BREVIBLOC®
(ESMOLOL HYDROCHLORIDE)

1 NAME OF THE MEDICINE

Esmolol hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Brevibloc Injection is supplied as 100 mg/10 mL vial.

Brevibloc Powder for Injection is supplied in a 50 mL vial containing 2.5 g esmolol hydrochloride.

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

100 mg/ 10 mL vial:

Brevibloc 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.

2.5 g vial:

Powder for concentrate for solution for infusion.

Esmolol hydrochloride powder is a white to almost white powder.

The reconstituted solution is a clear and colourless liquid free from visible particles.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Supraventricular tachycardia

Brevibloc 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.

4.2 DOSE AND METHOD OF 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. Product is for single use in one patient only. Discard any residue.

100 mg/ 10 mL 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.

2.5 g vial:

BREVIBLOC POWDER FOR INJECTION IS NOT FOR DIRECT INTRAVENOUS INJECTION. THIS DOSAGE FORM MUST BE RECONSTITUTED AND DILUTED PRIOR TO INFUSION. The administration of incorrectly reconstituted/diluted Brevibloc Powder for Injection may result in death (see section 4.4 Special Warnings and Precautions for Use and section 4.9 Overdose).

Dosage

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 minute 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 check and 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 dosages 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.

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

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.

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 alternative 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 in Table 1 but the physician should carefully consider the labelling instructions for the alternative agent selected.

Table 1. Recommended guideline for the transition to alternative antiarrhythmic agents

Oral Alternative Agent	Dosage
Propranolol hydrochloride	10 to 30 mg every 6-8 h
Digoxin	0.125 to 0.5 mg every 6 h (by mouth or intravenously)

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.

Method of Administration

Brevibloc Powder for Injection reconstitutes to a concentrated solution for infusion which **MUST BE DILUTED BEFORE ADMINISTRATION.** Each mL of the diluted solution for infusion contains 10 mg esmolol hydrochloride (10 mg/mL). INSTRUCTION FOR USE is provided in Table 2.

Table 2. **INSTRUCTION FOR USE** for a diluted solution for infusion (10 mg/mL) administered through standard infusion

Presentation	***Volume of diluent to be added***	***Final concentration of the reconstituted /diluted solution***	***Final volume of the reconstituted /diluted solution***	***Administration***
2.5 g esmolol powder	**Step 1** Reconstitute one vial with 50 mL of one of below mentioned solutions. **Step 2** Dilute immediately the reconstituted content of the vial (50 mL) to 250 mL with one of below mentioned solutions.	**10 mg/mL**	250 mL	Standard infusion with a volume of 250 mL

Brevibloc Powder for Injection must be reconstituted and diluted by a healthcare professional and administered as an IV infusion. Do not administer as an IV push or bolus.

Once the infusion solution is prepared, it should be administered immediately (see section 4.4 Special Warning and Precaution for Use). The reconstituted and diluted product is physiochemically stable during 24 hours at room temperature. From a microbiological point of view the reconstituted and diluted product must be used immediately. To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2 – 8 °C for not more than 24 hours. The white to almost white lyophilised powder will dissolve completely after reconstitution. Mix gently until a clear solution is obtained.

Reconstituted solutions should be visually examined for particulate matter and discoloration. Only a clear and colourless solution should be used.

Compatibility with commonly used intravenous fluids

100 mg/10 mL vial:

Brevibloc Injection was tested for compatibility with eight commonly used intravenous fluids at a final concentration of 10 mg esmolol hydrochloride 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

2.5 g vial:

Brevibloc Powder for Injection was tested for compatibility with three commonly used intravenous fluids at a final concentration of 10 mg esmolol hydrochloride per mL. Brevibloc Powder for Injection was found to be physically and chemically compatible with the solutions listed below for at least 24 hours when stored below 25°C. 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.

Sodium Chloride (0.9%) Injection USP

Glucose (5%) Injection USP

Lactated Ringer's Injection USP

4.3 CONTRAINDICATIONS

Patients with hypersensitivity to esmolol hydrochloride or any of the excipients should not be given Brevibloc.

Brevibloc is contraindicated in patients with sinus bradycardia, heart block greater than first degree, cardiogenic shock or overt heart failure (see Section 4.4 Special Warnings and Precautions for Use). Brevibloc is also contraindicated in patients with severe bradycardia (less than 50 beats per minute), sick sinus syndrome, severe AV-nodal conductance disorders (without pacemaker), second and third degree AV-block, severe hypotension, non-treated phaeochromocytoma, pulmonary hypertension, acute asthma attack and metabolic acidosis.

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.)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypotension

In clinical trials 20-50% of patients treated with Brevibloc 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 pre-treatment blood pressure is low. Decrease of dose or termination of infusion reverses hypotension, usually within 30 minutes. It is advised to continuously monitor the blood pressure and ECG in all patients treated with esmolol hydrochloride.

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 Section 4.9 Overdose.)

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. 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.

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.

Beta-blockers

Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block. The elderly should be treated with caution, starting with a lower dosage, but tolerance is usually good in the elderly.

Beta-blockers may increase the number and the duration of anginal attacks in patients with Prinzmetal's angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Non-selective beta-blockers should not be used for these patients and $beta_1$-selective blockers only with the utmost care.

If the patient is already on a $beta_2$-receptor stimulating agent, re-evaluate the dose of esmolol hydrochloride.

In patients with peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication), beta-blockers should be used with great caution as aggravation of these disorders may occur.

Beta-blockers may induce bradycardia. If the pulse rate decreases to less than 50-55 beats per minute at rest and the patient experiences symptoms related to bradycardia, the dosage should be reduced.

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.

Brevibloc should be used with caution in patients with a history of wheezing or asthma.

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.

Psoriasis

In patients with psoriasis or a history of psoriasis, the administration of esmolol hydrochloride should be carefully weighed.

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.

Use in renal impairment

Because the acid metabolite of Brevibloc is primarily excreted unchanged by the kidney, Brevibloc 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.

In all patients, it is advised to terminate the infusion of Brevibloc gradually because of the risk of rebound tachycardia.

Use in the elderly

See Section 4.4 Special Warnings and Precautions for Use, Beta-blockers.

Paediatric use

The safety and effectiveness of Brevibloc in children (under 18 years) have not been established.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

See also Section 6.2 Incompatibilities.

Calcium antagonists such as verapamil and to a lesser extent diltiazem, have a negative influence on contractility and AV-conduction. As with other beta-blocking agents esmolol hydrochloride should be used with caution in combination with verapamil in patients with impaired ventricular 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 Section 4.3 Contraindications). The combination should not be given to patients with conduction abnormalities and Brevibloc should not be administered within 48 hours of discontinuing verapamil.

Calcium antagonists such as dihydropyridine derivatives (e.g. nifedipine and amlodipine) may increase the risk of hypotension. In patients with cardiac insufficiency and who are being treated with a calcium antagonist, treatment with beta-blocking agents may lead to cardiac failure. Careful titration of Brevibloc and appropriate haemodynamic monitoring is recommended.

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 Section 4.4 Special Warnings and Precautions for Use).

Concomitant use of esmolol hydrochloride and class I antiarrhythmic agents (such as disopyramide and quinidine) and also amiodarone can increase the action of both on the AV-conductance time and induce negative inotropic effect.

Sympathomimetic agents may counteract the effect of beta-adrenergic blocking agents.

Catecholamine-depleting drugs, e.g. 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 were concomitantly administered intravenously to normal volunteers, there was a 10-20% increase in digoxin blood levels at some time points. The combination of digitalis glycosides and Brevibloc may increase AV-conduction time. Digoxin did not affect Brevibloc pharmacokinetics.

Concomitant use of clonidine and beta-blockers increases the risk of “rebound hypertension”. When clonidine is used in conjunction with non-selective beta-blockers, such as propranolol, treatment with clonidine should be continued for some time after treatment with the beta-blocker has been discontinued.

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.

Concomitant use of esmolol hydrochloride and insulin and oral antidiabetic drugs may intensify the blood sugar lowering effect (especially non-selective beta-blockers). Beta-adrenergic blockade may prevent the appearance of signs of hypoglycemia (tachycardia).

Anaesthetic medicines: In the situation where the patient's volume status is uncertain or concomitant antihypertensive drugs are utilized, there may be attenuation of reflex tachycardia and an increase of the risk of hypotension. Continuation of beta-blockade reduces the risk of arrhythmia during induction and intubation. The anaesthesiologist should be informed when the patient is receiving a beta-blocking agent in addition to esmolol hydrochloride.

The hypotensive effects of inhalation anaesthetic agents may be increased in the presence of Brevibloc. The dosage of either agent may be modified, as needed, to maintain the desired haemodynamics.

NSAIDs may decrease the hypotensive effects of beta-blockers.

Concomitant administration of tricyclic antidepressants, barbiturates and phenothiazines as well as other antihypertensive agents may increase the blood pressure lowering effect. Dosing of esmolol hydrochloride should be adjusted downward to avoid unexpected hypotension.

Special caution must be taken when using amisulpride concomitantly with beta-blockers.

The combination of Brevibloc with ganglion blocking agents can enhance the hypotensive effect.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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. Lactation is not advised during the use of esmolol hydrochloride.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No specific studies have been conducted to assess the direct effect of esmolol hydrochloride on the ability to drive and use machines. However, adverse effects of esmolol hydrochloride include dizziness which could affect the ability to drive or use machines. See Section 4.8 Adverse Effects (Undesirable Effects).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The adverse reaction rates provided in Table 3 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 Section 4.4 Special Warnings and Precautions for Use). Deaths have been reported in postmarketing experience occurring during complex clinical states where Brevibloc was presumably being used simply to control ventricular rate (see Section 4.4 Special Warnings and Precautions for Use, Cardiac failure).

Table 3. Adverse reaction rates in clinical trials

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%
	Thrombophlebitis	<1%
	Pulmonary oedema	<1%
	Heart block	<1%
	Asystole	<0.01%
	Severe bradycardia	<0.01%
	Sinus pause	<0.01%
CENTRAL NERVOUS SYSTEM		
	Dizziness	3%
	Somnolence	3%
	Confusion	~ 2%
	Headache	~ 2%
	Agitation	~ 2%
	Fatigue	~ 1%
	Paraesthesia	≥1%, <10%
	Asthenia	≥1%, <10%
	Depression	<1%
	Abnormal thinking	<1%
	Anxiety	<1%
	Anorexia	<1%
	Light headedness	<1%
	Convulsion	<1%
	Syncope	<1%
	Seizures (including one death)	<1%

RESPIRATORY		
	Bronchospasm	<1%
	Wheezing	<1%
	Dyspnea	<1%
	Nasal congestion	<1%
	Pulmonary oedema	<1%
	Rhonchi	<1%
	Rales	<1%
GASTROINTESTINAL		
	Nausea	7%
	Vomiting	~ 1%
	Dyspepsia	<1%
	Constipation	<1%
	Dry mouth	<1%
	Abdominal discomfort	<1%
	Taste perversion/Dysgeusia	<1%
SKIN (INFUSION SITE)		
	Diaphoresis	≥10%
	Infusion site reaction (including inflammation & induration)	~ 8%
	Oedema	<1%
	Erythema	<1%
	Skin discoloration	<1%
	Burning at infusion site	<1%
	Local skin necrosis (from extravasation)	<1%
	Psoriasis	reported
MISCELLANEOUS		
	Urinary retention	<1%
	Speech disorder	<1%
	Abnormal vision	<1%
	Midscapular pain	<1%
	Rigors	<1%
	Fever and chills	<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 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.

Esmolol hydrochloride can cause psoriasis in some situations or worsen it or cause rash in similar skin disorders.

In case of undesirable effects, the infusion of esmolol hydrochloride shall be reduced or interrupted. Most of these undesirable effects disappear within 30 minutes after discontinuation of the administration of esmolol hydrochloride.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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 625 to 2500 mg (12.5-50 mg/kg) have been fatal. Patients have recovered completely from overdoses as high as 1.75 g given over one minute or doses of 7.5 g 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

Nebulised beta$_2$-stimulating agent should be given. If this is not sufficient, intravenous administration of a beta$_2$-stimulating agent and/or a theophylline derivative can be considered.

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. In case further treatment is necessary, the following agents can be given intravenously:

- Atropine
- Inotropic agents
- Calcium ions

Symptomatic hypotension
Intravenous administration of fluids and/or pressor agents.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Brevibloc is a beta$_1$-selective (cardioselective) adrenergic blocking agent with rapid onset and a short duration of action (elimination half-life is approximately 9 minutes).

Mechanism of action

Brevibloc 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.

Pharmacodynamics

Clinical pharmacology studies in normal volunteers have confirmed the beta-blocking activity of Brevibloc, 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 pre-treatment 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).

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

No data available.

Distribution

Brevibloc has been shown to be 55% bound to human plasma protein, while the acid metabolite is only 10% bound.

Metabolism

Brevibloc 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.

Excretion

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 1/1,500 of the activity of esmolol hydrochloride 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 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

100 mg / 10 mL vial - Excipients in the 10 mL vial are sodium acetate trihydrate, glacial acetic acid, hydrochloric acid and water for injections.

2.5 g powder / vial – None

6.2 INCOMPATIBILITIES

Brevibloc MUST NOT be used in combination with sodium carbonate solutions or other medicinal products (e.g. furosemide, diazepam and thiopental) that are chemically incompatible with esmolol hydrochloride.

Brevibloc is not compatible with Sodium Bicarbonate (5%) Injection USP. Please refer to section 4.2 for list of compatible diluents.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the ARTG[1]. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Brevibloc is supplied as:

100 mg / 10 mL glass vials
Phebra product code : INJ168
It is supplied in a carton containing 5 or 20 vials.

2.5 g powder per glass vial
Phebra product code: INJ210
It is supplied in a carton containing 1 vial.

The vial stopper is not made with natural rubber latex.

Not all pack sizes may be marketed.

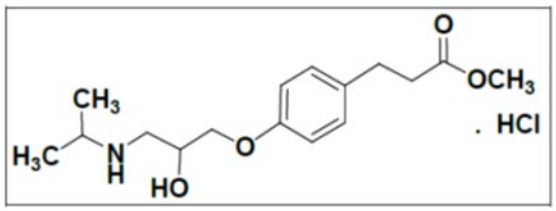
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Esmolol hydrochloride is ± methyl 3-[4-[2-hydroxy- 3-(isopropylamino) propoxy]phenyl] propionate hydrochloride. Esmolol hydrochloride has the empirical formula $C_{16}H_{25}NO_4$.HCl and a molecular weight of 331.8. It has one asymmetric centre and exists as a racemic mixture. 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.

Chemical structure



CAS number

81161-17-3

[1] AUST R 43494, AUST R 310943

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription only medicine

8 SPONSOR

Phebra[2] Pty Ltd,
19 Orion Road, Lane Cove West, NSW 2066, Australia.
Telephone: 1800 720 020

9 DATE OF FIRST APPROVAL

Brevibloc 100 mg / 10 mL Injection vial (AUST R 43494): 04 Mar 1993

Brevibloc 2.5 g Powder for Injection for infusion vial (AUST R 310943): 15 Nov 2019

10 DATE OF REVISION

22 Jan 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
NA	Addition of 100 mg/ 1mL mg glass vial information for PI.
2	Minor editorial changes – improved readability of presentations.
3	Minor editorial changes – improved readability of presentations.
4.1	Minor editorial changes – adjusted the product name as Brevibloc only.
4.2	Minor editorial changes – grammar correction and improved readability of presentations.
4.7	Minor editorial changes – updated AAN for esmolol hydrochloride
4.9	Minor editorial changes – grammar correction
5.1	Minor editorial changes – grammar correction and adjusted the product name as Brevibloc only.
5.2	Minor editorial changes – moved text in order to be in the correct sub-section.
6.1	Minor editorial changes – updated AAN for esmolol hydrochloride, grammar correction and improved readability of presentations.
6.5	Minor editorial changes – improved product code readability, availability of pack sizes and addition of safety statement for latex.
7.0	Minor editorial changes – standardization of content