

## Part II

### Summary of Product Characteristics

#### 1 NAME OF THE MEDICINAL PRODUCT

Brevibloc 100mg/10ml Solution for Injection.

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10ml vial contains 100mg esmolol hydrochloride (10mg/ml).

Excipients: Contains approximately 28 mg sodium per dose.

For a full list of excipients, see section 6.1.

#### 3 PHARMACEUTICAL FORM

Solution for Injection.

Clear, colourless to slight straw coloured solution.

The solution has a pH of 5 and osmolarity of 312 mOsmol/l.

#### 4 CLINICAL PARTICULARS

##### 4.1 Therapeutic Indications

- a) Supraventricular tachyarrhythmias, including atrial fibrillation, atrial flutter and sinus tachycardia or other circumstances where short-term control of ventricular rate with a short acting agent is desirable
- b) Perioperative tachycardia and hypertension including the management of tachycardia and hypertension associated with surgical procedures, such as endotracheal intubation, induction of anaesthesia, skin incision, sternotomy and aortic dissection

##### 4.2 Posology and method of administration

Intravenous Injection

Brevibloc 100mg is a ready-to-use preparation in vials at a concentration of 10mg/ml.

##### Supraventricular Tachyarrhythmia

The effective dose of Brevibloc for treatment of supraventricular tachyarrhythmia is 50 to 200mcg/kg/min, although doses as high as 300mcg/kg/min have been used. In a few patients a dosage of 25mcg/kg/min has been adequate. Brevibloc dosage in supraventricular tachyarrhythmia must be individualised by titration in which each step consists of a loading dosage followed by a maintenance dose.

##### **Flow Chart for Initiation and Maintenance of Treatment**

Loading dosage infusion of 500mcg/kg/min for 1 minute THEN maintenance infusion of 50mcg/kg/min for 4 minutes\*

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

NB: Maintenance doses above 200mcg/kg/min have not been shown to have significantly increased benefits, and the

safety of doses above 300mcg/kg/min has not been studied.

After achieving an adequate control of the heart rate and a stable clinical status in patients with supraventricular tachyarrhythmia, transition to alternative antiarrhythmic agents such as verapamil, propranolol or metoprolol, digoxin or quinidine 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:

<u>Alternative agent</u>	<u>Dosage</u>
Propranolol hydrochloride	10 - 20 mg 4 - 6 hourly (po)
Digoxin	0.125 - 0.5 mg 6 hourly (po or iv)
Verapamil	80mg 6 hourly po
Quinidine	200mg 2 hourly po

The dosage of Brevibloc should be reduced as follows:

1. Within the first hour after the first dose of the alternative agent, reduce the Brevibloc infusion rate 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 the Brevibloc infusion.

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

### **Perioperative tachycardia and hypertension**

1. In anticipation of a surgical event :  
Brevibloc should be infused as a loading dose of 500mcg/kg/min for 4 minutes followed by a maintenance dose of 300mcg/kg/min 2-5 minutes prior to the anticipated event
2. When treating tachycardia and / or hypertension in the perioperative setting, the following dose regimens may be used.
  - A) For the intraoperative treatment - during anaesthesia when immediate control is required, give an 80mg loading bolus over 15 - 30 seconds followed by a 150mcg/kg/min infusion. Titrate the infusion rate as required up to 300mcg/kg/min.
  - B) Upon awakening from anaesthesia, administer an infusion of 500mcg/kg/min for four minutes followed by a 300mcg/kg/min infusion.
  - C) For postoperative situations when time for titration is available give the 500mcg/kg/min loading dose over one minute before each titration step to produce a rapid onset of action. Use titration steps of 50, 100, 150, 200, 250 and 300mcg/kg/min given over four minutes, stopping at the desired therapeutic effect.

Additional dosing information: as the desired therapeutic effect or a safety endpoint (eg lowered blood pressure) is approached, omit the loading dose and reduce the incremental infusion to 12.5-25mcg/kg/min. Also, if desired, increase the interval between titration steps from five to ten 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

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

**Use in the elderly:** 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.

### 4.3 Contraindications

1. heart block greater than first degree
2. severe bradycardia
3. overt heart failure
4. cardiogenic shock

### 4.4 Special warnings and precautions for use

Patients with bronchospastic disease should, in general, not receive beta blockers. Because of its relative beta<sub>1</sub> selectivity and titratability, Brevibloc should be used with caution in patients with bronchospastic diseases. However, since beta<sub>1</sub> 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<sub>2</sub> agonist should be administered if necessary.

In patients with supraventricular tachyarrhythmia, Brevibloc has been shown to produce a decrease in systolic blood pressure. Accordingly patients with low pre-treatment systolic pressures should be carefully observed during titration and maintenance infusions with Brevibloc.

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, the dosage should be reduced or Brevibloc should be withdrawn and specific treatment should also be considered.

Brevibloc should be administered with caution to patients with impaired renal function because the acid metabolite of Brevibloc is primarily excreted unchanged by the kidney.

Brevibloc should be used with caution in diabetic patients.

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

Infusion concentrations of 20mg/ml have been associated with significant venous irritation and thrombophlebitis in animals and man, therefore concentrations greater than 10mg/ml should be avoided.

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

If a local infusion site reaction develops, an alternative infusion site should be used.

This medicinal product contains approximately 28 mg sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

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

Catecholamine-depleting agents 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.

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. 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 succinylcholine-induced neuromuscular blockade has been 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 are not of major clinical importance, Brevibloc should be titrated with caution in patients being treated concurrently with digoxin, morphine, succinylcholine or warfarin.

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.

There exist no data on the interactions of esmolol with calcium channel blockers; however, in common with other beta-adrenoceptor antagonists it is recommended that esmolol be used with caution in combination with verapamil in patients with impaired ventricular function. The combination should not be given to patients with conduction abnormalities and esmolol should not be administered within 48 hours of discontinuing verapamil.

## **4.6 Pregnancy and lactation**

No teratogenic effects have been observed in animal studies. However, there are no human data available and Brevibloc should only be used in pregnancy if the potential benefit outweighs the potential risk to the foetus.

It is not known whether Brevibloc is excreted in human milk, therefore caution should be exercised when Brevibloc is administered to nursing mothers.

## **4.7 Effects on ability to drive and use machines**

Not relevant.

## **4.8 Undesirable effects**

The most frequently observed side effect has been hypotension. Less frequently observed were sweating, nausea, peripheral ischaemia, confusion, somnolence, dizziness, fatigue, agitation, headache, vomiting, inflammation, induration or infiltration at the infusion site.

Rarely seen are oedema, wheezing, dyspnoea, anxiety, anorexia, constipation, urinary retention, speech disorder, abnormal vision, rigor and fever.

## **4.9 Overdose**

Overdoses of Brevibloc (esmolol hydrochloride) can cause cardiac arrest. In addition, overdoses can produce bradycardia, hypotension, electromechanical 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 2.5g (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 Brevibloc administration. Then general supportive measures should be instituted as appropriate.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Brevibloc (esmolol hydrochloride) is a beta-selective (cardioselective) adrenergic receptor blocking agent with a rapid onset, a very short duration of action and no significant intrinsic sympathomimetic or membrane stabilising activity at therapeutic doses.

### 5.2 Pharmacokinetic properties

Brevibloc (esmolol hydrochloride) is rapidly metabolised by hydrolysis of the ester linkage by esterases in the red blood cells. The distribution half-life after intravenous infusion is 2 minutes and the elimination half-life 9 minutes. Metabolism of Brevibloc results in the formation of the corresponding free acid ASL-8123 and methanol. The acid metabolite ASL-8123 has weak (less than 0.1% of esmolol) beat-blocking activity.

Consistent with the high blood-based metabolism of Brevibloc, less than 2% of the drug is excreted unchanged in the urine.

The acid metabolite has an elimination half-life of about 3.7 hours and is excreted in the urine.

Brevibloc has been shown to be 55% bound to human plasma protein compared with only 10% for the acid metabolite.

### 5.3 Preclinical safety data

Not applicable.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium acetate

Glacial acetic acid

Sodium Chloride

Sodium hydroxide or hydrochloride acid (for pH adjustment)

Water for injections

### 6.2 Incompatibilities

Brevibloc is not compatible with Sodium bicarbonate.

### 6.3 Shelf Life

Unopened: 2 years.

The product should be used immediately after opening.

### 6.4 Special precautions for storage

Store below 25°C.

### 6.5 Nature and contents of container

Type I Ph. Eur., amber glass vial with rubber stopper, 10ml. Pack sizes 3, 5, 10 and 20.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product**

For single use only.

Discard any unused contents.

## **7 MARKETING AUTHORISATION HOLDER**

Baxter Healthcare Limited  
Caxton Way  
Thetford  
Norfolk IP24 3SE  
United Kingdom

## **8 MARKETING AUTHORISATION NUMBER**

PA 0167/099/001

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 08 September 1994

Date of last renewal: 23 March 2008

## **10 DATE OF REVISION OF THE TEXT**

September 2008