AmBisome Injection

1. Background

AmBisome Injection contains the active ingredient, amphotericin B, an antifungal agent, entrapped in liposomes. AmBisome Injection is indicated for the treatment of severe systemic and/or deep mycoses in patients who fail to respond to conventional amphotericin B therapy and who develop nephrotoxicity after receiving conventional amphotericin B or in whom conventional amphotericin B is considered to be contra-indicated because of renal impairment. Registration applications have been submitted in Sweden, Norway, Finland, Ireland and Germany.

A conventional intravenous preparation containing the same active drug substance under the trade name Fungizone Intravenous (E.R. Squibb and Sons Limited PL/0034/5041) is already on the market.

2. Pharmaceutical Comment

Summary

AmBisome Injection contains the active ingredient, amphotericin B, encapsulated in liposomes. There are no major chemical and pharmaceutical problems;

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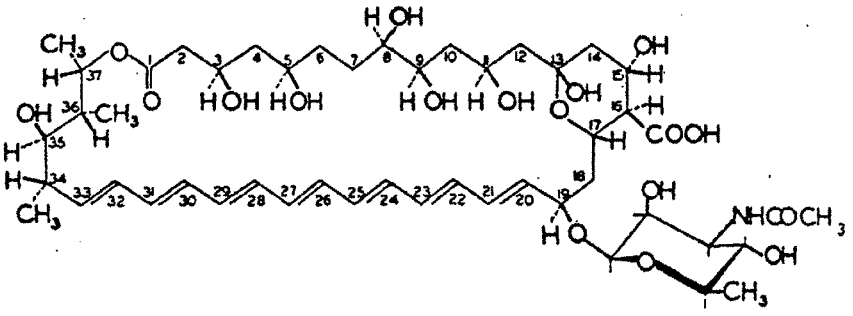

Drug Substance

A Drug Master File [redacted] was submitted separately by [redacted] and authorisation to access has been granted by the manufacturer.

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Amphotericin B is a macrocyclic polyene antibiotic and it is included in the British Pharmacopoeia and the United States Pharmacopoeia. The drug substance is produced by streptomycetes nodosus, supplied by [redacted]

Detailed description of the manufacturing process has been provided [redacted]

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Satisfactory in-process controls during manufacturing have been provided. These include batch, equipment and environmental monitoring. Detailed documentation of the analyses of the starting materials, intermediate products and the final bulk products have been tendered.

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A drug substance specification has been provided. [redacted]

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Dosage Form

AmBisome is a sterile lyophilised liposomal formulation of amphotericin B presented in 50ml, type I U.S.P. glass vials. The closure consists of West 4416/50 Gray butyl rubber stoppers and aluminium ring seals fitted with plastic flip-off caps. The components of AmBisome are hydrogenated soyabean lecithin (HSPC), cholesterol, distearoylphosphatidyl glycerol (DSPG) and amphotericin B; [redacted]

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[redacted]

A satisfactory finished product specification is provided.

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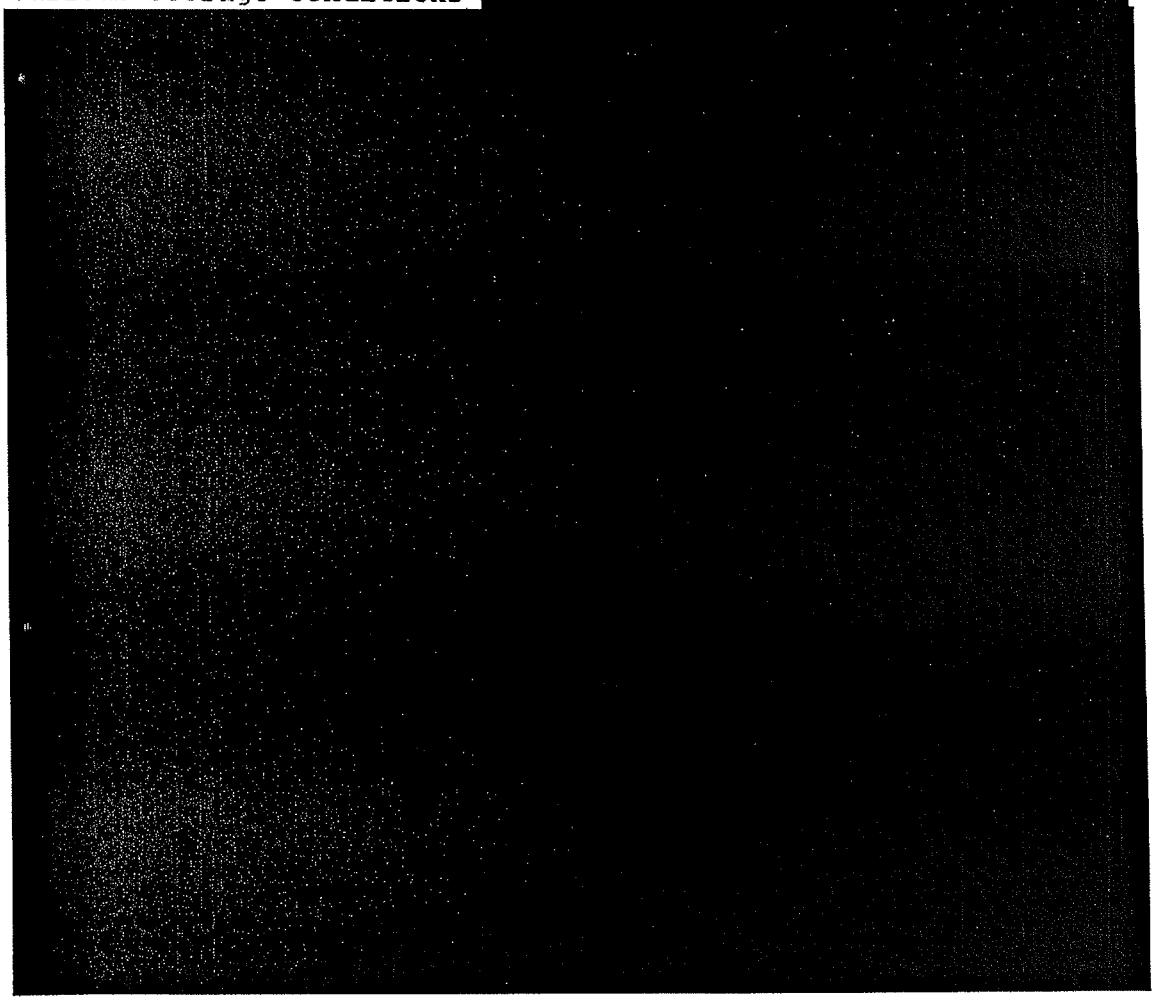
[redacted] batch analysis results [redacted] have been submitted to demonstrate consistency in the production batches. [redacted]

The stability of AmBisome Injection has been studied under various storage conditions [redacted]



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Pharmacokinetics

The disposition of AmBisome has been studied in both rodents and patients. [redacted] In mice, when AmBisome is administered at 1mg/kg by iv route, the peak plasma level of amphotericin B achieved is 7.8µg/ml, which is approximately five times higher than that for conventional dosage form (ca. 1.6µg/ml). The circulating plasma concentration of amphotericin B remains high (ca. 0.8µg/ml), twenty-four hours after the administration of AmBisome. However, the initial half life of amphotericin B is almost identical for both conventional and liposome formulations. The RES (reticuloendothelial system) clearance of AmBisome has also been investigated. Amphotericin B encapsulated in liposomes displays a broad tissue distribution; AmBisomes are highly sequestered in the liver and spleen where the levels of amphotericin B are respectively 5.4µg/g and 8.4µg/g, approximately four hours after drug administration at 1mg/kg via i.v. route. The concentration of amphotericin B is also high in the lung; a peak concentration at 7.6µg/g is achieved at 15 minutes after administration of AmBisome.

In patients, the plasma concentration of amphotericin B in AmBisome follow a biexponential decay with the distribution half life ranging from 1.07-2.62 hours and the elimination half-life ranged from 6.4 to 4.6 hours. Analogous to the murine pharmacokinetics, the levels of amphotericin B is high in the liver and spleen, a likely indication of reticuloendothelial uptake of AmBisome.

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Although this is an abridged application, the establishment of essential similarity is not necessary because relevant clinical and toxicological studies have been performed on this preparation.

3. Pharmaceutical Recommendation

It is recommended the grant of a product licence for this preparation [redacted]

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[redacted]
October 1990

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PRECLINICAL ASSESSMENT

INTRODUCTION

This is an abridged application for a new liposomal formulation of the established antifungal antibiotic, amphotericin B, the macrocyclic, polyene antibiotic produced by Streptomyces nodosus. The rationale for the development of this new formulation is to circumvent the toxicity of conventional amphotericin B while providing superior efficacy by allowing the administration of higher daily and cumulative doses. AmBisome for injection contains 50mg lyophilised amphotericin B per vial. The other components are hydrogenated soyabean lecithin (SSPC), cholesterol and disterearoylphosphatidyl glycerol (DSPG).

AmBisome is indicated for use in the treatment of severe systemic and/or deep mycoses in patients who fail to respond to conventional amphotericin B therapy, who develop nephrotoxicity after receiving conventional amphotericin B, or in whom conventional amphotericin B is considered to be contraindicated because of renal impairment.

AmBisome is administered by intravenous infusion over 30-60 minutes at a concentration of 0.5mg/ml amphotericin B. The maximum recommended human dose is 3mg/kg/day and a cumulative dose of 1 to 3g of amphotericin B as AmBisome over 3 to 4 weeks has been typical. The maximum recommended human dose of conventional amphotericin B is 1mg/kg/day

PRECLINICAL COMMENT

The preclinical evaluation of AmBisome was minimal.

AmBisome was shown to be more effective than conventional amphotericin B in murine models of systemic candidiasis and cryptococcosis as indicated by increased survival times and significantly enhanced clearance of the fungal pathogen from infected organs. Other model infections were not investigated since the models investigated were considered to provide adequate justification for the initiation of clinical trials with AmBisome.

The acute toxicity of AmBisome is some 20-fold lower than conventional amphotericin B. There were no conventional repeat dose toxicity studies with AmBisome. Several pharmacokinetic / tissue distribution studies were provided, one of which incorporated some haematological, clinical chemistry and histological investigations. The results indicated that higher circulating plasma levels of amphotericin B can be achieved when the drug is administered iv as AmBisome compared with conventional amphotericin B and also the tissue distribution was altered such that lower levels of amphotericin B were found in kidneys while higher levels were found in liver, lungs and spleen. Thus, although there is evidence that the potential for nephrotoxicity may be reduced by encapsulating amphotericin B in liposomes, the potential for enhanced toxicity in other organs such as the liver has not been addressed in the limited preclinical studies.

The particle size can influence the biodistribution of amphotericin B encapsulated in liposomes and, since batch analysis results including particle size distribution were not provided for the materials used in the preclinical evaluation, it is not clear whether the results of the preclinical studies have any clinical relevance.

There were no mutagenicity or reproductive toxicity studies but this is a well established drug indicated for a life-threatenning condition.

The safety of the components and excipients of AmBisome was addressed in the expert report and there would not appear to be any hazard associated with the liposome formulation itself which would prevent its use in the proposed indication.

CONCLUSION

The preclinical data are limited but further evaluation in animals is probably unnecessary in view of the proposed indication and the clinical experience with conventional amphotericin B.

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NOVEMBER 1990

MEDICAL ASSESSMENT

This is an abridged product licence application for a new formulation of Amphotericin B encapsulated in liposomes, and for intravenous use.

AmBisome is indicated for:

> "the treatment of severe systemic and/or deep mycoses in patients who fail to respond to conventional Amphotericin B, who develop nephrotoxicity after receiving conventional Amphotericin B, or in whom conventional Amphotericin B is considered to be contraindicated because of renal impairment."

Fungal infections due to: disseminated candidia, aspergillus, mucormycosis, chronic mycetoma and cryptococcal meningitis are said to have been treated successfully.

AmBisome is not indicated for "the common clinically inapparent forms of fungal disease which show only positive skin or serologic tests."

The recommended dosage regimen is:

> Starting dose 1mg/kg as an infusion over 30-60 minutes and increased stepwise to 3mg/kg "as required".
>
> The data sheet states that there are currently insufficient data to define total dosage and duration of treatment. "However a cumulative dose of 1-3gm over 3-4 weeks has been typical."

1. Introduction

This is a new formulation of Amphotericin B encapsulated in unilamellar liposomes made from soy phosphatidylcholine.

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[redacted]

The diameter of the liposomes is <150nm and they can be retained in the circulation for long periods without entrapment by the reticulo-endothelial system.

AmBisome is supplied in a lyophilised state and complicated instructions for reconstitution are provided.

The product has been designed to alter the tissue distribution of Amphotericin and reduce the toxicity which currently limits use of the product, especially renal toxicity.

AmBisome is not licensed in any country.

2. Pharmacokinetics (p 54)

14 patients received 5 day courses of daily infusions from 2-4mg/kg of AmBisome.

These patients did not have fungal infections, but were undergoing treatment for advanced, non-responsive cancer.

7 patients received concomitant dipyridamole and 7 doxorubicin.

Kinetics were dose dependent, but very variable, both within and between patients.

Steady state was reached by day 2, although higher levels were often seen after a 2nd five day course.

Dipyridamole appeared to reduce the clearance and increase the AUC of AmBisome, although no formal comparison was made. Trough levels were also higher for this combination.

The $T_{\frac{1}{2}\beta}$ of AmBisome was not dose dependent. Mean values ranged from 6.8 - 8.6hrs but the range of individual values was considerably greater.

Tissue levels were measured in 3 patients from the efficacy study who died shortly after a dose. Most of the Amphotericin was found in the liver and spleen, with low levels in brain lung and kidney.

3. Efficacy (p 60)

There are no controlled studies with AmBisome.

Efficacy is based on the results of a multinational compassionate use programme involving 80 patients with 84 incidences of fungal infection.

Only patients who could not be treated with conventional Amphotericin B for reasons of failure to respond, renal toxicity, or prior renal impairment were included.

Dosage recommendations varied for the different groups, but were within the recommendations for the licence.

A mean of 21.55 (1 - 94) days treatment, at a mean cumulative dose of 2.56g (0.05 - 16.7) was given.

The maximum daily dose received was 4mg/kg.

Most patients had a serious underlying disorder and many were seriously ill at the time of treatment.

3.1 Clinical efficacy (p 63)

64 patients were evaluable. Clinical efficacy was evaluated by the investigator and the criteria were rather soft.

Some patients had only fever as a symptom of fungal infection, others had several other infections concomitantly. Overall response (cure + improvement) was seen in 79% of patients with pulmonary and 77% of patients with extra-pulmonary infections.

Patients with Candidal infections had the highest clinical cure rate (78% in those treated for more than 8 days).

Patients who had organ transplants did best, but numbers were very small.

Patients with unresolved leukopenia did worst.

Clinical response was not related to dose or duration of therapy.

18 patients who failed to respond to other antifungal agents were evaluable for clinical efficacy and 80% responded (cure or improvement).

3.2 Mycological response (p66)

49 patients were evaluable. The majority had infections with Candida or Aspergillus spp. 59 pathogens were identified, 43 were cultured.

Over 80% of candidal infections were eradicated and 36% of Aspergillus.

Few non-candida or Aspergillus infections responded.

Once again organ transplant patients did best.

8/10 patients who failed to respond to previous anti-fungals, had eradication of their infection.

Clinical and mycological cure were correlated.

17 patients who died within 4 weeks of receiving AmBisome had tissue examined for fungi at PM and 8 had no evidence of infection.

Higher total dose and longer treatment were associated with mycological eradication in these cases.

2 patients received two courses of treatment and one patient 3, with good results.

4. Safety (p 71)

The compassionate and pharmacokinetic studies involved a total of 94 patients who received AmBisome.

4.1 Deaths

33 patients died within 4 weeks. All were due to underlying disease and none appeared to be due to AmBisome.

11 patients had a fungal infection cited as a cause of death.

4.2 Adverse events

The Commonest events in the Compassionate study related to laboratory monitoring.

Pancreatitis, cardiac arrhythmias and neuropathy were reported. Relationship to AmBisome could not be excluded.

In the Phase I study most patients reported chills, headache, nausea and fever.

4.3 Renal toxicity (p 79)

3 patients had minor transient elevations of creatinine in the Phase I study.

In the compassionate use study 40 patients entered with abnormal renal function. No patients withdrew because renal function worsened and in 9 it normalised on treatment with AmBisome.

Of 35 patients who entered with normal creatinine, 5 had increases. These tended to be minor increases

BUN and Potassium tended to follow creatinine levels.

Actual levels are not known since the figures referred to in the text have not been supplied.

In general the results are hopeful, and 40 patients who could not receive conventional Amphotericin because of renal impairment were able to tolerate AmBisome.

Although an effect on renal function cannot be ruled out, this formulation could be used in patients with renal impairment, with careful monitoring of renal function.

4.4 Hepatic function (p 84)

5 patients developed abnormalities of both transaminases, mostly due to underlying conditions.

Hepatic toxicity did not lead to withdrawal of AmBisome and some patients improved their hepatic function while on the drug.

4.5 Haematology

No remarkable results seen. The Company say there was no evidence of haemolysis, but no specific tests were carried out.

5. Expert Report (p 86)

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It contains a great deal of background information on fungal infections and conventional Amphotericin.

The conclusions are appended.

6. Data sheet (p 91)

6.1 Indications

AmBisome has ~~really only been shown useful in~~ Candida and Aspergillus infections. In particular it has not been shown effective in cryptococcal meningitis. This should be made clear and the list of other organisms should be removed.

6.2 The pregnancy warning should comply with the CRM guidelines.

7. Medical Comment

Although no controlled trials have been carried out, the data presented are encouraging for this group of severely ill patients who cannot tolerate conventional Amphotericin B.

Efficacy has been demonstrated for Candida and some Aspergillus infections.

Renal toxicity cannot be excluded, but an effective dose can be given without it, even to patients with underlying renal impairment.

A product licence should be granted subject to amendment of the data sheet.