

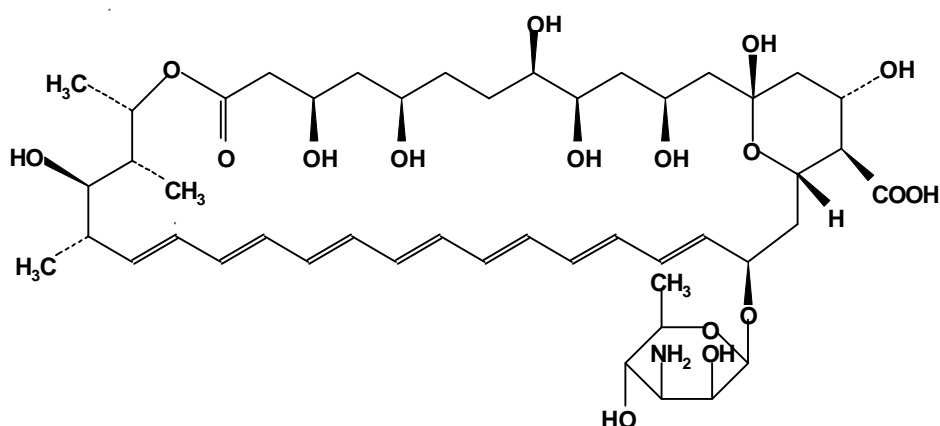
PRODUCT INFORMATION

Abelcet® (Amphotericin Lipid Complex)

NAME OF THE MEDICINE

The chemical structure of amphotericin B is as follows:

CAS Number: 1397-89-3



DESCRIPTION

ABELCET® is a sterile, pyrogen-free suspension in isotonic saline. It consists of amphotericin, of which amphotericin B is the major component, in a complex with phospholipids. Amphotericin is a macrocyclic, polyene, broad-spectrum antifungal antibiotic produced by *Streptomyces nodosus*. The lipophilic moiety of amphotericin B allows molecules of the drug to be complexed in a ribbon-like structure with the phospholipids.

ABELCET is supplied as a 20 mL suspension in a vial. Each vial contains the equivalent of 100 mg of amphotericin B. Before infusion, the suspension must be filtered using the filter needle provided (to remove any large particles present) and then diluted with 5.0% glucose injection, according to the Section below titled, *Preparation of the Suspension for Infusion*. Each mL of ABELCET suspension contains:

Amphotericin equivalent to amphotericin B	5.0 mg
Dimyristoylphosphatidylcholine	3.4 mg
Dimyristoylphosphatidylglycerol (as the sodium and ammonium salts)	1.5 mg
Sodium Chloride	9.0 mg
Water for Injections, sufficient to make	1.0 mL

PHARMACOLOGY

Pharmacokinetics

Amphotericin B is complexed to phospholipids in ABELCET. The pharmacokinetic properties of ABELCET and conventional amphotericin B are different. Amphotericin B when administered as ABELCET is rapidly distributed to tissues. Limited human autopsy data showed that, after administration of ABELCET, amphotericin B levels in tissue were highest in the liver, spleen and lung. Peak blood levels of amphotericin B were lower after administration of ABELCET than after administration of equivalent amounts of conventional drug.

Available data on the pharmacokinetics of amphotericin B in whole blood after the administration of ABELCET in humans, support an initial rapid fall in the concentration of amphotericin B from the blood followed by a long terminal decline in concentration. However, the physicochemical character of circulating amphotericin B and the pharmacological significance of the level of the drug in blood is not known.

The assay used to measure amphotericin B in the blood after the administration of ABELCET does not distinguish amphotericin B that is complexed with the phospholipids of ABELCET from amphotericin B that is uncomplexed.

The pharmacokinetics of amphotericin B after the administration of ABELCET are nonlinear. Volume of distribution and clearance from blood increase with increasing dose of ABELCET, resulting in less than proportional increases in blood concentrations of amphotericin B over a dose range of 0.6 to 5 mg/kg/day. The pharmacokinetics of amphotericin B in whole blood after the administration of ABELCET and amphotericin B desoxycholate are:

Pharmacokinetic Parameters of Amphotericin B in Whole Blood in Patients Administered Multiple Doses of ABELCET or Amphotericin B Desoxycholate		
Pharmacokinetic Parameter	ABELCET 5 mg/kg/day for 5-7 days Mean ± SD	Amphotericin B 0.6 mg/kg/day for 42 days^a Mean ± SD
Peak Concentration (µg/mL)	1.7 ± 0.8 (n=10) ^b	1.1 ± 0.2 (n=5)
Concentration at End of Dosing Interval (µg/mL)	0.6 ± 0.3 (n=10) ^b	0.4 ± 0.2 (n=5)
Area Under Blood Concentration-Time Curve (AUC _{0-24h}) (µg*h/mL)	14 ± 7 (n=14) ^{b,c}	17.1 ± 5 (n=5)
Clearance (mL/h*kg)	436 ± 188.5 (n=14) ^{b,c}	38 ± 15 (n=5)
Apparent Volume of Distribution (Vd _{area}) (L/kg)	131 ± 57.7 (n=8) ^c	5 ± 2.8 (n=5)
Terminal Elimination Half-Life (h)	173.4 ± 78 (n=8) ^c	91.1 ± 40.9 (n=5)
Amount Excreted in Urine Over 24 h After Last Dose (% of dose) ^d	0.9 ± 0.4 (n=8) ^c	9.6 ± 2.5 (n=8)

^a Data from patients with mucocutaneous leishmaniasis. Infusion rate was 0.25 mg/kg/h.

^b Data from studies in patients with cytologically proven cancer being treated with chemotherapy or neutropenic patients with presumed or proven fungal infection. Infusion rate was 2.5 mg/kg/h.

^c Data from patients with mucocutaneous leishmaniasis. Infusion rate was 4 mg/kg/h.

^d Percentage of dose excreted in 24 hours after last dose.

The large volume of distribution and high clearance value from the blood of amphotericin B after the administration of ABELCET probably reflect uptake by tissues. The long terminal elimination half-life probably reflects a slow redistribution from tissues. Although amphotericin B is excreted slowly, there is little accumulation in the blood after repeated dosing.

Tissue concentrations of amphotericin B have been obtained at autopsy from one heart transplant patient who received ABELCET at a dose of 5.3 mg/kg/day for three consecutive days immediately before death. The concentrations of amphotericin B ($\mu\text{g/g}$) reported were: 290, spleen; 222, lung; 196, liver; 7.6, lymph node; 6.9, kidney; 5, heart; 1.6, brain. The relationship of tissue concentrations of amphotericin B to its biological activity when administered as ABELCET is unknown.

Microbiological Activity

Amphotericin B, the active antifungal agent in ABELCET, 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 ergosterols than for the cholesterol of human cells.

Amphotericin B is active against many fungal pathogens in vitro, including *Candida* sp., *Cryptococcus neoformans*, *Aspergillus* sp., *Mucor* sp., *Sporothrix schenckii*, *Blastomyces dermatitidis*, *Coccidioides immitis* and *Histoplasma capsulatum*. Most strains are inhibited by amphotericin B concentrations of 0.03 to 1.0 $\mu\text{g/mL}$.

Amphotericin B has little or no activity against bacteria or viruses. ABELCET shows in vitro activity against *Aspergillus* sp. (n=3) and *Candida* sp. (n=10), with MICs generally $<1 \mu\text{g/mL}$. Depending upon the species and strain of *Aspergillus* and *Candida* tested, significant in vitro differences in susceptibility to amphotericin B have been reported (MICs ranging from 0.1 to $>10 \mu\text{g/mL}$). However, standardised techniques for susceptibility testing for antifungal agents have not been established, and results of susceptibility studies do not necessarily correlate with clinical outcome.

CLINICAL TRIALS

Two randomised comparative studies were conducted in systemic *Candida* and in cryptococcal meningitis. In addition, a comparison was made of open-label treatment of patients with aspergillosis with a retrospectively acquired control group. In the randomised comparative study in patients with invasive candidiasis (153 on 5 mg/kg/day of ABELCET vs 78 on 0.6 to 1.0 mg/kg/day of amphotericin B), the overall response rate was 63% for ABELCET vs 68% for amphotericin B. In the randomised comparative study in patients with cryptococcal meningitis (21 on 5 mg/kg/day of ABELCET vs 17 on 0.7 mg/kg/day of amphotericin B), the overall response rate (clinical and mycological success) was 43% for ABELCET vs 47% for amphotericin B.

A comparison was made of a group of patients with aspergillosis treated with ABELCET with a retrospectively acquired control group of patients treated with amphotericin B. Patients in the ABELCET-treated group were given the product for a variety of reasons which included failure of amphotericin B or another systemic antifungal therapy, nephrotoxicity due to amphotericin B or another drug, renal disease or acute amphotericin B toxicity. There were several differences in the characteristics of the two groups that may have influenced the comparison. Overall clinical response rate (complete and partial response) was 40% for ABELCET vs 20% for amphotericin B.

Information to support efficacy in other fungal infections, including fusariosis, coccidioidomycosis, zygomycosis and blastomycosis, is limited.

INDICATIONS

ABELCET is indicated for the treatment of invasive fungal disease caused by organisms susceptible to amphotericin B (see Clinical Trials).

CONTRAINDICATIONS

ABELCET is contraindicated in patients with known hypersensitivity to any of its constituents unless, in the opinion of the physician, the advantages of using ABELCET outweigh the risk of hypersensitivity.

PRECAUTIONS

Adverse reactions similar to those associated with conventional amphotericin B may occur with ABELCET. Patients should be monitored for any type of adverse reaction associated with conventional amphotericin B. Particular attention should be paid to patients receiving nephrotoxic drugs concomitantly with ABELCET. Renal function should be monitored closely in these patients.

Anaphylactoid reactions and asthma have been reported in patients given ABELCET. Facilities for cardiopulmonary resuscitation should be readily at hand when ABELCET is being administered. *If severe respiratory distress and/or anaphylaxis occur with the infusion of ABELCET, the infusion should be immediately discontinued. The patient should not receive further infusions of ABELCET.*

The recommended daily dose of ABELCET is 5.0 mg/kg. Use of other doses has not been supported by adequate information.

Use in Patients with Renal Impairment

Although ABELCET is generally less nephrotoxic than conventional amphotericin B, it should be remembered that ABELCET may on occasion be associated with worsening of renal function. In patients with serious systemic fungal infections and contraindications to conventional amphotericin B who were treated with ABELCET renal function remained stable in 50.5% of patients, improved in 21.8% and declined in 24.4% after 6 weeks of treatment. In the subpopulation of cases with baseline serum creatinine levels greater than 221 µmol/L, the mean serum creatinine decreased from 339 µmol/L at the start of treatment to 229 µmol/L after 6 weeks of treatment. Renal dysfunction that developed during treatment with conventional amphotericin B has been shown to stabilise or improve frequently during subsequent ABELCET treatment.

Use in Renal Dialysis Patients

ABELCET should be administered to renal dialysis patients only after the completion of dialysis. Serum potassium and magnesium levels should be monitored regularly. ABELCET may be given to patients with renal failure at the recommended adult dose.

Use in Fertility

There was no effect on fertility in rats dosed with ABELCET at up to 10 mg/kg/day amphotericin B (0.32 times the recommended human dose, based on body surface area).

Use in Pregnancy (Category B3)

Conventional amphotericin B has been used successfully to treat systemic fungal infections in pregnant women with no obvious effect on the foetus, but only a small number of cases have been reported. Reproductive studies of ABELCET in rats showed no evidence of embryotoxicity, foetotoxicity or teratogenicity at plasma drug exposures similar to those expected therapeutically. However, in rabbits, a dose-ranging teratogenicity study, but not the subsequent full study, indicated that ABELCET may have embryotoxic and foetotoxic effects at estimated plasma exposures (based on C_{max}) below those expected in patients. As uncertainty remains as to whether or not ABELCET can affect the developing embryo/foetus, the drug should be administered to pregnant women only for life-threatening disease when the likely benefit exceeds the risk to mother and foetus.

Use in Lactation

It is not known whether ABELCET is excreted in human milk, and there have been no relevant studies in animals. As many drugs are excreted in human milk and can be harmful to the baby, treatment of lactating women with ABELCET is not recommended.

Paediatric Use

Systemic fungal infections in children have been treated successfully with ABELCET. The dose to be given should be calculated using the same dose per kg of weight as is used to calculate the recommended adult dose.

Use in the Elderly

Systemic fungal infections in elderly patients have been treated successfully with ABELCET. The dose to be given should be calculated using the same dose per kg of weight as is used to calculate the recommended dose.

Carcinogenesis

There have been no animal studies conducted to assess the carcinogenic potential of ABELCET.

Genotoxicity

Gene mutation assays in *Salmonella typhimurium* and in mouse lymphoma cells *in vitro* were negative. There was no increase in the incidence of chromosomal aberrations in Chinese hamster ovary cells *in vitro* or in an *in vivo* micronucleus test in mice.

Interactions with Other Drugs

The interaction of ABELCET with other drugs has not been studied to date. Patients requiring concomitant medications should be closely observed. Specifically, in patients receiving nephrotoxic drugs, renal function should be closely monitored. Conventional amphotericin B has been reported to interact with antineoplastic agents, corticosteroids and corticotrophin (ACTH), digitalis glycosides and skeletal muscle relaxants.

In dogs, exacerbated myelotoxicity and nephrotoxicity were observed when ABELCET (1.5 or 5.0 mg/kg/day) was administered concomitantly with zidovudine for 30 days. If concomitant treatment with both agents is required, renal and haematologic function should be closely monitored.

Preliminary data suggest that patients receiving ABELCET concomitantly with high dose cyclosporin experience an increase in serum creatinine. The data also indicate that the increase in serum creatinine is caused by cyclosporin and not ABELCET. Until further

information is available, renal function should be monitored closely in patients who receive concomitant treatment with both drugs.

ADVERSE EFFECTS

Clinical Trial Data

The most common clinical adverse reactions have been chills and fever. Premedication (e.g. paracetamol) may be administered for the prevention of infusion related adverse reactions.

Adverse experiences reported among patients with invasive candidiasis treated with ABELCET (n=153) or amphotericin B (n=78) in a comparative clinical trial are shown in the table below. Included are all adverse events occurring with an incidence rate of greater than or equal to 5%.

Study AI800-017 Invasive Candidiasis Adverse Events (Regardless of Causality) Grouped by Body System with Incidence \geq 5%				
	ABELCET 5.0 mg/kg/day		Amphotericin B 0.6 mg/kg/day	
	Incidence \geq5%			
Body System/Adverse Events	n	(%)	n	(%)
No. of Patients Treated	153	(%)	78	(%)
No. of Patients Who Reported AEs	149		78	
Body as a Whole	116	(76)	57	(73)
Sepsis	38	(25)	14	(18)
Infection	32	(21)	19	(24)
Fever	30	(20)	13	(17)
Chills	19	(12)	3	(4)
Abdominal Pain	18	(12)	15	(19)
Pain	15	(10)	9	(12)
Generalised Oedema	12	(8)	9	(12)
Chest Pain	12	(8)	6	(8)
Headache	9	(6)	8	(10)
Injection Site Reaction	9	(6)	5	(6)
Asthenia	8	(5)	5	(6)
Injection Site Hypersensitivity	2	(1)	6	(8)
Cardiovascular System	99	(65)	42	(54)
Hypotension	49	(32)	15	(19)
Tachycardia	25	(16)	6	(8)
Heart Arrest	15	(10)	13	(17)
Hypertension	13	(8)	8	(10)
Heart Failure	12	(8)	6	(8)
Atrial Fibrillation	10	(7)	4	(5)
Phlebitis	7	(5)	2	(3)
Supraventricular Tachycardia	7	(5)	2	(3)
Electrocardiogram Abnormal	5	(3)	8	(10)

Study AI800-017				
Invasive Candidiasis				
Adverse Events (Regardless of Causality) Grouped by Body System				
with Incidence \geq 5%				
	ABELCET		Amphotericin B	
	5.0 mg/kg/day		0.6 mg/kg/day	
	Incidence \geq 5%			
Body System/Adverse Events	n	(%)	n	(%)
No. of Patients Treated	153	(%)	78	(%)
No. of Patients Who Reported AEs	149		78	
Digestive System	92	(60)	50	(64)
Diarrhoea	26	(17)	12	(15)
Nausea	24	(16)	11	(14)
Vomiting	20	(13)	8	(10)
Nausea and Vomiting	8	(5)	7	(9)
Gastrointestinal Haemorrhage	10	(7)	3	(4)
Constipation	9	(6)	8	(10)
Anorexia	8	(5)	0	
Liver Function Tests Abnormal	7	(5)	5	(6)
Haemic and Lymphatic System	57	(37)	40	(51)
Anaemia	26	(17)	14	(18)
Leukocytosis	15	(10)	12	(15)
Thrombocytopenia	12	(8)	5	(6)
Blood Dyscrasia	6	(4)	1	(1)
Thromboplastin Decreased	6	(4)	5	(6)
Leukopenia	5	(3)	7	(9)
Cyanosis	1	(1)	5	(6)
Metabolic and Nutritional Disorders	110	(72)	65	(83)
Creatinine Increased	51	(33)	35	(45)
Hypokalaemia	41	(27)	15	(19)
Urea Increased	29	(19)	20	(26)
Alkaline Phosphatase Increased	25	(16)	16	(21)
Hypomagnesaemia	18	(12)	8	(10)
Acidosis	15	(10)	6	(8)
Peripheral Oedema	15	(10)	9	(12)
Bilirubinaemia	14	(9)	7	(9)
Hyperkalaemia	12	(8)	6	(8)
Hypoxia	11	(7)	1	(1)
Hyperglycaemia	9	(6)	5	(6)
Hypernatraemia	9	(6)	5	(6)
Hyperphosphataemia	8	(5)	6	(8)
Hyponatraemia	8	(5)	5	(6)
Hyperchloraemia	6	(4)	5	(6)
SGPT Increased	5	(3)	5	(6)
Hypoglycaemia	2	(1)	7	(9)

Study AI800-017 Invasive Candidiasis Adverse Events (Regardless of Causality) Grouped by Body System with Incidence \geq 5%				
	ABELCET 5.0 mg/kg/day		Amphotericin B 0.6 mg/kg/day	
	Incidence \geq5%			
Body System/Adverse Events	n	(%)	n	(%)
No. of Patients Treated	153		78	
No. of Patients Who Reported AEs	149		78	
Nervous System	67	(44)	22	(28)
Confusion	16	(10)	4	(5)
Insomnia	12	(8)	5	(6)
Somnolence	12	(8)	5	(6)
Anxiety	11	(7)	3	(4)
Agitation	7	(5)	3	(4)
Respiratory System	99	(65)	56	(72)
Dyspnoea	37	(24)	26	(33)
Plural Effusion	24	(16)	5	(6)
Lung Disorder	22	(14)	14	(18)
Respiratory Disorder	19	(12)	9	(12)
Pneumonia	15	(10)	7	(9)
Hyperventilation	13	(8)	9	(12)
Asthma	11	(7)	3	(4)
Lung Oedema	10	(7)	3	(4)
Haemoptysis	9	(6)	1	(1)
Respiratory Failure	9	(6)	9	(12)
Cough Increased	8	(5)	1	(1)
Pharyngitis	7	(5)	2	(3)
Apnoea	1	(1)	6	(8)
Skin & Appendages	41	(27)	25	(32)
Rash	12	(8)	13	(17)
Pruritus	7	(5)	2	(3)
Skin Ulcer	5	(3)	5	(6)
Urogenital System	72	(47)	40	(51)
Haematuria	29	(19)	16	(21)
Urinary Tract Infection	16	(10)	9	(12)
Pyuria	15	(10)	8	(10)
Oliguria	11	(7)	5	(6)
Kidney Function Abnormal	9	(6)	5	(6)
Kidney Failure	7	(5)	6	(8)
Urinary Tract Disorder	1	(1)	4	(5)

Post-marketing Data

The following additional events were observed during post-marketing monitoring:

Body as a Whole	
Very Rare:	Anaphylaxis
	Vasodilation
Cardiovascular System	
$\geq 1/100$ and $< 1/10$:	Hypotension
$\geq 1/1000$ and $< 1/100$:	Shock
Very Rare:	Arrhythmia
	Asystole
	Bradycardia
	Haemorrhage
Digestive System	
$\geq 1/100$ and $< 1/10$:	Abdominal pain
	Nausea
	Vomiting
Very Rare:	Gastrointestinal Haemorrhage
	Liver Function Abnormal
	Peritonitis
Haemic and Lymphatic System	
Very Rare:	Pancytopenia
Metabolic System and Nutritional Disorders	
$\geq 1/100$ and $< 1/10$:	Electrolyte imbalance including blood potassium increased, blood magnesium decreased
Very Rare:	Hypoglycaemia
	Hyperammonaemia
Musculoskeletal System	
Very Rare	Myoclonus
$\geq 1/1000$ and $< 1/100$:	Myalgia
Nervous System	
Rare:	Neuropathy
Very Rare:	Agitation
	Confusion
	Convulsion
	Encephalopathy
	Stupor
Respiratory System	
$\geq 1/1000$ and $< 1/100$:	Respiratory failure
Rare:	Asthma
Very Rare:	Hypoxia
Not Known:	Bronchospasm
Skin and subcutaneous tissue disorders	
$\geq 1/100$ and $< 1/10$:	Rash
$\geq 1/1000$ and $< 1/100$:	Pruritus
Not Known:	Dermatitis exfoliative
Urogenital System	
Very Rare:	Anuria
	Incontinence
Not Known:	Hyposthenuria
	Renal Tubular acidosis

Infusion hypersensitivity reactions have been associated with abdominal pain, nausea, vomiting, myalgia, pruritus, maculopapular rash, fever, hypotension, shock, bronchospasm, respiratory failure.

Renal tubular acidosis has been reported including hyposthenuria and electrolyte imbalance such as increased potassium and decreased magnesium.

DOSAGE AND ADMINISTRATION

Dosage

The recommended daily dose is 5.0 mg/kg given as a single infusion. An initial test dose of 1.0 mg should be infused intravenously over 15 minutes. Facilities for resuscitation should be readily at hand. ABELCET should be administered by intravenous infusion at a rate of 2.5 mg/kg/h. An in-line filter may be used for intravenous infusion of ABELCET. The mean pore diameter of the filter should not be less than 5.0 microns. For severe systemic infections, treatment duration is typically at least 14 days. ABELCET has been administered for as long as 11 months, and cumulative doses have been as high as 56.6 g without significant toxicity.

Preparation of the Suspension for Infusion

Allow the suspension to come to room temperature. Shake gently until there is no evidence of any yellow sediment at the bottom of the vial. Withdraw the appropriate dose of ABELCET from the required number of vials into a sterile syringe using a 17 to 19 gauge needle. Remove the needle from the syringe filled with ABELCET and replace with the 5 micron high flow filter needle provided with each vial.

Insert the filter needle of the syringe into an IV bag containing 5.0% glucose injection and empty the contents of the syringe into the bag. The final concentration should be 1 mg/mL. Do not use the agent after dilution with 5.0% glucose injection if there is any evidence of foreign material. Vials are for single use in one patient on one occasion only. Unused material should be discarded. Aseptic technique must be strictly observed throughout handling of ABELCET since no bacteriostatic agent or preservative is present. The infusion is best administered by means of an infusion pump.

DO NOT DILUTE WITH SALINE SOLUTIONS OR MIX WITH OTHER DRUGS OR ELECTROLYTES. The compatibility of ABELCET with these materials has not been established. An existing intravenous line should be flushed with 5.0% glucose injection before infusion of ABELCET, or a separate infusion line should be used.

To reduce microbiological hazard, use as soon as practicable after preparation. If storage is necessary, hold at 2°C to 8°C for not more than 24 hours. Following storage in IV bags, the ready for use ABELCET suspension must be vigorously agitated prior to use.

OVERDOSAGE

No instance of overdose with ABELCET has been reported. One paediatric patient received a single dose of 13.1 mg/kg on one occasion, without adverse effects. Should an overdose occur, the patient should be treated as deemed appropriate by the physician.

For advice on the management of overdosage, please contact the Poisons Information Centre (telephone 13 11 26).

PRESENTATION

Amphotericin equivalent to amphotericin B 100 mg/20 mL; yellow, opaque suspension for infusion; 20 mL vials with filter needles are individually packaged.

STORAGE CONDITIONS

Store at 2°C to 8°C (Refrigerate. Do not freeze). Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Orphan Australia Pty. Ltd.
300 Frankston-Dandenong Road
Dandenong
VIC 3175
Australia
www.orphan.com.au

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF APPROVAL

Approved by the Therapeutic Goods Administration on 20 April 2004
Date of most recent safety-related notification: 25 May 2010

Manufacture by Sigma-Tau PharmaSource Inc., Indianapolis, IN, USA

AUST R 65406