BREVIBLOC® INJECTION

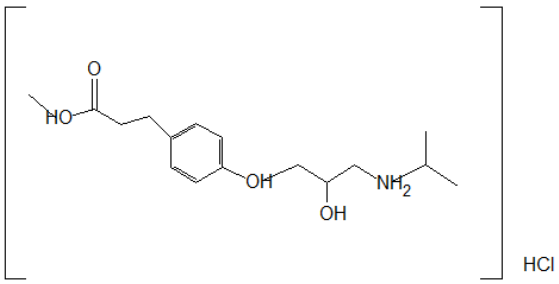
NAME OF THE MEDICINE

Esmolol hydrochloride

Esmolol HCl ± methyl 3-[4-[2-hydroxy-3-(isopropylamino) propoxy] phenyl] propionate hydrochloride.

Esmolol HCl has the empirical formula $C_{16}H_{25}NO_4$.HCl and a molecular weight of 331.8. The CAS registry number is 81161-17-3. It has one asymmetric centre and exists as a racemic mixture.

Structural Formula:



DESCRIPTION

Brevibloc (esmolol HCl) is a beta$_1$-selective (cardioselective) adrenergic receptor blocking agent with a very short duration of action (elimination half-life is approximately 9 minutes).
Esmolol HCl is a white to off-white crystalline powder. It is a relatively hydrophilic compound which is very soluble in water and freely soluble in alcohol. Its partition coefficient (octanol/water) at pH 7.0 is 0.42 compared to 17.0 for propranolol.
Brevibloc (esmolol HCl) Injection is a clear, colourless to light yellow, sterile, nonpyrogenic solution for intravenous infusion. The single dose vial has a pH range of 4.5 to 5.5.
Excipients in the 10mL vial are sodium acetate trihydrate, acetic acid, sodium hydroxide, hydrochloric acid and Water for Injection.

PHARMACOLOGY

Brevibloc (esmolol HCl) is a beta$_1$-selective (cardioselective) adrenergic blocking agent with rapid onset and a short duration of action.

Pharmacokinetics

Brevibloc (esmolol HCl) is rapidly metabolised by hydrolysis of the ester linkage, chiefly by the esterases in the cytosol of red blood cells and not by plasma cholinesterases or red cell membrane acetylcholinesterase. Total body clearance in man was found to be about 20 L/kg/hr, which is greater than cardiac output; thus the metabolism of Brevibloc is not limited by the rate of blood flow to metabolising tissues such as the liver or affected by hepatic or renal blood flow. Brevibloc has a rapid distribution half-life of about 2 minutes and an elimination half-life of about 9 minutes. Using an appropriate loading dose, steady-state blood levels of Brevibloc for dosages from 50 - 300 microgram/kg/min (0.05-0.3 mg/kg/min) are obtained within five minutes. (Steady-state is reached in about 30 minutes without the loading dose). Steady-state blood levels of Brevibloc increase linearly over this dosage range and elimination kinetics are dose-independent over this range. Steady-state blood levels are maintained during infusion but decrease rapidly after termination of the infusion. Because of its short half-life, blood levels of Brevibloc can be rapidly altered by increasing or decreasing the infusion rate and rapidly eliminated by discontinuing the infusion.
Consistent with the high rate of blood-based metabolism of Brevibloc, less than 2% of the drug is excreted unchanged in the urine. Within 24 hours of the end of infusion, approximately 73-88% of the dosage has been accounted for in the urine as the acid metabolite of Brevibloc.
Metabolism of Brevibloc results in the formation of the corresponding free acid and methanol. The acid metabolite has been shown in animals to have about 1/1500th the activity of esmolol and in normal volunteers its blood levels do not correspond to the level of beta-blockade. The acid metabolite has an elimination half-life of about 3.7 hours and is excreted in the urine with a clearance approximately equivalent to the glomerular filtration rate. Excretion of the acid metabolite is significantly decreased in patients with renal disease, with the elimination half-life increased to about ten-fold that of normal's and plasma levels considerably elevated. Methanol blood levels, monitored in subjects receiving Brevibloc for up to 6 hours at 300 microgram/kg/min (0.3 mg/kg/min) and 24 hours at 150 microgram/kg/min (0.15 mg/kg/min), approximated endogenous levels and were less than 2% of levels usually associated with methanol toxicity.
Brevibloc has been shown to be 55% bound to human plasma protein, while the acid metabolite is only 10% bound.

Pharmacodynamics

Clinical pharmacology studies in normal volunteers have confirmed the beta blocking activity of Brevibloc (esmolol HCl), showing reduction in heart rate at rest and during exercise and attenuation of isoprenaline-induced increases in heart rate. Blood levels of Brevibloc have been shown to correlate with extent of beta blockade. After termination of infusion, substantial recovery from beta blockade is observed in 10-20 minutes.
In human electro-physiology studies, Brevibloc produced effects typical of a beta blocker: a decrease in the heart rate, increase in sinus cycle length, prolongation of the sinus node recovery time, prolongation of the AH interval during normal sinus rhythm and during atrial pacing and an increase in antegrade Wenckebach cycle length.
In patients undergoing radionuclide angiography, Brevibloc, at dosages of 200 microgram/kg/min (0.2 mg/kg/min), produced reductions in heart rate, systolic blood pressure, rate pressure product, left and right ventricular ejection fraction and cardiac index at rest, which were similar in magnitude to those produced by intravenous propranolol (4 mg). During exercise, Brevibloc produced reductions in heart rate, rate pressure product and cardiac index which were also similar to those produced by propranolol, but produced a significantly larger fall in systolic blood pressure. In patients undergoing cardiac catheterisation, the maximum therapeutic dose of 300 microgram/kg/min (0.3 mg/kg/min) of Brevibloc produced similar effects, and, in addition, there were small, clinically insignificant increases in the left ventricular end diastolic pressure and pulmonary capillary wedge pressure. At thirty minutes after the discontinuation of Brevibloc infusion, all the haemodynamic parameters had returned to pretreatment levels.
The relative cardioselectivity of Brevibloc was demonstrated in 10 mildly asthmatic patients. Infusions of Brevibloc [100, 200 and 300 microgram/kg/min (0.1, 0.2 and 0.3 mg/kg/min)] produced no significant increases in specific airway resistance compared to placebo. At 300 microgram/kg/min (0.3 mg/kg/min), Brevibloc produced slightly enhanced bronchomotor sensitivity to dry air stimulus. These effects were not clinically significant and Brevibloc was well tolerated by all patients. Six of the patients also received intravenous propranolol and at a dosage of 1 mg, two experienced significant, symptomatic bronchospasm requiring bronchodilator treatment.
One other propranolol-treated patient also experienced dry air-induced bronchospasm. No adverse pulmonary effects were observed in patients with chronic obstructive pulmonary disease who received therapeutic dosages of Brevibloc for treatment of supraventricular tachycardia (51 patients) or in perioperative settings (32 patients).

Mechanism of Action

Brevibloc (esmolol HCl) is a $beta_1$-selective (cardioselective) adrenergic receptor blocking agent with rapid onset, a very short duration of action and no significant intrinsic sympathomimetic or membrane stabilising activity at therapeutic dosages. Its elimination half-life after intravenous infusion is approximately 9 minutes. Brevibloc inhibits the $beta_1$ receptors located chiefly in cardiac muscle, but this preferential effect is not absolute and at higher doses it begins to inhibit $beta_2$ receptors located chiefly in the bronchial and vascular musculature.

INDICATIONS

Supraventricular Tachycardia - Brevibloc (esmolol HCl) is indicated for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other emergent circumstances where short term control of ventricular rate with a short-acting agent is desirable. Brevibloc is also indicated in non compensatory sinus tachycardia where, in the physician's judgement, the rapid heart rate requires specific intervention. Brevibloc is not intended for use in chronic settings where transfer to another agent is anticipated or for treatment periods greater than 24 hours duration.

CONTRAINDICATIONS

Brevibloc (esmolol HCl) is contraindicated in patients with sinus bradycardia, heart block greater than first degree, cardiogenic shock or overt heart failure (See **Precautions**). Brevibloc is contraindicated in patients who require inotropic agents and/or vasopressors to maintain systemic blood pressure and cardiac output. The use of intravenous calcium channel antagonist agents with a beta-blocker may cause severe depression of myocardial function. Brevibloc should NOT be administered concomitantly with IV verapamil or within close proximity since fatal cardiac arrest has occurred in patients receiving both drugs. (The half-life of Brevibloc is approximately 9 minutes with a range of 5 - 23 minutes. In normal patients the elimination half-life of IV verapamil is 2 - 5 hours).

PRECAUTIONS

Hypotension: In clinical trials 20-50% of patients treated with Brevibloc (esmolol HCl) have had hypotension, generally defined as systolic pressure less than 90 mmHg and/or diastolic pressure less than 50 mmHg. About 12% of the patients have been symptomatic (mainly sweating or dizziness). Hypotension can occur at any dose but is dose-related so that maintenance doses beyond 200 microgram/kg/min (0.2 mg/kg/min) are not recommended. Patients should be closely monitored, especially if pretreatment blood pressure is low. Decrease of dose or termination of infusion reverses hypotension, usually within 30 minutes.

Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure.

Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure Brevibloc should be withdrawn. Although withdrawal may be sufficient because of the short elimination half-life of Brevibloc, specific treatment may also be considered. (See **Overdosage**).
The use of Brevibloc for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised haemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium.
Brevibloc should not be used to slow the heart rate in the presence of agents which are both inotropic and vasoconstrictive such as dopamine, adrenaline and noradrenaline because of the danger of blocking contractility when systemic vascular resistance is high. Despite the rapid onset and offset of the effects of Brevibloc, several cases of death have been reported in complex clinical states where Brevibloc was presumably being used to control ventricular rate.

Anaphylactic Reaction: While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reaction.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of its relative $beta_1$ selectivity and titratability, Brevibloc may be used with caution in patients with bronchospastic diseases. However, since $beta_1$ selectivity is not absolute, Brevibloc should be carefully titrated to obtain the lowest possible effective dose. In the event of bronchospasm, the infusion should be terminated immediately; a $beta_2$ stimulating agent may be administered if conditions warrant but should be used with particular caution as patients already have rapid ventricular rates.

Diabetes Mellitus and Hypoglycaemia: Brevibloc should be used with caution in diabetic patients requiring a beta-blocking agent. Beta-blockers may mask tachycardia occurring with hypoglycaemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Infusion concentrations of 20 mg/mL were associated with more venous irritation including thrombophlebitis than concentrations of 10 mg/mL. Concentrations greater than 10 mg/mL or infusion into small veins or through a butterfly catheter should be avoided. Extravasation may lead to a serious local reaction and possible skin necrosis. Care should be taken in the intravenous administration of Brevibloc as sloughing of the skin and necrosis have been reported in association with infiltration and extravasation of intravenous infusions. The use of the 2.5 g ampoule diluted to a 10 mg/mL concentration with diluents such as 5% glucose in lactated Ringer's, 5% glucose in Ringer's and 5% glucose in 0.9% sodium chloride results in hyperosmotic solutions which may produce venous irritation and/or tissue necrosis.

Because the acid metabolite of Brevibloc is primarily excreted unchanged by the kidney Brevibloc (esmolol HCl) should be administered with caution to patients with impaired renal function. The elimination half-life of the acid metabolite was prolonged ten-fold and the plasma level was considerably elevated in patients with end-stage renal disease.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Because of its short term usage no carcinogenicity, mutagenicity or reproductive performance studies have been conducted with Brevibloc.

Use in Pregnancy
Category C. There are no adequate and well controlled studies in pregnant women. Beta-adrenergic blocking agents may cause pharmacological effects such as bradycardia in the foetus and newborn infant.

Use in Lactation
It is not known whether Brevibloc is excreted in human milk, however, caution should be exercised when Brevibloc is administered to a nursing woman.

Use in Children
The safety and effectiveness of Brevibloc in children have not been established.

Interactions with other drugs
Caution should be exercised when considering the use of Brevibloc and verapamil in patients with depressed myocardial function. Fatal cardiac arrests have occurred in patients receiving both drugs. Both Brevibloc and verapamil decrease myocardial contractility and atrioventricular conduction. Serious adverse events with this combination are more likely to occur in patients with severe cardiac myopathy congestive heart failure or recent myocardial infarction (See **Contraindications**).
Brevibloc should not be used to slow the heart rate in the presence of agents which are both inotropic and vasoconstrictive such as dopamine, adrenaline and noradrenaline because of the danger of blocking contractility when systemic vascular resistance is high (See **Precautions**).
Catecholamine-depleting drugs, eg reserpine, may have an additive effect when given with beta- blocking agents. Patients treated concurrently with Brevibloc and a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.
A study of interaction between Brevibloc and warfarin showed that concomitant administration of Brevibloc and warfarin does not alter warfarin plasma levels. Brevibloc concentrations were equivocally higher when given with warfarin, but this is not likely to be clinically important.

When digoxin and Brevibloc (esmolol HCl) were concomitantly administered intravenously to normal volunteers, there was a 10-20% increase in digoxin blood levels at some time points. Digoxin did not affect Brevibloc pharmacokinetics.
When intravenous morphine and Brevibloc were concomitantly administered in normal subjects, no effect on morphine blood levels was seen, but Brevibloc steady state blood levels were increased by 46% in the presence of morphine. No other pharmacokinetic parameters were changed.
The effect of Brevibloc on the duration of succinylcholine-induced neuromuscular blockade was studied in patients undergoing surgery. The onset of neuromuscular blockade by succinylcholine was unaffected by Brevibloc, but the duration of neuromuscular blockade was prolonged from 5 minutes to 8 minutes.
Although the interactions observed in these studies do not appear to be of major clinical importance, Brevibloc should be titrated with caution in patients being treated concurrently with digoxin, morphine, succinylcholine or warfarin.

ADVERSE EFFECTS

The following adverse reaction rates are based on use of Brevibloc in clinical trials involving 369 patients with supraventricular tachycardia and over 600 intraoperative and postoperative patients enrolled in clinical trials. Most adverse effects observed in controlled clinical trial settings have been mild and transient. The most important adverse effect has been hypotension (See **Precautions**). Deaths have been reported in postmarketing experience occurring during complex clinical states where Brevibloc was presumably being used simply to control ventricular rate (See **Precautions**/*Cardiac Failure*).

CARDIOVASCULAR	
Symptomatic hypotension (diaphoresis, dizziness)*	12%
Asymptomatic hypotension*	~ 25%
Peripheral ischaemia	~ 1%
Pallor	<1%
Flushing	<1%
Bradycardia (heart rate less than 50 beats per minute)	<1%
Chest pain	<1%
Syncope	<1%
Pulmonary oedema	<1%
Heart block	<1%
CENTRAL NERVOUS SYSTEM	
Dizziness	3%
Somnolence	3%
Confusion	~ 2%
Headache	~ 2%
Agitation	~ 2%
Fatigue	~ 1%
Paraesthesia	<1%
Asthenia	<1%
Depression	<1%
Abnormal thinking	<1%
Anxiety	<1%
Anorexia	<1%
Light headedness	<1%
Seizures (including one death)	<1%
RESPIRATORY	
Bronchospasm	<1%
Wheezing	<1%
Dyspnea	<1%
Nasal congestion	<1%
Rhonchi	<1%
Rales	<1%

GASTROINTESTINAL		
	Nausea	7%
	Vomiting	~ 1%
	Dyspepsia	<1%
	Constipation	<1%
	Dry mouth	<1%
	Abdominal discomfort	<1%
	Taste perversion	Has been reported
SKIN (INFUSION SITE)		
	Infusion site reaction (including inflammation & induration)	~ 8%
	Oedema	<1%
	Erythema	<1%
	Skin discoloration	<1%
	Burning at infusion site	<1%
	Thrombophlebitis	<1%
	Local skin necrosis (from extravasation)	
MISCELLANEOUS		
	Urinary retention	<1%
	Speech disorder	<1%
	Abnormal vision	<1%
	Midscapular pain	<1%
	Rigors	<1%
	Fever	<1%

* Therapy was discontinued in about 11% of patients, about half of whom were symptomatic

Cardiovascular: Symptomatic hypotension (diaphoresis, dizziness) occurred in 12% of patients, and therapy was discontinued in about 11%, about half of whom were symptomatic. Asymptomatic hypotension occurred in about 25% of patients. Hypotension resolved during Brevibloc (esmolol HCl) infusion in 63% of these patients and within 30 minutes after discontinuation of infusion in 80% of the remaining patients. Diaphoresis accompanied hypotension in 10% of patients.

In two patients without supraventricular tachycardia but with serious coronary artery disease (post inferior myocardial infarction or unstable angina), severe bradycardia/sinus pause/asystole has developed, reversible in both cases with discontinuation of treatment.

The following experiences are based on spontaneous adverse event reports. Data are insufficient to establish an estimate of their incidence or to establish causation. Some of these events may occur as part of the underlying illness.
Cardiovascular: Death, cardiac arrest, hypertension, ventricular tachycardia and idioventricular rhythm.
Dermatological Reactions: Discolouration, blistering, rash, facial flushing and skin dryness.
Neurological: Cerebral hypoxia, anoxic encephalopathy, aphasia, coma, dysphagia, lethargy, somnolence and prolonged response to neuromuscular blockage.
Haematological: leucopenia, thrombocytopenia.
Respiratory: Apnoea, hypoxia, respiratory arrest, pneumonia.
Renal: Renal failure, metabolic acidosis.

DOSAGE AND ADMINISTRATION

Note: Parenteral drug products should be inspected visually prior to administration. Any solutions which contain visible particulate matter or are hazy or discoloured should not be used.

100 mg Vial: This dosage form is prediluted to provide a ready-to-use 10 mg/mL concentration recommended for Brevibloc intravenous administration. It may be used to administer the appropriate Brevibloc loading dosage infusions by hand-held syringe while the maintenance infusion is being prepared.
When using the 100 mg vial, a loading dose of 0.5 mg/kg for a 70 kg patient would be 3.5 mL.

Supraventricular Tachycardia: In the treatment of supraventricular tachycardia, responses to Brevibloc usually (over 95%) occur within the range of 50 to 200 microgram/kg/min (0.05 to 0.2 mg/kg/min). The average effective dosage is

approximately 100 microgram/kg/min (0.1 mg/kg/min) although dosages as low as 25 microgram/kg/min (0.025 mg/kg/min) have been adequate in some patients. Dosages as high as 300 microgram/kg/min (0.3 mg/kg/min) have been used, but these provide little added effect and an increased rate of adverse effects and are not recommended. Dosage of Brevibloc in supraventricular tachycardia must be individualised by titration in which each step consists of a loading dosage followed by a maintenance dosage.

To initiate treatment of a patient with supraventricular tachycardia, administer a loading infusion of 500 microgram/kg/min (0.5 mg/kg/min) over one minute followed by a 4 min maintenance infusion of 50 microgram/kg/min (0.05 mg/kg/min). If an adequate therapeutic effect is observed over the five minutes of drug administration, maintain the maintenance infusion dosage with periodic adjustments up or down as needed. If an adequate, therapeutic effect is not observed, repeat the same loading dosage infusion over one minute and increase the maintenance infusion to 100 microgram/kg/min (0.1 mg/kg/min).

Continue titration procedure as above, repeating the original loading dose of 500 microgram/kg/min (0.5 mg/kg/min) over 1 minute and further increasing the maintenance infusion rate over the subsequent four minutes by 50 microgram/kg/min (0.05 mg/kg/min) increments. As the desired heart rate or blood pressure is approached, reduce the maintenance infusion rate downward as appropriate. If desired increase the interval between steps from 5-10 minutes. Maintenance dosage above 200 microgram/kg/min (0.2 mg/kg/min) have not been shown to have significantly increased benefits and are not recommended. The interval between titration steps may be increased.

This specific dosage and administration regimen has not been studied intraoperatively and, because of the time required for titration, may not be optimal for intraoperative use.

The safety of maintenance dosages above 300microgram/kg/min (0.3mg/kg/min) has not been studied.

In the event of an adverse reaction, Brevibloc should be discontinued. If benefits outweigh risks, Brevibloc may be resumed at a lower infusion rate without a loading dose after the condition has subsided. If a local infusion site reaction develops, an alternate infusion site should be used and caution should be taken to prevent extravasation. The use of butterfly needles should be avoided.

Abrupt cessation of Brevibloc in patients has not been reported to produce the withdrawal effects which may occur with abrupt withdrawal of beta-blockers following chronic use in coronary artery disease (CAD) patients. However, caution should still be used in abruptly discontinuing infusions of Brevibloc in CAD patients.

After achieving an adequate control of the heart rate and a stable clinical status in patients with supraventricular tachycardia, transition to alternative antiarrhythmic agents such as propranolol, or digoxin, may be accomplished. A recommended guideline for such a transition is given below but the physician should carefully consider the labelling instructions for the alternative agent selected:

Oral Alternative Agent	Dosage
Propranolol hydrochloride	10 - 30mg q 6-8 h
Digoxin	0.125-0.5 mg q 6 h (p.o. or i.v.)

The dosage of Brevibloc should be reduced as follows:
1. Thirty minutes following the first dose of the alternative agent, reduce the infusion rate of Brevibloc by one-half (50%).
2. Following the second dose of the alternative agent, monitor the patient's response and if satisfactory control is maintained for the first hour, discontinue Brevibloc.

The use of infusions of Brevibloc up to 24 hours duration has been well documented.
Compatibility with Commonly Used Intravenous Fluids: Brevibloc (esmolol HCl) injection was tested for compatibility with eight commonly used intravenous fluids at a final concentration of 10 mg esmolol HCl per mL. Brevibloc injection was found to be physically and chemically compatible with the solutions listed below for at least 24 hours when stored below 25°C or under refrigeration. However in order to reduce microbial contamination hazards, infusion should be commenced as soon as practicable after preparation of the admixture. The resulting solutions should be used within 24 hours of preparation and any residue discarded.
Glucose (5%) Injection USP
Glucose (5%) in Ringer's Injection
Glucose (5%) in Lactated Ringer's Injection
Glucose (5%) and Sodium Chloride (0.45%) Injection USP
Glucose (5%) and Sodium Chloride (0.9%) Injection USP
Lactated Ringer's Injection USP
Sodium Chloride (0.45%) Injection USP
Sodium Chloride (0.9%) Injection USP
Brevibloc injection was NOT compatible with Sodium Bicarbonate (5%) Injection USP.

OVERDOSAGE

Acute Toxicity: Overdoses of Brevibloc can cause cardiac arrest. In addition, overdoses can produce bradycardia, hypotension, electro-mechanical dissociation and loss of consciousness. Cases of massive accidental overdoses of Brevibloc have occurred due to dilution errors. Some of these overdoses have been fatal while others resulted in permanent disability. Bolus doses in the range of 625mg to 2500mg (12.5 - 50mg/kg) have been fatal. Patients have recovered completely from overdoses as high as 1.75g given over one minute or doses of 7.5g given over one hour for cardiovascular surgery. The patients who survived appear to be those whose circulation could be supported until the effects of Brevibloc resolved. Because of its approximately 9-minute elimination half-life, the first step in the event of toxicity should be to discontinue the Brevibloc infusion. Then, based on the observed clinical effects, the following general measures should also be considered:
Bradycardia: Intravenous administration of atropine or another anticholinergic drug.
Bronchospasm: Intravenous administration of a $beta_2$ stimulating agent and/or a theophylline derivative.
Cardiac Failure: Intravenous administration of a diuretic and/or digitalis glycoside. In shock resulting from inadequate cardiac contractility, intravenous administration of dopamine, dobutamine or isoprenaline may be considered.
Symptomatic Hypotension: Intravenous administration of fluids and/or pressor agents.

Contact the Poisons Information Centre on 13 11 26 for further advice on overdose management.

PRESENTATION

Brevibloc Injection is supplied as-

100mg – 10mL vials INJ116

AUST R 43494

Store below 25°C. Short-term freezing (i.e. 24 hours) does not adversely affect the product, but exposure to elevated temperatures should be avoided.

NAME AND ADDRESS OF THE SPONSOR

Phebra Pty Ltd, 332 Burns Bay Road, Lane Cove NSW 2066, Australia.
Telephone: 1800 720 020

POISON SCHEDULE OF THE MEDICINE

Prescription only medicine - S4

Approved: February 25, 1993
Updated: December 12,1996
Safety related changes and minor amendments approved: January 10, 1997
Minor amendment approved: May 13, 1998
Amendment approved: December 6, 1999
Amendment approved: 5 November 2007
Date of most recent amendment: 10 October 2008

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