ABLC PL/13339/0001

1 Introduction

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ABLC contains the active ingredient, amphotericin B, complexed with lipids dimyristoylphosphatidylcholine and dimyristoylphosphatidylglycerol [redacted] The complex is suspended in normal saline.

ABLC is proposed to be indicated for first-line therapy of cryptococcal meningitis, and systemic cryptococcosis in patients with acquired immunodeficiency syndrome (AIDS). The other proposed clinical indication is for the treatment of severe systemic fungal infections in patients, who have not responded to treatment with conventional amphotericin B or other systemic antifungal agents, or who have renal impairment or other contraindications to conventional amphotericin B. ABLC is recommended to be use as an intravenous infusion at a rate of 2.5mg/kg/h. The recommended daily dose is 5.0mg/kg.

Amphotericin B is already currently marketed in Europe and the USA as a colloidal dispersion (Fungizone). There are other two amphotericin B lipid formulations available in the United Kingdom. One of them is a unilamellar liposome preparation (AmBisome) and the other is marketed in the UK as Amphocil, containing a colloidal dispersion of amphotericin B.

2 Legal Status

Prescription Only Medicine

3 Pharmaceutical Comment

Drug Substance-Amphotericin B

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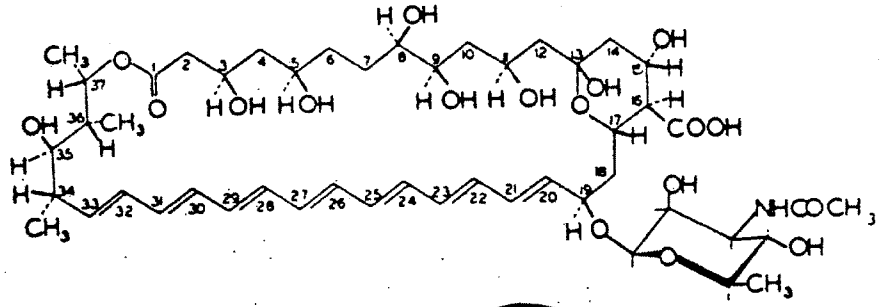
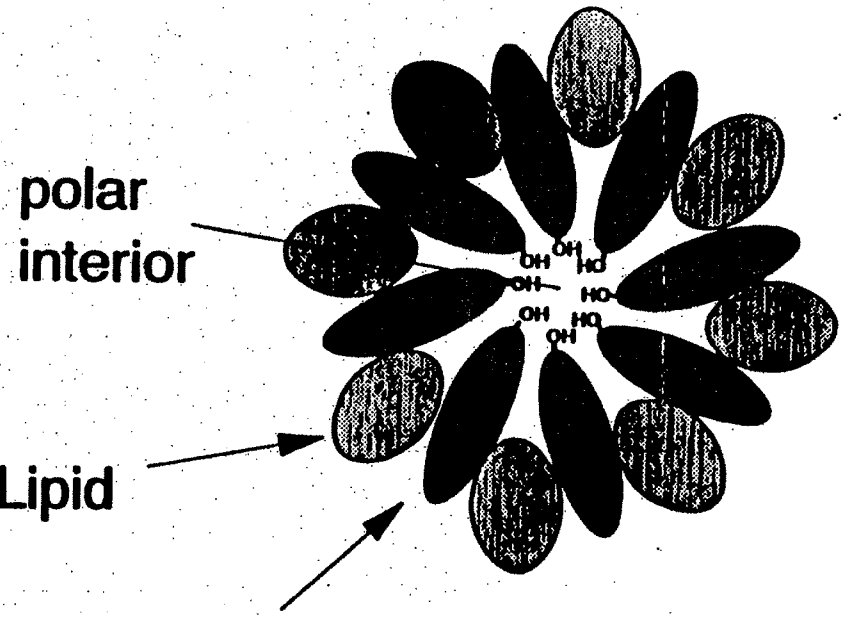
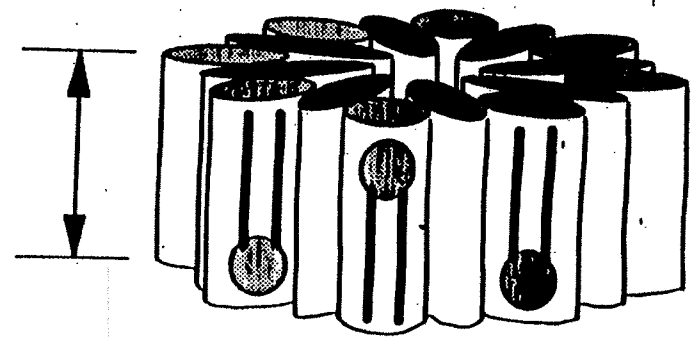
[redacted]

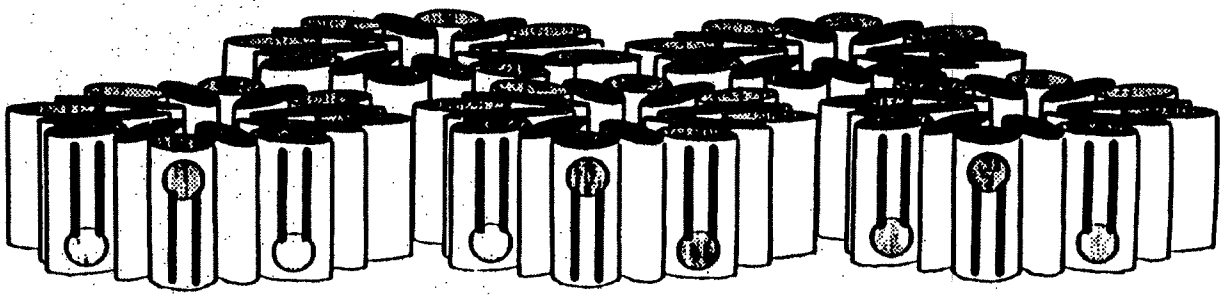
Top View of Single Complex







Side View



Membrane of Associated Complexes

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[redacted]

The preparation of the parenteral grade amphotericin B has been described in the DMF. [redacted]

[redacted]

[redacted]

A specification for the purified drug substance has been provided. In general, it is considered to be satisfactory.

[redacted]

The AIM have provided stability data for [redacted] batches of drug substance, which have been stored for [redacted] and [redacted] years respectively to support a retesting time of 24 months. Storage conditions for the drug substance have not been proposed.

Dosage Form

Whilst the company, Liposome Company Inc, have provided most of the relevant information in the dossier, it is presented in a rather confusing manner. The tabulated pharmaceutical expert report does not contain all the essential summary data necessary for the preparation for this committee paper, thus requiring the assessor to supplement the report with data contained in the dossier.

It is evident that some of the Part II data presented in the dossier have already been evaluated by the Food and Drug Administration (FDA) in the USA.

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[redacted] The dosage form consists of the active ingredient, amphotericin B, which is complexed with two lipids, namely dimyristoylphosphatidylcholine (DMPC) and dimyristoylphosphatidylglycerol (DMPG), in a [redacted] suspended in saline. The suspension is contained in a type I glass vials (PhEur) closed with grey butyl stoppers (PhEur). Both the vials and rubber closures are siliconised. Specifications for the packaging material have been provided.

[redacted]

The Committee may wish to note that there has been a report with regard to anaphylactic reactions to liposomal amphotericin (Lancet 1994 Vol 344 p.682). It is suggested by the authors that the lipid component of that preparation causes the "immediate, potentially fatal reactions". This specific point will be highlighted in the clinical assessment report.

[redacted]

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[redacted]

Validation of the process has been provided. [redacted]

[redacted]

Specifications for the pharmaceutical excipients and the active ingredient have been provided. [redacted]

[redacted]

A finished product specification has been proposed, encapsulating a range of physico-chemical control tests to ensure consistency of the quality of the finished products on a batch-to-batch basis. [redacted]

[redacted]

[redacted]

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[redacted]

Analytical results for batches manufactured at [redacted] were provided. [redacted]

[redacted]

[redacted]

Analytical methods employed are validated.

Pharmacokinetics

The in vivo disposition of ABLC has been investigated in rodents and in human subjects. In the murine pharmacokinetic studies, administration of ABLC at 1 and 5mg/kg iv doses of labelled amphotericin B resulted in dose-related increases in the concentrations of radioactivity in blood and liver, spleen, lung and brain. The results seem to be consistent with the interpretation that the administration of the lipid complex, vis-a-vis Fungizone, enhances the uptake of radioactivity in the reticuloendothelial system.

Human pharmacokinetics were carried out in a single study in five groups, each containing eight patients, with mucocutaneous leishmaniasis, against which the drug was evaluated. The submitted data demonstrated that the in vivo disposition profiles of ABLC were markedly different from that of Fungizone, the comparator. At 0.6mg/kg dose over a duration of 42 days, at steady state, the AUC value obtained for ABLC group (4.45 μg/ml) was lower than that obtained for the Fungizone group (17.06 μg/ml). The Cmax value for the ABLC group (0.86 μg/ml) was also lower than that for the Fungizone group (1.06μ

g/ml) whereas the $t_{1/2}$ for the ABLC group (113.14 hours) was longer than that for the amphotericin B group (91.06 hours). Clearance and volume of distribution for the ABLC group were significantly greater than that for the Fungizone group.

	Formulation	
Parameter	**ABLC™**	**Fungizone**
Tmax	0.304(0.008)	3.201(1.785)
Cmax	0.856(0.314)	1.056(0.145)
Beta (hr^{-1})	0.0006(0.001)	0.009(0.004)
T½ (hr)	113.141(20.604)	91.063(40.86)
AUC(µg*hr/ml)	4.449(0.896)	17.064(5.029)
AUC_{ss}(pred.)(µg*hr.ml)	4.447(0.892)*	17.151(5.013)
Clt (ml/hr/kg)	139.596(32.165)*	38.309(14.683)
Vdarea (l/kg)	23.228(8.357)*	5.014(2.505)

‡ Values expressed as Means (Std)
*Significant at $p < 0.5$
Data taken from Part IV Clinical Data

The analytical methods used in the in vivo studies has been validated.

Summary of Product Characteristics/Product Particulars

The Summary Product Characteristics should be amended:

- It should be emphasised that vigorous agitation should be avoided.
- Unit per mg of amphotericin B should be included on the label.
- The proposed trade name ABLC is not considered acceptable. A pronounceable trade name should be provided.

A patient information leaflet should be provided.

4 Pharmaceutical Conclusions

The applicant has provided a substantive amount of data on the development, manufacture and control of this product. The outstanding pharmaceutical issues are as follows:

PART I

1. **Summary of Product Characteristics and product particulars**

   1.1 It should be emphasised that vigorous agitation/shaking should be avoided.

   1.2 Unit per mg of amphotericin B should be included on the label.

   1.3 The proposed trade name ABLC is not considered acceptable. A pronounceable trade name should be provided.

2. A patient information leaflet should be provided.

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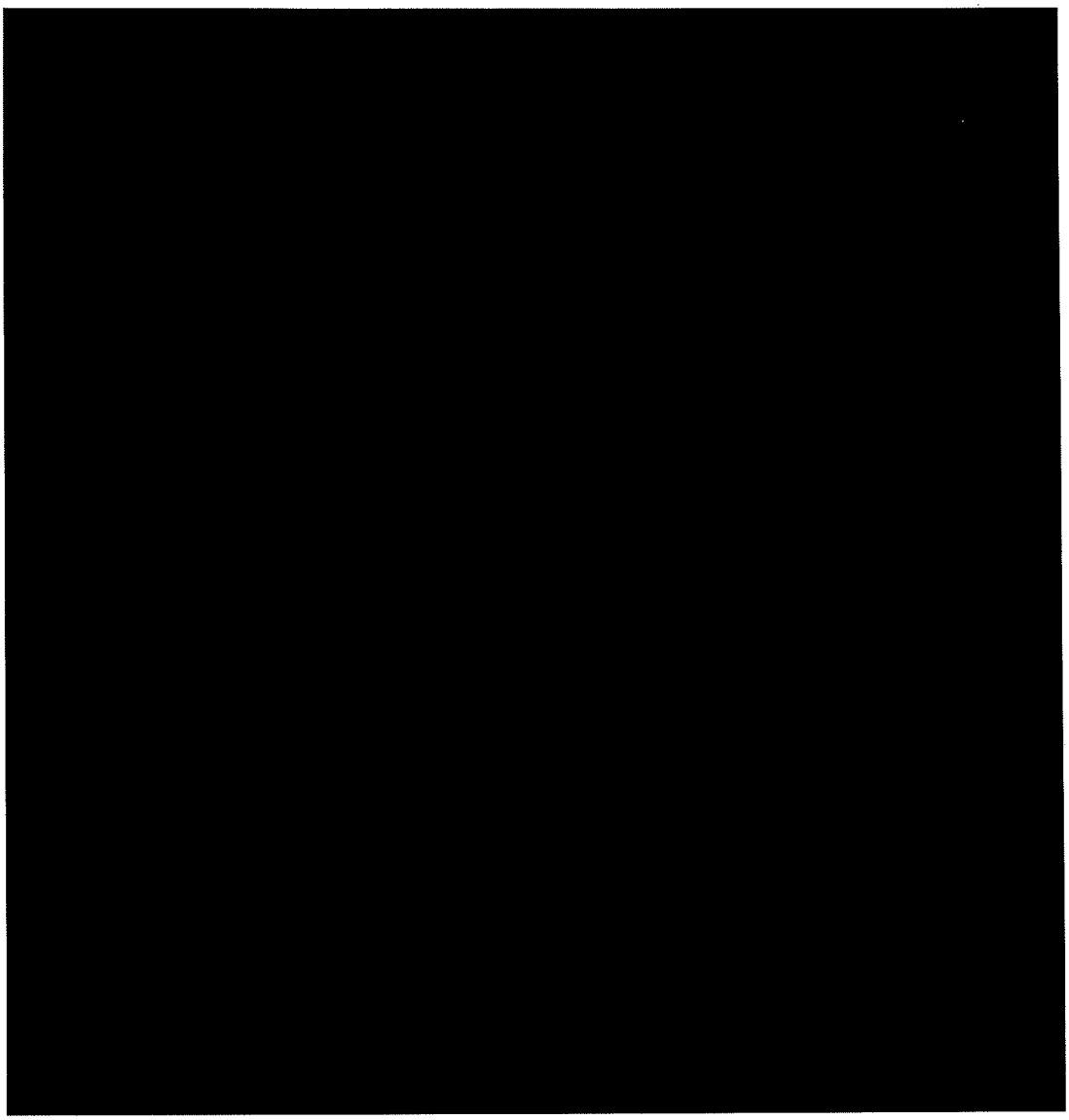

PART II E

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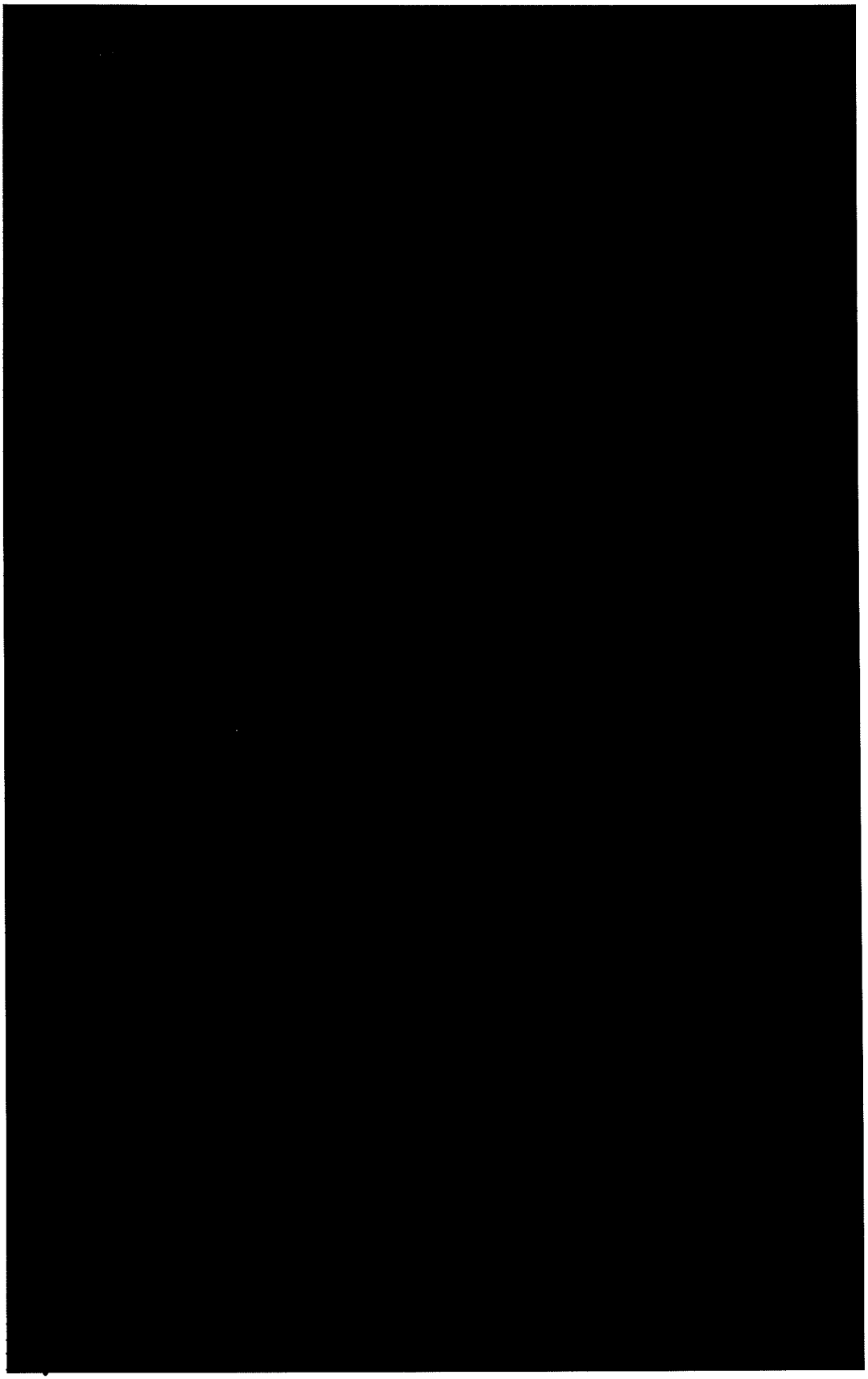

PRE-CLINICAL ASSESSMENT

1. Introduction

Amphotericin B is a broad spectrum polyene macrolide antifungal agent and has been shown to be effective in many systemic mycotic infections including cryptococcal meningitis. Longer term use is often associated with renal toxicity and anaemia and acute effects such as fever, chills, nausea and vomiting are common.

Amphotericin B Lipid Complex is a new formulation which has been developed in an attempt to improve the efficacy and reduce the toxicity of Amphotericin B. Other lipid formulations of Amphotericin B have been developed including Ambisome, a unilamellar liposome preparation. This has shown some improved efficacy and reduced toxicity and it is currently licensed in the UK along with Fungizone and Amphocil which both contain a colloidal dispersion of Amphotericin B.

Amphotericin B Lipid Complex (ABLC) consists of Amphotericin B complexed with 2 phospholipids dimyristoylphosphatidylcholine (DMPC) and dimyristoyl-phosphatidylglycerol (DMPG) in a [redacted] It is intended for iv administration and is suspended in physiological saline. The lipid complex appears to consist of non-liposomal ribbon like structures.

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It is indicated for the first-line therapy of cryptococcal meningitis in patients with AIDS and in systemic fungal infections in patients who have not responded to treatment with conventional Amphotericin B or other systemic fungal agents or who have renal impairment or other contraindications to conventional Amphotericin B.

Amphotericin B Lipid Complex is intended to have a maximum daily dose of 5mg/kg given by infusion .

The precautions and warnings given include the need for weekly monitoring of renal, hepatic and haematological function and mention some possible drug interactions. There is also the following statement with regard to pregnancy: "Safety for use in pregnant or lactating patients has not been established for ABLC. ABLC should only be used during pregnancy or lactation if the potential benefits exceed the possible risks.

The Expert report was of a reasonable quality and can be found as Appendix 1.

2. Pharmacodynamics

2.1 Effects relating to proposed Therapeutic Indications (See Appendix 2)

The efficacy of ABLC in systemic fungal-type infections in experimental animals (mostly mice) has been compared to that of a deoxycholate colloidal dispersion of Amphotericin B ie Fungizone. In these models both ABLC and Fungizone were able to increase survival and reduce the level of infection or even clear relevant organs of infection eg kidney or brain. Infections investigated included Candida, Aspergillus, Cryptococcus, Histoplasma and Blastomycosis in normal as well as immunosuppressed animals. As can be seen from the Appended tables ABLC was

generally effective at higher doses than Fungizone but because it is better tolerated considerably higher doses could be given. In some instances ABLC had a greater beneficial effect because Fungizone toxicity prevented an effective dose from being given. This was apparent in some C.neoformans infections in particular.

In summary then it appears that ABLC may offer some modest advantages over Fungizone in the treatment of some infections including cryptococcal meningitis. It was also clearly more effective than Fluconazole and other azole antifungal agents.

2.2 Resistance

One study of resistance appeared to suggest that in vitro some phospholipase deficient Candida species were resistant to ABLC. However in vivo this was not apparent presumably because other mechanisms for the release of the active Amphotericin B from the lipids then operate.

2.3 General Pharmacology

Single doses of ABLC of 1, 3 or 10mg/kg (iv) given to mice had no appreciable effects on the CNS or on intestinal propulsion. The same doses in rats had no appreciable effects on the CNS, sensory, neuromuscular or reflexive functions. Single doses of 0.5, 1.5 or 5mg/kg iv to rabbits had no antipyrogenic effect. Cardiovascular and renal function was evaluated after single iv doses to dogs. A dose of 6mg/kg had no appreciable effects, at higher doses (12-48mg/kg) changes in renal and cardiovascular function were seen. All the dogs survived.

2.4 Drug Interactions

a. Acute combination study with Cyclosporin in mice

ABLC at 25+ mg/kg iv was no more toxic when given with 90mg/kg cyclosporin than when given with saline.

b. Acute combination study with Pentamine in mice

ABLC at 25+ mg/kg iv was more toxic when given with 15mg/kg iv pentamine than when given alone. As ABLC (and Fungizone) gives similar toxic effects to pentamine there was probably an additive effect.

c. Acute combination toxicity with Zidovudine (ZDV) in mice

ABLC (25+ mg/kg iv) toxicity was not enhanced when given with 1500mg/kg ZDV. (LD_{50} values 60mg/kg ABLC, 65mg/kg ABLC + AZT.)

d. Repeat dose combination toxicity studies with Zidovudine

Species	Treatment	ABLC (mg/kg)	ZDV (mg/kg)	Doses	Animals	Comments
rats	1ABLC™+ZDV	10	500	30	8M	
	2 vehicle+ZDV	0	500	30	8M	
	3 vehicles only	0	0	30	8M	
dogs	1 ABLC™+ZDV	1.5	50	28-30	4M,4F	1 dead/moribund
	2 ABLC™+ZDV	5.0	50	28-30	4M,4F	5 dead/moribund
	3 vehicles only	0	0	28-30	4M,4F	
dogs	1 vehicle only	0	0	70	2M,2F	no deaths
	2 vehicle+ZDV	0	50	28	2M,2F	1 dead/moribund
	3 Fungizone®+ZDV	0.5	50	28	4M,4F	7 dead/moribund
	4 ABLC™+ZDV concurrent	5.0	50	28	2M,2F	2 dead/moribund
	5 ABLC™+ZDV sequential	5.0	50	28/28	2M,2F	no deaths
	6 ABLC™+ZDV (washout)	5.0	50	28/14/28	2M,2F	no deaths

ABLC was given iv and ZDV was given po in 2 divided doses/day. In the rats no enhancement of toxicity was seen. In the dogs given ABLC and ZDV concurrently enhanced toxicity was noted. The primary target organs were those normally associated with ABLC (kidney) and ZDV (bone marrow) and no novel toxicity was evident. Fungizone also had this effect. When administration was sequential some recovery of the appropriate target organs was seen. It appeared that serum ZDV levels were slightly elevated in the high-dose combination groups and it is suggested that the renal damage caused by ABLC hindered the excretion of ZDV.

e. In vitro combination study with Zidovudine

ABLC was toxic at 100µg/ml in HIV-infected Tcells (8166) and macrophages (U937). In combination with ZDV no significant interactions were noted.

3. Pharmacokinetics (See Appendix 3)

It was found that ABLC may sediment out when plasma or serum are obtained from whole blood and consequently the more accurate data are derived from whole blood. In measuring Amphotericin B, lipid complexed, protein-bound, free etc were not distinguished.

Single dose iv studies were carried out in mice and dogs using ^{14}C Amphotericin B. Blood levels and AUC values after a dose of ABLC were lower than when the same dose of Fungizone was given to mice and dogs. The blood levels also decreased more slowly after ABLC was given eg t½ in dogs Fungizone 0.5mg/kg - 18.5h, ABLC 0.5mg/kg 19.9h, ABLC 5mg/kg 76.5h. It is suggested that ABLC may be rapidly taken up by the reticuloendothelial system (RES). In mice given ^{14}C-ABLC radioactivity levels were proportionally higher after a 5mg/kg dose than after a 1mg/kg dose. In dogs a greater than

proportional increase was seen between 0.5 and 5mg/kg for both blood levels and AUC values. Tissue levels generally exceeded blood levels and were higher in ABLC treated mice than in Fungizone treated. ABLC treatment resulted in particularly high radioactivity levels in spleen, liver, lungs and kidneys. Brain levels were very low. Tissue levels declined slowly, more slowly after ABLC than Fungizone and this was reflected in the rate of excretion in urine and faeces. In the dog urinary excretion predominated while in the mouse faecal and urinary excretion were both important. Over 10 days greatest recoveries were found for Fungizone and lowest recoveries for the high dose of ABLC.

A single dose study was also carried out in rats using doses of 3 or 10mg/kg ip or 3mg/kg iv. The systemic availability of the ip dose was about 52% and there were no major differences in distribution or elimination between the ip + iv doses.

Repeat dose studies were available for mice (4 days), rats (1 month) and dogs (1 month). Here unlabelled drug was used and detection was by HPLC. Some accumulation was seen but a steady state appeared to be reached after 7-10 days (dogs). After cessation of dosing, blood and tissue levels persisted eg in rats 28 days post-dose (10mg/kg) blood levels fell to about 35% of values found at cessation of dosing. In the dog Amphotericin B was detected in blood 15 days, and in tissues 29 days post-dose.

In the dog it was apparent that ABLC resulted in much lower kidney concentrations of Amphotericin B (approx $^1/_{20}$) than Fungizone when given at the same dose level which is consistent with the lower renal toxicity seen.

Table of Comparative Pharmacokinetics (in blood) of ABLC

Species	Dose details (mg/kg x time)	Cmax (µg/ml)	AUC (µg.h/ml)	t½ (h)
Mouse	iv 1 x 1 day	2.2	4.4	
	iv 5 x 1 day	1.4	6.5	
Rat	iv 3 x 1 day	0.85	14.3	
	ip 3	0.24	7.36	
Dog	iv 0.5 x 1 day	2.74	4.2	19.9
	5 x 1 day	35.0	175	76.5
Rat	iv 1 x 1 month	0.11	-	
	3 x 1 month	0.13	-	
Dog	iv 5 x 1 month	-	-	(3.63 days)
Man	iv 0.6 x 42 days	0.86	4.45	113.1
	2.5 x 10 days*	2.41	6.77	187.2
	5.0 x 5 days*	1.70	9.5	173.4

* **steady state was probably not reached.**

Comment

The pharmacokinetic studies are a little limited. They have not included all the usual investigations such as metabolism, distribution in pregnancy etc. They have provided comparative data between ABLC and Fungizone and indicated that ABLC is largely taken up by the reticuloendothelial system, and only slowly eliminated from the body. However Amphotericin B is a well known drug-substance and the information may be regarded as adequate, particularly in view of the proposed indications.

4. Toxicity Studies

4.1 Acute studies

	LD50 ABLC (mg/kg)		LD50 Fungizone (mg/kg)	
	M	F	M	F
Mice iv	54	45	5	3
Rats iv	68	51	3	2

The no-effect level for both sexes of rats and mice was 15mg/kg iv.

4.2 Repeat dose studies

a. Sub-acute studies

Rats were dosed with ABLC for 4 weeks at 1, 3 or 10mg/kg iv.

Dogs were dosed with ABLC for 2 weeks at 2.5, 5 or 10mg/kg iv and for 4 weeks with 0.5, 1.5 or 5.0mg/kg iv.

b. Chronic studies

Rats were dosed with ABLC 6 days/week for 6 months, iv and ip alternately, at 1, 3 or 10mg/kg. (Note bioavailability ip/iv approx ½ in rats).

Dogs were similarly treated except at the lower dose levels of 0.5, 1.5 or 5mg/kg.

The results of all these studies indicated that ABLC related toxicity occurred at the injection sites, kidney, liver and spleen.

i. **Injection sites**

Inflammatory changes were greater in ABLC treated groups than in controls and severity increased with dose suggesting that ABLC had an irritant effect.

ii. **Kidney**

This appeared to be the main target organ in rats and dogs. At even the lowest doses administered (0.5mg/kg in dogs and 1mg/kg in rats) changes were seen in the urine eg increased output, decreased specific gravity etc. At slightly higher doses eg 1.5mg/kg in dogs, 3mg/kg in rats elevated serum urea nitrogen and creatinine were noted and some pathological changes were found in the kidneys eg tubular epithelial degeneration in dogs seen after 0.5 + mg/kg for 1 month and hyperplasia of the transitional epithelium of the renal pelvis seen after 3 + mg/kg for 1 month in rats and tubular cytoplasmic eosinophilic droplets seen after 1 + mg/kg for 6 months in rats. The renal lesions decreased in severity in animals allowed a drug free period prior to sacrifice. It was claimed that the nephrotoxicity of ABLC was about 10 fold less than that of Fungizone on a mg/kg basis in dogs.

iii. **Liver**

The main effect on the liver appeared to be on the RE cells presumably as a result of uptake of Amphotericin B and the lipid complex. Some high dose dogs had inflammatory changes in the liver and elevated serum transaminases which may have been related to the fairly marked uraemia in these animals.

iv. **Spleen**

Again the main effect appeared to be on the RE cells. Some increase in extramedullary haemotopoesis was also seen in rats where decreases in erythrocyte parameters were noted.

v. **Platelets**

In dogs dosed at 2.5mg/kg for 1 month or longer and in rats dosed at 10mg/kg iv platelets were decreased. Recovery was seen in rats and dogs post-treatment, suggesting reversibility.

Comments

ABLC showed a similar toxicity profile to Amphotericin B itself but at higher doses. Nephrotoxicity is very likely to occur in man as it has been seen in 2 animal species at doses lower than the maximum human dose but this has been addressed by renal function monitoring in the clinical trials. The [redacted] particle size [redacted] did not appear to cause any particular toxicity in the animals.

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4.3 Additional Toxicity Studies (See Appendix 4)

ABLC was shown to have no significant immunotoxicological effects in mice, it did not cause appreciable arterial irritation, it did not cause haemolysis of human erythrocytes and interfered less with normal human leukocyte function than Fungizone although it did increase the oxidative burst of PMN a little. The toxicity of the phospholipid component was evaluated in rats (acute 28 day iv studies). Although some effects were seen these were reversible and probably of little toxicological significance. The small depression of erythrocyte related parameters and platelets may have contributed to the findings with ABLC but this did not appear to be a cause for concern. The possible contaminants Amphotericin A and Amphotericin X had considerably greater LD_{50} values than Amphotericin B and trace amounts appeared unlikely to present any problems.

5. Mutagenic Potential

A standard battery of tests was conducted with ABLC to a reasonable standard. The tests included an Ames test, gene mutation in mouse lymphoma L5178Y cells, chromosomal aberrations in CHO cells and an in vivo mouse micronucleus test (dosing 3, 10, 25mg/kg iv). They all gave negative results suggesting an absence of mutagenic potential.

6. Carcinogenic Potential

No studies were conducted and this appears reasonable.

7. Reproduction Studies

Two main studies were presented, both were preceded by dose-range studies. One of the studies was an iv teratology study in rats. Dosing (1, 3 or 10mg/kg) was from day 6-17 of gestation and in one arm of the study the pregnant dams were delivered by caesarean section at day 20 and the fetuses were evaluated for malformations. In the second arm, the dams delivered naturally and the offspring were fully evaluated for post-natal development. There was evidence of slight maternal toxicity at 10mg/kg iv (the top dose) but there were no adverse effects on the offspring, other than a marginal and reversible increase in pup growth retardation.

The other study was a standard iv rabbit teratology study with doses of 0.03, 0.3 or 3mg/kg given from day 6-18 of gestation. The dose range study had suggested an increase in fetuses with enlarged kidneys at 0.3 + mg/kg and an overall increase in fetal defects. The main study again suggested a small increase in the number of fetuses with enlarged kidneys (3mg/kg) but did not show any teratogenic effects or marked embryotoxicity or fetotoxicity at up to 3mg/kg. One high dose doe died and was found to have renal tubular degeneration. There were no other indications of maternotoxicity except an increase in spleen weight at 3mg/kg. Fungizone was used as a comparator and maternotoxicity and fetotoxicity were seen at 1mg/kg iv.

These studies gave no real cause for concern.

There were no other studies eg on fertility, general reproduction or the effect of dosing late in pregnancy, as in a standard peri-post-natal study. This is probably acceptable for the indications requested.

8. Conclusions

The animal studies suggest that ABLC may be an effective antifungal agent which could offer some advantages over the colloidal dispersion formulation of Amphotericin B in that high enough doses to be effective may be given without undue toxicity in some instances. There was some enhancement of ZDV toxicity when this was given concurrently suggesting a need for caution in combination therapy but this may have been due to renal impairment. ABLC gave lower blood levels of Amphotericin B and higher tissue levels than the colloidal dispersion suggesting a difference in distribution. The drug persisted in the tissues for some time (detectable for 29 days after a month of dosing in dog) with highest levels being found in liver, spleen, kidneys and lungs. It did appear that at equal dose levels kidney concentrations of Amphotericin B were lower after ABLC than after the colloidal dispersion. The pharmacokinetic section was incomplete and concentrated primarily on comparative data. The absence of eg metabolism data does not appear to be too significant for this product. The toxicity studies showed the kidney to be the main target organ but the toxicity occurred at higher doses than seen with uncomplexed Amphotericin B. ABLC did not appear to be mutagenic or teratogenic. Although the reproductive toxicity package was not complete, adequate reassurance was probably provided for a product of this nature. There would not appear to be any Preclinical objections to the grant of a licence for this product.

[redacted]
October 1994

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III. MEDICAL ASSESSMENT OF ABLC™ (Amphotericin B lipid complex)

1. INTRODUCTION

Appendix 5
page 81

Regulatory Status of Amphotericin B Preparations

ABLC™, (Liposome Co.) : A complex abridged product licence application for a novel formulation of amphotericin B that is currently not licensed for use in any country.

Fungizone™, (Squibb) : conventional amphotericin B (containing the bile acid sodium desoxycholic acid) and in clinical use in the UK since the early 1960s.

AmBisome™, (Vestar) : a liposomal preparation of amphotericin B that was given a UK licence in December 1991.

Amphocil™, (Zeneca) : an amphotericin B lipid complex (containing sodium cholesteryl sulphate) given a UK licence in August 1993.

Formulation

ABLC™ consists of amphotericin B complexed with the lipids dimyristoylphosphatidylcholine (DMPC) and dimyristoylphosphatidylglycerol (DMPG), suspended in saline. Prior to infusion ABLC™ is mixed with 5% dextrose.

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Pharmacological Rationale

ABLC™ has been developed to alter the systemic distribution of amphotericin B, and thus reduce the toxicity and extend the anti-fungal efficacy of amphotericin B.

It is postulated that ABLC™ is readily taken up by phagocytes of the reticulo-endothelial system, and that amphotericin B will be released within phagocytes that have ingested fungal components.

Indications

ABLC™ is recommended for :

"First line therapy of cryptococcal meningitis and systemic cryptococcus in patients with acquired immunodeficiency syndrome (AIDS).

Therapy of severe systemic fungal infections in patients who have not responded to treatment with conventional amphotericin B, or who have renal impairment, or other contraindications to conventional amphotericin B."

Dosage Regimen

"ABLC™ should be administered by intravenous infusion at a rate of 2.5 mg/kg/hr. The recommended daily dose is 5.0 mg/kg."

"Most successful treatment courses have been 12 to 15 days long."

"Special patient groups : no adjustment of dosage is required for special patient groups."

2. PHARMACOKINETICS

A pharmacokinetic analysis was performed as an adjunct to a study on the safety and efficacy of ABLC™ in the treatment of cutaneous leishmaniasis in Peru.

The study was open-label, parallel group, sequential, ascending multiple dose.
5 groups of 8 patients were studied:
4 groups receiving ABLC™ and a single group receiving Fungizone™.
2 groups were comparable since they received doses of ABLC™ and Fungizone™ respectively at 0.6 mg/kg/day for 42 days.
Following the last dose of ABLC™ or Fungizone™ treatment blood samples were taken for the pharmacokinetic analysis.

Following administration of 0.6 mg/kg the AUC_{0-24} was significantly lower (4-fold) for ABLC™ than Fungizone™.
However, the $t_{1/2}$ was similar at 113 hours for ABLC and 91 hours for Fungizone.
Hence, both clearance and volume of distribution may be greater for ABLC™ than for Fungizone.
The AUC_{0-24} of the different doses of ABLC™ was not proportional, probably because of the widely differing numbers of days of treatment, which did not allow the steady state to be reached in some groups.
Based on compartmental and non-compartmental predictions, there would be linearity of AUC_{0-24} with doses reaching steady state.

CRITICAL COMMENT
The results of this study are consistent with the pharmacological rationale that ABLC is rapidly cleared from the peripheral blood by uptake into phagocytes of the reticuloendothelial system.

There are deficiencies regarding this pharmacokinetics study :
1. Number of subjects :
There were apparently only 5 subjects in the Fungizone™ control group, which is insufficient for reliable statistical analysis.
The company report is inconsistent since it refers to both 5 and 8 subjects in this group.
2. The pharmacokinetics of the recommended therapeutic dose of 5.0 mg/kg/day of ABLC was studied after an administration period of only 5 days. This administration period should be longer, since at least 14 days of treatment with ABLC is generally required for severe systemic fungal infections.
3. Infusion times were variable between groups :
ABLC™ (0.6 mg/kg) infusions were performed over 0.3 hours.
Fungizone™ (0.6 mg/kg/day) infusions were given over 2.4 hours.
Hence, pharmacokinetic data is not "strictly comparable" for these groups.
4. Blood samples were taken for only 72 hours in most cases, and this does not seem long enough when ABLC has a $t_{1/2}$ of 113 hours.

5. Studies in healthy volunteers and patients with renal and hepatic impairment were not described.

3. EFFICACY

Analysis of the risk benefit profile of ABLC™ was complicated because life-threatening fungal infections generally occur in patients as a consequence of underlying severe systemic disease. In addition, double-blind, placebo-controlled trials of the efficacy of ABLC in treatment of severe fungal infections would not be ethical.
Three main clinical investigations were performed with ABLC™, involving administration of ABLC™ to a total of 239 subjects.

3.1. **Cryptococcal Meningitis in AIDS**

· Appendix 7.1
· page 86

A multicentre comparative study of 3 different dosage regimens of ABLC™ with Fungizone™ for the treatment of 55 AIDS patients with cryptococcal meningitis. There

Clinical responses were assessed by Karnofsky performance score, neurologic assessment score, headache severity and weight. Responses were classed as success, failure, relapse or undeterminable.
Mycological response was determined in terms of CSF, blood and urine cultures for C. neoformans. Responses were classed as success, improved, failure, undeterminable.

Clinical response rates (resolution of signs and symptoms) were 80.9% for ABLC™ Group III and 70.6% for Fungizone™.
Mycological response rates were 42.9% for ABLC™ and 47.0% for conventional amphotericin B.
The overall success rate (clinical plus mycological success) was 42.9% for ABLC™ and 47.0% in the Fungizone™ group.

For the treatment of cryptococcal meningitis in AIDS, while clinical response rates were greater for ABLC™ compared with Fungizone™, mycological response rates and overall success rates were not. ABLC™ has equivalent efficacy to Fungizone™ in the treatment of cryptococcal meningitis in AIDS.

3.2. **Advanced Systemic Fungal Infections**

Appendix 7.2
page 87

An open-label, non-comparative, non-placebo-controlled study on the efficacy of using ABLC™ for 135 patients in 109 US centres with advanced fungal infections. These patients had been unsuccessfully treated with at least 1000mg of conventional amphotericin B, or had experienced severe nephrotoxicity due to conventional amphotericin B, or had renal disease.

Treatment was with ABLC™ at 5.0 mg/kg/day for 4 weeks, with reduced dosage where nephrotoxicity developed.
The overall clinical response rate (cure plus improvement) was 66.7%, while the overall mycological response rate was 55.2%.
For candidiasis the clinical response rate was 73.2% and the mycological response rate 75.0%.
For aspergillosis the clinical response rate was 59.5% and the mycological response rate 40.9%.

The results of this study suggest that ABLC™ is a useful adjunct in severely ill subjects with systemic fungal infections following failure of conventional amphotericin B therapy or with renal disease.
Interpretation of the efficacy of ABLC™ is limited due to lack of appropriate controls.

3.3. **Mucocutaneous Leishmaniasis**

Appendix 7.3
page 89

An open-label randomised escalating dose comparison of ABLC™ with Fungizone™ conducted with 77 patients with mucocutaneous leishmaniasis at one site in Lima, Peru. There were 5 ABLC™ dosing groups and a single Fungizone™ group. This was primarily a safety study that was to provide preliminary efficacy data.
ABLC was of only partial efficacy in the treatment of mucocutaneous leishmaniasis, since at the end of therapy all patients still had some lesions, while 3 months after therapy numerous subjects had no change or deterioration in their disease state.
In contrast, Fungizone caused absence of lesions by the end of therapy in the majority of subjects.
Localisation of ABLC™ in splenic and hepatic phagocytes of the reticulo-endothelial system may favour use of ABLC™ in visceral rather than muco-cutaneous leishmaniais.
In summary, ABLC was of only partial efficacy in the treatment of mucocutaneous leishmaniasis, and clearly less effective than Fungizone.

4. **SAFETY**

The 3 described clinical studies involved a total of 239 patients receiving ABLC™.

4.1 **Deaths**

Appendix 8.1
page 91

A total of 64 patients died either during ABLC therapy or within 4 weeks of the final dose of ABLC™.
A. In the study of AIDS with cryptococcal meningitis, the mortality of ABLC™ treated patients was 17.9%, while the mortality of the Fungizone treated patients was 18%. These are typical mortality rates in this subgroup of patients.
In one case ABLC™ was considered to have been possibly related to death from hypotension and cardiac arrest (described in appendix, p. 94).

B. In the study of severe systemic fungal infections with underlying AIDS, malignancy or organ transplantation, the 41.5% of cases ending in death was also to be expected. In a case of pulmonary embolism and another with renal failure death was considered by the investigators to have been possibly related to ABLC™ (described in appendix, p. 95)
C. No deaths occurred in the study on patients with cutaneous leishmaniasis.

4.2 **Withdrawals From Therapy Due To Adverse Events** Appendix 8.2 page 96

Of 239 cases treated with ABLC™, 17 (7.1%) were withdrawn from therapy due to adverse events. In 3 of these cases the adverse events were considered related to ABLC™.

4.3 **Clinical Adverse Events**

Among the 239 cases receiving ABLC™ a total of 1153 clinical adverse events were recorded : Appendix 8.3 page 98

331 (28.7%) were considered unrelated to ABLC™
317(27.5%) were considered possibly related to ABLC™
243 (21.1%) were considered related to ABLC™
262 (22.7%) could not be given a degree of relationship

There were 243 drug-related clinical adverse events in a total of 5931 infusions :

65 (26.7%) were considered mild
148 (60.9%) moderate
30 (12.3%) severe

The most prevalent types of drug-related adverse events were those referable to the body as a whole (206/243 episodes, 84.8%) and the digestive system (25/243 episodes, 10.3%).

4.4 **Early Acute Adverse Events** Appendix 8.3 page 98

The most frequent early adverse events consisted of chills, fever, nausea and vomiting. These events occurred soon after the initiation of therapy ; generally only in relation to the first or second days of therapy.
Out of a total of 239 patients treated with ABLC™ :
44 (18.4%) had chills, 2 (0.8%) had chills with fever, 27 (11.3%) had fever
11 (4.6% had nausea, 1 (0.4%) had nausea with vomiting, 6 had vomiting.
These mild acute adverse events responded to antihistamines and/or hydrocortisone.

4.5 **Renal Toxicity** Appendix 8.4 page 102

Renal toxicity is the most serious dose-limiting toxicity of conventional amphotericin B. Evaluation of nephro-toxicity in severely ill patient populations was complicated due to underlying and concurrent illnesses, other infections, and nephrotoxic concomitant medications.

Among the total of 239 patients, only 5 were withdrawn because of decreases in renal function : all 5 subjects being involved in the non-comparative study of advanced systemic fungal infections.
Serum creatinine was monitored in a total of 233 patients, creatinine increased significantly in 17.6%, while with conventional amphotericin B serum creatinine has been reported to increase in 83%.
Blood urea nitrogen increased in 35.2% of subjects
Serum hypokalaemia developed in 13.2% of subjects
In general, ABLC™ causes significantly less nephrotoxicity than conventional amphotericin B.

4.6. **Hepatic Toxicity** Appendix 8.5 page 104

Hepatotoxicity is an unusual adverse effect of conventional amphotericin B. Data from the clinical studies on ABLC™ demonstrated that ABLC™ does not cause dose-limiting hepatotoxicity.

4.7. **Laboratory Tests**
The blood haemoglobin level is the primary index to detect haematologic toxicity of standard amphotericin B. Amphotericin B can cause haemolytic anaemia with raised blood urea and increased platelet counts. In all 3 clinical studies with ABLC™ haemoglobin levels, platelet conts and leukocyte counts all tended to remain stable.

5. CLINICAL EXPERT REPORT Appendix 9 page 105

Deleted according to Section 40, FOI Act

The clinical expert report was compiled by [redacted] A detailed review of the treatment of serious fungal infections with anti-fungal drugs is presented. It is concluded that "ABLC™ appears to fill a niche in antifungal treatment in cryptococcal infections in AIDS patients or in severe fungal infections where therapy is currently constrained either by drug toxicity or failure of existing treatment, in many cases conventional amphotericin B."
The entire clinical expert report is appended.

6. PRODUCT PARTICULARS Appendix 10 page 140

A completed MLA 201 was evaluated, but neither a draft SPC nor draft patient information leaflet was submitted.

6.1 **Clinical Indications** (MLA 201 page 4)
There is inadequate efficacy data to support the indication for :
"First line therapy of cryptococcal meningitis and systemic cryptococcus....."
This should be replaced by :
"Therapy of cryptoccal meningitis and systemic cryptococcus....."

The following text should be deleted :
"ABLC™ may be particularly indicated for treatment of fusariosis, which has been reported to respond very poorly to conventional amphotericin B."

6.2 **Recommended Dosage Schedule** (MLA 201 page 5)
The following sentence should be deleted :
"The drug is well tolerated when treatment is begun with 5.0 mg/kg on the first day. Accordingly, no dose escalation procedure is necessary."

Initial Test Dose Appendix 11 page 152

Due to the incidence of 2 cases of anaphylactic reactions soon after commencing infusion of liposomal amphotericin B (Lancet (1994) 344:682), it is recommended that the following text should be inserted :
"The initial dose of ABLC™ should be given as a single 1 mg test dose given over 15 mins. with facilities for resuscitation readily available"
Due to the incidence of early adverse events, the following should be inserted :
"Chills, fever, nausea and vomiting may occur in relation to the first 2 days of therapy. "
Dose Intervals
It should be specified that a single daily dose is recommended..
Duration Of Treatment
It should be more directly stated that :
"At least 14 days of ABLC™ treatment is generally required for severe systemic fungal infections."

Special Patient Groups (MLA 201 page 5)
The following text should be deleted :
"No adjustment of dosage is required."
State dose recommendations for children and the elderly, refer to renal disease.

6.3 **Contraindications, Precautions and Warnings**

Interactions (MLA 201 page 6A)
Omit :
" Although interaction of ABLC™ with other drugs has not been observed to date"
Replace by :
Interaction of ABLC™ with other drugs has not been studied to date."
Insertion :
"Particular attention should be paid to patients receiving nephrotoxic drugs. Renal function should be closely monitored in these patients."

Other Undesirable Effects (MLA 201 page 6A)
The anticipated frequency of adverse events should be provided.
Delete :
"Adverse events generally do not require dose reduction or alternate day dosing, and have not prevented patients from receiving prolonged treatment and a high cumulative dose."

Pregnancy & Lactation (MLA 201 page 6B)
Delete :
"Consequently ABLC should only be used during pregnancy or lactation if the potential benefits exceed the possible risks.
Insert :
"Only therapy for life-threatening disease should be carried out during pregnancy or lactation, when the likely benefit exceeds the risk incurred by mother and foetus."

7. SUMMARY OF MEDICAL ASSESSMENT

Pharmacokinetics

The results of a pharmacokinetics study are consistent with the pharmacological rationale for ABLC as a formulation that is readily cleared from the peripheral blood due to uptake by the reticuloendothelial system. However, a number of deficiencies were identified in the design of the pharmacokinetics study,.

Efficacy

- ABLC & Fungizone have equivalent efficacy in cryptococcal meningitis in AIDS
- ABLC was effective in the treatment of severe fungal infections for which Fungizone is ineffective or contraindicated. This study had neither placebo nor comparator controls, but showed encouraging efficacy for the treatment of severely ill patients with sysytemic fungal infections who cannot tolerate conventional amphotericin B.
- ABLC is less effective than Fungizone in the treatment of mucocutaneous leishmaniasis.

Safety

ABLC™ has an adverse event profile similar to currently marketed amphotericin B formulations that contain lipid complexes or liposomes. In particular, it causes less nephrotoxicity compared with equivalent doses of conventional amphotericin B.
Renal toxicity cannot be excluded, but an effective dose of ABLC can be given to patients with underlying renal impairment.

Amendment of Product Particulars

A series of modifications are proposed.

Medical Assessor's Conclusion

On grounds of safety, quality and efficacy it is considered that ABLC is suitable for a product licence, subject to appropriate amendment of product particulars.

Request to Committee

The Committee and the Sub-Committee are requested to consider the evidence in the clinical expert report and this assessment, and to advise the Licensing Authority of the suitability of ABLC for a Product Licence.

Deleted according to Section 40, FOI Act [redacted]
Medical Assessor
12th October 1994