Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

Amphotericin B
Amphocil

Abelcet

DE/W/009/pdWS/001

Rapporteur:	Germany
Finalisation procedure (day 120):	24.11.2017

TABLE OF CONTENTS

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VI
INN (or common name) of the active substance(s):	Amphotericin B
MAH (s):	See section VI
Pharmaco-therapeutic group (ATC Code):	J02AA01
Pharmaceutical form(s) and strength(s):	concentrate for suspension for infusion

I. EXECUTIVE SUMMARY

This is a data submission for two amphotericin B containing products 'Amphocil' and 'ABELCET' in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use. The member state DE is the rapporteur for this procedure.

The MAHs did not propose any update to the product information, which is not supported.
The submitted clinical studies and literature on efficacy and safety of Amphocil and ABELCET confirm the limited data for the paediatric population of all age groups. The MAHs stated that the submitted data do not influence the benefit/risk ratio for Amphocil and ABELCET. This is agreed in general, but based on the review of the submitted paediatric data updates - especially regarding the differences within the member states on the appropriate wording for the paediatrics in the product information - are proposed (see section II. and V.).

Summary of outcome

☐ No change

☐ New study data: <section(s) xxxx, xxxx>

☐ New safety information: <section(s) xxxx, xxxx>

☒ Paediatric information clarified:
SmPC sections 4.2, 4.4 and 4.5 for **Amphoci**l and sections 4.2 and 4.8 for **ABELCET**

☐ New indication: <section(s) xxxx, xxxx>

II. RECOMMENDATION

The following information related to paediatric use of Amphocil and ABELCET is recommended to be implemented in the product information

Amphocil:
If not already mentioned, the very limited data on efficacy and safety of Amphocil for the use in children and adolescents should be addressed in the relevant sections of the SmPC/PL. Based on the wording of the approved product information in the member states DK, NL and SE, the following wording for the sections 4.2 and 4.4 is proposed:

4.2 Posology and method of administration

Initially, the following advice should be given:

‘Treatment with /…/ should be initiated by physicians experienced in the treatment of systemic fungal infections.’

and during the section under the appropriate subheading:

‘Use in children and adolescents:
Experience with /…/ in children is very limited. Use should therefore be discouraged unless life-threatening infections without other treatment options exist. The very limited experience seems to indicate that the dose per kilogram of body weight may be comparable to adults (see section 4.4).’

4.4 Special warnings and precautions for use

‘The efficacy and safety of /…/ in children is limited. In clinical studies, children (including children less than 3 years) were treated with /…/ with daily doses (mg / kg) similar to adult doses without any unexpected adverse events reported.’

If applicable, consideration should be given to the infusion-related reactions, in particular to the infusion time.

4.5 Interaction with other medicinal products and other forms of interaction

Furthermore, the influence of concomitant medication (cyclosporine or tacrolimus) on the nephrotoxicity in adults and children were reported in section 4.5 of the SmPC only in the MSs GR and SK. The MAH should update all approved SmPCs regarding this interaction.

ABELCET:
Not all of the Abelcet approved SmPC within the European states includes this information. Therefore the MAH is requested to harmonize the wording via variation procedure as follows (proposed additions are red colored):

4.2 Posology and method of administration
…
Use in children and adolescents
Systemic fungal infections in children (ranging from 1 month to 16 years of age) have been treated successfully with Abelcet at doses comparable to the recommended adult dose on a body weight basis.
There are no sufficient data on efficacy and safety available in children less than one month.

No data on the efficacy and safety of Abelcet in preterm newborn infants suffering from fungal infections due to aspergillus species are available.

4.8 Undesirable effects
…
Adverse events are similar to those seen in adults.

III. INTRODUCTION

For the work-sharing procedure for paediatric studies according to Article 45 of the Regulation No 1901/2006 as amended on medicinal products for paediatric use, data for the following two medicinal products has been submitted:

- **Amphocil** (former name was **ABCD**), an **A**mphotericin **B** **C**olloidal **D**ispersion with sodium cholesteryl sulphate (molar ratio = 1 :1)

- **ABELCET** (= **ABLC**), an Amphotericin B complex with two phospholipids in a 1:2 drug-to-lipid molar ratio. The two phospholipids, L-α-dimyristoylphosphatidylcholine (DMPC) and L-α dimyristoyl-phosphatidylglycerol (DMPG), are present in a 7:3 molar ratio.

In addition, the following documentation has been included as per the procedural guidance:

- A short critical expert overview

- A line listing

- Published information relevant to the paediatric population

- SmPC wording of sections 4.1 - 5.3 and related PL wording for the EU countries where a marketing authorization is granted for Amphocil and ABELCET

Rapporteur's comment:
*It should be pointed out that this assessment report does not cover the medicinal products '**Ambisome'** the liposomal formulation of amphotericin B with defined liposomes and ''**Fungizone'** the so-called conventional amphotericin B formulation.*

Amphocil and ABELCET
For both medicinal products, the applicant stated that the submitted paediatric studies do not influence the benefit risk assessment for Amphocil and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical studies

Both medicinal products (Amphocil and ABELCET) are concentrates for suspension for infusion.

Amphocil
Amphocil is administered via an intravenous infusion. It is available in 50mg or 100mg vials.

ABELCET
ABELCET is a 5 mg/ml concentrate for suspension for infusion.
According to the studies submitted the final infusion concentration should be 1 mg/ml. For paediatric patients and patients with cardiovascular diseases, the drug may be diluted with 5% dextrose injection to a final infusion concentration of 2 mg/ml may be used.

Rapporteur's comment:
The two Amphotericin B products differ in their composition resulting in dissimilar structures for the finished product. This will influence the pharmacokinetic properties. Some pharmacokinetics data of each product are available but insufficient to compare them in particular for the paediatric population. Differences of pharmacokinetics of conventional amphotericin B and Amphocil and/or ABELCET have been described in section 5.2 of the SmPC.
An influence of the different composition of the finished product on the efficacy can not be excluded as comparable studies have not been conducted.
Thus, these ***both medicinal products are separately assessed in this report****.*

Orally applied Amphotericin B formulations are not worthwhile to develop due to the low bioavailability below 5 %. Amphotericin B should be intravenously administered in order to achieve effective tissue and serum concentrations. Therefore, a specific paediatric formulation is not necessary.

Licensing status:

<u>Amphocil</u>

Amphocil has been indicated since 1993 in several European countries.

Currently the product is authorized in DK, NL and SE.
Licenses have been withdrawn/cancelled by the Marketing Authorisation Holder (MAH)in BE, FI, IS, UK, and DE.

<u>ABELCET</u>
ABELCET was approved in the United States in November 1995 with a different MAH.
ABELCET is registered in EU via the mutual recognition procedure (MRP) in three countries with UK as the Reference Member State (RMS) and Italy and Austria as Concerned Member States (CMS). Additional European countries (BE, CZ, CY, DE, DK, ES, FI, FR, GR, HU, IS, IE, LU, NL,

NO, PL, PT, SE, SK) registered ABELCET via national procedures. Cephalon is the (MAH) in Europe.

Clinical background
Amphotericin B is the active ingredient of Amphocil and ABELCET.

Amphotericin B is a macrocyclic, polyene, broad-spectrum antifungal antibiotic produced by *Streptomyces nodosus*.
Amphotericin B dispersed with deoxycholate (conventional amphotericin B), available since 1958, has been considered the 'gold-standard' for the treatment of serious systemic fungal infections. It is active against a broad spectrum of fungal pathogens, including *Candida* and *Aspergillus* species, *Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis* and *Cryptococcus neoformans.* Most strains are inhibited by Amphotericin B concentrations of 0.03-1.0 µg/ml. Amphotericin B has little or no activity against bacteria or viruses.

Amphotericin B may be fungistatic or fungicidal, depending on its concentration and on fungal susceptibility. The drug probably acts by binding to ergosterol in the fungal cell membrane causing subsequent membrane damage. As a result, cell contents leak from the fungal cell, and, ultimately, cell death occurs. Binding of the drug to sterols in human cell membranes may result in toxicity, although amphotericin B has greater affinity for fungal ergosterol than for the cholesterol of human cells.

Depending on the kind, site and severity of infection, the usual daily dose of conventional Amphotericin B (=Amphotericin B Deoxycholate; not lipid-based preparation) is0.5 – 0.7 mg/kg with a maximum dose of 1 mg/kg or up to 1.5 mg/kg when given on alternate days. At all these doses, amphotericin B causes a high incidence of acute reactions, including fever, chills, shaking, headache, nausea, vomiting,
Impairment of renal function is the dose-limiting toxicity of amphotericin B. The majority of patients who receive multiple doses of amphotericin B experience drug-induced renal insufficiency that may last months after completion or may be permanent, requiring renal dialysis.

In order to reduce its toxicity, various lipid-based formulations of amphotericin B, ranging from lipid complexes, lipid emulsions to small unilamellar liposomes, were developed and licensed during the 1990s.

Indications:

Amphocil:
Amphocil has been indicated in several European countries for the treatment of:

> *Severe systemic and/or deep mycoses in patients, where conventional amphotericin B is precluded in effective doses because of toxicity or reduced renal function*

As the medicinal product is authorised through national procedures, the specific indication wording may vary between the Member States.

Paediatric wording in the SmPC

The submitted line listing presents the wording in section 4.2 and 4.5 of the SmPC related to the paediatric use.
All SmPCs have the following similar wording:

> 'A limited number of children received Amphocil in daily doses (mg/kg bodyweight) similar to those used in adults. No unexpected adverse events were reported.'

Rapporteur's comment:
Only in the SmPCs of CZ, GR, and SK the daily dose is specified to 3-4 mg/kg bodyweight. Furthermore, no age restriction – e. g. regarding neonates – is given in any SmPC. No data on different paediatric age groups were submitted.
The influence of concomitant medication (cyclosporine or tacrolimus) on the nephrotoxicity in adults and children were reported in section 4.5 of the SmPC only in the MSs GR and SK.
The MAH should update all approved SmPCs regarding this interaction (see: section II. and V.).

ABELCET
ABELCET is indicated in several European countries for the treatment of:

- *ABELCET is indicated for the treatment of severe invasive candidiasis.*
- *ABELCET is also indicated as second line therapy for the treatment of severe systemic fungal infections in patients who have not responded to conventional amphotericin B or other systemic antifungal agents, in those who have renal impairment or other contra-indications to conventional amphotericin B, or in patients who have developed amphotericin B nephrotoxicity.*
- *ABELCET treatment is indicated as second line treatment for invasive aspergillosis, cryptococcal meningitis and disseminated cryptococcosis in HIV patients, fusariosis, coccidiomycosis, zygomycosis and blastomycosis.*

Rapporteur's comment:
As ABELCET is mainly approved via national procedures, the wording for the indication may vary within the Member States. For example the approved indication in Germany is as follows:

> *'Abelcet is indicated for the treatment of invasive fungal infections due to Candida or Aspergillus species in patients who have not responded to conventional amphotericin B (amphotericin B sodium desoxycholate complex) treatment, do not tolerate such treatment or who have contra-indications to conventional amphotericin B.'*

IV.2 Non-clinical aspects

No additional data are provided.
Information on non-clinical aspects is depicted in the relevant sections of the SmPC.

IV.3 Clinical aspects

1. Introduction

Amphocil

The MAH refers in the clinical overview to the following clinical studies:

- Study 07-16: A double-blind, randomised comparison of Amphocil and amphotericin B deoxycholate in patients with invasive aspergillosis
- Study 07-26: A double-blind, randomised comparison of Amphocil and amphotericin B deoxycholate in febrile neutropenic patients unresponsive to antibacterial therapy
- Study 07-28: Amphocil in patients with aspergillosis compared to a historical control group1 receiving amphotericin B deoxycholate
- Open-label studies (07-03, 07-00/10, 07-15, 07-14A, 07-14B)
- Two published studies by Dietze *et al* (1993 [Study 07-08] and 1995) on the treatment of Brazilian kala-azar (leishmaniasis) with a short course of Amphocil.

In addition, an extensive literature search has been undertaken in October 2009 using EMBASE, BIOSIS and MEDLINE databases.

ABELCET

According to the letter from 'Cephalon GmbH' (dated 23rd of November 2009) the following documentation on ABELCET on paediatric population was submitted:

- Bibliography: 35 publications
- Clinical expert overview together with the cover letter dated 23rd of November 2009
- Clinical study reports:

  Study A01002-A
  Study A01007-0
  AI800-900901
  AI800-900901 (non aspergillosis subset)
  A93-D-01
  A93-D-01 (non aspergillosis subset)
  AI800-022 (publications Walsh TJ et al. 1997)

- Paediatric information displayed in the following PSURs:

  01 Mar 2003 - 23 Apr 2008
  08 Sep 2008 - 01 Mar 2009
  08 Sep 2005 - 07 Sep 2009

2. Clinical studies

Amphocil

Clinical studies:
The MAH stated that the clinical studies (see above) have previously been submitted as part of the original national MAAs. The studies were performed in adults and children. No specific studies limited to the paediatric population only have been conducted.
The MAH concluded that these studies included limited numbers of children. Based on these data a paediatric indication for Amphocil was granted.

By request, only the synopsis of the following studies 07-16, 07-26, 07-28; 07-03, 07-00/10, 07-15, 07-14A and 07-14B were submitted. A subset analysis of the paediatric population regarding the efficacy and safety including a comparison of the safety data between adults and paediatric patients has not been undertaken to date.
A brief information on the submitted synopses is given below:

Synopsis of Study No.:

CONTROLLED STUDIES
07-16
A double-blind, randomised comparison of AMPHOCIL® (ABCD) and Fungizone® in the treatment of invasive aspergillosis
(January 1993 – February 1997)
Total Number of subjects: 213 (Intent-to-treat)

07-26
A double-blind, randomised pilot study comparing ABCD (Amphotericin B colloidal dispersion) and Fungizone® in the treatment of febrile neutropenic patients failing broad spectrum antibacterial therapy.
(March 1994 – June 1996)
Total Number of subjects: 213 (Intent-to-treat)

07-28
ABCD (Amphotericin B Colloidal Dispersion or Amphocil™) in patients with systemic *Aspergillus* infection: Comparison of Amphocil with amphotericin B historical controls.
Comparison of open-label (Phase I/II/III) studies with an historical control group.
(For Amphocil: 1991 – 1994; for Amphotericin B: 1990 – 1994)
Total Number of subjects: 506 (Intent-to-treat)

NON-CONTROLLED STUDIES
07-03
Phase I dose escalating study to evaluate the safety of amphotericin B colloidal dispersion (ABCD or Amphocil) in marrow transplant patients with Candidiasis, Aspergillosis or Torulopsis.
(March 6, 1991 – June 25, 1994)
Total Number of subjects: 213

07-00/10
Amphocil (ABCD; Amphotericin B Colloidal Dispersion) for the treatment of systemic mycoses in cases when conventional amphotericin B is contraindicated: A Phase II/III clinical study.
(Oct 1991 – Sept 1992)
Total Number of subjects: 168

07-15
Open label randomised comparison of two dose levels of Amphocil™ (ABCD) in patients who have failed prior therapy with Amphotericin B for systemic fungal infections.
(Aug 1992 – June 1994)
Total Number of subjects: 42

07-14A
Open label treatment with Amphocil in patients with renal impairment who have a systemic fungal infection.
(June 1992 – Nov 1993)
Total Number of subjects: 133

07-14B
Open label treatment with Amphocil in patients with renal impairment who have a systemic fungal infection.
(June 1993 – Sept 1994)
Total Number of subjects: 155

No information on the age of the subjects was available from any synopsis.

Rapporteur's comment:
The mentioned studies have not been submitted with this dossier. Thus, they can not be sufficiently assessed in this report. Amphocil is not approved in Germany. However, data on the above mentioned studies which became available to the BfArM in 2005, reveal that - regarding the 5 non-controlled studies - about 8.5% (N = 49) out of 572 patients (Intent-To-Treat group) were children less than 12 years. Further information e. g. on different age groups is lacking. This also applies to the controlled studies. Only the age range of 0 – 81 years of the included patients is given.
Thus, if not already mentioned, the very limited data on efficacy and safety of Amphocil for the use in children and adolescents should be addressed in the relevant sections of the SmPC/PL.

Literature / publications:
The literature search resulted in about 275 publications and is presented as abstracts with one exception (no. 10) . A great number of the abstracts do not refer to the treatment of fungal infections with Amphocil in the paediatric population.
A search by the assessor within these citations with the key words 'Amphocil','Amphotec', 'colloidal' and 'ABCD' reveal the following 10 out of these 275 abstracts:

1. *Successful treatment of aspergillus brain abscess in a child with acute lymphoblastic leukemia and liver failure. Sterba J. Prochazka J. Ventruba J. Kren L. Valik D. Burgetova*

D. Mudry P. Skotakova J. Blatny J. Pediatric Hematology & Oncology. 22(8):649-55, 2005 Dec.

Invasive fungal infection continues to pose a significant threat to immunocompromised patients, with cerebral aspergillosis being among the most feared ones. The authors describe **an adolescent girl** with acute lymphoblastic leukemia (ALL) with subsequent acute liver failure, who developed an aspergillus brain abscess. The patient was treated with combined antifungal therapy using amphotericin B local instillation, **prolonged systemic amphotericin B colloidal dispersion** along with vinca alkaloids-containing chemotherapy, followed by neurosurgical debridement and oral voriconazole in the setting of ongoing antileukemic maintenance chemotherapy. Her ALL remains now in complete remission 30 months from diagnosis, with no evidence of fungal infection.

2. *Experience with community-based amphotericin B infusion therapy. Malani PN. Depestel DD. Riddell J. Bickley S. Klein LR. Kauffman CA. Pharmacotherapy. 25(5):690-7, 2005 May.*

STUDY OBJECTIVES: To identify the types and frequencies of adverse events associated with community-based amphotericin B infusion therapy. A second objective was to validate the effectiveness of a monitoring system, based on guidelines from the Infectious Diseases Society of America (IDSA). DESIGN: Retrospective medical record review. SETTING: Outpatient clinic at a tertiary care center. PATIENTS: One hundred five patients who received amphotericin B therapy from a home care provider between January 1997 and July 2002. MEASUREMENTS AND MAIN RESULTS: A total of 113 courses of amphotericin B formulations were administered: liposomal amphotericin B, 41 courses (36%), amphotericin B deoxycholate, 31 courses (27%), amphotericin B lipid complex, 31 courses (27%), and **amphotericin B colloidal dispersion, 3 courses (3%)**; an additional 7 courses consisted of sequential therapy with two different formulations. Nephrotoxicity was associated with 46 (41%) courses, electrolyte abnormalities with 40 (35%) courses, venous access device complications with 12 (11%) courses, and infusion reactions with 13 (12%) courses. Nephrotoxicity occurred most frequently in adults aged 60 years or older, solid organ transplant recipients, and those receiving concomitant cyclosporine. **Only two (12%) of 17 courses in children younger than 13 years were associated with nephrotoxicity**. Thirteen of all 113 courses resulted in patients requiring hospital admission due to their adverse events. Monitoring of electrolyte, serum creatinine, and blood urea nitrogen levels 2 or 3 times/week was adequate for identifying these events. CONCLUSION: Significant rates of adverse events occurred in patients who received community-based amphotericin B infusion therapy. A monitoring system based on IDSA guidelines was effective in facilitating the detection and management of these adverse events.

3. *[Change in human visceral leishmaniasis treatment in Italy: retrospective study of 630 patients]. [Review] [6 refs] [Italian] Gradoni L. Gramiccia M. Scalone A. Parassitologia. 46(1-2):199-201, 2004 Jun.*

Since the 1940s meglumine antimoniate (MA) has been the only first-line drug for **visceral leishmaniasis (VL)** treatment in Italy. From 1991 through 1994**, several patients of all ages**, representing 1/3 of all immunocompetent VL patients reported during that period, were enrolled in clinical trials of liposomal amphotericin B (L-AmB), which led to a novel, safe, short course of VL treatment as an alternative to MA. In the same period, other lipid-associated AmB drugs were registered in Italy for the treatment of fungal infections, i.e**., AmB colloidal dispersion (ABCD)** and AmB lipid complex (ABLC). A retrospective analysis was performed on data collected at the Unit of Protozoology of Istituto Superiore di Sanita, Rome, to assess whether changes have occurred in first-line drug regimens adopted in Italy for routine VL treatment, during the 1995-2002- period. The sample consisted of immunocompetent individuals clinically suspected for VL,

in whom the disease was confirmed by the examination of serum and bone marrow specimens sent to the Unit by hospitals from throughout the country. Relevant information on patients was then recorded, which included drug regimens used and post-therapy results. We recorded treatment information for 630 patients, representing a large proportion (55.5%) of 1,135 immunocompetent individuals with VL reported in Italy from 1995 through 2002. About half were children (306). Every year, patients were referred by 19 to 42 hospitals, with a range of 1 to 30 patients per hospital. MA was the first-line drug used in 159 patients (25.2%). However, the proportion of MA-treated patients has steadily decreased from 55.9% in 1995 to 1.0% in 2002. We recorded the failure of MA therapy in 16 patients (10.1%), who were successfully retreated with a L-AmB regimen. The rate of MA failures significantly increased in recent years, from 5.3% in 1995 to 36.4% in 2000 (p = 0.01). AmB drugs have been the only alternative drugs used in the remaining 471 patients (74.8%). L-AmB accounted for most regimens (441, 93.6%). The proportion of patients treated with any AmB-based drugs increased from 44.1% in 1995 to 99.0% in 2002. Drug treatment was unsuccessful in 15 patients (3.2%), who were successfully retreated with a high-dose L-AmB regimen. This rate was significantly lower than the MA failure rate (p = 0.001). Results have shown a countrywide change in therapy over the period considered. A traditionally effective, but moderately toxic drug (MA) has been almost fully replaced by a new compound (L-AmB) with negligible toxicity, in an epidemiologic context of disease reemergence. Furthermore, short courses of 6 to 7 days, as required for lipid-associated AmB, are highly cost-effective if compared with 21- to 28-day courses needed for standard MA treatment.

4. *Amphotericin B nephrotoxicity in children. [Review] [70 refs] Goldman RD. Koren G. Journal of Pediatric Hematology/Oncology. 26(7):421-6, 2004 Jul.*

Amphotericin B is the treatment of choice for severe systemic fungal infections. Nephrotoxicity is the most clinically significant adverse effect, but studies examining **nephrotoxicity in children** are scarce. Nephrotoxicity includes decreased glomerular filtration rate and distal tubulopathy with urinary loss of potassium and magnesium, renal tubular acidosis, loss of urine concentrating ability, and sometimes Fanconi's syndrome. The mechanisms involved in nephrotoxicity include the use of deoxycholate, the vehicle for amphotericin, reduction in renal blood flow and glomerular filtration rate, increased salt concentrations at the macula densa, interaction of amphotericin with ergosterol in the cell membrane, and apoptosis in proximal tubular cells and medullary interstitial cells. Some risk factors for amphotericin nephrotoxicity have been determined over the years. Cumulative dosage, treatment duration, and dosing schedule as well as the combination of amphotericin with other nephrotoxic drugs, such as diuretics and cyclosporine, are important risk factors. Mechanisms to prevent nephrotoxicity include the use of lipid formulations such as amphotericin B lipid complex, **amphotericin B colloidal dispersion**, and liposomal amphotericin B and the concurrent use of volume repletion. Amiloride can be considered in serious potassium loss.

5. *Use of amphotericin B colloidal dispersion in children. Sandler ES. Mustafa MM. Tkaczewski I. Graham ML. Morrison VA. Green M. Trigg M. Abboud M. Aquino VM. Gurwith M. Pietrelli L. Journal of Pediatric Hematology/Oncology. 22(3):242-6, 2000 May-Jun.*

PURPOSE: To describe the experience with a new lipid-based amphotericin product (**amphotericin B colloidal dispersion or ABCD**) in **children with fever and neutropenia** who are at high risk for fungal infection. PATIENTS AND METHODS: **Forty-nine children** with febrile neutropenia were treated in a prospective, randomized trial comparing ABCD with

amphotericin B. **An additional 70 children with presumed or proven fungal infection were treated with 5 different open-label studies of ABCD**. Patients were registered into these studies for reasons of: 1) failure to respond to amphotericin B; 2) development of nephrotoxicity or preexisting renal impairment; or 3) willingness to participate in a dose-escalation study. Extensive data detailing response and toxicity were collected from each patient. RESULTS: In the randomized trial, there was significantly less renal toxicity in the children receiving ABCD than in those receiving amphotericin B (12.0% vs. 52.4% [P = 0.003]). Other adverse symptoms were not significantly different. In the additional open label studies, although 80% of patients receiving ABCD reported some adverse symptom, the majority of these were infusion related, and nephrotoxicity was reported in only 12% of these patients.
CONCLUSIONS: ABCD was well-tolerated at doses up to 5 times greater then those usually tolerated with amphotericin B. Renal toxicity was markedly less than expected, and there were no other unexpected severe toxicities. Further randomized studies are needed to further define the role of this and other liposomal products in children.

6. *A comparative review of conventional and lipid formulations of amphotericin B. [Review] [33 refs] Robinson RF. Nahata MC. Journal of Clinical Pharmacy & Therapeutics. 24(4):249-57, 1999 Aug.*

Over the past 15 years, factors such as corticosteroid treatment, cytotoxic chemotherapy, excessive use of broad spectrum antibiotics and HIV have led to an increased risk of serious fungal infections in both adults and pediatric patients. This increase in invasive fungal infections poses increasing difficulty in their treatment. Three new lipid formulations of amphotericin B are now available in the U.S.: amphotericin B lipid complex (Abelcet), **amphotericin B colloidal dispersion (Amphotec),** and liposomal amphotericin B (AmBisome). These newer formulations are substantially more expensive, but allow patients to receive higher doses for longer periods of time with decreased renal toxicity than conventional amphotericin B. The properties of these new agents are summarized in this review. Discussion of current national guidelines as well as those used at our institution are presented to provide guidance for the development of institution specific guidelines for the most cost-effective drug for most patients, some may benefit more from one of the newer lipid formulations.

7. *Treatment of **visceral leishmaniasis** with amphotericin B colloidal dispersion. [Review] [29 refs] Berman J. Dietze R. Chemotherapy. 45 Suppl 1:54-66, 1999 Jun.*

Amphotericin B is an effective antileishmanial agent whose use is limited by drug toxicity. The development of less toxic, lipid encapsulated formulations of amphotericin B as antimycotic agents has made these formulations available for testing against visceral leishmaniasis, a disease ideally suited for 'liposomal' therapy since the parasites are only found within reticuloendothelial macrophages. In phase **II experiments of Amphotericin B Colloidal Dispersion (ABCD)** for Brazilian kala-azar, **10 of 10 patients** were cured with 2 mg/kg/day for 10 days; 9 of 9 patients were cured with 2 mg/kg/day for 7 days; 9 of 10 patients were cured with 2 mg/kg/day for 5 days. The ability to cure 90% of kala-azar patients with a regimen of merely 5 days is remarkable considering that 20-40 days of treatment with pentavalent antimonials and a 28-40 day course of (every-other-day) amphotericin B desoxycholate therapy are otherwise needed. **Although ABCD did frequently cause a syndrome of fever and respiratory distress during infusion for children less than 6 years of age**, the virtual absence of kidney toxicity was striking.

8. *Review of lipid-amphotericin B formulations in the treatment of candidiasis and personal experience. Herbrecht R. Journal de Mycologie Medicale. 6(SUPPL. 1)(pp 11-16), 1996. Date of Publication: Aug 1996.*

There are now many reports on the efficacy and tolerance of lipid based formulations of amphotericin B in various types of invasive fungal infections. Liposomal amphotericin B has proven to be effective in the treatment of invasive candidiasis. Cases of acute and chronic disseminated infection, endocarditis, meningitis, ophthalmic infection, hepatic candidiasis and urinary tract infection have been successfully treated even in patients who had failed conventional amphotericin B. Response rates as high as 84% have been obtained in large uncontrolled studies in patients with invasive candidiasis. The success rate seems to be higher for Candida infections than for aspergillosis. Although numerous uncontrolled studies are encouraging and suggest that the lipid based formulations of amphotericin B may become major drugs in the antifungal armamentarium, only one randomised comparative trial versus amphotericin B in the treatment of confirmed invasive Candida infections had been presented to date. This study demonstrated that amphotericin B lipid complex is as effective as amphotericin B and is significantly less toxic. Liposomal amphotericin B (AmBisome) is more effective than amphotericin B in the treatment of fever persisting after 96 hours of broad spectrum antibiotic therapy in neutropenic children. Again the tolerance is significantly better for the lipid based form of amphotericin B. Efficacy of liposomal amphotericin B in prophylaxis of fungal infections has also been clearly established, especially in liver transplant recipients. It is obvious from all publications that the tolerance, especially renal tolerance, of liposomal amphotericin B, amphotericin B lipid complex or **amphotericin B colloidal dispersion** is much better than the tolerance of conventional amphotericin B. This improved tolerance has also been proven in subgroups of patients with preexisting renal toxicity or receiving concomitantly a nephrotoxic drug such as cyclosporin or an aminoglycoside. We have treated **48 patients** with a lipid based formulation of amphotericin B in our hospital. All but three patients were treated in a clinical trial setting. As the inclusion criteria were not the same for the different studies, we can not make any comparisons between the three drugs. All patients had a confirmed mycosis. Most of the patients were treated because of the failure of, or contra-indication to conventional amphotericin B. Overall 24 patients responded favourably to the treatment. As it has been suggested in the literature the response rate was higher for candidiasis than for aspergillosis. No major toxicity was observed in our patients and no treatment had to be stopped due to side effects. This data made us decide to recommend the use of lipid based formulation of amphotericin B in our hospital in patients with confirmed invasive fungal infections who failed to respond to conventional amphotericin B or with a contra-indication to amphotericin B. Until additional data is available, first line treatment will be considered in our hospital only in transplant patients with an Aspergillus or a Mucorales infection.

9. *Amphotericin B for the treatment of systemic fungal infections: Meta-analysis of conventional versus lipid formulations. Macaulay, S. S. , ; Martin, J. E. , ; Zarnke, K. B. , Abstracts of the Interscience Conference on Antimicrobial Agents & Chemotherapy. 42 2002. 393.*

Background: Lipid formulations of amphotericin B (AmB) may be superior to conventional amphotericin B for fungal infection treatment. Objectives: To determine whether lipid AmB formulations, in aggregate, are superior to conventional AmB for the treatment of suspected or documented fungal infections. Methods: Medline, Cochrane Library, , and IPA were searched for randomized comparative trials of any language. Unpublished data were sought from authors, manufacturers, and databases of abstracts. Bibliographies of identified trials were handsearched. Included studies were randomized controlled trials comparing any lipid formulation of amphotericin

B with conventional amphotericin B in adults or children with suspected or documented systemic fungal infections reporting relevant outcomes. Outcomes included death, nephrotoxicity (NTOX), hypokalemia (HK), and infusion-related reactions (IRR). Odds ratios were determined using the rando effects and fixed effect models. Results: **Sixteen studies met the inclusion criteria, including 2,345 patients and four lipid formulations.** Compared to conventional AmB, lipid formulations in aggregate were associated with an OR of 0.75 (95%CI 0.55 to 1.02) for death, 0.36 (95%CI 0.29 to 0.45) for NTOX, 0.32 (95%CI 0.16 to 0.65) for IRR, and 0.51 (95% CI 0.37 to 0.69) for HK. Subanalysis showed liposomal AmB caused significantly less death (OR 0.66, 95%CI 0.45 to 0.98), NTOX, HK, and IRR compared to conventional AmB. Lipid complex caused significantly less NTOX compared to conventional AmB. Intralipid(R) formulations caused less NTOX and IRR compared to conventional AmB. **Insufficient data were available for comparison of colloidal dispersion with conventional AmB.**
Conclusion: As a group, lipid formulations caused less NTOX, IRR, and HK compared to conventional AmB, with a trend toward reduced death. Sub-analyses revealed significant reduction in all endpoints, including death, with liposomal AmB.

10. Amphotericin B colloidal dispersion therapy for invasive mycosis: Report of successful therapy in *two pediatric patients Mustafa, Mahmoud M. ; Sandler, Eric S. ; Bernini, Juan Carlos ; Aquino, Victor M. Pediatric Infectious Disease Journal. 13(4). 1994. 326-328.*

No abstract available.

Rapporteur's comment:
As the MAH has already stated, the specific data on use of Amphocil in the paediatric population were sparse.

Safety results
Periodic Safety Update Reports (time period 20 August 1993 - 19 August 2009) have been submitted to the various relevant national regulatory authorities according to their individual submission schedules. Amphocil (amphotericin B colloidal dispersion) has been approved in the UK since 20 August 1993 and has since been marketed in over 26 countries worldwide.
For ease of review, the Three Rivers Pharmaceuticals safety database for Amphocil has also been searched in October 2009 to create a line listing of all cases reported specifically for the paediatric population. The line listing is attached as Appendix 2. Very few new cases have been received since the datalock point of the last PSUR. Close review of this line listing confirms the previous statements in the PSURs that no new safety signals (for the adult or paediatric population) have been noted from the post-marketing data received since 1993. The current SmPC captures the safety data adequately.

No publications specifically concerning the paediatric safety of Amphocil have been identified. The safety findings reported in the various publications retrieved in the literature search have been reported in previous PSURs and, where relevant, the safety data for Amphocil have already been captured in the SmPC.

Rapporteur's comment:
The data reveal no new safety issues regarding the paediatric population.

ABELCET (ABLC)

A) Paediatric information from the original application dossier

Study No. 6, Protocol No. AI800-900/901
Emergency-Use-Protocol; Amphotericin B Complex (ABLC) In Patients With Progressive, Potentially Fatal, Fungal Diseases (Subset: Patients with Fungal Infections Other Than Aspergillosis); May 3, 1995

- **Description**

The study was conducted to investigate the efficacy and safety of ABLC which was designed to reduce the drug-related toxicity, especially nephrotoxicity, of amphotericin B (AmB). The patient population for this emergency-use study consisted of seriously ill patients with advanced systemic fungal infections.

- **Methods**

- Objective(s)

The objective of this program was to assess the safety and efficacy of ABLC, which was made available on an emergency-use basis to patients who had progressive, potentially fatal fungal infections (confirmed or presumptive)

- Study design
  This was a multicenter, open-label, emergency-use, noncomparative study with 'single patient' enrollment.

- Study population /Sample size
  A total of 225 individuals with all types of fungal infections received ABLC; 3 enrolled twice, for a total of 228 cases. Data from the subset of 141 patients who had fungal infections other than aspergillosis and who had received at least one dose of ABLC are presented in this report.
  Data from 84 patients with aspergillosis are presented in a separate report (see study No.1 below).

- Treatments
  The recommended dose of 5 mg/kg/day of ABLC were administered intravenously over two hours at a rate of 2.5 mg/kg/hr. The investigator could increase or decrease the rate, depending on the patient's tolerance to the rate of infusion. The daily ABLC dose was to be reduced if nephrotoxicity developed (indicated by an increase in serum creatinine of 0.5 mg/dl above the baseline level) or if the investigator considered the reduction to be necessary for any other reason.

- Outcomes/endpoints

Efficacy assessments:

- Clinical response (cure, improvement, failure, not evaluable) at end of therapy and at post-therapy follow-up at weeks 1and 4 (additionally relapse)
- Mycological response (eradication, persistence, not evaluable) at end of therapy and at post-therapy follow-up at weeks 1and 4 (additionally new infections)

- Correlations with cofactors (underlying conditions, neutrophil trend, reasons for enrollment, pathogen, site of infection, duration of treatment with ABLC, cumulative dose of ABLC, gender and age, relation between clinical and mycological efficacy at end of therapy and at the follow-up visits)

Safety assessments:

- Adverse events (all adverse events were categorized and tabulated by body system)
- Laboratory data

- Statistical Methods
  Statistical tests were applied whenever appropriate to determine correlation among factors or changes from baseline. The sample size of the study was not predetermined. Two groups were evaluated for efficacy: the intent-to-treat (ITT) population included all patients who received at least the 1- mg test dose and the evaluable group included patients who had a positive culture at baseline, received at least four doses of study drug, and received less than four doses of concomitant antifungal medication.
  Any patient who received at least one dose of ABLC (incl. the 1-mg test dose) was included in the safety analysis.

➢ **Results**

- Recruitment/ Number analysed
  A total of 118 investigators from the United States, 3 from Canada, and 1 each from Australia, Mexico, and the Netherlands enrolled 141 patients with fungal infections other than aspergillosis.
  Three patients enrolled twice. Forty-eight (34%) completed the study, as specified by the investigator. Ninety-three patients (66%) discontinued therapy for the following reasons:
  - Death (n = 35)
  - Severe clinical adverse events (n = 14)
  - Progression of fungal infection (n = 13)
  - Investigator's discretion (n = 10)
  - Patient's request (N = 9)
  - Administrative reasons (n = 8)
  - Development of opportunistic (n = 1), central line (n = 1) infections, end-stage pulmonary toxicity (n = 1), and transfer to VAMC (n = 1).

<u>Paediatric population:</u>

Twenty patients (14%) were children (≤ 12 years). Children less than 2 years of age were to be excluded from the study. According to the protocol deviations two premature infants (3 months and 1 month of age) and 2 two-month-old- infants were enrolled.

- Baseline data
  A total of 20 children were enrolled (≤ 12 years) with 4 children less than 2 years of age (see above).

- Efficacy results
  For the 14 out of 20 children for whom clinical response could be assessed, 5 (36%) were clinically cured and 5 (36%) had clinical improvement, for an overall response rate of 71%. Seven of nine children (78%) for whom mycological response could be assessed

had eradication of the fungal pathogen.
An evaluation by age is demonstrated in the table below:

Table VII.26
ABLC / STUDY AI800-900/901 (Non-Aspergillosis - Intent-to-Treat)

End-of-Therapy Clinical Efficacy by Age

Age	Clinical Efficacy (1) Cured	Improved	Failed	Not Eval.	Total (2)	Response (3) n1/n2 (%)
0 < 2 Yrs	2	0	0	2	4	2/2 (100%)
2 <= 12 Yrs	3	5	4	4	16	8/12 (66.7%)
13 <= 64 Yrs	28	31	21	25	105	59/80 (73.8%)
>= 65 Yrs	4	7	1	4	16	11/12 (91.7%)
Total :	37 (26.2%)	43 (30.5%)	26 (18.4%)	35 (24.8%)	141	80/106 (75.5%)

- Safety results
  The most common adverse events were increased serum creatinine (n=5), fever (n=4) and chills (n=3).

Study No. 1, Protocol No. AI800-900/901
Emergency-Use-Protocol; Amphotericin B Complex (ABLC) In Patients With Progressive, Potentially Fatal, Fungal Diseases (Subset: All Patients with Aspergillosis); April 11, 1995

- **Description**
  Please see study above.

- **Methods**
  Please see study above.

- Objective(s)
  Please see study above.
- Study design
  Please see study above.
- Study population /Sample size
  Data from 84 patients (subset of study No.6 above) who had aspergillosis and who received at least one dose of ABLC are presented in this report.
- Treatments
  Please see study above.
- Outcomes/endpoints
  Please see study above.
- Statistical Methods
  Please see study above.

- **Results**
- Recruitment/ Number analysed
  A total of 61 investigators from the United States and 1 from Canada enrolled 84 patients with aspergillosis in this emergency-use study.

74 patients were considered to have definite (n=57) or probable (n=17) aspergillosis and were included in the efficacy analysis.

Paediatric population:

- 14 patients (18%) were children (≤ 12 years). Children less than 2 years of age were to be excluded from the study. According to the protocol deviations a one-year-old infant was enrolled.

- Baseline data
  Fourteen children (≤ 12 years) were enrolled in this study; 10 had definite, 3 probable and 1 had neither definite nor probable aspergillosis.

- Efficacy results
  At the end of therapy seven of 13 children (54%) who had definite or probable aspergillosis responded to ABLC. One of these seven patients, a one-year-old infant, had a complete response.

- Safety results
  All 14 children comprised the safety population. Eleven children had adverse events, the most common of which were fever and respiratory failure (each in 2 patients).
  Three children had events considered related to study drug: fever (1 patient), increased BUN and serum creatinine (1 patient), and hypokalemia (1 patient). Four patients have events considered probably related to study drug: fever and confusion (1), chills and kidney failure (1), hyperbilirubinemia (1) and vomiting (1).

Study No. 3, Protocol No. A93-D-05
A Phase III Open Label, Non-comparative Study of Amphotericin B lipid Complex (ABLC) In The Treatment Of Definite or Probable Invasive Aspergillosis

- **Description**
  Please see study above.
- **Methods**
  Please see study above.

- **Results**

- Recruitment/ Number analysed
  Five patients out of 30 were children (≤ 12 years).

- Efficacy results
  At the end of therapy 4 of 5 children failed and one responded to ABLC

- Safety results
  All of five children have adverse events, the most common of which was hypokalemia (3). Three children were reported to have events considered drug-related. One patient had hypokalemia (probably related), hypomagnesemia (probably), and thrombocytopenia (possibly). Another patient had fever, hypokalemia (four events), and hyperkalemia. The third patient had fever (three events, chills, fever, hypocalcemia, hypokalemia,

hypophosphatemia, and vomiting.

Study No. 2, Protocol No. A93-D-01
Open Label Single Patient Emergency-Use-Protocol; Amphotericin B Complex (ABLC) In Patients With Progressive, Potentially Fatal, Fungal Diseases (Subset: All Patients with Aspergillosis); April 11, 1995

- **Description**
  Please see study above.
- **Methods**
  Please see study above.

- **Results**

- Recruitment/ Number analysed
  Five patients out of 77 with definite and 1 with probable aspergillosis were children (≤ 12 years).

- Efficacy results
  Two of five paediatric patients (40%) with definite aspergillosis responded to ABLC.

- Safety results
  All of six children had adverse events, the most common of which were diarrhea, fever, headache, hypokalemia, myalgia, and vomiting (each in two patients . one children was withdrawn due to bilirubinemia considered probably study drug-related.

Study No. 7, Protocol No. A93-D-01
Open Label Single Patient Emergency-Use-Protocol; Amphotericin B Complex (ABLC) In Patients With Progressive, Potentially Fatal, Fungal Diseases (Subset: All Patients with Aspergillosis); April 11, 1995

- **Description**
  Please see study above.

- **Methods**
  Please see study above.

- **Results**

- Recruitment/ Number analysed
  Eleven patients out of 89 with definite and 1 with probable aspergillosis were children (≤ 12 years).

- Efficacy results
  Efficacy data were not analyzed for this interim report.

- Safety results
  Seven children had adverse events. One child had two events of chills that were considered probably related to stud< drug. Three patients had events considered possibly related to study drug: renal failure (1), hypokalemia (1), and hyperbilirubinemia, increased AKT, perinatal disorder, and respiratory congenital anomaly (1).

Protocol AI800-022
Safety pharmacokinetics and Antifungal Response of Amphotericin B Lipid Complex in the Treatment of Hepatosplenic Candidiasis in Paediatric patients with Neoplastic Diseases ; Dec 1994 (Investigator: Thomas Walsh, M.D.)

An abstract of this study is given below (source: study report AI800-022):

The objectives of this study are to investigate the safety, pharmacokinetics, and antifungal response of three dosing regimens of ABLC® for the treatment of hepatosplenic candidiasis in pediatric patients with neoplastic diseases. This report is an interim summary containing *only* the pharmacokinetic results obtained for three patients at a single dose level (Cohort 1: 2.5 mg/kg-day for 42 doses).

Three patients (Pt. 2,3, and 4) were treated at 2.5 mg amphotericin B/kg-day as ABLC®. The underlying neoplastic disease in each case was acute promyelocytic leukemia. Patients 2 and 4 completed ABLC® therapy (42 doses). Patient 3 was discontinued after 17 doses due to tumor relapse requiring antineoplastic therapy. Two patients were female; one was male. They ranged in age and baseline weight from 10-16 years and 32.3-66.0 kg respectively.

ABLC® was administered daily by intravenous infusion. For this cohort, infusion times were 1 hr on the first treatment day and 0.5 hr on the remaining days. A test dose of 1 mg preceded the therapeutic dose on day 1 only. Amphotericin B concentrations were determined in heparinized whole blood. Dosing interval profiles were obtained on days 1, 7, and 42 (except Pt. 3). Peak and trough values were also obtained for study day 14, 21, 28, and 35. Follow-up samples were obtained where possible.

Pharmacokinetic parameters are summarized in the table below. Concentration-time profiles demonstrated the multiexponential disposition of ABLC®. Although few samples were obtained beyond the last dosing interval (Pts. 2 and 4 only), their pattern was consistent with a terminal half-life in excess of 5 days. Little change was observed in trough concentrations and in day 7 and 42 values for AUCτ (area under the curve during the 24 hr dosing interval) for those patients for whom data was available (Pts. 2 and 4). These data suggest mean clearance value of 9.96 ± 0.067 L/hr or 0.219 ± 0.67 L-kg/hr (mean ± sd) and that average drug concentrations of 0.492 ± 0.16 ug/ml are attained by day 7 of the 42 day regimen.

Rapporteur's comment:
In conclusion, data on the paediatric population is limited:
39 out of 54 children below the age of 12 years included in the clinical trials could be evaluated. Only 3 children were below the age of 2 years.
The pharmacokinetic data obtained from three children are too limited for including in section 5.2 of the current SmPC.

Overall safety results from the original dossiers compiled by the MAH

Paediatric safety information (**see table 2 below**) was collected from:

- three open-label emergency use studies involving 556 patients with life-threatening systemic fungal infections, amongst them 111 children (studies AI800-900/901, A93-D-01, A93-D-05)
- an open-label study involving six paediatric cancer patients with hepatosplenic candidiasis (study AI800-022).

Table 2: Adverse events reported in paediatric and adult patients with life-threatening systemic fungal infections and treated with ABELCET (combined data from studies A1800-900/901, A93-D01 and A93-D05) Observed Adverse events

	Paediatric population		Adult population
	0 to <2 years (N=12)	2 to 16 years (N=99)	17 to 64 years (N=396)
Chills	0%	17%	18%
Fever	0%	19%	12%
Multiple organ failure	8%	8%	12%
Headache	0%	8%	6%
Infection	0%	4%	5%
Pain	0%	6%	5%
Abdominal pain	0%	3%	4%
Asthenia	0%	2%	3%
Chest pain	0%	2%	3%
Hypotension	0%	3%	9%
Hypertension	0%	4%	5%
Tachycardia	0%	1%	2%
Nausea	0%	8%	9%
Vomiting	0%	9%	8%
Diarrhoea	0%	6%	6%
Thrombocytopenia	0%	7%	6%
Leucopoenia	0%	5%	5%
Anaemia	0%	5%	3%
Creatinine increase	0%	15%	9%
Bilirubinemia	0%	4%	3%
Respiratory failure	0%	5%	9%
Dyspnoea	0%	4%	7%
Respiratory disorder	0%	3%	4%
Rash	0%	2%	5%
Kidney failure	8%	4%	4%
Kidney functions abnormal	0%	1%	3%

Injection site reactions, i.e. chills and fevers, were the most common occurrences reported in children, with incidence rates roughly similar to the adult population.
During treatment with ABELCET, serum creatinine increases were more frequently reported in children than in adults (13% versus 9% of patients, respectively). The clinical significance of this difference remains unclear since it was not associated with an increase in the reporting of other renal abnormalities and absolute values for serum creatinine levels were not reported. The impact of ABELCET on renal function was investigated in a 2005 study by Alexander et al. and revealed no differences between adult and paediatric patients.

They reported a retrospective analysis of records from 3514 ABELCET-treated patients with fungal infections, enrolled from 1996 to 2000 in the Collaborative Exchange of Antifungal Research (CLEAR) registry. Patients received ABELCET at a median daily dose of 4.4 mg/kg/day (range: 0.2-10.0 mg/kg/day) for a median duration of 12 days (range: 1-378 days), resulting in a median cumulative dose of 3200 mg (range: 5.3-74000 mg).

Renal function parameters were evaluated at baseline and at the end of therapy (*please see table 3*). The median change in predicted creatinine clearance (Cl_{Cr}) from baseline to the end of therapy was -3 mL/min (range: -119 to +118 mL/min); doubling of serum creatinine (S-Cr) level occurred in 13% of patients, and new dialysis was needed for 3% of patients.
Compared to patients under 18, adult patients (18 years old and older) showed a significantly greater decrease of Cl_{Cr} (-3 versus 0 ml/min respectively p=0.008), and a significantly higher incidence of increase S-Cr level to $\geq$2.5 mg/dl (13% versus 6%, p<0.001) at the end-of-therapy. However, the two age groups showed similar incidence.

Table 3: Renal function in ABELCET-treated patients with fungal infections in the Collaborative Exchange of Antifungal Research database

All Patients		Age group <18 years (N=454) (N=3048)	≥18 years
Baseline S-Cr level (mg/dL)			
• median (range)	1.4 (0.08; 6)	0.7 (0.1; 6)	1.6 (0.08; 6)
End-of-therapy renal function parameter			
Change in Cl_{Cr} (mL/min)			
• Median (range)	-3 (-119; 118)	0 (-105; 108)	-3 (-119; 118)
• p-value	…	…	**0.008**
Doubling of baseline S-Cr level			
• Number (%) of patients	468 (13)	71 (16)	396 (13)
• p-value	…	…	0.110
Increase in S-Cr level to ≥2.5 mg/dL			
• Number (%) of patients-	412 (12)	27 (6)	385 (13)
• p-value …	…		**<0.001**
New dialysis			
Number (%) of patients	92(3)	12(3)	80(3)
• • p-value	…	…	0.975

The association of several factors with the development of nephrotoxicity was analysed in a multivariate logistic regression analysis (Table 4). In ABELCET-treated patients, concomitant treatment with potentially nephrotoxic agents and a baseline S-Cr level below 2 mg/dl were factors predisposing for the development of nephrotoxicity. The underlying condition of HSCT or haematological malignancy, use of ABELCET as first-line therapy, age below 18 years old, average daily dose above 5 mg/kg/day, and duration of therapy above 114 days were not.

Table 4: Logistic regression analysis of risk for nephrotoxicity in ABELCET-treated patients with fungal infections in the Collaborative Exchange of Antifungal Research database

Covariate	OR (95% CI)	p-value

Baseline S-Cr level <2 mg/dL	**1.72 (1.40–2.12)**	**<0.001**
Concomitant nephrotoxic agents [2]	**1.26 (1.06–1.51)**	**0.011**
HSCT or haematologic malignancy [1]	1.18 (0.99–1.41)	0.072
Duration of therapy >14 days	0.85 (0.72–1.02)	0.074
ABELCET dose >5 mg/kg/day	1.20 (0.97–1.48)	0.098
Age <18 years	**0.81 (0.62–1.05)**	**0.112**
First-line therapy with ABELCET [3]	0.90 (0.75–1.07)	0.238

NOTE: Nephrotoxicity was defined as doubling of serum creatinine (S-Cr) level from baseline or increase to ≥2.5 mg/dL by end of therapy.

[1] Hematopoietic stem-cell transplant (HSCT) or haematologic malignancy included patients with leukaemia, lymphoma, multiple myeloma, aplastic anaemia, myelodysplastic syndrome, allergenic HSCT (including patients with graft-vs.-host disease), autologous HSCT, and peripheral stem-cell transplant recipients.

[2] Concomitant nephrotoxic agents included calcineurin inhibitors, aminoglycosides, foscarnet, cidofovir, or amphotericin B colloidal dispersion.

3 First-line therapy included patients with no prior antifungal treatment and no underlying renal disease or patients with underlying renal disease and no prior antifungal treatment.

Rapporteur's comment:
The MAH stated that there were no major differences in the reported adverse events between children and adults. Considering the analysis of Alexander et al., 2005 (see above) the conclusion is supported.

B) Paediatric information from published studies

Multiple age groups

In 1998 and 1999, Walsh TJ et al. reported data from an open-label, emergency use, multicentre study of 556 patients, including 111 paediatric patients (**21-day to 16-year old**). Patients with IFIs enrolled if mycoses refractory to conventional antifungal therapy intolerant of previous systemic antifungal therapy or concomitant nephrotoxic drugs or pre-existing renal disease. Mean age was 9.3 years. Mean duration of treatment was 38.9 days. The mean daily dose was 4.85 mg/kg and the mean cumulative dose was 165.2 mg/kg. The most common underlying conditions were haematological malignancies (37%), bone marrow transplantation (28%) and prematurity (15%). Efficacy was evaluable in 25 patients. A complete or partial therapeutic response was obtained in 70% (38/54) of the patients, with response in 56% (14/25) of children with aspergillosis and 81% (22/27) of patients with candidiasis. Efficacy results were 70% (n=20) for haematological malignancies**,** 60% (n=15) in those with bone marrow transplants and 88% (n=8) in premature infants. No significant change in mean serum creatinine between baseline and end of therapy 1.23±0.11 vs. 1.32±0.12 mg/dl. No significant change in the hepatic transaminases, alkaline phosphatase but mild rise in total bilirubin in 83 evaluable cases 3.66 ± 0.73 vs. 5.31 ± 1.09 mg/dL (p=0.054) respectively between baseline and end of therapy.

Herbrecht et al (2001) evaluated the safety and efficacy of ABELCET in a retrospective multicentre study of 46 paediatric patients (**3-month to 18-year old**) with invasive fungal infections (54% with mould infection and 41% candidiasis). 57% of the patients failed previous conventional Amphotericin B treatment and 20% had renal impairment due to conventional Amphotericin B. The mean age of the patients was 9.7±4.8 years. Primary underlying conditions included mainly haematopoietic stem cell transplantation, leukaemia and lung transplantation. The mean daily dose given was 4.11 mg/kg for a mean duration of 38.7 days. At the end of

therapy, 38 of 46 (83%) patients responded successfully to treatment with ABELCET, including 18 of 23 (78%) with aspergillosis and 17 of 19 (89%) with candidiasis. ABELCET was well tolerated, with a low incidence of adverse events. The mean creatinine value was 74.5 µmol/L at baseline and 78.2 µmol
/L at the end of therapy; 7% doubled serum creatinine and 13% normalized serum creatinine.

Le Guyader et al. (2004) reported a study of 14 paediatric patients (**5-month to 15-year old**), treated with ABELCET (21 treatments) for a median duration of 8 days (1–48 days). ABELCET was administered to infants with either a history of deterioration of the renal function (DRF) (10 episodes: group A) or DRF occurrence during a treatment with conventional Amphotericin B (7 episodes: group B), and for age lower than 1 year (3 episodes).The clinical tolerance was good in 90% of the cases, with a premedication in half of the cases. The study of the renal function showed a good renal tolerance for 6 episodes out of 9 evaluable in group A, 3 resolutions and 2 stabilisations of the renal failure for the 5 evaluable episodes of the B group. Seven to ten days of treatment by ABELCET were necessary to obtain the renal failure resolved.

Wiley et al. (2005) evaluated the efficacy and safety of ABELCET in 548 paediatric patients (**0- to 20-year old**) who were enrolled from 1996 to 2000 in the Collaborative Exchange of Antifungal Research (CLEAR) registry. This was the largest series of paediatric patients treated for invasive mycoses with a single agent. All patients had cancer or had received a bone marrow, cord blood or solid organ transplant and were treated with ABELCET for documented or suspected fungal infection.
Most patients were either intolerant of or refractory to conventional antifungal therapy, and almost one-half were neutropenic at treatment onset. Of the 548 patients, 300 (54.7%) were transplant recipients and 393 (71.7%) had received one or more concomitant nephrotoxins. *Candida* and *Aspergillus* were the most commonly isolated species in patients with proven or probable infections. Response data were evaluable for 255 of the 285 patients with documented single or multiple pathogens. A complete (cured) or partial (improved) response was achieved in 54.5% of patients, with an additional 16.9% of patients having a stable outcome.
There were few clinically significant deleterious effects on renal function. There was no significant difference between the rates of new haemodialysis versus baseline haemodialysis. Elevations in serum creatinine of >1.5 x baseline and >2.5 x baseline values were seen, respectively, in 24.8% and 8.8% of all patients. In comparison to patients with prior therapy, patients with no prior therapy had a high percentage of elevations in serum creatinine of >1.5 x baseline, suggesting that, in children, de novo treatment with ABELCET will cause an initial rise in serum creatinine over the course of the first 7 to 10 days of therapy, but then creatinine levels will stabilize. This is not true for conventional amphotericin B desoxycholate.

Preterm newborn infants

Adler-Shohet et al (2001) conducted a phase II open-label, multicentre clinical trial to evaluate the safety and efficacy of ABELCET in first line therapy in neonates with invasive Candida infections at dosages of 2.5 and 5.0 mg/kg A total of **30 infants** with invasive *Candida* infections were enrolled in the study, of which 26 (87%) had *Candida* spp. detected in blood. **The majority of patients was preterm and weighted less than 1.5 kg at birth.** The first 15 neonates received 2.5 mg/kg/day of ABELCET: 13 infants were evaluable for a mycological response, 11 neonates had eradication of infection with a complete clinical response. Four infants died; none of these had evidence of fungal disease at the time of death. The second 15 neonates received 5 mg/kg/day: 13 infants were evaluable for a mycological response; 12 had eradication of infection with a complete clinical response. Serum creatinine levels were unchanged or

decreased in 27 of 30 patients, including 6 of 7 patients with pre-existing renal disease. Three patients had infusion reaction (fever and hypotension) that resolved with increased infusion time and premedication. Serum potassium decreased to less than 3.3 mg/dL during therapy in 50% of patients, and incidence of hypokalemia did not differ between the 2 dosage groups.

Knoppert et al (2001) reported a case study describing eradication of severe neonatal candidiasis with ABELCET **in a preterm infant**. The infant did not respond to conventional amphotericin B alone or in combination with fluconazole. After therapy was changed to ABELCET at a dose of 5 mg/kg/day the infant improved significantly, and subsequently recovered.

Adler-Shohet F et al. (2001) treated **11 neonates and infants** with ABELCET for invasive candidiasis. Patients ranged in **age from 3 to 14 weeks** (median: 7 weeks) and weighted from 0.7 to 5 kg. ABELCET was given at 4.9 mg/kg/day (range 3.2-6.5) for a median of 23 days (range: 4-41). Response to therapy was observed in 82% of patients (9/11 neonates with mycological cure). One neutropenic patient with histiocytosis died with disseminated candidiasis. Another child died of multisystem failure due to extreme prematurity, although candidemia had cleared prior to death. No surviving babies experienced a relapse. Median creatininaemia was 80 µmol/L at baseline and 44 µmol/L at the end of therapy. Creatinine levels improved or did not significantly change in eight of the 11 patients. All 5 patients who experienced acute nephrotoxicity with amphotericin B tolerated amphotericin B lipid complex.

Lopez-Sastre et al. (2003) conducted a prospective multicentre study to assess the epidemiology of neonatal invasive candidiasis in Spain. In a total of 20,565 admissions to the 27 participating neonatal units over an 18-month period, systemic candidiasis was diagnosed in **118 (0.57%) neonates**. Candida species were isolated from the blood in 79 infants, from the urine in 33, and from the cerebrospinal fluid in 4; in 2 cases, histologic evidence of deep tissue candidiasis was found at autopsy. Liposomal amphotericin B, **ABELCET** and amphotericin B were respectively given to 81, **29** and 7 infants. Amphotericin B had to be stopped in 3/7 infants (43%) due to nephrotoxicity. ABELCET was used as first-line treatment because of prematurity (n=26) or renal failure (n=2) and secondary to amphotericin B nephrotoxicity (n=1). Initial dose was 2.6±1.5 mg/kg and maximal daily dose was 4.2±1.0 mg/kg. Mean infusion time was 2.2±1.4 hours with a mean duration of treatment of 15±6 days. Out of 29 patients treated with **ABELCET, 25 (86%) clinically recovered**. The mean duration of therapy was significantly shorter with ABELCET than with liposomal amphotericin B (15 versus 19 days, respectively; $p<0.05$). No differences between liposomal amphotericin B and ABELCET were observed in terms of mortality rate and incidence of adverse effects related to treatment.
The **mortality rate was 14% with ABELCET** and 6% with liposomal amphotericin B, this difference was not significant. **All deaths occurred in the very low birth weight cohort with candidemia**. There was no significant difference in laboratory abnormalities or mean time to recovery between groups.

Yalaz et al. (2003) reported **a case of fatal invasive Acremonium** infection in a preterm neonate treated with amphotericin B. The authors concluded that this infection is difficult to treat and the outcome is generally poor. The newborn infant, especially the preterm neonate, is at increased risk for development of a considerable spectrum of opportunistic infections, due to molecular, cellular and functional deficiency of both cellular and humoral immunity. Optimal treatment of Acremonium species infections is not well-defined, due to the limited number of reported cases and conflicting results obtained in different studies. In a review, there was general resistance to most antifungals, excluding amphotericin B and ketoconazole. Therefore,

amphotericin B therapy, in combination with ketoconazole or another new azole or allylamine, is advocated.

Würthwein et al. (2005) studied the **pharmacokinetics** of ABELCET in whole blood and drug concentrations in urine and cerebrospinal fluid (CSF) in **twenty-eight neonates** with invasive *Candida* infections. There were 18 boys and 10 girls, with a median gestational age of 27 weeks (range, 24 to 41 weeks) and a median birth weight of 910 g (range, 460 to 4,600 g). **Fifteen infants received ABELCET at 2.5 mg/kg, and 13 infants received ABELCET at 5.0 mg/kg once daily for a median duration of 21 days** (range, 4 to 47 days). The disposition of ABELCET in neonates was not substantially different from that observed in other age groups, and weight was the only factor that influenced the clearance of amphotericin B from blood. Random sampling demonstrated substantial drug exposure in urine and, as with other amphotericin formulations, low concentrations in CSF.
Based on the results of this study, previously published safety and efficacy data, and the results of a comparative randomized clinical trial with adults, a dosage between 2.5 and 5.0 mg/kg/day of ABELCET administered as an intravenous infusion over 2 h has been recommended for the treatment of invasive *Candida* infections in neonates.

Cetin et al. (2005) reported a retrospective survey that **compared ABELCET to liposomal** amphotericin B (Ambisome). **Ten neonates were treated with ABELCET** and 9 treated with Ambisome for a mean duration of 21 and 18 days. The mean gestational age of the patients was 30.9 ± 4.2 weeks and mean birth weight was 1536±714 g. Treatment failure rate was similar in both groups (2 patients died in the ABELCET group and 1 in the liposomal amphotericin B group). Fungal eradication was achieved in all the 16 surviving infants. No patient showed severe side-effects from the antifungal therapy; the incidence of minimal side-effects were similar in both groups and they were elevated serum transaminase levels in six patients, increased serum creatinine in one patient and hypokalemia in one patient. The authors concluded that both preparations have the same benefits for the treatment of neonatal fungal sepsis and they can be used safely in neonates including very low birth weight infants. However, the clinician must keep in mind the cost of treatment.

Auron et al. (2009) conducted a retrospective case-control study to determine the effect of the amphotericin B lipid complex (ABLC) on serum creatinine (SCr), blood urea nitrogen (BUN), sodium (Na), and potassium (K) **in very low birth weight (VLBW) infants**. Medical records of **35 VLBW** infants who received ABLC for at least 2 weeks were reviewed for patient demographics, use of medications, fluid intake, urinary output, and serum electrolytes and compared to 35 patients matched by gestational age (GA) not treated with ABLC.
Infants who received ABLC had an average GA of 25.7±2.1 weeks and a birth weight of 764±196 g. Between day 1 and 14 of ABLC treatment, the BUN decreased from 17.5±11.5 to 10.5±6.8 mg/dl (p=0.01), the SCr varied between 0.78±0.32 and 0.69±0.32 mg/dl, Na varied between 136.6±5.8 and 137.8±3.6 mEq/l, and K varied between 4.8±0.9 and 4.9±0.6 mEq/l, respectively. In the ABLC group, 66% of patients (23/35) had hypokalemia (versus 46% in the control group -16/35-, *p*=0.09), and 14% of patients (5/35) had hyponatremia (versus 6% in the control group -2/35-, *p*=0.42).
Based on these results, we conclude that treatment with ABLC for 2 weeks did not increase BUN or SCr, nor decrease Na or K in VLBW infants.

Conclusion on benefit/risk by the MAH
Published data support the use of ABELCET for the treatment of candidiasis in preterm neonates, including very low birth weight infants at doses comparable to the recommended adult dose on bodyweight basis.

Rapporteur's comment:
Main indication for the use of ABELCET in preterm newborn infants was candidiasis. Data on efficacy and safety of ABELCET in this age group suffering from fungal infection due to aspergillus species are not available.
This information should be reflected in section 4.2 of SmPC as recommended below.

C) Post- marketing paediatric information (short summaries)

PSUR: 01 March 2003 to 23 April 2008
More than 26,848 patients received Abelcet worldwide during the five-year reporting period covered by this PSUR.
In total, 111 pediatric patients were investigated in the open-label emergency use studies (A1800-900/90165, A93-D-0166, A93-D-0567). In addition, Abelcet was administered to 548 children and adolescents who formed a subset of patients within a large, observational, post-marketing study. In these studies, Abelcet was used at doses comparable to the recommended adult dose adjusted for body weight. There appeared to be no major differences in the AEs reported in children, compared with adults, in the emergency-use studies even though they were treated with the adult dose. Infusion-related reactions i.e., chills and fevers, were the most common occurrences reported, with incidence rates roughly similar to the adult population.

PSUR: 08 September 2005 to 07 September 2008
More than 18,094 patients received Abelcet worldwide during the three-year reporting period covered by this PSUR.
Overall, 36 (24 %) fatal reports were received during this reporting period. Infusion reactions associated with Abelcet administration may present with a variety of signs and symptoms including fever, chills, respiratory distress, wheezing, hypotension, hypertension, and tachycardia. Both the RSI and the 2007 CCSI contain a warning about infusion related reactions and advise that appropriate medical support including the ability to provide cardiopulmonary resuscitation be present during Abelcet infusion.
No new relevant safety findings were identified.

PSUR: 08 September 2008 to 01 March 2009
Sales data is reported on the basis of each calendar month. For the period of 01 September 2008 to 28 February 2009, an estimated 1,454 patients worldwide were exposed to amphotericin B lipid complex.
The most frequent adverse events reported during this reporting period were classified in the Cardiac Disorders SOC (tachycardia), General disorders and administration site conditions SOC (Chills, Pyrexia, and Peripheral coldness), Investigations SOC (Oxygen saturation decreased, and blood pressure increased), and Vascular Disorders SOC (Hypertension).
Although a listed event, the MAH will continue to monitor and discuss case reports of infusion-related reaction.

Rapporteur's comment:
The conclusion of the submitted PSURs can support conditionally, because the evaluation of these PSURs was under process via national renewal procedure at the time of this assessment.

3. Discussion on clinical aspects and conclusion

Amphocil
There are limited data from the available clinical studies and literature on efficacy and safety of Amphocil in the paediatric population of all age groups. This should be more addressed in the relevant sections of the product information (*see below chapter V. recommendation*).

ABELCET
Data from emergency-use-studies (severe fatal fungal infections due to *Candida* and *Aspergillus* species) as well as from published studies indicated that the use of ABELCET in paediatrics older than 2 years of age would appear to be justified with the recommended dose as given. Insufficient data for neonates are addressed in the SmPC but should be amended regarding neonates treated for aspergillosis. Additional updates in the SmPC are required (*see below chapter V. recommendation*).

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

Following the circulation of the Day 70 and 90 PPdAR, there were no additional issues raised by the Concerned Member States.

- **Overall conclusion**

In general, the benefit-risk balance of Amphocil and ABELCET remains unchanged for the paediatric population. However, some updates of the SmPC and PL are necessary in order to reflect and/or amend insufficient data on efficacy and safety for the paediatric population.

- **Recommendation**

A Type IB variation is requested from the MAH(s) to update the SmPCs and PLs of Amphocil and ABELCET within 60 days of this report.

Amphocil:
If not already mentioned, the very limited data on efficacy and safety of Amphocil for the use in children and adolescents should be addressed in the relevant sections of the SmPC/PL. Based

on the wording of the approved product information in the member states DK, NL and SE, the following wording for the sections 4.2 and 4.4 is proposed:

4.2 Posology and method of administration

Initially, the following advice should be given:

> 'Treatment with /…/ should be initiated by physicians experienced in the treatment of systemic fungal infections.'

and during the section under the appropriate subheading:

> *'Use in children and adolescents:*
> Experience with /…/ in children is very limited. Use should therefore be discouraged unless life-threatening infections without other treatment options exist. The very limited experience seems to indicate that the dose per kilogram of body weight may be comparable to adults (see section 4.4).'

4.4 Special warnings and precautions for use

> 'The efficacy and safety of /…/ in children is limited. In clinical studies, children (including children less than 3 years) were treated with /…/ with daily doses (mg / kg) similar to adult doses without any unexpected adverse events reported.'

If applicable, consideration should be given to the infusion-related reactions, in particular to the infusion time.

4.5 Interaction with other medicinal products and other forms of interaction

Furthermore, the influence of concomitant medication (cyclosporine or tacrolimus) on the nephrotoxicity in adults and children were reported in section 4.5 of the SmPC only in the MSs GR and SK. The MAH should update all approved SmPCs regarding this interaction.

ABELCET:
Not all of the Abelcet approved SmPC within the European states includes this information. Therefore the MAH is requested to harmonize the wording via variation procedure as follows (proposed additions are red colored):

4.2 Posology and method of administration
…
Use in children and adolescents
Systemic fungal infections in children (ranging from 1 month to 16 years of age) have been treated successfully with Abelcet at doses comparable to the recommended adult dose on a body weight basis.
There are no sufficient data on efficacy and safety available in children less than one month.

No data on the efficacy and safety of Abelcet in preterm newborn infants suffering from fungal infections due to *aspergillus* species are available.

4.8 Undesirable effects

…

Adverse events are similar to those seen in adults.

VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

The list can be taken from the spreadsheet compiled from the EMA