injection, USP. In contradistinction, pulmonary phycomycosis, which is more common in association with hematologic malignancies, is often an incidental finding at autopsy. A cumulative dose of at least 3 g of amphotericin B is recommended. Although a total dose of 3 to 4 g will sometimes cause lasting renal impairment, this would seem a reasonable minimum where there is clinical evidence of invasion of the deep tissues. Since rhinocerebral phycomycosis usually follows a rapidly fatal course, the therapeutic approach which often includes surgical intervention must necessarily be more aggressive than that used in more indolent mycoses.

The duration of treatment for deep-seated mycoses may be 6 to 12 weeks or longer.

Candidiasis: In disseminated and/or deep-seated *Candida* infections, usual doses of Amphotericin B for Injection, USP range from 0.4 to 0.6 mg/kg/day for four or more weeks. Doses up to 1 mg/kg/day may need to be employed depending upon the severity of infection. Treatment is given until obvious clinical improvement is seen and total cumulative doses up to 2 to 4 g in adults may need to be administered. Lower doses (0.3 mg/kg/day) may be employed in special circumstances, e.g., *Candida* esophagitis that is resistant to local therapy or when amphotericin B is used in combination with other antifungal agents.

Cryptococcosis: Therapy with Amphotericin B for Injection, USP in cryptococcosis in non-immunosuppressed patients typically may require doses of 0.3 mg/kg/day for periods approximating 4-6 weeks or until cultures demonstrate evidence of eradication. In immunosuppressed patients and/or in those with meningitis, amphotericin B may be given in combination with other antifungal agents for 6 weeks. Daily doses of amphotericin B may need to be increased in severely ill patients or in patients receiving amphotericin B alone.

In patients with cryptococcal meningitis and acquired immune deficiency syndrome (AIDS), higher doses (0.7-0.8 mg/kg/day) may need to be employed, and treatment courses may extend to 12 weeks. In AIDS patients who are culture negative after a standard course of therapy, chronic suppressive therapy, e.g., 1 mg/kg weekly should be considered.

Coccidioidomycosis: In primary coccidioidomycosis requiring treatment, Amphotericin B for Injection, USP in doses to a maximum of 1.5 mg/kg/day is given to total cumulative doses of 0.5 to 2.5 g in adults depending on the severity and site of infection. In coccidiodal menigitis, due to the poor penetration of Amphotericin B into the CSF, alternative anti-fungal therapy or alternate route of administration should be considered.

Blastomycosis: In seriously ill patients with blastomycosis, Amphotericin B for Injection, USP in doses of 0.3 to 1 mg/kg/day to a total cumulative dose of 1.5 to 2.5 g in adults are recommended.

Histoplasmosis: In chronic pulmonary or disseminated histoplasmosis, doses approximating 0.5 to 1 mg/kg/day to a total cumulative dose of 2 to 2.5 g in adults are generally recommended.

Preparation of Solutions

Reconstitute the dry powder as follows: an initial concentrate of 5 mg amphotericin B per mL is first prepared by adding 10 mL Sterile Water for Injection U.S.P. without a bacteriostatic agent to the vial of dry powder and shaking the vial until the liquid is clear.

The infusion liquid, providing 0.1 mg amphotericin B per mL is then obtained by further dilution (1:50) with 5% Dextrose Injection U.S.P. of pH above 4.2 to a volume of 500 mL. The pH of each container of Dextrose Injection should be ascertained before use. Commercial Dextrose Injection usually has a pH above 4.2; however, if it is below 4.2, 1 or 2 mL of sterile buffer should be added to the Dextrose Injection before it is used to dilute the concentrated solution of amphotericin B. The Dextrose Injection should then be retested to ascertain that the pH has been adjusted to the required range.

The recommended buffer has the following composition:

Dibasic sodium phosphate (anhydrous)		1.59 g
Monobasic sodium phosphate (anhydrous)		0.96 g
Water for Injection U.S.P.	q.s	100.0 mL

The buffer should be sterilized before it is added to the Dextrose Injection, either by filtration through a bacterial retentive stone, mat or membrane (maximum pore size of 0.45 microns), or by autoclaving for 30 minutes at 15 pounds pressure (121°C).

Caution: Aseptic technique must be strictly observed in all handling, since no preservative or bacteriostatic agent is present in the antibiotic or in materials used to prepare it for administration. Entry into the single use vial or into the diluents must be made with a sterile needle. Do not reconstitute with saline solutions. Single use. Discard unused portion.

The use of any diluent other than the ones recommended or the presence of a bacteriostatic agent (eg, benzyl alcohol) in the diluent may cause precipitation of the antibiotic. Do not use the initial concentrate or the infusion solution if there is any evidence of precipitation or foreign matter in either one.

An in-line membrane filter may be used for intravenous infusion of amphotericin B; however, the mean pore diameter of the filter should not be less than 1.0 micron in order to assure passage of the antibiotic dispersion.

PHARMACEUTICAL INFORMATION

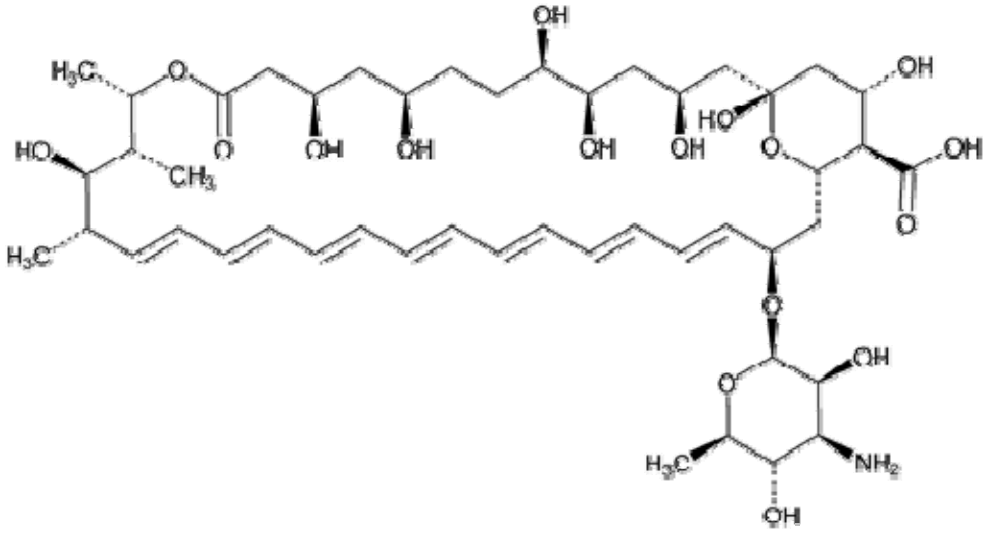
I. DRUG SUBSTANCE

Common Name: Amphotericin B

Chemical Name:

[1*R*(1*R**,3*S**,5*R**,6*R**,9*R**,11*R**,15*S**,16*R**,17*R**,18*S**,19*E*,21*E*,23*E*,25*E*,27*E*,29*E*,31*E*, 33*R**,35*S**,36*R**,37*S**)]-33- [(3-Amino-3,6-dideoxy-β-D-mannopyranosyl)oxy]-1,3,5,6,9,11,17,37-octahydroxy-15,16,18-trimethyl-13-oxo-14,-39-dioxabicyclo[33.3.1]nonatriaconta-19,21,23,25,27,29,31-heptaene-36-carboxylic acid

Structural Formula



Molecular Formula: $C_{47}H_{73}NO_{17}$

Molecular Weight: 924 g/ mol

Description

Amphotericin B is a polyene antifungal agent derived from a strain of *Streptomyces nodosus*, containing the moiety mycosamine. Crystalline amphotericin B is insoluble in water; the antibiotic is, therefore, "solubilized" by preparing a mixture of amphotericin B - deoxycholic acid which, on reconstitution, provides a colloidal dispersion for parenteral administration. Maximal antifungal effects of the antibiotic occur between pH 6.0 and 7.5 and decrease at low pH.

II. STABILITY AND STORAGE RECOMMENDATIONS

Prior to reconstitution, Amphotericin B for Injection, USP should be stored in the refrigerator (2°C - 8°C), protected against exposure to light. The concentrate (5 mg amphotericin B per mL after reconstitution with 10 mL Sterile Water for Injection U.S.P.) may be stored in the dark, at room temperature for 24

hours, or at refrigerator temperature (2°C - 8°C) for one week with minimal loss of potency and clarity. Any unused material should then be discarded. Solutions prepared for intravenous infusion (0.1 mg or less amphotericin B/mL) should be used promptly after preparation and should be protected from light during administration.

AVAILABILITY OF DOSAGE FORMS

Amphotericin B for Injection, USP is available as a sterile lyophilized powder in vials providing 50 mg amphotericin B, 38.8 mg deoxycholic acid, 19.9 mg sodium phosphates (consisting of mono and dibasic sodium phosphate) and phosphoric acid and sodium hydroxide as needed.

At the time of manufacture the air in the vial is replaced by nitrogen.

MICROBIOLOGY

Amphotericin B shows a high order of *in vitro* activity against a large number of fungi.

The M.I.C.'s for relevant fungal organisms are listed below:

Organism	MIC* (mcg/mL)
Aspergillus fumigatus	1.9
Blastomyces brasiliensis	0.2
Blastomyces dermatitidis	0.06 - 0.07
Candida albicans	0.2 - 0.5
Candida parakrusei	1.1
Candida parapsilosis	0.2 - 4.0
Candida pseudotropicalis	0.2 - 0.9
Candida tropicalis	3.7
Coccidioides immitis	0.16 - 1.0
Cryptococcus neoformans	0.2
Histoplasma capsulatum	0.04
Mucor hiemalis	2.5
Mucor rouxii	0.06
Rhizopus arrhizus	1.0 - 5.0
Rhizopus microsporus	0.03 - 5.0
Rhizopus nigricans	0.4
Rhizopus stolonifer	0.03 - 0.06
Sporotrichum schenckii (yeast phase)	0.07

* MIC = Minimal Inhibitory Concentration after 24 to 48 hours incubation, tested by agar dilution method.

The following fungi have also shown sensitivity to amphotericin B, with MIC's ranging from 0.1 to 14.7 mcg/mL:

Aspergillus flavus, Aspergillus niger, Epidermophyton floccosum, Fusarium bulbigenum, Geotrichum sp., *Microsporum audouini, Microsporum canis, Monosporium apiospermum, Rhodotorula cerevisiae, Rhodotorula glutinis, Rhodotorula mucilaginosa, Saccharomyces cerevisiae, Trichophyton gallinae, Trichophyton megnini, Trichophyton mentagrophytes, Trichophyton rubrum, Trichophyton tonsurans.*

The following organisms exhibit MIC values of greater than 40.0 mcg/mL:

Cephalosporium recifei, Cladosporium carrionii, Cladosporium wernecki, Fonsecaea compactum, Fonsecaea pedrosoi, Microsporum gypseum, Nocardia asteroides, Nocardia brasiliensis, Nocardia madurae, Phialophora verrucosa, Sporotrichum schenckii (mycelial phase).

Amphotericin B has also shown anti-protozoal activity *in vitro* against the following:

Organism	MIC (mcg/mL)
Leishmania brasiliensis	0.01
Leishmania donovani	0.1
Trypanosoma cruzi	2.5
Trypanosoma congolense	25.0
Trichomonas vaginalis	12.5

Strains of *C. albicans*, *C. guilliermondi, C. krusei,* and *C. parakrusei* have been shown to develop resistance to amphotericin B as have two strains of *Coccidioides immitis*. *Candida tropicalis* is resistant to the drug.

Amphotericin B is inactive against bacteria, rickettsiae and viruses.

PHARMACOLOGY

Human Pharmacology

In humans, an initial intravenous injection of 1 to 5 mg of amphotericin B per day, followed by gradual increase of the daily dose to 0.65 mg/kg yields peak plasma concentrations of approximately 2-4 mcg/mL. These concentrations are well maintained between doses, since the initial plasma half-life is about 24 hours. The terminal phase of amphotericin B elimination only becomes apparent when dosing is discontinued, since the final elimination phase is not reached for almost 6 days. This terminal elimination phase has a half-life of approximately 15 days. The long terminal elimination-phase half-life of amphotericin B implies that a long time will be required to attain pharmacokinetic steady state conditions with repeated doses of this drug.

Peak and "valley" (just prior to the next infusion) serum concentrations of amphotericin B were measured in 15 patients undergoing either daily or alternate-day treatment, after at least 3 consecutive infusions at the same dosage level. As expected, mean peak concentrations in patients undergoing alternate-day infusions of up to 90 mg were higher than those obtained with daily therapy with half the dose. However, despite the longer time lapse post infusion, alternate day valley serum concentrations were not significantly lower than those obtained following daily infusions. At doses above 50 mg during daily or alternate-day therapy, the valley concentrations during daily therapy and peak concentrations during either daily or alternate day therapy showed a tendency to plateau. Over the dosage range studied, the valley concentrations during alternate day therapy differed very little from one dose to another. Increasingly higher serum concentrations did not occur after the same dose was given repeatedly.

Most of the antibiotic is probably bound to sterol-containing membranes in many different tissues. Although actual details of distribution within the tissues and possible metabolic pathways are as yet unknown, the liver appears to be the major tissue storage site. Amphotericin B circulating in plasma is

highly bound (> 90%) to plasma proteins and is poorly dialyzable. Approximately two thirds of concurrent plasma concentrations have been detected in fluids from inflamed pleura, peritoneum, synovium, and aqueous humor. Concentrations in the cerebrospinal fluid seldom exceed 2.5 percent of those in the plasma or are non-detectable. Little amphotericin B penetrates into vitreous humor or normal amniotic fluid.

Amphotericin B is excreted very slowly by the kidneys, and less than 10% of an administered dose is excreted in the urine in a biologically active form. The percentage of injected drug excreted in the urine of patients without severe renal disease decreases as the dose increases. Excretion in the bile may represent an important route of elimination.

When therapy is discontinued, serum and urine concentrations of the drug fall rapidly during the first day, due to the short initial half-life, and then decline much more slowly during subsequent weeks. Levels of amphotericin B can be detected in the urine for at least seven to eight weeks.

The concentration of amphotericin B in the urine is roughly parallel to that in the plasma, and this represents such a small amount of the administered dose, that impaired renal function has no recognizable effect on plasma drug concentrations, nor on excretion of the drug by the kidneys. Plasma levels are also not affected by renal or hepatic disease.

Very little amphotericin B penetrates into the cerebrospinal fluid, parotid-gland fluid, aqueous humor or hemodialysis solutions.

TOXICOLOGY

Acute Toxicity

Mice

The $LD_{50's}$ in mice treated intravenously with preparations of amphotericin B-sodium desoxycholate complex were found to range from 3.3 - 4.6 mg/kg in several studies. Toxic signs included ataxia and convulsions.

Rabbits

The approximate LD_{50} in rabbits treated with single intravenous infusions of amphotericin B sodium desoxycholate was 5.0 - 6.0 mg/kg. The deaths usually occurred 10 to 30 minutes after completion of the infusion, and were preceded by tremors and convulsions.

Dogs

Amphotericin B preparations administered intravenously are generally more toxic in dogs than in other species due to an apparent species-specific gastrointestinal reaction (hemorrhage). One to 5 mg intravenous infusions administered to dogs in single or repeated doses (up to 3 days) resulted in bradycardia, emesis, hematemesis, polydipsia, bloody diarrhea, bloody stools, anorexia, depressed activity, emaciation, intestinal hemorrhage, an increase in blood urea nitrogen, reduced renal excretion of phenolsulfonphthalein and reduced liver detoxification of bromsulphonphthalein.

Subacute Toxicity

Species	No. of Animals per Group	No. of Groups	Dose mg/ kg/ day	Duration of Study	Route of Administration	Toxic Signs
Rat	NR*	NR*	2.5 – 6.0	3 weeks	IP	High Dose Group: Extensive nephrocalcinosis; increased calcium concentration in kidney
Dog	1 or 3	7	0.11 – 0.84	1 - 4 days	Intrathecal	One dog died after 4th injection of 2.25 mg dose. At single doses of 4.5 & 6.75 mg, 3 dogs under local anesthesia showed general discomfort, hind leg rigidity, salivation and micturition for 30 – 120 minutes. Two nembutalized dogs showed ocular damage at these doses.
Rabbit	3	5	1, 0.1 0.25, 0.625, 1.56	11 days	IV	Some elevation of BUN in low dose group after eleventh dose. Elevated values in only 1 or 0.25 mg/kg/ dose group. High Dose Groups: Marked incidences of BUN elevation after 24 hours.
Dog	3	4	0, 1, 2, 4, 3 times / week	13 weeks	IV	Focal, basophilic, tubular deposits in both kidneys of all groups, with marked areas of proximal tubular degeneration in high dose group. Mid & High Dose: Slight decrease in erythrocyte count, hematocrit & hemoglobin values; marked increase in BUN values. High Dose Group Only: Emesis; 2 deaths preceeded by desquamation, vertigo and dry scaly skin in one and depigmentation in other. "Button ulcers" present in ileocecal valve and in caecum. Two of the animals exhibited widespread areas of mucosal necrosis compatible with necrotic enteritis.
Dog	1	7	1.6 – 3.5	2 – 5 days	IV	Four dogs showed loss of appetite & general discomfort after initial doses of 1.6 and 1.9 mg/kg. Two of these periodically showed traces of blood in stools. The other 3 dogs vomited and 1 high dose dog had hemorrhage in duodenum, jejunum and ileum. Low Dose Group: One showed moderate congestion of duodenum and slight congestion in jejunum and ileum. Another showed congestion of stomach mucosa and slight hemorrhage in the intestines.
Monkey	1 or 2	4	2.0	10 – 21 days (5 days/ week)	IV	By tenth day, one monkey exhibited depression, anorexia, emaciation, dehydration, increased blood sugar, and an unusually high BUN level. Another exhibited a number of tubercular lesions in lung, moderate fatty and granular degeneration of liver. All monkeys experienced occasional emesis within 1 hour after dose, sclerosis of veins at site of injection and persistent elevation of BUN.

* Not reported

Chronic Toxicity

Species	No. of Animals per Group	No. of Groups	Dose mg/ kg/ day	Duration of Study	Route of Administration	Toxic Signs
Rat	8 M 8 F	4 4	0, 250, 500 or 1000	91 days	PO	Slight nasal discharge in all groups. Non-significant weight loss in high dose males.
Dog	3	3	0, 250 or 500 (1)	48 days	PO	All dogs gained weight. Occasional emesis in one low dose dog. Lungs of 4 dogs showed either a slight alveolar infiltration, or a small encapsulated nodule of histocytes, lymphocytes or plasma cells with or without polymorphonuclear leukocytes.
Dog	4	4	0, 125, 250 or 500 (2)	187 days	PO	All groups exhibited slight weight gain & rare instances of emesis. High Dose Group: 2 inbred dogs had hematuria at irregular intervals after 15th week; also had petechiae in urinary bladder mucosa and one had embedded calculi. Slight kidney cirrhosis in 2 dogs and kidney infarction in one.
Mice	10	5	5, 10, 25, 50, 100	71 days	IP	No instances of toxicity related to drug.

(1) Crystalline Amphotericin B suspended in 0.2% lecithin.

(2) Crystalline Amphotericin B suspended in 0.25% agar.

Chronic Renal Toxicity

Species	No. of Animals	Dose mg/ kg/ day	Duration of Administration (days)	Route of Administration	Toxic Signs
Dog	15	0.5, 2.0	4	IV	Increase in BUN.
Dog	6	0.25 – 1.0*	12 – 191	IV	Weight loss; terminal hematemesis or melena (4 dogs) with hemorrhagic gastritis; temporary thrombophlebitis (1 dog).
Dog	10	0.25 – 4.0	4 – 187	IV	0.5 mg/kg non-lethal; tubular necrosis and calcification thickening of tubular basement membranes; increase in BUN.
Dog	18	0.25 – 2.0	2 – 18	IV	Increase in BUN and progressive uremia; two deaths.

***** Every other day in half the dogs.

Reproduction and Teratology

Species	Sex	No. of Animals per Group	No. of Groups	Dose mg/ kg/ day	Duration of Study	Route of Administration	Toxic Signs
Mice	F	60 – 110	4	0, 50, 100 or 200	Immediately after coitus up to Day 17 of gestation or to full term	PO	Incidence of resorption at all doses higher than controls
Rat	F	40	4	0, 50, 100 or 200	Immediately after coitus & up to Day 19 of gestation or to full term	PO	Incidence of resorptions at 200 mg/kg/day and 100 mg/kg/day higher than controls. Higher incidences of stillborns in high dose group.
Rabbit	F	13 - 30	4	0, 25, 50 or 100	Immediately after coitus & up to Day 29 of gestation or to full term	PO	Increased number of deaths of dams in mid & high dose groups; only 1 dam delivered in high dose and of 3 of 7 in mid-dose group. One dam in mid-dose group delivered a stillborn fetus on Day 27 of gestation; at necropsy, this dam held 5 dead fetuses, two of which were undeveloped.
Rat	F	19 – 22	4	0, 0.6, 1.5 or 3.75	Days 6 – 15 of gestation	IP	No drug related abnormalities
Rabbit	F	15	5	0, 0.24, 0.6 or 1.50	Days 6 – 18 of gestation	IV	Dose related decrease in neonatal survival thought to be due to dextrose vehicle.
Rat	F	25	4	0, 0.6, 1.5 or 3.75	Day 15 of gestation to 21 days post-partum	IP	Higher incidence of stillborns in high dose group possibly due to dextrose vehicle since incidence of stillborns in low & mid dose groups similar to dextrose-only treated individuals.

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