MEDICAL OFFICER'S CONSULTATIVE REVIEW OF NDA
NDA 50-740

INDICATION: VISCERAL LEISHMANIASIS

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Date of Submission	July 3, 1996
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Date Received by Medical Officer	August 13, 1996
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Drug Identification	
Generic name	liposomal amphotericin B
Proposed trade name	AmBisome
Molecular Formula	$C_{47}H_{73}NO_{17}$
Pharmacologic Category	liposomal polyene antifungal
Dosage Form	suspension
Route of Administration	intravenous

Note on fonts: This review is written in Times New Roman. Courier font is used for direct quotes from the Applicant's NDA or IND submissions.

Proposed INDICATIONS AND USAGE section

In adult and pediatric patients, AmBisome is indicated for the following:

treatment of visceral leishmaniasis

Proposed DOSAGE AND ADMINISTRATION section

AmBisome should be administered using the following dosage schedules for each indication for adult and pediatric patients:

Visceral Leishmaniasis	3.0 (for 5 days)	
	3.0 day 14, 21	

Dosing should be individualized to the needs of the specific patient.

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ON ORIGINAL

Proposed CLINICAL STUDIES section

Treatment of Visceral Leishmaniasis: In open-labeled studies, 108 immunocompetent patients (70 pediatric and 38 adult) and 21 immunocompromised patients (primarily male adults with AIDS) received therapy with AmBisome for proven visceral leishmaniasis.

Success was defined as the complete clearance of parasites from the bone marrow aspirates by Day 21. The success rate among the immunocompetent patients was 99% and among the immunocompromised patients, 95%.

Materials reviewed

1. NDA 50-740, volume 1.1 and Study Report for Protocol 104-012 and supporting data which consisted of three published papers and one manuscript in press at the time of submission:

1. Davidson, et al. 1994. Liposomal amphotericin B (AmBisome) in visceral leishmaniasis: a multi-centre trial. *Quarterly Journal of Medicine.* 87: 75-81.

2. Davidson, et al. 1996. Short-course treatment of visceral leishmaniasis with liposomal amphotericin B (AmBisome). *Clinical Infectious Diseases.* 22: 938-43.

3. Russo, et al. Visceral leishmaniasis in HIV infected patients: treatment with high dose liposomal amphotericin B (AmBisome). *Journal of Infection.* In press at the time of submission.

4. Seaman, et al. 1995. Liposomal amphotericin B (AmBisome) in the treatment of complicated kala-azar under field conditions. *Clinical Infectious Diseases.* 21: 188-93

2. NDA 50-740, volumes 19.1-19.4 consisting of Case Report Forms for all patients described in papers 1,2, and 3 above

Scientific and Regulatory Background

The genus *Leishmania*, protozoan parasites belonging to the order Kinetoplastida, includes several species that are pathogenic to humans. Extracellular, flagellated *Leishmania* promastigotes live in the gut of female phlebotomine sandflies and are injected into the skin of humans and other mammals when the sandfly feeds. In most areas where disease occurs, it is zoonotic. Once in the human host, promastigotes invade the mononuclear phagocytes and multiply as intracellular amastigotes. Disease in humans is characterized as cutaneous leishmaniasis (CL) or visceral leishmaniasis (VL).

There are three species of the genus *Leishmania* associated with visceral disease in humans, *L. donovani, L. infantum,* and *L. chagasi.* Each of these is associated with a specific geographic distribution as described below:

L. infantum	Mediterranean basin, including southern Europe and North Africa Iran, Central Asia
L. donovani	India*, East Africa
L. chagasi	South and Central America

The infections caused by the genus *Leishmania* are best viewed as a complex of diseases rather than a single entity. In each of the geographic foci listed above the sandfly vector and the mammal reservoir of parasite differ. In India, no animal reservoir has been found, thus suggesting that the disease there is anthroponotic. Only a minority of

infections with *Leishmania* species progress to clinical disease. Response to infection with *Leishmania* is determined in part by the immune status of the host. Experience with VL in patients coinfected with HIV has shown that these patients can present quite atypically and do not respond to treatment as well as the immunocompetent host. Occasionally *Leishmania* species that are generally associated with cutaneous disease such as *L. tropica* and *L. major* are isolated from patients with classic visceral leishmaniasis. While the presentation of VL is fairly uniform throughout the world, response to treatment is not. Reports of resistance to standard treatments such as antimonials are increasing in parts of Europe, India, and East Africa (Torre-Cisneros et al, 1993 Clin Inf Dis; 17:625-7; Gokhale et al, 1994 Trans Royal Soc Trop Med Hyg; 88:228: Pearson and de Queiroz Sousa, 1996 Clin Inf Dis; 22:1-13). Thus it becomes necessary to carefully define the geographic distribution of the population of patients to be studied in this disease.

In cutaneous disease the amastigotes are confined to the site of initial infection. In visceral disease the amastigotes disseminate throughout the reticuloendothelial system and multiply in cells of the liver, spleen, and bone marrow. In these organs they induce hyperplasia that manifests clinically as visceral leishmaniasis- fever, cachexia, hepatomegaly, splenomegaly, and anemia, leukopenia, and thrombocytopenia. In some areas a hyperpigmentation of the skin is a prominent feature of visceral leishmaniasis, giving rise to the Hindi name for the disease, kala azar (black fever). The onset of symptoms is usually insidious, the course protracted and, if untreated, is usually fatal.

The diagnosis of VL is confirmed by the visualization of intracellular amastigotes in aspirates of tissue taken from spleen or bone marrow or by growing promastigotes in culture. Leishmanial antibody detection is supportive but not diagnostic. The leishmanin skin test (Montenegro test), which is positive in those who have had asymptomatic or successfully treated infection, is negative in patients with VL.

There are no FDA-approved drugs for the treatment of visceral leishmaniasis. Early treatment for VL was with the trivalent antimonials. The less toxic pentavalent antimonials were introduced in the 1920s. This class of drugs, which includes sodium stibogluconate (Pentostam) and meglumine antimonate (Glucantime), has been the mainstay of treatment for VL since its introduction. However clinical treatment failures have become increasingly common. Other drugs shown to have efficacy in treating the leishmaniases include aminosidine (paromomycin), pentamidine, and amphotericin B. Amphotericin B is thought to act by intercalation with parasite episterol precursors of ergosterol in preference to host cholesterol and interruption of parasite cell wall synthesis. While this drug has shown excellent *in vitro* activity against *Leishmania,* the toxicity of Amphotericin B has limited its use in the treatment of visceral leishmaniasis.

AmBisome, a liposomal amphotericin B, has been thought to have potential utility in visceral leishmaniasis because of its ability to reach the intracellular targets where the amastigotes reside. The first clinical case report of successful treatment of VL with AmBisome was published in 1991. Animal studies have demonstrated efficacy of AmBisome in experimentally infected mice and naturally infected dogs with VL. The studies included in the publications that constitute this NDA submission are the subsequent trials of dose-ranging with AmBisome in the treatment of 108 patients with parasitologically documented visceral leishmaniasis who were treated and followed-up for 6-12 months..

* The original case description was by Major Leishman, RAMC (1903), in the Indian cantonment of Dum-dum, giving rise to the name Dum-dum fever.

APPEARS THIS WAY
ON ORIGINAL

Study No. VS104-012

AmBisome in the Treatment of Visceral Leishmaniasis in Non-Immunocompromised and Immunocompromised Patients

Objectives

1. To determine the safety and efficacy of AmBisome in the treatment of Mediterranean visceral leishmaniasis in immunocompetent adults and children

2. To determine the safety and efficacy of AmBisome in the treatment of Mediterranean visceral leishmaniasis in the immunocompromised patient population

3. To determine the safety and efficacy of AmBisome for the treatment of severe, complicated or drug resistant visceral leishmaniasis under third world field conditions

Design

This was a multi-center, open study comprised of individual component studies designed to test regimens of AmBisome in selected patient populations with a parasitologically confirmed diagnosis of visceral leishmaniasis. There were two types of settings where the studies were conducted. There were several study centers which were hospitals experienced in the treatment of visceral leishmaniasis in Naples, Rome, Genoa, Palermo, Catagna, and Caserta, Italy, Lisbon, Portugal, Sao Paolo, Brazil, and London, UK. There was an additional cohort of patients treated under field conditions in the Sudan. The patient populations included immunocompetent patients, both adult and pediatric, and immunocompromised patients who were coinfected with HIV, had a malignancy, or were receiving immunosuppressive drugs. All component studies were open-label. They included patients with and without prior treatment for visceral leishmaniasis. The European and Brazilian studies were approved by local institutional review boards under formal protocols conducted in accordance with Good Clinical Practices. Informed consent was obtained from all treated patients in Europe, Brazil, and the Sudan. The following discussion of study design distinguishes between immunocompetent patients, immunosuppressed patients, and severely ill patients treated under field conditions in the Sudan.

AmBisome was studied in immunocompetent patients infected in one of two areas of endemicity, Southern Europe (Mediterranean basin) or Brazil. The studies were conducted from 1991 to 1994. These clinical trials began with a dose that was adequate to cure without subsequent relapse. The rationale was then to treat further patient cohorts with progressively lower doses or shorter courses of therapy while maintaining efficacy. In total, there were six cohorts of patients studied; the intravenous doses of AmBisome administered ranged from 30 mg/kg (total) to 12 mg/kg (total) given over a period of 21 to 4 days. Initial assessment of response at 21 days was both parasitologic and clinical. Patients were followed for 6-12 months after treatment to assess for clinical relapse.

The clinical trials in immunosuppressed patients enrolled patients infected in the Mediterranean basin including Europe and North Africa. The studies were conducted from 1991 to 1994. Intravenous regimens were administered over a period of 10 to 21days. Because of the high relapse rate in the first cohort receiving doses of 29 mg/kg (total) to 39 mg/kg (total), a second, more intensively treated cohort was studied at a dose of 40 mg/kg (total). Initial assessment of response at 21 days was both parasitologic and clinical. Patients were followed for 6-12 months after treatment to assess for clinical relapse.

In the West Upper Nile area of the Sudan an epidemic of VL has been in progress since 1984. The patients who had failed prior therapy or who were severely ill were enrolled and treated with doses ranging from 9-30 mg/kg (total) over a period of 3-10 days at remote, temporary field stations without electricity or running water from February 1993 to January 1994. Initial assessment of response was both parasitologic and clinical. Follow-up was passive; patients returned if they experienced new symptoms.

MO COMMENT: The studies undertaken in the Sudan were quite different from those in Europe and Brazil. The Sudanese patients were more severely ill with both VL and other concurrent diseases, epidemic conditions prevailed in a setting with severely compromised infrastructure, the dosing regimens studied were designed for short-course therapy with doses generally less than the 21 mg/kg total recommended in the draft labeling, there was no laboratory data, and follow-up was passive and limited to those patients who returned if they did not feel well. For the purposes of this review, these studies are supportive rather than pivotal.

PROTOCOL OVERVIEW
Population

The patients studied may be in one of three categories as described below. It was planned that ten patients were to be enrolled in the first instance in each of the three categories:

(a) Visceral leishmaniasis patients recently diagnosed and untreated. These patients were to receive 10 days of AmBisome at the higher dose of 3-4 mg/kg/day.

(b) Visceral leishmaniasis patients who have shown primary drug unresponsiveness (failure to clear parasites), or who have relapsed after a full course of another standard antileishmanial drug. These patients will receive 21 days of AmBisome at the lower dose of 1-2 mg/kg/day.

(c) Visceral leishmaniasis patients with coexisting HIV infection. These patients will receive 21 days of AmBisome at the lower dose of 1-2 mg/kg/day.

MO COMMENT: It should be noted that the dosing regimens described in (a), (b), and (c) were starting points and for each of these categories of patients, data were reported for other regimens as well. For patients in categories (a) and (b) the doses described in the protocol were the highest doses used, and progressively lower doses were tried in a systematic attempt to identify the lowest effective dose and/or the shortest effective regimen. For patients in category (c) the dose described in the protocol was the lowest dose used. It should also be noted that this protocol did not distinguish between adult and pediatric patients. Indeed, visceral leishmaniasis in the immunocompetent host in the Mediterranean basin is often a pediatric disease. Table 1 summarizes dosing regimens used in the various cohorts of immunocompetent and immunosuppressed patients (treated in referral centers in Europe and Brazil) and in severely ill patients treated under field conditions (Sudan). Patients who were in category (a) above are represented by Cohort II, patients who were in in category (b) by Cohort I, and patients who were in category (c) above are represented by Cohort VII.

TABLE 1
DOSING REGIMENS OF AMBISOME IN VISCERAL LEISHMANIASIS IMMUNOCOMPETENT AND IMMUNOSUPPRESSED PATIENTS, EUROPE AND BRAZIL FIELD CONDITIONS, WESTERN UPPER NILE, SUDAN

IMMUNOCOMPETENT PATIENTS

COHORT	SCHEDULE	TOTAL DOSE
I.	1 mg/kg/day or 100 mg/day x 21 days	21-29 mg/kg
II.	3 mg/kg/day x 10 days	30 mg/kg
III.	4 mg/kg/day days 1-5, day 10	24 mg/kg ⇒proposed dose = 21 mg/kg
IV.	3 mg/kg/day days 1-5, day 10	18 mg/kg
V.	3 mg/kg/day days 1-4, day 10	15 mg/kg
VI.	3 mg/kg/day days 1-3, day 10	12 mg/kg

IMMUNOCOMPROMISED PATIENTS

COHORT	SCHEDULE	TOTAL DOSE
VII.	100 mg/day x 21 days	29.0-38.9 mg/kg
VIII.	4 mg/kg/day days 1-5, 10, 17, 24, 31, 38	40 mg/kg

PATIENTS TREATED UNDER FIELD CONDITIONS, SUDAN

COHORT	SCHEDULE	TOTAL DOSE
IX.	3-5 mg/kg/day days 0, 3, 10	9-15 mg/kg
X.	3-5 mg/kg/day days 0,3,6,8,10,13	18-30 mg/kg
IX.	4-5 mg/kg/day days 0,2,5	12-15 mg/kg

Inclusion/Exclusion Criteria of Note
Inclusion Criteria

At entry, all patients must have parasitological proof of visceral leishmaniasis by one of the following methods:

- Presence of amastigotes of leishmania on smears of bone marrow aspirate, or smears of splenic aspirate, or histology of liver, marrow, or spleen
- Culture of leishmania from one of the above sites

A typical history and clinical examination plus positive serology are NOT adequate diagnostic criteria for admission to this therapeutic trial.

Exclusion Criteria

- Pregnancy and lactation
- Patient (or guardian in under 16 years) unable to give informed consent

Procedures

Patients with clinically evident visceral leishmaniasis had aspirates and/or cultures performed. Proven cases for whom consent was obtained were enrolled in the study. Once the patient was enrolled the following data were recorded: site and method of diagnosis of leishmaniasis, country of infection, leishmania serology, leishmanial species (if known), prior anti-leishmanial treatment, HIV status (serology results and CDC clinical stage if applicable) , name, age, sex, height, weight, race.

Indirect Parameters
Clinical and laboratory parameters were recorded at regular intervals determined by the number of days of treatment in the regimen. For patients receiving 21 days of treatment, these parameters were recorded on days 0, 7, 14, and 21. For patients receiving 10 days of treatment, these parameters were recorded on days 0, 5, 10 and 21. The patients in Cohort VIII who received 10 days of treatment over a 38 day interval were evaluated on days 1,5,10, 17, 24, 31, and 38. The clinical parameters recorded were fever (oral temperature > 37.5° C in previous 24 hours), spleen size (maximum span below the R [sic] costal margin during quiet breathing, and weight. The laboratory parameters recorded were serum albumin and total protein, liver enzymes (alkaline phosphatase, AST, ALT), BUN, creatinine, electrolytes, hemoglobin, white blood cell count, platelet count, and ESR or C-reactive protein.

Direct Parasite Response

In all cases, it was required that a specimen for parasitological diagnosis be taken at the end of treatment for microscopy and culture. This was scheduled at or near day 21, irrespective of whether the treatment had been for 10 or for 21 days. The patients in Cohort VIII were studied on a different schedule; their post-treatment parasitology was performed on day 45. Usually this was an aspirate of the tissue from which the diagnosis was originally made (e.g. spleen or bone marrow). This aspirate taken at day 21 (or 45 for Cohort VIII) was considered the Test of Cure. Splenic or bone marrow aspirate was quantified by the method of Chulay and Bryceson (1983 Am J Trop Med Hyg 32(3): 475-79):

GRADE	AVG PARASITE DENSITY
6+	>100 parasites/field
5+	10-100 parasites/field
4+	1-10 parasites/field
3+	1-10 parasites/10 fields
2+	1-10 parasites/100 fields
1+	1-10 parasites/1000 fields
0	0 parasites/1000 fields

Field is 10x ocular and 100x oil immersion lens.

Follow-up Post Treatment
Follow-up visits were scheduled at 1 month, 3 months, 6 months, and 12 months after treatment. The assessments at these visits included clinical and laboratory parameters described above. Parasitology was to be obtained if any of these indirect parameters were not satisfactory and relapse was suspected.

Evaluability Criteria

There was not a formal statement of evaluablity criteria in the original protocol. From the above discussion of the protocol, it can be seen that patients of all ages were eligible for enrollment, a history of prior treatment for visceral leishmaniasis was possible among study patients, and patients may have become infected with leishmania in a wide variety of geographical locations.

MO COMMENT: The reviewing Medical Officer accepted patients of all ages as evaluable. Because visceral leishmaniasis is largely a pediatric disease in Southern Europe, the discussion of results below will distinguish between adult and pediatric responses to treatment. A history of prior treatment for leishmaniasis, if recent enough, could make it difficult to determine if the observed response to treatment were the result of AmBisome alone or the result of a combination of AmBisome plus the prior treatment. The reviewing Medical Officer regarded patients with a history of prior treatment for visceral leishmaniasis as evaluable if that treatment ended one month or more before enrollment. A considerable body of literature suggests that leishmania parasites causing visceral disease from different geographic locations may respond differently to drug treatment (see section SCIENTIFIC AND REGULATORY BACKGROUND). Whether this is due to frank drug resistance remains to be determined. In different geographic regions visceral leishmaniasis is caused by different species of the genus *Leishmania*. Traditionally *L. donovani* has been associated with disease in subSaharan Africa, the Middle East, and South Asia, *L. infantum* with disease in the Mediterranean basin (Southern Europe and North Africa), and *L. chagasi* with New World visceral leishmaniasis. For the purposes of evaluating efficacy of AmBisome in visceral leishmaniasis, the reviewing Medical Officer regarded as evaluable those patients who had become infected in the Mediterranean basin with documented or presumed *Leishmania infantum*. The reviewing Medical Officer regarded as evaluable patients who had parasitologic (microscopy or culture) and clinical assessments at day 21, and were followed for six months or longer after completion of treatment. The reasons patients were made unevaluable by the MO are listed below:

Therapy with antileishmanial drug $\leq$ 1 month prior to enrollment

Infected outside Mediterranean basin (*L. donovani* or *L. chagasi*)

No parasitologic diagnosis documented

No parasitology at 21 days documented

Clinical follow-up < 6 months

Unable to complete study, died for reason(s) that could not be attributed to drug failiure

Refused treatment and/or procedure

Endpoints

The following excerpt from the protocol discusses endpoints:

There are five possible end points

1. cure (clinically and parasitologically free of leishmania when the test of cure aspirate is performed). At follow-up at 1, 3, 6, and 12 months these may prove to have (a) a relapse (b) no relapse
2. drug failure - the patient is clinically or parasitologically nonresponsive or inadequately responsive to treatment such that AmBisome has been discontinued or another anti-leishmanial drug added

3. adverse event/toxicity leading to discontinuation of AmBisome
4. patient dies before assessment of drug efficacy can be made
5. patient defaults from treatment before assessment of drug efficacy can be made

MO COMMENT: The combination of the requirement for parasitologic diagnosis, the large number of patients studied, and the length of time patients were followed after treatment make these studies unusual in the published literature of drug treatment of visceral leishmaniasis.

MO COMMENT: The reviewing MO concurs with the requirement of parasitologic and clinical resolution in order for a patient to be considered a cure. While there is little consensus in the literature regarding the importance of a positive splenic aspirate in a treated patient who is clinically well, it has been shown that among treated patients who are clinically well, there is a lower risk of relapse in those with a negative follow-up smear compared to those with a positive smear.

MO COMMENT: The reviewing MO did not require documentation of discontinuation of AmBisome or of addition of another antileishmanial drug in order to score an inadequate response or a non-response a failure. The MO defined two separate endpoints: 1) acute clearance of parasites as determined by microscopy and/or culture of aspirated spleen or bone marrow at 21 days (End of Therapy) and 2) overall success which included those patients who cleared parasites at 21 days **and** who remained relapse free in the follow-up period of 6-12 months after completion of therapy. The MO regarded as failures patients in whom parasites were found upon repeat aspiration of tissue at the completion of therapy and patients who relapsed following acute clearance of parasites.

Statistical Methods

These studies were open-label studies of various AmBisome dosing schedules in the treatment of visceral leishmaniasis. The numbers of patients were not based on comparative sample size estimates. Patients served as their own controls in evaluating disease response and changes in safety parameters. For non-parametric data, Wilcoxon signed rank tests and Mann-Whitney Utests were used. For parametric data paired student's t-tests, X^2 and Fisher's exact tests were used.

MO COMMENT: Since there are no drugs approved for use in the US for the treatment of visceral leishmaniasis, it is not possible to study the efficacy of AmBisome in a controlled trial with an approved active comparator. Untreated, the disease is regarded as ultimately fatal. A review of the literature and personal communications with experts suggests that an effective drug should have a rate of primary response of 90%-95%.

MO COMMENT: The statement 'patients served as their own controls' referred to patients who had been previously treated for visceral leishmaniasis.

STUDY RESULTS

Demographics and Evaluability

A total of 108 immunocompetent patients and 21 immunocompromised patients were enrolled in the clinical trials carried out in European and Brazilian centers. Screen failure information was not provided in the study publications. Forty-nine patients were studied in the Sudan. Table 2 presents demographic data on the European and Brazilian patients and evaluability at day 21 and at one year according to the Applicant. The Roman numerals refer to the same treatment groups described in Table 1. Table 3 presents demographic data on the Sudanese patients.

TABLE 2
DEMOGRAPHICS AND EVALUABILITY PER APPLICANT
IMMUNOCOMPETENT AND IMMUNOCOMPROMISED PATIENTS-EUROPE AND BRAZIL

COHORT	PATIENTS (CHILDREN)	MALES/ FEMALES	PREVIOUS THERAPY	NO. EVALUABLE AT DAY 21 (%)	NO. EVAL AT 1 YEAR
IMMUNOCOMPETENT PATIENTS					
I.	10 (6)	8/2	4	10	10
II.	10 (9)	2/8	0	10	10
III.	13 (10)	7/6	2	13	10
IV.	42 (26)	24/18	1	42	41
V.	32 (19)	18/14	1	32	31
VI.	1 (0)	1/0	0	1	1
TOTAL	108 (70)	60/48	8	108 (100)	103 (95.4)

COHORT	PATIENTS (CHILDREN)	M/F	HIV+	PREVIOUS THERAPY	NO. EVALUABLE AT 21 DAYS (%)	NO. EVAL AT F/U (%)
IMMUNOCOMPROMISED PATIENTS						
VII.	11 (0)	7/4	7	8	11	11
VIII.	10 (0)	9/1	10	5	9	7
TOTAL	21 (0)	16/5	17	13	20 (95.2)	18 (85.7)

MO COMMENT: Among the immunocompetent patients, approximately 65% were children, and 56% were male, and 7% had had prior therapy for visceral leishmaniasis. Among the immunocompromised patients, 62% had had prior therapy for visceral leishmaniasis.

TABLE 3
DEMOGRAPHICS AND EVALUABILITY PER APPLICANT
PATIENTS IN THE SUDAN

COHORT	NO. PTS	M/F	MEDIAN AGE in yrs (RANGE)	NO. EVALUABLE AT 21 DAYS	NO. EVALUABLE AT F/U
IX.	18	10/8	8	16/18	8
X.	19	11/8	18	16/19	2
XI.	12	6/6	10	1/12	4
TOTAL	49	27/22		43/49 (87.8)	14/49 (28.6)

The Sudanese patients were described as in generally poor condition when they presented for treatment. Patients who received regimens IX. and X. were selected because they had relapsed after treatment with pentavalent antimony and aminosidine (many had relapsed more than once), they had had an incomplete parasitologic response to antimony and aminosidine, or because they had severe illness defined by a body mass index below a certain value, age >50 years, bleeding, intractable vomiting, and/or moribund condition. Patients who received regimen XI were presenting for the first time with VL.

The reviewing Medical Officer used somewhat different evaluability criteria as described above (see Evaluability Criteria, MO COMMENT). Table 4 presents evaluability according to the MO's critieria. All case report forms for patients in European and Brazilian centers were reviewed. Because there were no patient level data on the Sudanese studies, MO analysis was limited to the submitted publication. In general, the MO concurred with the data in Table 3. Patients who were scored as clinically and parasitologically evaluable by the MO were patients who were infected in the Mediterranean basin, had no prior treatment with antileishmanial drugs or, if they did, had treatment one month or more before enrollment in the present trial, had a record of a repeat study of tissue at 21 days to assess for parasites by microscopy and/or culture, and who were followed up at 6 months after treatment or longer. Unevaluable patients are listed by reason.

TABLE 4
EVALUABILITY PER MEDICAL OFFICER
IMMUNOCOMPETENT PATIENTS-EUROPE AND BRAZIL

COHORT/ TOTAL DOSE	NUMBER ENROLLED	CLINICALLY AND PARASITOLOGICALLY EVALUABLE (%)
I. 21-29 mg/kg x 21days	10	5 (50)
II. 30 mg/kg	10	10 (100)
III. 24 mg/kg	13	10 (76.9)
IV. 18 mg/kg	42	33 (78.6)
V. 15 mg/kg	32	28 (87.5)
VI. 12 mg/kg	1	1 (100)
TOTAL	108	87 (80.6)

UNEVALUABLE PATIENTS BY REASON*	
Therapy with antileishmanial drug ≤ 1 month prior to enrollment	N=2; Cohort I: #1EP, #3RP
Infected outside Mediterranean basin (L. chagasi) and clinical follow-up < 6 months	N=3; Cohort III: #9ER, #10SJ, #12a
No parasitologic diagnosis documented	N=3; Cohort IV: #41IG; Cohort V: #3RL, #31MA
No parasitology at 21 days documented	N=10; Cohort I: #6VC, #7LI, #13VV; Cohort IV: #1MD, #6TL, #17SS, #32GR, #34CB, #40LR; Cohort V: #32GC
Clinical follow-up < 6 months	N=2; Cohort IV: #32GR, #37AS; Cohort V: #11AD
Total	N=21

* Within a cohort patients were numbered sequentially 1,2,3... In order to distinguish between patients with the same number, they are identified by cohort and by initials assigned at enrollment.

The Medical Officer's assessment of the evaluability of the immunocompromised patients is presented in Table 5. Again, unevaluable patients are listed by reason.

TABLE 5
EVALUABILITY PER MEDICAL OFFICER
IMMUNOCOMPROMISED PATIENTS- EUROPE

COHORT/ TOTAL DOSE	NUMBER ENROLLED	CLINICALLY AND PARASITOLOGICALLY EVALUABLE (%)
VII.	11	10 (90.9%)
VIII.	10	8 (80%)
TOTAL	21	18 (85.7%)
UNEVALUABLE PATIENTS BY REASON		
Unable to complete study, died of bacterial sepsis		N=1; Cohort VII: #29ES
Refused treatment and/or procedure		N=2; Cohort VIII: #5, #10
Total		N=3

Efficacy

Parasitologic and Clinical-Immunocompetent Patients

The discussion of the efficacy of AmBisome in VL must distinguish between the immunocompetent and the immunocompromised host. Table 6 presents the Applicant's assessment of efficacy in 108 immunocompetent patients. These trials began with a cohort that received a dose that was thought to be adequate to cure patients treated without subsequent relapse. Progressively lower doses or shorter courses of therapy are represented in the subsequent cohorts. The diagnosis of VL required positive microscopy or culture of bone marrow or splenic aspirates, and the criterion for a successful initial response was complete clearance of parasites from the Test of Cure aspirate taken on day 21. The presence of any residual parasites by microscopy or culture at day 21 was considered a failure of the primary therapeutic regimen. Patients were then followed clinically for relapse up to one year. Relapse was also cause to classify the patient as a failure.

TABLE 6
EFFICACY PER APPLICANT
IMMUNOCOMPETENT PATIENTS

COHORT	NO. PATIENTS	SUCCESS DAY 21(%) PARASITOLOGIC	NO RELAPSE F/U ≥ 6 MO (%) CLINICAL
I.	10	10/10 (100)	10/10 (100)
II.	10	10/10 (100)	10/10 (100)
III.	13	13/13 (100)	10/10 (100)
IV.	42	42/42 (100)	40/41 (97.6)
V.	32	31/32 (96.9)	29/31 (93.5)
VI.	1	1/1(100)	1/1(100)
TOTAL	108	107/108 (99.1)	100/103 (97.1)

One Cohort V (15 mg/kg) patient, a child, had residual parasites seen in bone marrow aspirate at day 21. This patient had responded clinically but was considered a failure because of residual parasites. Accordingly the patient was retreated with AmBisome 3 mg/kg for an additional 10 days with a documented complete response; the patient remained free of relapse at one year. There were three relapses, one child in the 18 mg/kg group and two children in the 15 mg/kg group. All three were retreated with AmBisome 3 mg/kg for 10 days, and all three had a complete response and remained free of relapse for one year. The investigator attributed the failures/relapses to inadequate dosing rather than resistance since the patients were cured with higher dosing. It was noted that the failures occurred in children, where there is a proportionally larger reticuloendothelial system, the site of the parasite burden. It was suggested that in the adult population doses lower than 15 mg/kg might be curative.

MO COMMENT: The Applicant's efficacy rates show that the parasitologic cure rate and the follow-up (clinical) cure rate are well within the range expected of an antileishmanial drug. The 95% confidence interval around the point estimate for efficacy at 21 days is {97.3, 100.0}. The 95% CI around the point estimate for efficacy at follow-up is {93.8, 100.0}. The Applicant defined relapse rate as the number of patients with disease recurrence during 6 months or more of follow-up divided by the number who achieved parasitologic cure at the end of therapy (relapse rate = # recurrence after EOT/# cure at EOT). All failures were observed in the cohorts that received less than 21 mg/kg total, the dose recommended in the draft labeling. While it is noteworthy that all failures occurred in children, it should be kept in mind that 70% of all immunocompetent patients studied were children and that perhaps failures were observed in the pediatric population because they were so well represented in the study population. Whether or not immunocompetent adults would respond to doses less than 15 mg/kg would require systematic study in a larger population.

In addition to the overall efficacy reported, the Applicant noted that immunocompetent patients achieved a rapid clinical improvement when given AmBisome. A number of parameters were monitored during the follow-up of these patients. Table 6A presents a summary of the changes observed in clinical parameters for patients in Cohorts III-VI. The Applicant reported that the data available for Cohorts I and II did not permit the same quantitation of these parameters, and instead presented graphic representations of clinical parameters for patients in Cohorts I and II.

TABLE 6A
CHANGES IN CLINICAL PARAMETERS IN IMMUNOCOMPETENT PATIENTS PER APPLICANT

Parameter	Day 0		Day 5		Day 10		Day 21	
Fever	67/88		2/88		0/88		0/88	
Spleen size[1]	7.1	±0.4	5.0	±0.3*	3.9	±0.2*	2.6	±0.2*
Serum Albumin[2]	32.6	±0.6	33.1	±0.4	36.5	±0.5*	40.6	±0.6*
ESR[3]	90.0	±3.2	74.5	±3.7*	58.1	±3.7*	47.1	±3.5*

[1] cm below LCM, mean ± SEM
[2] g/L, mean ± SEM
[3] mm/1st hour, mean ± SEM
* $p < 0.001$

MO COMMENT: Review of Table 6A shows that 65/67 (97.0%) of febrile patients in Cohorts III-VI defervesced by day 5 of treatment, and that all febrile patients defervesced by day 10 of treatment and no fevers were documented in any of the patients after day 10. Spleen size and ESR were observed to normalize and serum albumin observed to increase with increasing drug exposure. Review of CRFs shows that the data available for Cohorts I and II did not permit similar quantification. Graphic representations of the changes in spleen size, ESR and albumin for Cohorts I and II showed similar trends.

The reviewing MO used somewhat more exclusive evaluability criteria and found 87 patients were clinically and parasitologically evaluable. According to the protocol, failure included those who had positive parasitologic studies at day 21 (microscopy and/or culture of tissue aspirates) and those who relapsed during the follow-up period. Failures at 21days were carried forward and included in the final analysis of efficacy. The efficacy results per MO are presented in Table 7.

TABLE 7
EFFICACY PER MEDICAL OFFICER
IMMUNOCOMPETENT PATIENTS

COHORT	NO. PATIENTS EVALUABLE	SUCCESS DAY 21 (%) (PARASITOLOGIC)	RELAPSE FREE F/U ≥ 6 MO (%) (OVERALL SUCCESS)
I.	5	5/5 (100)	5/5 (100)
II.	10	10/10 (100)	10/10 (100)
III.	10	10/10 (100)	10/10 (100)
IV.	33	33/33 (100)	32/33 (97.0)
V.	28	27/28 (96.4)	25/28 (89.3)
VI.	1	1/1(100)	1/1 (100)
TOTAL	87	86/87 (98.9)	83/87 (95.4)

MO COMMENT: Efficacy rates were obtained using the reviewing MO's more exclusive evaluability criteria and by using the overall success rate (success = patients cured at EOT plus patients who did not relapse/ total number of patients evaluable). The overall success rate is a more stringent measurement of efficacy. By the MO criteria efficacy rates for AmBisome in immunocompetent patients with VL remain in the range of 90%-95% expected of an effective antileishmanial agent. The 95% CI around the point estimate for efficacy at 21 days is {96.6, 100.0}. The 95% CI around the point estimate for efficacy at follow-up is {91.0, 99.8}.

The draft labeling states that the dose for visceral leishmaniasis is a total of 21 mg/kg given on 7 days over a 21 day period. Cohorts I, II, and III received doses of 21-29 mg/kg, 30 mg/kg, and 24 mg/kg, respectively. The efficacy rate of AmBisome in VL at 21 days among patients who received ≥ 21 mg/kg was 33/33 (100%) according to the Applicant and 25/25 (100%) according to the MO. The efficacy rate among these patients at follow-up was 30/30 (100%) per Applicant and 25/25 (100%) per MO. The patients in Cohort IV received a total dose of 18 mg/kg, which is less than the dose recommended in the draft labeling. The cure rates in Cohort IV at 21 days were 42/42 (100%) per Applicant and 33/33 (100%) per MO; at follow-up the cure rates for this cohort were 40/41(97.6%) per Applicant and 32/33 (97.0%) per MO. Efficacy remains above the expected rate in patients receiving less than the recommended dose.

Immunocompromised Patients

The response to treatment among the first cohort of immunocompromised patients (Cohort VII, received 100 mg/kg/day x 21 days for a total dose of 29-39 mg/kg) was characterized by a higher rate of relapse than seen in the immunocompetent patients. Because of this relapse rate, a second cohort of immunocompromised patients was treated with a more intensive regimen (Cohort VIII, received 4 mg/kg/day days 1-5 with weekly follow-up doses on days 10, 17, 24, 31, and 38 for a total dose of 40 mg/kg). The relapse rate remained high in these patients. Table 8 presents the efficacy of AmBisome in treating VL in these populations as reported by the Applicant.

TABLE 8
EFFICACY IN IMMUNOCOMPROMISED PATIENTS
PER APPLICANT

Cohort	Schedule	Number	Clinical Response	Bone Marrow Aspirate Neg., Day 21	Subsequeent Relapse
VII.	100 mg/day x 21d	11	11/11	11/11(100%)	8/11 (72.7%)
VIII.	4 mg/kg/d, Day 1-5, 10, 17, 24, 31, 38	10	10/10	8/9 (88.9%)	7/7 (100%)
TOTAL		21	21/21	19/20 (95%)	15/18 (833.3%)

MO COMMENT: Patients in Cohort VIII underwent repeat bone marrow aspiration at day 45.

MO COMMENT: Following review of the submitted publications and the CRFs, the MO analyssis of the efficacy among immunocompromised patients is generally in agreement with the data presented in Table 8, with the exception that in Cohort VII, there were only 10 evaluable patients at day 21 since one patient, #29ES, died at day14 of staphylococcal sepsis and was considered unevaluable by the MO. Of those 10 patients remaining, two had amastigotes visualized on repeat bone marrow aspirates, but these failed to grow in culture. This suggests that the parasites were not viable and the MO agrees with scoring the day 21 aspirates negative for these two patients. Since one patient died before completing the study, the MO considered only 10 evaluable, and therefore the relapse rate of Cohort VII by MO analysis is 80%, and the relapse rate for the total population is 15/17 (88.2%).

The Applicant commented that the clinical parameters of the patients in Cohort VII improved, but more sslowly than in the immunocompetent patients studied concurrently (Cohorts I and II). Splenomegaly persisted to a greeater degree, ESRs fell but the mean remained above normal. The clinical response was similar in Cohort VIII. While there was some initial improvement in weight, elevated ESR, and splenomegaly, the responses were slower than in the immunocompetent patients, the parameters under study did not always normalize, and the improvements were not reliably sustained. Nonetheless there was some clinical benefit achieved and parasitologic studies following treatment showed high rates of acute parasite clearance. These rates were lower than those observed in immunocompetent patients, but with a sample size of 20 it is difficult to draw a firm conclusion. The investigator suggested that the high relapse rate among the immunocompromised patients might respond to repeat courses of AmBisome or might require long-term secondary prophylaxis.

MO COMMENT: While the above regimens achieved some level of clinical response and clearance of parasites in most patients, the high relapse rates of 80% and 100% are remarkable. These patient cohorts are small and a significant number (13/21= 61.9%) received prior therapy, suggesting a longer duration of disease and possibly greater difficulty in achieving a cure. These data strongly suggest that the immunosuppressed host with VL is not able to achieve the same response rates with AmBisome in long term follow-up. Animal models of VL have shown that drug alone cannot clear amastigotes, and that an intact cellular immune response is necessary to control the parasite. Indeed some of the findings among the immunosuppressed patients studied here suggest a huge parasite burden that multiplies uncheckeed in the host with impaired cellular immunity. *Leishmania* amastigotes are usually found in the tissues of the reticuloendothelial system (spleen, liver, bone marrow) of those with visceral disease. Among the HIV coinfected patients studied, parasites were seen in the duodenal biopsy of one and in the circulating granulocytes of two others, suggesting an overwhelming organism load that is able to parasitize tissues outside of the RES as well. Case reports in the medical literature have documented extensive gastrointestinal and pleuropulmonary involvement in VL patients coinfected with HIV (Alvar et al, 1997

Clin Micro Rev; 10 (2):298-319). The study of patients in Cohorts VII and VIII did demonstrate acute parasite clearance but did not identify a curative dose of AmBisome for the treatment of VL in the immunosuppressed host. Rather, these studies highlighted the difference between immunocompetent and immunocompromised hosts of *Leishmania.* The MO concurs with the investigator's suggestion that multiple courses of treatment and/or long-term maintenance therapy may be needed to prevent relapse in the immunocompromised patient.

Patients Treated under Field Conditions in the Sudan

Efficacy rates in severely ill patients treated under field conditions in the Sudan with short course regimens are presented per Applicant in Table 9.

TABLE 9
EFFICACY IN SUDANESE PATIENTS
PER APPLICANT

Group	Number	Early Deaths	Cured Day 21 (%)	Salvaged (%)
IX.	18	2/18	8/16 (50.0)	3/8 (37.5)
X.	19	3/19	14/16 (87.5)	1/2 (50.0)
XI.	12	1/12	7/11 (63.6)	3/4 (75.0)
TOTAL	49	6/49	n.a.	n.a.

n.a. = not applicable because of differences in disease severity and treatment intensity.

MO COMMENT: The MO reviewed the submitted publication that provided these data on the patients studied in the Sudan; there were no supporting data or CRFs submitted. Salvaged patients were those who did not fully respond to the regimen initially given, but did respond to 3 mg/kg/day x 10 days. The MO analysis generally concurs with that of the Applicant. .

The Applicant reported that there were six early deaths among the Sudanese patients and it was thought that these patients died from intercurrent illnesses. In five of the cases the patients died before treatment with AmBisome was complete. From the available information, it appears that two of these patients (both in Cohort X) died with jaundice and hematemesis on days 2 and 3, respectively. The third early death in Cohort X occurred in the context of severe diarrhea and dehydration; that patient died after three doses (day 10) of AmBisome. One child died in Cohort XI after completing treatment but before being checked for parasites. His death was thought to be due to malaria. The two other early deaths occurred in Cohort IX; both of these patients died after receiving two doses of AmBisome. Salvage regimens consisted of 3 mg/kg daily for 10 days, and these were given to the patients who self referred for recurrent illness.

MO COMMMENT: Analysis of the early deaths data highlights the difficulty in drawing conclusions about the efficacy of AmBisome in the patients treated in the Sudan. The majority of the early deaths (5/6) occurred in the Cohorts made up of sicker patients, many of whom, out of necessity, received doses lower than that recommended in the draft labeling. There were suggestions of other ongoing illnesses in these patients who died. These observations do point toward reasons other than the failure of AmBisome in explaining these patients' deaths. However the lack of definitive diagnoses makes it difficult to draw a firm conclusion. That some parasite clearance was attained in these patients who generally received abbreviated regimens supports the efficacy documented at higher doses among immunocompetent patients in European referral centers. The data on salvaged patients is particularly interesting. Those from Cohorts IX and X who did not clear parasites at day 21 included patients who had failed other regimens, some of whom had failed multiple times; a small number were successfully treated with 'rescue' doses of AmBisome.

MO COMMENT: The Sudanese experience may be most instructive in pointing out the shortcomings of lower doses and irregular follow-up in patients with severe disease.

Safety

The safety database for AmBisome in visceral leishmaniasis includes 178 patients. There were 108 immunocompetent patients (70 of them children), 21 immunocompromised patients, and 49 patients treated under field conditions in the Sudan. The drug exposure and safety data on the Sudanese patients is limited because the dosing for individual patients was not available and the study conditions lacked the facilities for laboratory testing. The Sudanese safety data are discussed separately below with this in mind. The doses given to the 108 immunocompetent and 21 immunosuppressed (total n= 129) patients ranged from a total dose of . The daily doses ranged from Table 10 shows the numbers of patients exposed to each total dose and daily dose according to the MO analysis.

TABLE 10
DRUG EXPOSURE BY TOTAL DOSE AND BY DAILY DOSE
IMMUNOCOMPETENT AND IMMUNOCOMPROMISED PATIENTS
PER MEDICAL OFFICER

TOTAL DOSE	NO. PTS (%)	DAILY DOSE	NO.PTS (%)
40 mg/kg	10 (7.8)	4.0 mg/kg/day	23 (17.8)
30-39 mg/kg	21 (16.3)	3.0 mg/kg/day	85 (65.9)
21-29 mg/kg	23 (17.8)	1.0-2.0 mg/kg/day	21 (16.3)
10-20 mg/kg	75 (58.1)		
TOTAL	129	TOTAL	129

MO COMMENT: Table 10 shows that 54/129 (41.9%) of patients received total doses equal to or greater than 21mg/kg, the dose for VL recommended in the draft labeling. Table 10 also shows that 108/129 (83.7%) patients received daily doses equal to or greater than 3.0 mg/kg/day, the daily dose for VL recommended in the draft labeling.

Clinical Safety

As mentioned above, this discussion will first focus on clinical adverse events observed among immunocompetent patients and immunocompromised patients studied in hospital centers experienced in the care of patients with VL. A discussion of clinical AEs seen in the Sudanese patients will follow.

Among the 108 patients whose dosing regimens are listed in Table 10, there were 9 (8.3%) treatment-emergent AEs reported. Assessment of relationship to study drug was not made in all cases, but no patient had a treatment regimen changed because of toxicity. There was one episode of mild arterial hypotension after the first dose reported in an 18 year old man. There was one patient aged 2 years in whom fever (40°C) was reported on days 3 and 4. Rashes were observed in 3 patients, one of whom had rash that predated the start of therapy with AmBisome. The other two patients had rashes that were noted some time during the first week of therapy and resolved within one week. Nausea and/or vomiting were noted in two patients, one of whom had underlying liver disease. Headache was noted in two patients, and in one this was severe and associated with low back pain. These symptoms responded to treatment with acetominophen. Enlarged cervical lymph nodes were noted in a 14 month-old child on days 5-17. There were no episodes of phlebitis associated with infusion.

Among the 49 Sudanese patients there were two who had seizures during the period of treatment though not during the time of infusion. One seizure was thought to be due to hypoglycemia. Two patients had jaundice early in treatment with regimen XI and were switched to regimen X. However the subsequent appearance of jaundice in a

number of patients at the same treatment center who had not received the drug suggested that the condition was not related to therapy with AmBisome.

Laboratory Safety

The laboratory parameters that were analyzed for safety were chosen in part because of what is known about the toxicity of Amphotericin B. The Applicant presented safety data on renal function, electrolyte abnormalities, and liver function tests. No regimens among the immunocompetent or immunosuppressed patients treated in European or Brazilian referral centers were modified because of abnormal laboratory data.

Among the patients receiving high-dose, short course therapy (Cohorts III-VI) there was a transient increase in serum creatinine that peaked at day 5. On day 0 the serum creatinine was 66.1 ± 3.3 μM/L (± SEM), on day 5, 73.2 ± 5.2 μM/L ($p < 0.05$), on day 10, 68.6 ± 4.9 μM/L, and on day 21, 62.6 ± 3.1 μM/L. A similar trend to a transient increase in serum creatinine was observed in the HIV positive patients treated intensively (Cohort VIII). In the earlier experience in immunologically competent patients with a 21 day course of therapy at 1 mg/kg/day (Cohort I), a rise in serum creatinine was not seen.

Hypokalemia was also a potential concern. Analysis of the pooled data for immunocompetent patients showed that there was no significant change in mean serum potassium during or after treatment. In the short course therapy patients (Cohorts III-VI), of 88 patients only one patient had a serum potassium of less than 2.5 mEq/L and that was observed on Day 10. All others were either within normal limits or had minimal depression below the lower limit of normal. Two HIV positive patients from Cohort VII also showed evidence of significant hypokalemia (≤ 2.5 mEq/L) but the interpretation of this finding is more difficult. There was no summary data regarding serum magnesium levels.

Liver function tests were monitored in patients in all of these studies. Serum transaminases decreased in concert with improvement in the underlying disease. In pediatric patients there was a consistent elevation in the serum alkaline phosphatase post therapy. The authors speculated that this finding, restricted to the pediatric population may be related to renewed bone growth rather than a hepatic abnormality.

> MO COMMENT: The MO reviewed the individual publications and the CRFs and, in general concurs with the above summary statements by the Applicant. The significance of the observed hypokalemia in a small number of patients must be viewed in the context of the larger safety database. It suggests there may be a role for following serum potassium and magnesium levels in patients receiving AmBisome.

Reviewer's Conclusions

The studies submitted demonstrate the efficacy of AmBisome in the treatment of visceral leishmaniasis in immunocompetent patients, both adult and pediatric, infected in the Mediterranean basin with documented or presumed *Leishmania infantum*. Data documenting clinical efficacy in visceral leishmaniasis caused by other species of the genus *Leishmania* and from other geographic foci was not submitted in this NDA. It is noteworthy and perhaps helpful to the prescribing physician that *in vitro* data do demonstrate activity of AmBisome against *L. donovani*.

The markedly higher relapse rate noted among the immunosuppressed patients with VL warrants some distinction between immunocompetent and immunocompromised patients when discussing the efficacy of AmBisome in this disease. Again, it could be helpful to the prescribing physician to provide information from these clinical studies regarding higher relapse rates, the likely need for retreatment, and/or continuous secondary prophylaxis for immunocompromised patients.

AmBisome was generally well tolerated in these studies.

Reviewer's Recommendations

I recommend approval for AmBisome in the treatment of visceral leishmaniasis. Recommendations regarding specific aspects of the label are discussed separately below.

Labeling Recommendations

The **INDICATIONS AND USAGE** section:
AmBisome is indicated for the following:

Treatment of visceral leishmaniasis.
In immunocompromised patients with visceral leishmaniasis treated with AmBisome, relapse rates were high following initial clearance of parasites. While case reports have suggested there may be a role for long-term therapy to prevent relapses in HIV coinfected patients (Lopez-Dupla, et al. J Antimicrob Chemother 1993 Oct; 32 (4):657-9), there are no data to date documenting the efficacy or safety of repeat courses of AmBisome or of maintenance therapy with this drug among immunocompromised patients. For additional information, see CLINICAL TRIALS section.

The **CLINICAL STUDIES** section:
AmBisome was studied in patients with visceral leishmaniasis who were infected in the Mediterranean basin with documented or presumed *Leishmania infantum.* Clinical studies have not provided conclusive data regarding efficacy against *L. donovani* or *L. chagasi.*

AmBisome achieved high rates of acute parasite clearance in immunocompetent patients when total doses of 12-30 mg/kg were administered. Most of these immunocompetent patients remained relapse-free during follow-up periods of 6 months and longer. While acute parasite clearance was achieved in most of the immunocompromised patients who received total doses of 30-40 mg/kg, the majority of these patients were observed to relapse in the six months following the completion of therapy. Of the 21 immunocompromised patients studied, 17 were coinfected with HIV; approximately half of the HIV infected patients had AIDS. The following table presents a comparison of efficacy rates among immunocompetent and immunocompromised patients infected in the Mediterranean basin who had no prior treatment or remote prior treatment for visceral leishmaniasis. Efficacy is expressed as both acute parasite clearance at the end of therapy (EOT) and as overall success (clearance with no relapse) during the follow-up period (F/U) of $\geq$ 6 months for immunocompetent and immunocompromised patients:

AMBISOME EFFICACY IN VISCERAL LEISHMANIASIS
IMMUNOCOMPETENT PATIENTS

NO. PTS	PARASITE (%) CLEARANCE AT EOT	OVERALL SUCCESS (%) AT F/U
87	86/87 (98.9)	83/86 (96.5)

IMMUNOCOMPROMISED PATIENTS

REGIMEN	TOTAL DOSE	PARASITE CLEARANCE AT EOT(%)	OVERALL SUCCESS AT F/U (%)
100 mg/day x 21 days	29.0-38.9 mg/kg	10/10 (100)	2/10 (20.0)
4 mg/kg/day, days 1-5, and days 10, 17, 24, 31, 38	40 mg/kg	8/9 (88.9)	0/7 (0.0)
TOTAL		18/19 (94.7)	2/17 (11.8)

When followed for 6 months or more after treatment, the overall success rate among immunocompetent patients was 96.5% and the overall success rate among immunocompromised patients was 11.8%. While case reports have suggested there may be a role for long-term therapy to prevent relapses in HIV coinfected patients (Lopez-Dupla, et al. J Antimicrob Chemother 1993 Oct; 32 (4):657-9), there are no data to date documenting the efficacy or safety of

repeat courses of AmBisome or of maintenance therapy with this drug among immunocompromised patients.

The **DOSAGE AND ADMINISTRATION** section:

AmBisome should be administered using the following dosage schedules for each indication:

Visceral Leishmaniasis (immunocompetent patients):	3.0 mg/kg/day (for 5 days), then 3.0 mg/kg/day days 14, 21

For immunocompetent patients who do not achieve parasite clearance with the recommended dose, repeat therapy has been attempted. For such patients, expert advice regarding further treatment is recommended.

Visceral Leishmaniasis (immunocompromised patients)	Regimens of 100 mg/day x 21 days and 4 mg/kg/day for days 1-5, 10, 17, 24, 31, and 38 (total doses 30-40 mg/kg) have achieved high rates of initial parasite clearance among immunocompromised patients.

High rates of relapse have also been observed with the doses that achieve initial parasite clearance in immunocompromised patients. For patients who experience such relapses, expert advice regarding further treatment is recommended. For additional information, see CLINICAL TRIALS section.

/S/

Andrea Meyerhoff MD MSc DTMH
Medical Officer, DSPIDP

Concurrence Only:
HFD-590/DivDir/Goldberger /S/ 8/8/01
HFD-590/TmLdrMO/Hopkins

cc: Orig NDA 50-740
HFD-590
HFD-590/DepDir/Albrecht
HFD-590/MO/Meyerhoff
HFD-590/MO/Korvick
HFD-530/MO/Murray
HFD-590/Pharm/McMaster
HFD-590/Micro/Bala
HFD-590/Chem/Schmuff
HFD-590/Biopharm/Kumi
HFD-590/PM/Frank
HFD-590/PM/Fogarty

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050740

CHEMISTRY REVIEW(S)

Division of Special Pathogen and Immunologic Drug Products HFD–590
Review of Chemistry, Manufacturing and Controls

NDA #: 50-740

Chemistry Review#: 1 **Date Reviewed:** 8/8/97

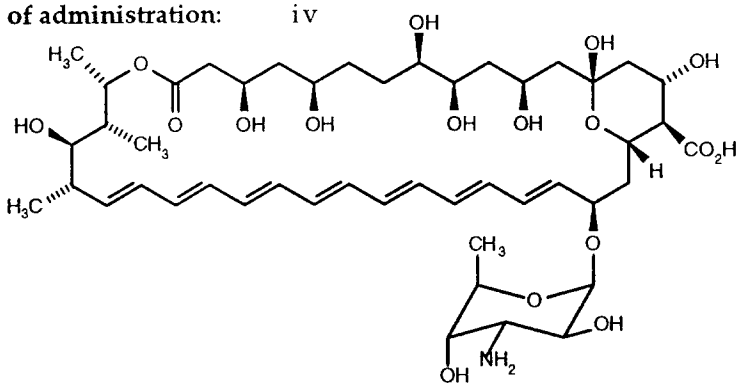
Submission Type	Document date	Date CDER recd	Date assigned
Original	11/8/96	11/12/96	11/15/96
	1/7/97	1/8/97	
	1/21/97	1/22/97	
	2/12/97	2/13/97	
	2/18/97	2/19/97	
	2/19/97	2/20/97	

Name & Address of Applicant: Fujisawa Pharmaceutical Company
Division of Fujisawa USA
Parkway North Center
3 Parkway North
Deerfield, IL 60015-2548

Drug Product Name(s):
Proprietary: AMBISOME
Non-proprietary: (amphotericin B) liposome for injection

Indication: Empirical therapy for presumed fungal infections in febrile neutropenic patients
Treatment of Aspergillus, Candida, Cryptococcus refractory to amphotericin B
Treatment of visceral leismaniasis

Dosage form/Strength: 50 mg lyophilized powder
Route of administration: iv



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

Mol. wgt.: 924.1

Chemical Name:
Amphotericin B

Conclusions/Recommendations
This NDA references NeXstar's for the drug product. This has been found to be acceptable.

/S/ 8/11/97

Copy to:
CChen HFD-830
EFrank HFD-890
MGoldberger HFD-890

APPEARS THIS WAY
ON ORIGINAL

Norman R. Schmuff, Ph.D.
Acting Team Leader, HFD-830

Concurrence:
CChen, Div Director, HFD-830 /S/ 8/11/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050740

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

Environmental Assessment and Finding of No Significant Impact for

NDA 50-740
AMBISOME® (amphotericin B)
liposomal for injection
50 mg

Center for Drug Evaluation and Research
Division of Special Pathogens and
Immunologic Drug Products
(HFD-590)

Finding of No Significant Impact for NDA 50-740 AMBISOME® (amphotericin B) liposomal for injection, 50 mg

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for AmBisome, Fujisawa USA has prepared an environmental assessment (attached) in accordance with 21 CFR § 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

AmBisome is a liposomal formulation of amphotericin B.
. The drug product is manufactured by NeXstar, San Dimas, CA
As a parenteral, the finished drug product will be used primarily in hospitals, clinics with some limited useage by patients in their homes.

Amphotericin B will be excreted into publicly owned treatment works (POTW). Amphotericin B may also enter POTWs due to manufacture of the drug substance and drug product. Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Rejected or returned drug product will be disposed of at by a licensed waste disposal contractor. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system while some unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

7/21/97 /S/

DATE PREPARED BY
Norman R. Schmuff, Ph.D.
Acting Chemistry Team Leader, HFD-830, DNDC III
Division of Special Pathogens and Immunologic Drug Products
HFD-590

7/21/97 /S/

DATE DIVISION CONCURRENCE
Chi-wan Chen, Ph.D.
Director, Division of New Drug Chemistry III

.....

7/25/97 /S/

DATE CONCURRED
Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Material Safety Data Sheet (drug substance)

APPEARS THIS WAY
ON ORIGINAL

FDA ADDENDUM

Clarification of information provided in the EA for 50-740:

Fujisawa USA, Inc is the applicant for NDA 50-740. NeXstar Pharmaceuticals, Inc. is the manufacturer of the drug product. In a separate communication to CDER, the applicant has certified that the information presented is true, accurate and complete to the best of the knowledge of Fujisawa USA, Inc.

Environmental Assessment

AmBisome®
(liposomal amphotericin B for injection)

FOI Copy

Submitted by:

Fujisawa USA, Inc.
Three Parkway North
Deerfield, IL 60015-2548

Applicant

Prepared by:

ICF Kaiser Engineers, Inc.
602 East Georgia Avenue
Ruston, LA 71270

For:

NeXstar Pharmaceuticals, Inc.
650 Cliffside Drive
San Dimas, CA 91773

Manufacturer

May 30, 1996

1. Date: May 30, 1996

2. Name of manufacturer 7/25/97 : NeXstar Pharmaceuticals, Inc.

3. Address: 650 Cliffside Drive
San Dimas, CA 91773

4. Description of Proposed Action

a. Requested Approval

Fujisawa USA Inc. has filed an NDA pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for AmBisome® (liposomal amphotericin B for injection). AmBisome is presented with an equivalent of 50 mg of amphotericin B, The New Drug Application number assigned by FDA is 50-740. This EA has been submitted pursuant to 21 CFR 25.31 (a).

7/25/97

b. Need for Action

AmBisome (liposomal amphotericin B for injection) is intended for the treatment of systemic fungal infection, visceral leishmaniasis, cryptococcal meningitis, candidiasis, aspergillosis This treatment is to be short-term, usually ranging from 7 to 21 days. The current patient population in the United States is small, less than 200,000 patients. The current patient population for most single indications is expected to remain small. Orphan Drug Applications have been filed for the indication of visceral leishmaniasis, cryptococcal meningitis The patient population for these indications is anticipated to remain Overall use of AmBisome is expected to eventually exceed this number in total.

c. Production Locations

The production and packaging facilities are NeXstar Pharmaceuticals, Inc. (650 Cliffside Drive, San Dimas, CA 91773) NeXstar Pharmaceuticals is located within the Walnut Creek Business Park, which is situated at the junction of the Foothill (I-210) Freeway and Covina Boulevard. The immediate area surrounding the site is a business park containing offices, businesses, and parking areas. To the south is a slope, which is undeveloped. Outside the business park, there are residential and non-residential areas, including restaurants and shopping areas. The population, income, and age distribution information based on the U.S. Census data for 1990, a 1995 update, and estimates for the year 2000 are given in Appendix A (CACI 1996a). The population within a 1-mile radius of the facility was 3,920 in 1995, and the forecasted population for the year 2000 is 4,055 (CACI 1996a). The 1995 population included 1,066 households and 732 families with a median age of 32.4. In a 2-mile radius of the facility the population in 1995 was 51,520 with a forecast for the year 2000 being 53,409. The 1995 population, within a 2-mile radius, included 16,360 households and 11,951 families with the median age being 31.2. At a distance of 10 miles from the plant the population in 1995 was 1,034,539 and is projected to be 1,087457 in the year 2000. According to the 1995 update of the U.S. Census data, there are 74,623 people 65 years of age or older and 87,391 children newborn to 4 years of age who live within a 10-mile radius of the plant. Children between the ages of 5 and 14 years make up the third largest group in this area with 157,820

people.

The facility is located within an industrial park. The surrounding topography consists mainly of flatlands. is located in the immediate vicinity. The population within a 1-mile radius of the facility was 2,971 in 1995, and the forecasted population for the year 2000 is 3,136 (CACI 1996b). The 1995 population included 1,061 households and 899 families with a median age of 35.1. In a 2-mile radius of the facility the population in 1995 was 26,959 with a forecast for the year 2000 being 28,941. The 1995 population, within a 2-mile radius, included 8,561 households and 6,764 families with the median age being 33. At a distance of 10 miles from the facility, the population in 1995 was 624,798 and is projected to be 679,494 in the year 2000. According to the 1995 update of the U.S. Census data, there are 55,476 people 65 years of age or older and 41,504 children newborn to 4 years of age who live within a 10-mile radius of the plant. Adults between the ages of 25 and 34 years make up the largest group in this area with 110,117 people.

Two of the intermediates in the production of AmBisome, AmBisome and AmBisome , are NeXstar proprietary materials. AmBisome AmBisome are manufactured by NeXstar Pharmaceuticals (650 Cliffside Dr., San Dimas, CA 91773). The active ingredient in AmBisome, amphotericin B, is manufactured by a independent manufacturing firm. Certification of the manufacturer's compliance with permits and environmental laws is provided in Appendix B.

and packaging operations are conducted at the As production increases, following FDA approval of the NDA, these operations will be conducted primarily at the NeXstar Pharmaceuticals site, with the site taking a back-up role.

d. Locations of Use

The product will be used nationwide only in hospitals and/or clinics. The product may eventually be used in the medically supervised home health care market, in addition to the hospital and clinic settings.

e. Disposal Sites

Process waste drug substance generated during the production of AmBisome will be disposed of via the sewer system, which connects to the Publicly Owned Treatment Works (POTW). Prior to disposal, the waste is monitored by for parameters described in Appendix C, to insure compliance with permits listed Appendix D. Potential air emissions from the production process are discussed in Section 6b.

Rejected, expired, or returned drug product will be disposed of by high temperature incineration at a facility licensed by EPA to destroy hazardous materials. The facility currently being used is This facility is licensed by EPA under RCRA permit number 90-3-TS-001 and EPA ID number CAD050806850 (permit is currently under renewal).

Hospitals, pharmacies, and clinics will dispose of empty or partially empty packages according to accepted procedures, although minimal quantities of unused drug may be disposed of in the sewer system.

5. Identification of Chemical Substances That are the Subject of the Proposed Action

The following chemicals are used in the production of AmBisome: amphotericin B.

Information regarding each of these chemical substances is provided in Appendix E, as required by the Center for Drug Evaluation and Research (CDER) for submission of an EA. Two other chemicals used as intermediates in the process are AmBisome AmBisome As previously mentioned, these are NeXstar proprietary materials, comprised of materials described in the list above.

6. Introduction of Substances into the Environment

a. Substances Expected to be Emitted

It is anticipated that low levels of solvent will be emitted into the environment through the air waste stream These emissions are not expected to have a significant environmental effect (Appendix F).

b. Controls Exercised

Liquid waste streams: Two liquid waste streams are generated at the NeXstar facility during the production of AmBisome. The first of these waste streams consists of rinsate generated during the steam cleaning of carbon filters, as discussed below (Air Waste Streams). This rinsate consists of 70 percent water, 30 percent solvent and is considered hazardous. The wastes generated per week are collected and disposed of as described below (Solid Waste Streams). The second of the waste streams consists of rinsate generated during the triple rinsing of all equipment following each production run. This rinsate consists of percent water and percent AmBisome. These process wastes, 20 to 50 gallons per week, are disposed of via the sewer system, which connects to the POTW. Prior to disposal, the waste is monitored by for parameters described in Appendix C, to insure compliance with permits listed in Appendix D.

Bulk, liquid AmBisome produced at the NeXstar facility is transported to the facility via sealed tanks for filling into vials, and packaging. The cleaning of equipment used during the packaging of AmBisome at the facility produces a rinsate waste stream which is disposed of via the sewer system, which connects to the POTW. Prior to disposal, the waste is monitored by for parameters described in Appendix C to ensure compliance with permits listed in Appendix D.

Air waste streams: The air waste streams are regulated through an air pollution control system, a intermediate production system, and a solvent recovery system at NeXstar's production facility. All solvent use during the manufacture of AmBisome is conducted under fume hoods which exhaust via an activated carbon filtration system. A pm detection limit for solvents is set for the carbon filter analytical systems. The process is only conducted if no solvent has been detected from the last process run. If the detection limit is reached during one production run, carbon filters are cleaned or replaced prior to the next run in order to insure that solvent emissions do not exceed the detection limit. Rinsate generated during the cleaning of the carbon filters is disposed of as described elsewhere (Liquid Waste Streams and Solid Waste Streams).

The air pollution control system consists of two carbon beds and an exhaust system containing a 1-

HP blower. The carbon beds are in a series and each contain pounds of carbon. Chemical analysis of the carbon beds is conducted by gas chromatography or a calibrated hand-held analyzer in the third run after a bed has been replaced. A chemical analysis is conducted in each run thereafter. If the carbon bed closest to the dryer is saturated, indicated by solvent vapors, then it is removed and replaced with the second carbon bed from behind. A new carbon bed is then installed in series with the second carbon bed. (Permit #D28504)

The intermediate production system contains an atomizer which consists of a intermediate production, a bag filter with a filter area of 26 square feet, and a carbon adsorber containing pounds of active carbon and a built-in cooler/condenser. Once the carbon bed is renewed, the vent gas is analyzed by or a hand-held analyzer in the third, fourth, and fifth drying runs and is regenerated after every fifth run or sooner if indicated. (Permit #D28505)

The solvent recovery system consists of a NIRO bag filter with a total filter area of square feet, a NIRO carbon adsorber containing pounds of activated carbon, and an exhaust system containing a 1-HP blower. Closed containers are used to retrieve dust discharged from the dust collectors and the filter bags are cleaned once a month. According to the the CTC number for activated carbon in the adsorber shall not be Once a year, the carbon in the adsorber is replaced unless a replacement is needed sooner. Vapor tight containers are used to store spent carbon and then disposed of in the appropriate manner. (Permit #D81597)

Minimal air emissions are generated during the packaging of AmBisome at the No air quality permit is required due to the small quantity of emissions.

Solid waste streams: Wastes generated during the cleaning and eventual disposal of carbon filters at the NeXstar facility are collected in 55 gallon drums, which are transported off-site and disposed of by . This facility is licensed by EPA under RCRA permit number 90-3-TS-001 and EPA ID number CAD050806850 (permit is currently under renewal).

No known solid waste streams are generated during the packaging of AmBisome at the facility.

c. Citation of and Statement of Compliance with Applicable Emission Requirements

Applicable Federal, State and Local Emission requirements are listed in Appendix G. NeXstar and Gensia are in compliance with all emissions requirements set forth in permits (Appendix D) applicable to the manufacturing operations. Materials Safety Data Sheets (MSDS) are provided in Appendix H.

A list of emission permits and/or licenses are provided in Appendix D along with the number, authorizing agency and expiration dates.

d. Discussion of the Effect of Approval on Compliance with Current Emission Requirements

Approval is not expected to affect compliance with current emission requirements since emissions controls were designed to handle maximum production capacity. Liquid wastes would be increased following increased production; however, the volume of this waste is not restricted by current permits. Air emissions of chloroform and methanol would remain constant since a 4 ppm

detection limit for each compound is set for the carbon filter analytical systems. These filters may need to be cleaned and/or replaced more often. This would increase the amount of solid waste transported off-site for disposal, but would not impact compliance.

As production increases, AmBisome will be manufactured and packaged in a new location, 502 Cliffside Drive, adjacent to the present NeXstar facility. Controls exercised at the new facility will be virtually identical to those at the present facility. Therefore, no effect on compliance with current emission requirements is expected. New permits will be required for the new facility.

e. Expected Introduction Concentrations

The total fifth year production is anticipated to be _____ kg.

I. Expected Introduction Concentration from Use

The expected introduction concentration (EIC) for AmBisome in the aquatic environment, assuming all drug product produced is used and deposited in the sewer system and no metabolism or depletion occurs. The EIC was calculated as follows:

$$\text{EIC Aquatic (ppm)} = \text{kg/yr} \times \frac{1}{\text{liters/day}} \times \frac{\text{year}}{365 \text{ days}} \times \frac{10^6}{\text{kg}}$$

Since the EIC from AmBisome use is ppb, the Tier 0 approach will be used; therefore items 7, 8, 9, 10, 11, and 15 are not provided. Since only minimal amounts of AmBisome used by hospitals and/or clinics may be disposed of through the sewer system, impacts on the terrestrial environment from the application of sludge from waste water treatment facilities to land will not be considered.

It is expected that normal air dispersion will decrease methanol concentrations to prior to reaching the site boundary.

ii. Expected Introduction Concentration from Disposal

An EIC for the disposal of AmBisome will not be calculated since AmBisome is not expected to be disposed of in the sewer system.

12. List of Preparers

Individuals involved in the preparation of this document for ICF Kaiser Engineers, Inc. were as follows:

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- 1967 A.B., Bacteriology/Chemistry minor, DouglassCollege, Rutgers University

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1994 B.S., Toxicology, Northeast Louisiana University

Additional Persons or Agencies Consulted Included:

Nancy B. Sager, Center for Drug Evaluation and Research, Rockville, MD

13. Certification

The undersigned official certifies that the information presented is true, accurate and complete to the best of the knowledge of ICF Kaiser Engineers, Inc.

/S/

Annette M. Shipp, Ph.D.
Vice President
ICF Kaiser Engineers, Inc.

5-30-96
Date

The undersigned official certifies that the AmBisome® (liposomal amphotericin B for injection) Environmental Assessment summary document and Appendices A-G contain non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR § 1506.6.

/S/

Stephen A. Campbell
Director, Regulatory Affairs
NeXstar Pharmaceuticals, Inc.

6/4/96
Date

14. References

Demographic and Income Forecast, Los Angeles County, CA.
La Jolla, CA. March 15, 1996.

APPEARS THIS WAY
ON ORIGINAL

LIST OF APPENDICES
APPENDICES NOT ATTACHED

Appendix A - Demographic and Income Surveys

Appendix B - Letter of Reference from amphotericin B manufacturer.

Appendix C - Monitoring Information Regarding Emissions From NeXstar Pharmaceuticals Production Facility and Gensia Packaging Facility

Appendix D - Emissions Permits

Appendix E - Chemical Substance Identification

Appendix F - Calculation of solvent Emissions

Appendix G - Federal, State, and Local Emissions Requirements

Appendix H - Material Safety Data Sheets

Material Safety Data Sheet
May be used to comply with OSHA's Hazard Communication Standard, 29 CFR 1910.1200. Standard must be consulted for specific requirements.

U.S. Department of Labor
Occupational Safety and Health Administration
(Non-Mandatory Form)
Form Approved
OMB No. 1218-0072

IDENTITY (As Used on Label and List)
AMPHOTERICIN B

Note: Blank spaces are not permitted. If any item is not applicable, or no information is available, the space must be marked to indicate that.

Section I

Manufacturer's Name

Emergency Telephone Number

Address (Number, Street, City, State, and ZIP Code)

Telephone Number for Information

Date Prepared
November 24, 1988

Signature of Preparer (optional)
Knud Andersen

Section II — Hazardous Ingredients/Identity Information

Hazardous Components (Specific Chemical Identity; Common Name(s))	OSHA PEL	ACGIH TLV	Other Limits Recommended	% (optional)
Amphotericin B				
CAS no. 1397-89-3				
Amphotericin B USP				

Section III — Physical/Chemical Characteristics

Boiling Point	NA	Specific Gravity (H_2O = 1)	NI
Vapor Pressure (mm Hg.)	NA	Melting Point	Decomposed above 170°C.
Vapor Density (AIR = 1)	NA	Evaporation Rate (Butyl Acetate = 1)	NA

Solubility in Water: Neutral insoluble, pH 2 and 11: About 0.1 mg/ml

Appearance and Odor: Yellow to orange powder, no specific odor.

Section IV — Fire and Explosion Hazard Data

Flash Point (Method Used)	NI	Flammable Limits	LEL NI	UEL NI

Extinguishing Media: Normal

Special Fire Fighting Procedures: No special fire hazard

Unusual Fire and Explosion Hazards: When heated to decomposition it emits toxic NO_x fumes. No special explosion hazard

(Reproduce locally)

5-8-86

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Stability			Conditions to Avoid
	Unstable	X	Heat - moisture - air exposure
	Stable		To be stored cold (below 8°C)

Incompatibility (Materials to Avoid): NI

Hazardous Decomposition or Byproducts: No reactivity hazard known

Hazardous Polymerization			Conditions to Avoid
	May Occur		
	Will Not Occur	X	

Section VI — Health Hazard Data

Route(s) of Entry: Inhalation? 1 Skin? 2 Ingestion? 3

Health Hazards (Acute and Chronic)

1. Irritation, coughing, breathlessness. May be absorbed through lungs
2. May provoke itching & rash, allergic reactions in sensitive persons
3. Little or no absorption. Large amount poison if swallowed. LD50 ora mi 8

Carcinogenicity: NI NTP? No IARC Monographs? No OSHA Regulated? No

Signs and Symptoms of Exposure

Coughing, breathlessness, itching, gastrointestinal disturbances, if large amounts absorbed, unconsciousn

Medical Conditions Generally Aggravated by Exposure

Reduced pulmonary function. Sensitivity to the drug itself.

Emergency and First Aid Procedures

Flush exposed areas with water, drink plenty of water, if unconscious: Artificial respiration.

Section VII — Precautions for Safe Handling and Use

Steps to Be Taken in Case Material Is Released or Spilled

Spilled product is swept up and collected in closable containers

Waste Disposal Method

Product is disposed of in accordance with governmental and local regulations.

Precautions to Be Taken in Handling and Storing

Avoid inhalation of dust and contact with skin and eyes. In case of contact, flush immediately with plenty of water.

Other Precautions

Must be stored in airtight containers under dry and cold conditions (below 8°C) protected from sun and UV-light.

Section VIII — Control Measures

Respiratory Protection (Specify Type)

An approved mask with particle filter (class P2)

Ventilation				
	Local Exhaust	YES	Special	NI
	Mechanical (General)	YES	Other	NI

Protective Gloves: Yes, no preference known.

Eye Protection: Safety goggles or face shield

Other Protective Clothing or Equipment

Provide easy access to plenty of water and eye washing.

Work/Hygienic Practices

Avoid spreading dust of the product.