

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Rx Liposomal Amphotericin B Injection 50 mg GALENSOME™

COMPOSITION

Each vial contains:
Amphotericin B IP (lyophilised) intercalated into Liposomal membrane 50 mg
To be reconstituted with 12.0 ml of sterile Water for Injections IP

DOSEAGE FORM

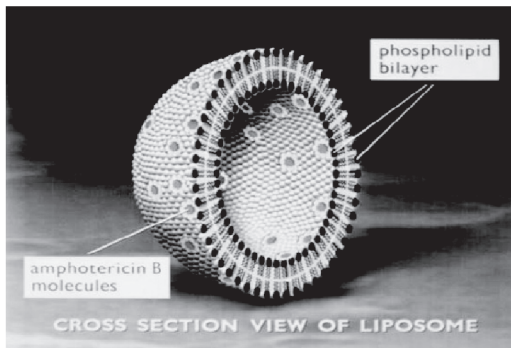
Injectable powder (lyophilised) for liposomal suspension.

DESCRIPTION
GALENSOME™ for Injection is a sterile, non-pyrogenic lyophilised product for intravenous infusion. Each vial contains 50 mg of amphotericin B IP intercalated into a liposomal membrane.

Sr. No.	Ingredients	GALENSOME™ 50 for Injection
1	Amphotericin B	50 mg
2	Distearyl phosphatidyl glycerol sodium	84 mg
3	Hydrogenated soy Phosphatidylcholine	213 mg
4	Cholesterol	52 mg
5	Sucrose	900 mg
6	Sodium succinate hexahydrate	27 mg
7	All-rac-alpha-tocopherol	0.64 mg

GALENSOME™ is a true single bilayer liposomal drug delivery system. Liposomes are closed, spherical vesicles created by mixing specific proportions of amphiphilic substances such as phospholipids and cholesterol so that they arrange themselves into multiple concentric bilayer membranes when hydrated in aqueous solutions. Single bilayer liposomes are then formed by the microemulsification of multilamellar vesicles using a homogenizer. **GALENSOME™** consists of these unilamellar bilayer liposomes with amphotericin B intercalated within the membrane. Due to the nature and quantity of amphiphilic substances used, and the lipophilic moiety in the amphotericin B molecule, the drug is an integral part of the overall structure of the **GALENSOME™** liposomes. **GALENSOME™** contains true liposomes that are less than 100 nm in diameter.

A schematic depiction of the liposome is presented below:



Amphotericin B is a macrocyclic, polyene, antifungal antibiotic produced from a strain of *Streptomyces nodosus*.

Note: Liposomal encapsulation or incorporation into a lipid complex can substantially affect a drug's functional properties relative to those of the unencapsulated drug or the non-lipid-associated drug. In addition, different liposomal or lipid-complex products with a common active ingredient may vary from one another in the chemical composition and physical form of the lipid component. Such differences may affect the functional properties of these drug products.

PHARMACOLOGY

Pharmacodynamics

Mechanism of Action

Amphotericin B, the active ingredient of liposomal amphotericin B, acts by binding to the sterol component, ergosterol, of the cell membrane of susceptible fungi. It forms transmembrane channels leading to alterations in the cell permeability through which monovalent ions (Na⁺, K⁺, H⁺, and Cl⁻) leak out of the cell resulting in cell death. While amphotericin B has a higher affinity for the ergosterol component of the fungal cell membrane, it can also bind to the cholesterol component of the mammalian cell, leading to cytotoxicity. The liposomal preparation of amphotericin B has been shown to penetrate the cell wall of both extracellular and intracellular forms of susceptible fungi.

Activity in Vitro and In Vivo

Liposomal amphotericin B has shown in vitro activity against the following organisms: *Aspergillus fumigatus* and *Aspergillus flavus*, *Candida albicans*, *Candida krusei*, *Candida lusitanae*, *Candida parapsilosis*, *Candida tropicalis*, *Cryptococcus neoformans*, *Blastomyces dermatitidis*, most strains of *Histoplasma capsulatum*, *Coccidioides immitis*, *Rhodotorula*, *Sporothrix schenckii*, *Penicillium marneffii*, and members of the mucormycetes group of moulds, including *Mucor mucedo*, *Rhizoglyphus* and *Rhizopus oryzae*.

The majority of clinically important fungal species seem to be susceptible to amphotericin B, although intrinsic resistance has, rarely, been reported, e.g. for some strains of *S. schenckii*, *C. glabrata*, *C. krusei*, *C. tropicalis*, *C. lusitanae*, *C. parapsilosis* and *Aspergillus terreus*.

Liposomal amphotericin B has been shown to be effective in animal models of visceral leishmaniasis (caused by *Leishmania infantum* and *Leishmania donovani*).

Standardized methods of in vitro antifungal susceptibility testing have been developed for testing yeasts and filamentous fungi. The clinical relevance of the test results is not always clear.

Drug Resistance

Intrinsic resistance, though rare, maybe primarily due to a decrease in ergosterol or a change in the target lipid, leading to reduced binding of amphotericin B to the cell membrane. Mutants with decreased susceptibility to amphotericin B have been isolated from several fungal species after serial passage in culture media containing the drug, and from some patients receiving prolonged therapy. Drug combination studies in vitro and in vivo suggest that imidazoles may induce resistance to amphotericin B. However, the clinical relevance of drug resistance has not been established.

Pharmacokinetics

The assay used to measure amphotericin B in the serum after administration of liposomal amphotericin B does not distinguish amphotericin B that is complexed with the phospholipids of liposomal amphotericin B from the amphotericin B that is uncomplexed. The pharmacokinetic profile of amphotericin B after administration of liposomal amphotericin B is based upon the total serum concentrations of amphotericin B. The pharmacokinetic profile of amphotericin B was determined in febrile neutropenic cancer and bone marrow transplant patients who received 1–2 hour infusions of 1–5 mg/kg/day liposomal amphotericin B for 3–20 days. The pharmacokinetics of amphotericin B after administration of liposomal amphotericin B is non-linear such that there is a greater than proportional increase in the serum concentrations with an increase in dose from 1–5 mg/kg/day.

Distribution

Based on total amphotericin B concentrations measured within a dosing interval (24 hours) after administration of liposomal amphotericin B, the mean half-life was 7–10 hours. However, based on the total amphotericin B concentration measured up to 49 days after dosing of liposomal amphotericin B, the mean half-life was 100–153 hours. The long terminal elimination half-life is probably a slow redistribution from the tissues. Steady-state concentrations were generally achieved within 4 days of dosing.

Mean trough concentrations of amphotericin B, although variable, remained relatively constant with repeated administration of the same dose over the range of 1–5 mg/kg/day, indicating no significant drug accumulation in the serum.

Metabolism

The metabolic pathways of amphotericin B after administration of liposomal amphotericin B are not known.

Excretion

The mean clearance at the steady state was independent of dose. The excretion of amphotericin B after the administration of liposomal amphotericin B has not been studied.

The pharmacokinetics of liposomal amphotericin B in paediatric patients has not been studied; however, it has been used in paediatric patients.

INDICATIONS

GALENSOME™ is indicated in the following:

For invasive fungal infection in patients who are refractory to or intolerant of conventional amphotericin B therapy

DOSEAGE AND ADMINISTRATION

Dosage

Adults and Paediatric

The recommended initial dose of **GALENSOME™** for indication for adult and paediatric patients is as follows:

Indication	Dose (mg/kg/day)
Systemic fungal infections	3–5
Aspergillus	
Candida	
Cryptococcus	

Dosing and rate of infusion should be individualized to the needs of the specific patient to ensure maximum efficacy while minimizing systemic toxicities or adverse events.

Particulars as to the optimal dosage and the eventual development of resistance are as yet incomplete. The product should be administered under strict medical supervision.

Systemic fungal infections in children have been successfully treated with liposomal amphotericin B, without reports of unusual adverse events. Liposomal amphotericin B has been studied in paediatric patients aged 1 month to 18 years. Doses used in these clinical studies were the same as those used in adults on a mg/kg body weight basis.

GALENSOME™ is not recommended for use in children below 1 month of age due to lack of data on safety and efficacy.

Elderly Patients

No alteration in dose or frequency of dosing is required.

Renal Impairment

No alteration in dose or frequency of dosing is required (see **WARNINGS AND PRECAUTIONS**).

Hepatic Impairment

No data are available on which to make a dose recommendation for patients with hepatic impairment (see **WARNINGS AND PRECAUTIONS**).

Method of Preparation

Read this entire section carefully before beginning reconstitution.

GALENSOME™ must be reconstituted using Sterile Water for Injections, IP (without a bacteriostatic agent). Vials of **GALENSOME™** containing amphotericin B are prepared as follows:

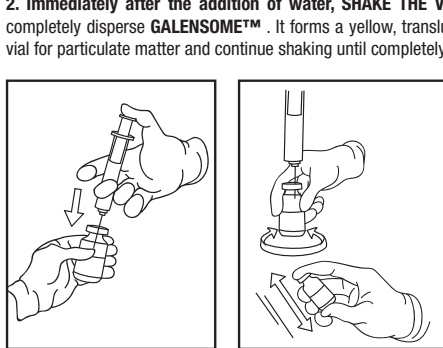
Reconstitution

1. Aseptically add Sterile Water for Injection, IP, to each **GALENSOME™** vial to yield a preparation containing 4 mg amphotericin B/mL. Sterile Water for injections to be used for reconstitution: 12 mL.

CAUTION: DO NOT RECONSTITUTE WITH SALINE OR ADD SALINE TO THE RECONSTITUTED CONCENTRATION, OR MIX WITH OTHER DRUGS.

The use of any solution other than those recommended, or the presence of a bacteriostatic agent in the solution, may cause precipitation of **GALENSOME™**.

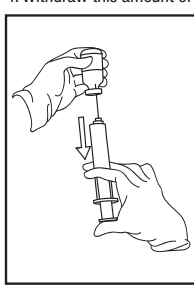
2. Immediately after the addition of water, SHAKE THE VIAL VIGOROUSLY for 30 seconds to completely disperse **GALENSOME™**. It forms a yellow, translucent suspension. Visually inspect the vial for particulate matter and continue shaking until completely dispersed.



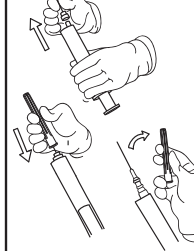
Filtration and Dilution

3. Calculate the amount of reconstituted (4 mg/mL) **GALENSOME™** to be further diluted.

4. Withdraw this amount of reconstituted **GALENSOME™** into a sterile syringe.



5. Attach the Sterile 18G blunt fill needle with 5-micron filter, provided, to the syringe. Inject the syringe contents through the blunt filter into the appropriate amount of Dextrose Injection.



6. **GALENSOME™** must be diluted with 5% Dextrose Injection to a final concentration of 1–2 mg/mL prior to administration. Lower concentrations (0.2–0.5 mg/mL) may be appropriate for infants and small children, so as to provide sufficient volume for infusion. **DISCARD PARTIALLY USED VIALS.**

Method of Administration

GALENSOME™ should be administered by intravenous infusion, using a controlled infusion device, over a period of approximately 120 minutes.

An in-line membrane filter should be used for the intravenous infusion of **GALENSOME™**. The pore diameter of the filter should be 5 microns or larger.

Note: An existing intravenous line must be flushed with 5% Dextrose Injection prior to the infusion of **GALENSOME™**. If this is not feasible, it must be administered through a separate line.

Infusion time may be reduced to approximately 60 minutes in patients in whom the treatment is well-tolerated. If the patient experiences discomfort during the infusion, the duration of infusion may be increased.

CONTRAINDICATIONS

GALENSOME™ is contraindicated in those patients who have demonstrated or have known hypersensitivity to amphotericin B deoxycholate or any other constituents of the product unless, in the opinion of the treating physician, the benefit of the therapy outweighs the risk.

WARNINGS AND PRECAUTIONS

General

Anaphylaxis and anaphylactoid reactions have been reported in association with liposomal amphotericin B infusion. Allergic type reactions, including severe infusion-related reactions, can occur during administration of amphotericin-containing products, including liposomal amphotericin B (see **UNDESIRABLE EFFECTS**). Therefore, administration of a test dose is still advisable before a new course of treatment. For this purpose a small amount (e.g. 1 mg) of an infusion of liposomal amphotericin B can be administered for about 10 minutes, the infusion stopped and the patient observed carefully for the next 30 minutes. If there have been no severe allergic or anaphylactoid/anaphylactoid reactions, the infusion of liposomal amphotericin B dose can be continued. If a severe allergic or anaphylactoid/anaphylactoid reaction occurs, the infusion should be immediately discontinued and the patient should not receive further infusion of liposomal amphotericin B.

Other severe infusion-related reactions can occur during administration of amphotericin B-containing products, including liposomal amphotericin B (see **UNDESIRABLE EFFECTS**). Although infusion-related reactions are not usually serious, consideration of precautionary measures for the prevention or treatment of these reactions should be given to patients who receive liposomal amphotericin B therapy. Slower infusion rates (over 2 hours) or routine doses of diphenhydramine, paracetamol, pethidine and/or hydrocortisone have been reported as successful in their prevention or treatment.

Liposomal amphotericin B has been shown to be substantially less toxic than conventional amphotericin B, particularly with respect to nephrotoxicity; however, adverse reactions, including renal adverse reactions, may still occur.

In studies comparing liposomal amphotericin B 3 mg/kg daily with higher doses (5, 6 or 10 mg/kg daily), it was found that the incidence rates of increased serum creatinine, hypokalaemia and hypomagnesaemia were notably higher in the high dose groups.

Regular laboratory evaluation of serum electrolytes, particularly potassium and magnesium as well as renal, hepatic and haematopoietic function should be performed, at least once weekly. This is particularly important for patients receiving prolonged therapy or those receiving concomitant nephrotoxic medications (see **Drug Interactions**). Renal function should be closely monitored in these patients. Due to the risk of hypokalaemia, appropriate potassium supplementation may be required during the course of liposomal amphotericin B administration. If clinically significant reduction in renal function or worsening of other parameters occurs, consideration should be given to dose reduction, treatment interruption or discontinuation.

Acute pulmonary toxicity has been reported in patients given amphotericin B (as sodium deoxycholate complex) during or shortly after leucocyte transfusions. It is recommended that these infusions are separated by as long a period as possible and pulmonary function should be monitored.

In the Treatment of Diabetic Patients

It should be noted that liposomal amphotericin B contains approximately 900 mg of sucrose in each vial.

False elevations of serum phosphate may occur when samples from patients receiving liposomal amphotericin B are analysed using the PHOSm assay (e.g. used in Beckman Coulter analysers, including the Synchron LX20). This assay is intended for the quantitative determination of inorganic phosphorus in human serum, plasma or urine samples.

Drug Interactions

No formal clinical studies of drug interactions have been conducted with liposomal amphotericin B. However, the following drugs are known to interact with amphotericin B and may interact with liposomal amphotericin B:

Antineoplastic Agents

Concurrent use of antineoplastic agents may enhance the potential for renal toxicity, bronchospasm and hypotension. Antineoplastic agents should be given concomitantly with caution.

Corticosteroids and Corticotropin (ACTH) and Diuretics

Concurrent use of corticosteroids, ACTH and diuretics (loop and thiazide) may potentiate hypokalaemia, which could predispose the patient to cardiac dysfunction. If used concomitantly, serum electrolytes and cardiac function should be closely monitored.

Digitalis Glycosides

Concurrent use may induce hypokalaemia and may potentiate digitalis toxicity. When administered concomitantly, serum potassium levels should be closely monitored.

Antifungals

No evidence of benefit from the use of fluconazole with liposomal amphotericin B has been observed. Whilst synergy between amphotericin and fluconazole has been reported, concurrent use may increase the toxicity of fluconazole by possibly increasing its cellular uptake and/or impairing its renal excretion.

In vitro and in vivo animal studies of 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.

Leucocyte Transfusions

Acute pulmonary toxicity has been reported in patients simultaneously receiving intravenous amphotericin B and leucocyte transfusions. It is recommended these infusions are separated by as long a period as possible and pulmonary function should be monitored.

Other Nephrotoxic Medications

Concurrent administration of liposomal amphotericin B with other nephrotoxic agents (e.g. ciclosporin, aminoglycosides, polymyxins, tacrolimus and pentamidine) may enhance the potential for drug-induced renal toxicity in some patients. However, in patients receiving concomitant ciclosporin and/or aminoglycosides, liposomal amphotericin B was associated with significantly less nephrotoxicity compared to amphotericin B. Regular monitoring of renal function is recommended in patients receiving liposomal amphotericin B along with any nephrotoxic medications.

Skeletal Muscle Relaxants

Amphotericin B-induced hypokalaemia may enhance the curariform effect of skeletal muscle relaxants (e.g. tubocurarine). When administered concomitantly, serum potassium levels should be closely monitored.

Renal Impairment

The effect of renal impairment on the disposition of amphotericin B after administration of liposomal amphotericin B has not been studied. However, liposomal amphotericin B has been successfully administered to patients with pre-existing renal impairment.

Hepatic Impairment

The effect of hepatic impairment on the disposition of amphotericin B after administration of liposomal amphotericin B is not known.

Pregnancy

Pregnancy Category B

Teratogenicity studies in animals have concluded that liposomal amphotericin B had no teratogenic potential. There have been no adequate and well-controlled studies on safety of liposomal amphotericin B in pregnant women. Systemic fungal infections have been successfully treated in pregnant women with amphotericin B deoxycholate, but the number of cases reported has been small.

Liposomal amphotericin B should be used during pregnancy only if the possible benefits to be derived outweigh the potential risks involved.

Lactation

Many drugs are excreted in human milk. However, it is not known whether liposomal amphotericin B is excreted in human milk. Due to the potential for serious adverse reactions in breastfed infants, a decision should be made whether to discontinue nursing or whether to discontinue the drug, taking into account the importance of the drug to the mother.

Paediatric Use

The pharmacokinetics of amphotericin B, after the administration of liposomal amphotericin B in paediatric patients, has not been studied; however, liposomal amphotericin B has been used in paediatric patients.

Paediatric patients, aged 1 month to 16 years, Confirmed systemic fungal infections have been successfully treated with liposomal amphotericin B there was no evidence of any differences in the efficacy or safety of liposomal amphotericin B compared to adults.

Since paediatric patients have received liposomal amphotericin B at doses comparable to those used in adults on a per kilogram body weight basis, no dosage adjustment is required in this population.

Safety and effectiveness in paediatric patients below the age of 1 month have not been established.

Geriatric Use

The pharmacokinetics of amphotericin B after the administration of liposomal amphotericin B in elderly patients has not been studied; however, liposomal amphotericin B has been used in elderly patients. No alteration in dose or frequency of dosing is required. As with most other drugs, elderly patients receiving liposomal amphotericin B should be carefully monitored.

Gender and Ethnicity

The effect of gender or ethnicity on the pharmacokinetics of amphotericin B after the administration of liposomal amphotericin B is not known.

UNDESIRABLE EFFECTS

Fever and chills/rigors are the most frequent infusion-related reactions expected to occur during liposomal amphotericin B administration. Less frequent infusion-related reactions may consist of one or more of the following symptoms: chest tightness or pain, dyspnoea, bronchospasm, flushing, tachycardia, hypotension and musculoskeletal pain (described as arthralgia, back pain or bone pain). These resolve rapidly on stopping the infusion and may not occur with every subsequent dose or when slower infusion rates (over 2 hours) are used. In addition, infusion-related reactions may also be prevented by the use of premedication. However, severe infusion-related reactions may necessitate the permanent discontinuation of liposomal amphotericin B therapy (see **WARNINGS AND PRECAUTIONS**).

In two double-blind, comparative studies, liposomal amphotericin B-treated patients experienced a significantly lower incidence of infusion-related reactions, as compared to patients treated with conventional amphotericin B or amphotericin B lipid complex.

In pooled study data from randomized, controlled clinical trials comparing liposomal amphotericin B with conventional amphotericin B therapy in more than 1,000 patients, reported adverse reactions were considerably less severe and less frequent in liposomal amphotericin B-treated patients as compared with conventional amphotericin B treated patients.

Nephrotoxicity occurs to some degree with conventional amphotericin B in most patients receiving the drug intravenously. In a double-blind study involving 687 patients, the incidence of nephrotoxicity with liposomal amphotericin B (as measured by serum creatinine increase greater than 2.0 times baseline measurement), was approximately half that for conventional amphotericin B. In another double-blind study involving 244 patients, the incidence of nephrotoxicity with liposomal amphotericin B (as measured by serum creatinine increase greater than 2.0 times baseline measurement) is approximately half that for amphotericin B lipid complex.

In paediatric patients (16 years of age or less) in this double-blind study, compared to amphotericin B deoxycholate, liposomal amphotericin B had a lower incidence of hypokalaemia (3.7% versus 55%), chills (29% versus 68%), vomiting (27% versus 55%), and hypertension (10% versus 21%). Similar trends, although with a somewhat lower incidence, were observed in an open-label, randomized study (104-14) involving 205 febrile neutropenic paediatric patients (141 treated with liposomal amphotericin B and 64 treated with amphotericin B deoxycholate). Paediatric patients appear to have more tolerance than older individuals for the nephrotoxic effects of amphotericin B deoxycholate.

In addition to the above mentioned adverse events, procedural complications, phlebitis and leucopenia were observed in HIV-positive patients with cryptococcal meningitis based on the experience of 267 patients (1 paediatric), of whom 94 received a dose of 6 mg/kg/day.

The following adverse reactions have been attributed to liposomal amphotericin B, based on clinical trial data and postmarketing experience. The frequency is based on analysis from pooled clinical trials of 688 liposomal amphotericin B-treated patients; the frequency of adverse reactions identified from postmarketing experience is not known.

Adverse reactions are listed below by body system organ class using MedDRA and are sorted by frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Frequencies are defined as follows:

Very common	(≥1/10)
Common	(≥1/100 to <1/10)
Uncommon	(≥1/1,000 to <1/100)
Very rare	(<1/10,000), not known (cannot be estimated from the available data)

Blood and Lymphatic System Disorders

Common: Thrombocytopenia

Not known: Anaemia

Immune System Disorders

Uncommon: Anaphylactoid reaction

Not known: Anaphylactic reactions, hypersensitivity

Metabolism and Nutrition Disorders

Very common: Hypokalaemia

Common: Hyponatremia, hypocalcaemia, hypomagnesaemia hyperglycaemia

Nervous System Disorders

Common: Headache

Uncommon: Convulsion

Cardiac Disorders

Common: Tachycardia

Not known: Cardiac arrest, arrhythmia

Vascular Disorders

Common: Hypotension, vasodilatation, flushing

Respiratory, Thoracic and Mediastinal Disorders

Common: Dyspnoea

Uncommon: Bronchospasm

Gastrointestinal Disorders

Very common: Nausea, vomiting

Common: Diarrhoea, abdominal pain

Hepatobiliary Disorders

Common: Liver function tests abnormal, hyperbilirinaemia, alkaline phosphatase increased

Skin and Subcutaneous Disorders

Common: Rash

Not known: Angioneurotic oedema

Musculoskeletal and Connective Tissue Disorders

Common: Back pain

Not known: Rhabdomyolysis (associated with hypokalaemia), musculoskeletal pain (described as arthralgia or bone pain)

Urogenital System Disorders

Common: Increased creatinine, blood urea increased, abnormal renal function, acute kidney failure, acute renal failure, dysuria, kidney failure, toxic nephropathy, urinary incontinence, and vaginal hemorrhage.

General Disorders and Administration Site Conditions

Very common: Rigors, pyrexia,

Common: Chest pain

Interference with Phosphorus Chemistry Assay

False elevations of serum phosphate may occur when samples from patients receiving liposomal amphotericin B are analysed using the PHOSm assay (e.g. used in Beckman Coulter analysers, including the Synchron LX20). This assay is intended for the quantitative determination of inorganic phosphorus in human serum, plasma or urine samples.

Clinical Laboratory Values

The effect of liposomal amphotericin B on renal and hepatic function and on serum electrolytes was assessed from laboratory values measured repeatedly in a double-blind randomized study. The frequency and magnitude of hepatic test abnormalities were similar in the liposomal amphotericin B and amphotericin B groups. Nephrotoxicity was defined as creatinine values increasing 100% or more over pre-treatment levels in paediatric patients