1. NAME OF THE MEDICINAL PRODUCT

Brevibloc Premixed 10 mg/ml Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Brevibloc Premixed 10 mg/ml Solution for Injection contains 10 mg of esmolol hydrochloride per ml. Each vial of 10 ml contains 100 mg of esmolol hydrochloride.

Excipients: This medicinal product contains approximately 1.22 mmol (or 28 mg) of sodium per vial. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection.
Clear colourless to light yellow solution.
The solution has a pH between 4.5 to 5.5 and osmolarity of approximately 300 mOsm/l.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Supraventricular tachycardia (except for pre-excitation syndromes) or non-compensatory sinus tachycardia

Brevibloc is indicated for for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other circumstances where short-term control of the ventricular rate with a short acting agent is desirable.
Brevibloc is also indicated for non-compensatory sinus tachycardia where, in the physician's judgement the rapid heart rate requires specific intervention.

- Tachycardia and hypertension occurring in the perioperative phase

Treatment of tachycardia and hypertension that occur during induction of anesthesia and tracheal intubation, during surgery, on emergence from anesthesia, and in the postoperative period, when in the physician's judgment such specific intervention is considered indicated.

Brevibloc is not indicated for use in children aged up to 18 years (see section 4.2). Brevibloc is not intended for use in chronic settings.

4.2. Posology and method of administration

Posology

Brevibloc Premixed 10 mg/ml Solution for Injection is a ready-to-use 10 mg/ml solution recommended for intravenous administration.

This dosage form is used to administer the appropriate Brevibloc loading dose or bolus dose by hand held syringe.

SUPRAVENTRICULAR TACHYARRYTHMIA (except for pre-excitation syndromes) OR NON-COMPENSATORY SINUS TACHYCARDIA

The Brevibloc dosage in supraventricular tachyarrhythmias should be individually titrated as indicated in the below flow chart.

Flow Chart for Initiation and Maintenance of Treatment

Loading dosage infusion of 500 micrograms /kg/minute for 1 minute THEN a maintenance infusion of 50 micrograms/kg/minute for 4 minutes

↓ → **Response**
Maintain the infusion at
50 micrograms/kg/minute

Inadequate response within 5 minutes
Repeat the dose of 500 micrograms/kg/minute for 1 minute
Increase the maintenance infusion to
100 micrograms/kg/minute for 4 minutes

↓ → **Response**
Maintain the infusion at
100 micrograms/kg/minute

Inadequate response within 5 minutes
Repeat the dose of 500 micrograms/kg/minute for 1 minute
Increase the maintenance infusion to
150 micrograms/kg/minute for 4 minutes

↓ → **Response**
Maintain the infusion at
150 micrograms/kg/minute

Inadequate response
Repeat the dose of 500 micrograms/kg/minute for 1 minute
Increase the maintenance infusion to
200 micrograms/kg/min and maintain

Loading dose
Loading dose adjustment may be necessary depending on the haemodynamic response (heart rate, blood pressure)

Maintenance dose
For a continuous and progressive dosage an effective maintenance dose is between 50 to 200 micrograms/kg/minute. 25 micrograms/kg/minute doses may be used.
Maintenance dose adjustment may be necessary depending on the desired haemodynamic response.

Administration of doses greater than 200 mcg/kg/min provides little added heart rate-lowering effect, and the rate of adverse reactions increases.

Loading dose and maintenance doses of Brevibloc to administer for different patient weights are outlined in Table 1 and Table 2 respectively.

Table 1
Volume of Brevibloc 10 mg/ml required for an
INITIAL LOADING DOSE of 500 mcg/ kg / minute

	Patient weight (kg)								
	40	50	60	70	80	90	100	110	120
Volume (ml)	2	2.5	3	3.5	4	4.5	5	5.5	6

Table 2
Volume of Brevibloc 10 mg/ml required to provide
MAINTENANCE DOSES at infusion rates between 12.5 and 300 mcg/kg/minute

Patient weight (kg)	**Infusion Dose Rate**						
	12.5 mcg/kg/min	**25 mcg/kg/min**	**50 mcg/kg/min**	**100 mcg/kg/min**	**150 mcg/kg/min**	**200 mcg/kg/min**	**300 mcg/kg/min**
	Amount to administer per hour to achieve the dose rate (ml / hr)						
40	3 ml/hr	6 ml/hr	12 ml/hr	24 ml/hr	36 ml/hr	48 ml/hr	72 ml/hr
50	3.75 ml/hr	7.5 ml/hr	15 ml/hr	30 ml/hr	45 ml/hr	60 ml/hr	90 ml/hr
60	4.5 ml/hr	9 ml/hr	18 ml/hr	36 ml/hr	54 ml/hr	72 ml/hr	108 ml/hr
70	5.25 ml/hr	10.5 ml/hr	21 ml/hr	42 ml/hr	63 ml/hr	84 ml/hr	126 ml/hr
80	6 ml/hr	12 ml/hr	24 ml/hr	48 ml/hr	72 ml/hr	96 ml/hr	144 ml/hr
90	6.75 ml/hr	13.5 ml/hr	27 ml/hr	54 ml/hr	81 ml/hr	108 ml/hr	162 ml/hr
100	7.5 ml/hr	15 ml/hr	30 ml/hr	60 ml/hr	90 ml/hr	120 ml/hr	180 ml/hr
110	8.25 ml/hr	16.5 ml/hr	33 ml/hr	66 ml/hr	99 ml/hr	132 ml/hr	198 ml/hr
120	9 ml/hr	18 ml/hr	36 ml/hr	72 ml/hr	108 ml/hr	144 ml/hr	216 ml/hr

1ml of Brevibloc is equivalent to 10mg of esmolol.

As the desired heart rate or safety end-point (e.g., lowered blood pressure) is approached, OMIT the loading dose and reduce the incremental dose in the maintenance infusion from 50 micrograms/kg/minute to 25 micrograms/kg/minute or lower. If necessary, the interval between the titration steps may be increased from 5 to 10 minutes.

PERIOPERATIVE TACHYCARDIA AND HYPERTENSION

For perioperative tachycardia and hypertension the dosing regimen may vary as follows:
For intraoperative treatment - during anaesthesia when immediate control is required:

- A bolus injection of 80 mg is given over 15 to 30 seconds followed by a 150 micrograms/kg/minute infusion. Titrate the infusion rate as required up to

300 micrograms/kg/minute. The volume of infusion required for different patient weights is provided in Table 2.

Upon awakening from anaesthesia

- An infusion of 500 micrograms/kg/minute is given for 4 minutes followed by a 300 micrograms/kg/minute infusion. The volume of infusion required for different patient weights is provided in Table 2.

For post-operative situations when time for titration is available

- A loading dose of 500 micrograms/kg/minute is given over 1 minute before each titration step to produce a rapid onset of action. Use titration steps of 50, 100, 150, 200, 250 and 300 micrograms/kg/minute given over 4 minutes and stopping at the desired therapeutic effect. The volume of infusion required for different patient weights is provided in Table 2.

Recommended maximum dose:

- For adequate control of blood pressure, higher dosages (250-300 mcg/kg/min) may be required. The safety of dosages above 300 mcg/kg/min has not been adequately studied.

Potential effects to be aware of during dosing with Brevibloc:

In the event of an adverse reaction, the dosage of Brevibloc may be reduced or discontinued. Pharmacological adverse reactions should resolve within 30 minutes.

If a local infusion site reaction develops, an alternative infusion site should be used and caution should be taken to prevent extravasation.

The administration of Brevibloc for longer than 24 hours has not been thoroughly evaluated. Infusion durations greater than 24 hours should only be used with caution.

It is advised to terminate the infusion gradually because of the risk of rebound tachycardia and rebound hypertension. As with all beta-blockers, because withdrawal effects cannot be excluded, caution should be used in abruptly discontinuing Brevibloc administration in coronary artery disease (CAD) patients.

Replacing Brevibloc therapy by alternative drugs

After patients achieve an adequate control of the heart rate and a stable clinical status, transition to alternative drugs (such as antiarrhythmics or calcium antagonists) may be accomplished.

Reducing the dosage:

When Brevibloc is to be replaced by alternative drugs, the physician should carefully consider the labeling instructions of the alternative drug selected and reduce the dosage of Brevibloc as follows:

- Within the first hour after the first dose of the alternative drug, reduce the Brevibloc infusion rate by one-half (50%).

- After administration of the second dose of the alternative drug, monitor the patient's response and if satisfactory control is maintained for the first hour, discontinue the Brevibloc infusion.

Additional dosing information

As the desired therapeutic effect or a safety endpoint (e.g., lowered blood pressure) is approached, omit the loading dose and reduce the incremental infusion to 12.5 to 25 micrograms/kg/minute.
Also, if desired, increase the interval between titration steps from 5 to 10 minutes.
Brevibloc should be discontinued when heart rate or blood pressure rapidly approach or exceed a safety limit, and then restarted without a loading infusion at a lower dose after the heart rate or blood pressure has returned to an acceptable level.

Special populations

Elderly
The elderly should be treated with caution, starting with a lower dosage.
Special studies in the elderly have not been conducted. However, analysis of data from 252 patients over 65 years of age indicated that no variations in pharmacodynamic effects occurred as compared with data from patients under 65.

Patients with renal insufficiency
In patients with renal insufficiency caution is needed when Brevibloc is administered by infusion, since the acid metabolite of Brevibloc is excreted unchanged through the kidneys. Excretion of the acid metabolite is significantly decreased in patients with end-stage renal disease, with the elimination half-life increased to about ten-fold that of normal, and plasma levels considerably elevated.

Patients with liver insufficiency
In case of liver insufficiency no special precautions are necessary since the esterases in the red blood cells have a main role in the Brevibloc metabolism.

Paediatric population
The safety and efficacy of Brevibloc in children aged up to 18 years have not yet been established. Therefore, Brevibloc is not indicated for use in the paediatric population (see section 4.1). Currently available data are described in section 5.1 and 5.2 but no recommendation on a posology can be made.

4.3. Contraindications

- Hypersensitivity to the active substance, to any of the excipients or other beta-blockers (cross sensitivity between beta-blockers is possible);
- Severe sinus bradycardia (less than 50 beats per minute);
- Sick sinus syndrome; severe AV-nodal conductance disorders (without pacemaker); 2nd or 3rd degree AV-block;
- Cardiogenic shock;
- Severe hypotension;

- Decompensated heart failure;
- Concomitant or recent intravenous administration of verapamil. Brevibloc must not be administered within 48 hours of discontinuing verapamil (see section 4.5);
- Non-treated phaeochromocytoma;
- Pulmonary hypertension;
- Acute asthmatic attack;
- Metabolic acidosis.

4.4. Special warnings and precautions for use

Warnings

It is recommended to continuously monitor the blood pressure and the ECG in all patients treated with Brevibloc.

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, severe reactions may occur, including loss of consciousness, cardiogenic shock, cardiac arrest. Several deaths have been reported in complex clinical states where Brevibloc was presumably being used to control ventricular rate.

The most frequently observed side effect is hypotension, which is dose related but can occur at any dose. This can be severe. In the event of a hypotensive episode the infusion rate should be lowered or, if necessary, be discontinued. Hypotension is usually reversible (within 30 minutes after discontinuation of administration of Brevibloc). In some cases, additional interventions may be necessary to restore blood pressure. In patients with a low systolic blood pressure, extra caution is needed when adjusting the dosage and during the maintenance infusion.

Bradycardia, including severe bradycardia, and cardiac arrest has occurred with the use of Brevibloc. Brevibloc should be used with special caution in patients with low pretreatment heart rates and only when the potential benefits are considered to outweigh the risk.

Brevibloc is contraindicated in patients with pre-existing severe sinus bradycardia (see section 4.3). 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 or administration stopped.

Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure. 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.

Caution should be exercised when using Brevibloc in patients with compromised cardiac function. 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). Brevibloc is contraindicated in patients with decompensated heart failure (see section 4.3).

Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block or other cardiac conduction disturbances (see section 4.3).

Brevibloc should be used with caution and only after pre-treatment with alpha-receptor blockers in patients with pheochromocytoma (see section 4.3).

Caution is required when Brevibloc is used to treat hypertension following induced hypothermia.

Patients with bronchospastic disease should, in general, not receive beta-blockers. Because of its relative beta-1 selectivity and titratability, Brevibloc should 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 and a beta-2-agonist should be administered if necessary.

If the patient already uses a beta-2-receptor stimulating agent, it may be necessary to re-evaluate the dose of this agent.

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

Precautions

Brevibloc should be used with caution in diabetics or in case of suspected or actual hypoglycaemia. Beta-blockers may mask the prodromal symptoms of a hypoglycaemia such as tachycardia. However, dizziness and sweating may not be affected. Concomitant use of beta-blockers and antidiabetic agents can increase the effect of the antidiabetic agents (blood glucose–lowering) (see section 4.5).

Infusion site reactions have occurred with the use of both Brevibloc 10 mg/ml and 20 mg/ml. These reactions have included infusion site irritation and inflammation as well as more severe reactions such as thrombophlebitis, necrosis, and blistering, in particular when associated with extravasation (see section 4.8). Infusions into small veins or through a butterfly catheter should be avoided. If a local infusion site reaction develops, an alternative infusion site should be used.

Beta-blockers may increase the number and the duration of anginal attacks in patients with Prinzemetal'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 should only be used with the utmost care.

In hypovolemic patients, Brevibloc can attenuate reflex tachycardia and increase the risk of circulatory collapse. Therefore, Brevibloc should be used with caution in such patients.

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.

Some beta-blockers, especially those administered intravenously, including Brevibloc, have been associated with increases in serum potassium levels and hyperkalemia. The risk is increased in patients with risk factors such as renal impairment and those on haemodialysis.

Beta-blockers may increase both the sensitivity toward allergens and the seriousness of anaphylactic reactions. Patients using beta-blockers may be unresponsive to the usual doses of epinephrine used to treat anaphylactic or anaphylactoid reactions (see section 4.5).

Beta-blockers have been associated with the development of psoriasis or psoriasiform eruptions and with aggravation of psoriasis. Patients with a personal or family history of psoriasis should be administered beta-blockers only after careful consideration of expected benefits and risks.

Beta-blockers, such as propranolol and metoprolol, may mask certain clinical signs of hyperthyroidism (such as tachycardia). Abrupt withdrawal of existing therapy with beta-blockers in patients at risk or suspected of developing thyrotoxicosis may precipitate thyroid storm and these patients must be monitored closely.

This medicinal product contains approximately 1.22 mmol (or 28 mg) of sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

4.5. Interaction with other medicinal products and other forms of interaction

Care should always be exercised whenever Brevibloc is used with other antihypertensive agents or other drugs that may cause hypotension or bradycardia: the effects of Brevibloc may be enhanced or the side-effects of hypotension or bradycardia may be exacerbated.

Calcium antagonists such as verapamil and to a lesser extent diltiazem have a negative influence on contractility and AV conduction. The combination should not be given to patients with conduction abnormalities and Brevibloc should not be administered within 48 hours of discontinuing verapamil (see section 4.3).

Calcium antagonists such as dihydropyridine derivatives (e.g., nifedipine) 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.

Concomitant use of Brevibloc and Class I anti-arrhythmic drugs (e.g., disopyramide, quinidine) and amiodarone may have potentiating effect on atrial-conduction time and induce negative inotropic effect.

Concomitant use of Brevibloc and insulin or oral anti-diabetic drugs may intensify the blood sugar lowering effect (especially non-selective beta-blockers). Beta-adrenergic blockade may prevent the appearance of signs of hypoglycaemia (tachycardia), but other manifestations such as dizziness and sweating may not be masked.

Anaesthetic drugs: in situations where the patient's volume status is uncertain or concomitant antihypertensive drugs are utilized, there may be attenuation of the reflex tachycardia and an increased the risk of hypotension. Continuation of beta-blockade reduces the risk of arrhythmia during induction and intubation. The anaesthetist should be informed when the patient is

receiving a beta-blocking agent in addition to Brevibloc. 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.

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

NSAIDs may decrease the hypotensive effects of beta-blockers.

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

Concomitant administration of tricyclic antidepressants (such as imipramine and amitriptyline), barbiturates or phenothiazines (such as chlorpromazine), as well as other antipsychotic agents (such as clozapine) may increase the blood pressure lowering effect. Dosing of Brevibloc should be adjusted downward to avoid unexpected hypotension.

When using beta-blockers, patients at risk of anaphylactic reactions may be more reactive to allergen exposure (accidental, diagnostic, or therapeutic). Patients using beta-blockers may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions (see section 4.4).

The effects of Brevibloc may be counteracted by sympathomimetic drugs having beta-adrenergic agonist activity with concomitant administration. The dose of either agent may need to be adjusted based on patient response, or use of alternate therapeutic agents considered.

Catecholamine-depleting agents, 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.

Use of beta-blockers with moxonidine or alpha-2-agonists (such as clonidine), increases the risk of withdrawal rebound hypertension. If clonidine or moxonidine are used in combination with a beta-blocker and both treatments have to be discontinued, the beta blocker should be discontinued first and then the clonidine or moxonidine after a few days.

The use of beta-blockers with ergot derivatives may result in severe peripheral vasoconstriction and hypertension.

Data from an interaction study between Brevibloc and warfarin showed that concomitant administration of Brevibloc and warfarin does not alter warfarin plasma levels. Brevibloc concentrations, however, were equivocally higher when given with warfarin.
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.

When intravenous morphine and Brevibloc interaction was studied in normal subjects, no effect on morphine blood levels was seen. The Brevibloc steady-state blood levels were increased by 46% in the presence of morphine, but no other pharmacokinetic parameters were changed.

The effect of Brevibloc on the duration of suxamethonium chloride-induced or mivacurium-induced neuromuscular blockade has been studied in patients undergoing surgery. Brevibloc did not affect the onset of neuromuscular blockade by suxamethonium chloride, but the duration of neuromuscular blockade was prolonged from 5 minutes to 8 minutes. Brevibloc moderately prolonged the clinical duration (18.6%) and recovery index (6.7%) of mivacurium.

Although the interactions observed in studies of warfarin, digoxin, morphine, suxamethonium chloride or mivacurium are not of major clinical importance, Brevibloc should be titrated with caution in patients being treated concurrently with warfarin, digoxin, morphine, suxamethonium chloride or mivacurium.

4.6. Fertility, Pregnancy and lactation

Pregnancy
There are limited amount of data from the use of esmolol hydrochloride in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Esmolol hydrochloride is **not recommended during pregnancy.**

Based on the pharmacological action, in the later period of pregnancy, side effects on the foetus and neonate (especially hypoglycemia, hypotension and bradycardia) should be taken into account.

If treatment with Brevibloc is considered necessary, the uteroplacental blood flow and foetal growth should be monitored. The newborn infant must be closely monitored.

Breastfeeding
Esmolol hydrochloride should not be used during breast-feeding.

It is not known whether esmolol hydrochloride/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded.

Fertility
There are no human data on the effects of esmolol on fertility.

4.7. Effects on ability to drive and use machines

Not relevant.

4.8. Undesirable effects

In case of undesirable effects, the dose of Brevibloc can be reduced or discontinued.

Most of the undesirable effects observed have been mild and transient. The most important one has been hypotension. The following undesirable effects are ranked according to MedDRA System Organ Class (SOC) and to their frequency.

Note: The frequency of occurrence of adverse events is classified as follows:

Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1000 to < 1/100)
Very rare (<1/10000)
Not known (Cannot be estimated from the available data)

System Organ Class	Frequency				
	Very common	**Common**	**Uncommon**	**Very rare**	**Not known**
Metabolism and nutrition disorders		Anorexia			Hyperkalemia Metabolic acidosis
Psychiatric disorders		Depression Anxiety	Thinking abnormal		
Nervous system disorders		Dizziness [1] Somnolence Headache Paraesthesiae Disturbance in attention Confusional state Agitation	Syncope Convulsion Speech disorder		
Eye disorders			Visual impairment		
Cardiac disorders			Bradycardia Atrioventricular block Pulmonary arterial pressure increased Cardiac Failure Ventricular extrasystoles Nodal rhythm Angina pectoris	Sinus arrest Asystole	Accelerated idioventricular rhythm Coronary arteriospasm Cardiac arrest.
Vascular disorders	Hypotension		Peripheral ischaemia Pallor Flushing	Thrombophlebitis [2]	

[1] Dizziness and diaphoresis are in association with symptomatic hypotension. [2] In association with Injection and Infusion site reactions.

System Organ Class	Frequency				
	Very common	**Common**	**Uncommon**	**Very rare**	**Not known**
Respiratory, thoracic and mediastinal disorders			Dyspnoea Pulmonary oedema Bronchospasm Wheezing Nasal congestion Rhonchi Rales		
Gastrointestinal disorders		Nausea Vomiting	Dysgeusia Dyspepsia Constipation Dry mouth Abdominal pain		
Skin and subcutaneous tissue disorders	Diaphoresis [1]		Skin discolouration [2] Erythema [2]	Skin necrosis [2] (due to extravasation)	Psoriasis [3] Angioedema Urticaria
Musculoskeletal and connective tissue disorders			Musculoskeletal pain [4]		
Renal and urinary disorders			Urinary retention		
General disorders and administration site conditions		Asthenia Fatigue Injection site reaction Infusion site reaction Infusion site inflammation Infusion site induration	Chills Pyrexia Oedema [2] Pain [2] Infusion site burning Infusion site ecchymosis		Infusion site phlebitis Infusion site vesicles Blistering [2]

[1] Dizziness and diaphoresis are in association with symptomatic hypotension. [2] In association with Injection and Infusion site reactions.
[3] Beta-blockers as a drug class can cause psoriasis in some situations, or worsen it. [4] Including midscapular pain and costochondritis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9. Overdose

Cases of massive accidental overdoses with concentrated solutions of Brevibloc have occurred. Some of these overdoses have been fatal while others have resulted in permanent disability. Loading doses in the range of 625 mg to 2.5 g (12.5 to 50 mg/kg) have been fatal.

Symptoms
In case of overdose the following symptoms can occur: severe hypotension, sinus bradycardia, atrioventricular block, heart insufficiency, cardiogenic shock, cardiac arrest, bronchospasm, respiratory insufficiency, loss of consciousness to coma, convulsions, nausea, vomiting, hypoglycaemia and hyperkalaemia.

Treatment
Because of the short elimination half-life of Brevibloc (approximately 9 minutes), the first step in the management of toxicity should be to discontinue the administration of the drug. The time taken for symptoms to disappear following overdosing will depend on the amount of Brevibloc administered. This may take longer than the 30 minutes seen with discontinuation at therapeutic dose levels of Brevibloc. Artificial respiration may be necessary. Based on the observed clinical effects, the following general measures should also be considered:

Bradycardia: atropine or another anticholinergic drug should be given i.v. When the bradycardia cannot be treated sufficiently a pacemaker may be necessary.

Bronchospasm: nebulised beta-2-sympathomimetics should be given. If this is not sufficient intravenous beta-2-sympathomimetics or aminophylline can be considered.

Symptomatic hypotension: fluids and/or pressor agents should be given i.v.

Cardiovascular depression or cardiac shock: diuretics or sympathomimetics can be administered. The dose of sympathomimetics (depending on the symptoms: dobutamine, dopamine, noradrenaline, isoprenaline, etc.) depends on the therapeutic effect.

In case further treatment is necessary, the following agents can be given i.v. based on the clinical situation and judgement of the treating healthcare professional:

- Atropine;
- Inotropic agents;
- Calcium ions.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Beta-blocking agents, selective.
ATC code: C07AB09

Brevibloc is a beta-selective (cardioselective) adrenergic receptor blocking agent. At therapeutic doses Brevibloc has no significant intrinsic sympathomimetic activity (ISA) or membrane stabilising activity.

Esmolol hydrochloride, the active ingredient of Brevibloc, is chemically related to the phenoxy propanolamine class of beta-blockers.

Based on the pharmacological properties Brevibloc has a rapid onset and a very short duration of action by which the dose can be quickly adjusted.

When an appropriate loading dose is used, steady state blood levels are obtained within 5 minutes. However, the therapeutic effect is achieved sooner than the stable plasma concentration. The infusion rate can then be adjusted to obtain the desired pharmacological effect.

Brevibloc has the known haemodynamic and electrophysiologic effect of beta-blockers:

- Reduction of the heart frequency during rest and exercise;
- Reduction of the isoprenaline caused increase of the heart frequency;
- Increase of the recovering time of the SA-node;
- Delay of the AV-conductance;
- Prolonging the AV-interval with normal sinus rhythm and during atrium stimulation without delay in the His-Purkinje tissue;
- Prolonging of PQ time, induction of AV block grade II;
- Prolonging the functional refractory period of atria and ventricles;
- Negative inotropic effect with decreased ejection fraction;
- Decrease in blood pressure.

Children
An uncontrolled pharmacokinetic/efficacy study was undertaken in 26 paediatric patients aged 2 to 16 years with supraventricular tachycardia (SVT). A loading dose of 1000 micrograms/kg of Brevibloc was administered followed by a continuous infusion of 300 micrograms/kg/minute. SVT was terminated in 65% of patients within 5 minutes of the commencement of esmolol.

In a randomised but uncontrolled dose comparison study, efficacy was assigned in 116 paediatric patients aged 1 week to 7 years with hypertension following repair of coarctation of the aorta. Patients receiving an initial infusion of either 125 micrograms/kg, 250 micrograms/kg, or 500 micrograms/kg, followed by a continuous infusion of 125 micrograms/kg/minute, 250 micrograms/kg/minute, or 500 micrograms/kg/minute respectively. There was no significant

difference in hypotensive effect between the 3 dosage groups. 54% of patients overall required medication other than Brevibloc to achieve satisfactory blood pressure control. No difference was apparent in this regard between the different dose groups.

5.2. Pharmacokinetic properties

Absorption
The kinetics of esmolol are linear in healthy adults, the plasma concentration is proportional to the dose. If a loading dose is not used then steady-state blood concentrations are reached within 30 minutes with doses of 50 to 300 micrograms/Kg per minute.

Distribution
The distribution half-life of esmolol hydrochloride is very fast, about 2 minutes.
The volume of distribution is 3.4 l/kg.Esmolol hydrochloride is 55% bound to human plasma protein compared with only 10% for the acid metabolite.

Biotransformation
The metabolism of esmolol hydrochloride is independent when the dose is between 50 and 300 micrograms/kg/minute.

Esmolol hydrochloride is metabolised by esterases into an acid metabolite (ASL-8123) and methanol. This occurs through hydrolysis of the ester group by esterases in the red blood cells.

Elimination
The elimination half-life after intravenous administration is approximately 9 minutes.
The total clearance is 285 ml/kg/minute; this is independent of the circulation of the liver or any other organ. Esmolol hydrochloride is excreted by the kidneys, partly unchanged (less than 2% of the administered amount), partly as acid metabolite that has a weak (less than 0.1% of esmolol) beta-blocking activity. The acid metabolite is excreted in the urine and has a half-life of about 3.7 hours.

Children
A pharmacokinetic study was undertaken in 22 paediatric patients aged 3 to 16 years. A loading dose of 1000 micrograms/kg of Brevibloc was administered, followed by a continuous infusion of 300 micrograms/kg/minute. The observed mean total body clearance was 119 ml/kg/minute, the mean volume of distribution 283 ml/kg and the mean terminal elimination half-life 6.9 minutes, indicating that Brevibloc kinetics in children are similar to those in adults. However, large inter-individual variability was observed.

5.3. Preclinical safety data

No teratogenic effect has been observed in animal studies. In rabbits an embryo toxic effect has been observed (increase in fetal resorption) which was probably caused by Brevibloc. This effect was observed at doses at least 10 times higher than the therapeutic dose. No studies have been done on the effect of Brevibloc on the fertility and on peri- and postnatal effects. Brevibloc was

found to be not mutagenic in several in vitro and in vivo test systems. The safety of Brevibloc has not been examined in long-term studies.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium acetate
Glacial acetic acid
Sodium chloride
Sodium hydroxide and/or hydrochloric acid for pH adjustment
Water for injections

6.2. Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products or sodium bicarbonate solutions.

6.3. Shelf life

2 years.

The opened product is physicochemically stable for 24 hours at 2 to 8 °C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless opening has taken place in controlled and validated aseptic conditions.

6.4. Special precautions for storage

Do not store above 25°C.
For storage conditions of the solution see section 6.3.

6.5. Nature and contents of container

10 ml Type I amber glass vial with a bromobutyl rubber stopper. Pack sizes of 3, 5, 10 and 20 vials. Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Each vial is intended for single use only. Avoid contact with alkali. The solution should be visually inspected for particulate matter and discolouration prior to administration. Only a clear and colourless or slightly coloured solution should be used. Any unused solution and the containers should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Baxter Holding B.V.
Kobaltweg 49,
3542CE Utrecht,
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

PA2299/021/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/09/2012

10. DATE OF REVISION OF THE TEXT

March 2019

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