BREVIBLOC
(Esmolol Hydrochloride)
Injection

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BREVIBLOC safely and effectively. See full prescribing information for BREVIBLOC injection.

BREVIBLOC (Esmolol Hydrochloride) injection, for intravenous use

Initial U.S. Approval: 1986

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3.3 Then 50 mcg per kg per min for gradual control (150 mcg per kg per minute for immediate control) adjusted to a maximum of 200 (tachycardia) or 300 (hypertension) mcg per kg per min (2.2)

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Revised: [04/2014]
4 CONTRAINDICATIONS
BREVIBLOC (Esmolol Hydrochloride) is contraindicated in patients with:
- Severe sinus bradycardia: May precipitate or worsen bradycardia resulting in cardiogenic shock and cardiac arrest (see Warnings and Precautions (5.2)).
- Heart block greater than first degree: Second- or third-degree atrioventricular block may precipitate or worsen bradycardia resulting in cardiogenic shock and cardiac arrest (see Warnings and Precautions (5.2)).
- Sick sinus syndrome: May precipitate or worsen bradycardia resulting in cardiogenic shock and cardiac arrest (see Warnings and Precautions (5.2)).
- Depreciated heart failure: May worsen heart failure.
- Cardiogenic shock: May precipitate cardiovascular collapse and cause cardiac arrest.
- IV administration of calcium-potassium channel antagonists (e.g., verapamil) and BREVIBLOC in close proximity (i.e., while cardiac effects from the other are still present); fatal cardiac arrests have occurred in patients receiving BREVIBLOC and intravenous verapamil.
- Pulmonary hypertension: May precipitate cardiopulmonary compromise.
- Hypersensitivity reactions, including anaphylaxis, to esmolol or any of the inactive ingredients of the product (cross-sensitivity between beta blockers is possible).

5 WARNINGS AND PRECAUTIONS
5.1 Hypotension
Hypotension can occur at any dose but is dose-related. Patients with hemodynamic compromise or on interacting medications are at particular risk. Severe reactions may include loss of consciousness, cardiac arrest, and death. For control of ventricular rate, dosages greater than 200 mcg per kg per min are not recommended. Monitor patients closely, especially if pretreatment blood pressure is low. In cases of an unexpected drop in blood pressure, reduce or stop BREVIBLOC injection. Decrease of dose or termination of infusion reduces hypotension, usually within 30 minutes.

5.2 Bradycardia
Bradycardia, including sinus pause, heart block, severe bradycardia, and cardiac arrest have occurred with the use of BREVIBLOC injection. Patients with first-degree atrioventricular block, sinus node dysfunction, or conduction disorders may be at particular risk. Decrease of heart rate and rhythm in patients receiving BREVIBLOC (see Contraindications (4)).

5.3 Cardiac Failure
Beta blockers, like BREVIBLOC injection, can cause depression of myocardial contractility and may precipitate heart failure and cardiogenic shock. At the first sign or symptom of impending cardiac failure, stop BREVIBLOC and start supportive therapy (see Overtreatment (10)).

5.4 Intraoperative and Postoperative Tachycardia and/or Hypertension
Monitor vital signs closely and titrate BREVIBLOC slowly in the treatment of patients whose blood pressure is primarily driven by vasocostriction associated with hypothermia.

5.5 Reactive Airways Disease
Patients with reactive airways disease should, in general, not receive beta blockers. Because of its relative beta, selectivity and titratability, titrate BREVIBLOC to the lowest possible effective dose. In the event of bronchospasm, stop the infusion immediately; a beta2 stimulating agent may be administered with appropriate monitoring of ventricular rates.

5.6 Use in Patients with Diabetes Mellitus and Hypoglycemia
In patients with hypoglycemia, or diabetics patients (especially those with lability diabetes) who are receiving insulin or other hypoglycemic agents, beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be masked.

5.7 Infusion Site Reactions
Infusion site reactions have occurred with the use of BREVIBLOC injection. They include irritation, inflammation, and severe reactions (thrombophlebitis, necrosis, and blistering), in particular when associated with extravasation (see Adverse Reactions (6)). Avoid infusions into small veins or through a butterfly catheter. If a local infusion site reaction develops, use an alternative infusion site and avoid extravasation.

5.8 Use in Patients with Prinzmetal’s Angina
Beta blockers may exacerbate anginal attacks in patients with Prinzmetal’s angina because of unopposed alpha receptor–mediated coronary artery vasospasm. Do not use nonselective beta blockers.

5.9 Use in Patients with Phaeochromocytoma
Use in Patients with Phaeochromocytoma is being prepared.

5.10 Use in Hypovolemic Patients
In hypovolemic patients, BREVIBLOC injection can attenuate reflex tachycardia and increase the risk of hypotension.

5.11 Use in Patients with Peripheral Circulatory Disorders
In patients with peripheral circulatory disorders (including Raynaud’s disease or syndrome, and peripheral occlusive vascular disease), BREVIBLOC may aggravate peripheral circulatory disorders.

5.12 Abrupt Discontinuation of BREVIBLOC Injection
Severe exacerbations of angina, myocardial infarction, and ventricular arrhythmias have been reported in patients with coronary artery disease upon abrupt discontinuation of beta blocker therapy. Observe patients for signs of myocardial ischemia when discontinuing BREVIBLOC.

5.13 Hyperkalemia
Beta blockers, 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. Intravenous administration of beta blockers has been reported to cause potentially life-threatening hyperkalemia in hemodialysis patients. Monitor serum electrolytes during therapy with BREVIBLOC.

5.14 Use in Patients with Metabolic Acidosis
Beta blockers, including BREVIBLOC, have been reported to cause hyperkalemic renal tubular acidosis. Acidosis in general may be associated with reduced cardiac contractility.

5.15 Use in Patients with Hypothyroidism
Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hypothyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, monitor patients for signs of thyrotoxicosis when withdrawing beta blockers.

5.16 Use in Patients at Risk of Severe Acute Hypersensitivity Reactions
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 or anaphylactoid reactions (see Drug Interactions (7)).

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The following adverse reaction rates are based on use of BREVIBLOC (Esmolol Hydrochloride) in clinical trials involving 269 patients with supraventricular tachycardia and/or ventricular arrhythmias and conduction disorders and postoperative and postpartum patients enrolled in clinical trials. Most adverse effects observed in controlled clinical trial settings have been mild and transient. The most important and common adverse effect has been hypotension (see Warnings and Precautions (5.1)). Deaths have been reported in post-marketing experience occurring during or after surgery, it is not clear whether BREVIBLOC was a contributing factor.
at the low end of the dosing range, reflecting greater frequency of decreased renal or cardiac function and of concomitant
in responses between the elderly and younger patients. In general, dose selection for an elderly patient should usually start
whether they responded differently from younger subjects. Other reported clinical experience has not identified differences
Clinical studies of BREVIBLOC injection did not include sufficient numbers of subjects aged 65 and over to determine
The safety and effectiveness of BREVIBLOC in pediatric patients have not been established.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Esmolol hydrochloride has been shown to produce increased fetal resorptions with minimal maternal toxicity in rabbits when given in doses approximately 8 times the maximum human maintenance dose (300 mcg/kg/min). There are no adequate and well-controlled studies in pregnant women. BREVIBLOC injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenicity studies in rats at intravenous dosages of esmolol hydrochloride up to 3000 mcg/kg/min (10 times the maximum human maintenance dosages) for 30 minutes daily produced no evidence of maternal toxicity, embryotoxicity or teratogenicity, while a small number of rats receiving 10,000 mcg/kg/min produced maternal toxicity and lethality in some litters. After subcutaneous dosages up to 1000 mcg/kg/min for 30 minutes daily produced no evidence of maternal toxicity, embryotoxicity or teratogenicity, while 2500 mcg/kg/min produced minimal maternal toxicity and increased fetal resorptions.

8.2 Labor and Delivery

Although there are no adequate and well-controlled studies in pregnant women, use of esmolol in the last trimester of pregnancy or during labor and delivery has been reported to cause fetal bradycardia, which continued after termination of drug infusion. BREVIBLOC injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from BREVIBLOC, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of BREVIBLOC in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of BREVIBLOC injection did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger patients. In general, dose selection for an elderly patient should usually start at the low end of the dosage range, reflecting greater frequency of decreased renal or cardiac function and of concomitant disease or other drug therapy.
In patients undergoing radionuclide angiography, BREVIBLOC, at dosages of 200 mcg/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 mcg/kg/min). During exercise, BREVIBLOC produced reductions in heart rate, rate pressure product and cardiac index which were also similar to those produced by propranolol, but BREVIBLOC produced a significantly larger fall in systolic blood pressure. In patients undergoing cardiac catheterization, the maximum therapeutic dose of 300 mcg/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 30 minutes after the discontinuation of BREVIBLOC infusion, all of the hemodynamic parameters had returned to pretreatment levels.

The relative cardioselectivity of BREVIBLOC was demonstrated in 10 mildly asthmatic patients. Infusions of BREVIBLOC at 100, 200 and 300 mcg/kg/min produced no significant increases in specific airway resistance compared to placebo. At 300 mcg/kg/min, BREVIBLOC produced slightly enhanced bronchomotor sensitivity to dry air stimuli. 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 mcg/kg/min they 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 COPD who received therapeutic dosages of BREVIBLOC for treatment of supraventricular tachycardia (31 patients) or in perioperative settings (32 patients).

12.3 Pharmacokinetics

Esmolol is rapidly metabolized 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/hr/kg, which is greater than cardiac output; thus the metabolism of esmolol is not limited by the rate of blood flow to metabolizing tissues such as the liver or affected by hepatic or renal blood flow. Esmolol has a rapid distribution half-life of about 2 minutes and a half-life of about 8 minutes.

Using an appropriate loading dose, steady-state blood levels of BREVIBLOC for dosages from 50-300 mcg/kg/min are obtained within five minutes. Steady-state is reached in about 30 minutes without the loading dose. Steady-state blood levels of esmolol 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 esmolol 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 esmolol, less than 2% of the drug is excreted unchanged in the urine. Within 24 hours of the end of infusion, the acid metabolite of esmolol in urine accounts for approximately 73-88% of the dosage.

Metabolism of esmolol results in the formation of the corresponding free acid and methanol. The acid metabolite has been shown in animals to have negligible activity 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. After a 4 hour maintenance infusion of 150 mcg/kg, the plasma concentrations of esmolol are similar in subjects with normal renal function and in patients with ESRD on dialysis. The half-life of the acid metabolite of BREVIBLOC, which is primarily excreted unchanged by the kidney, is increased about 12-fold to 48 hours in patients with ESRD. The peak concentrations of the acid metabolite are doubled in ESRD.

Methanol blood levels, monitored in subjects receiving BREVIBLOC for up to 6 hours at 300 mcg/kg/min and 24 hours at 150 mcg/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.

13 NONCLINICAL TOXICOLOGY

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

14 CLINICAL STUDIES

Supraventricular Tachycardia

In two multicenter, randomized, double-blind, controlled comparisons of BREVIBLOC injection with placebo and propranolol, maintenance doses of 50 to 200 mcg/kg/min of BREVIBLOC were found to be more effective than placebo and about as effective as propranolol, 3-6 mg given by bolus injections, in the treatment of supraventricular tachycardia, principally atrial fibrillation and atrial flutter. The majority of these patients developed their arrhythmias postoperatively. About 60-75% of the patients treated with BREVIBLOC developed either a 20% reduction in heart rate, a decrease in heart rate to less than 100 bpm, or, rarely, conversion to normal sinus rhythm and about 95% of these patients did so at a dosage of 200 mcg/kg/min or less. The average effective dosage of BREVIBLOC was approximately 100 mcg/kg/min in the two studies. Other multicenter baseline-controlled studies gave similar results. In the comparison with propranolol, about 50% of patients in both the BREVIBLOC and propranolol groups were on concomitant digoxin. Response rates were slightly higher with both beta blockers in the digoxin-treated patients. In all studies significant decreases of blood pressure occurred in 20-50% of patients, identified either as adverse reaction reports by investigators, or by observation of systolic pressure less than 90 mmHg or diastolic pressure less than 50 mmHg. The hypotension was symptomatic (mainly hypotension or dizziness) in about 12% of patients, and therapy was discontinued in about 11% of patients, half of whom were symptomatic. Hypotension was more common with BREVIBLOC (53%) than with propranolol (17%). The hypotension was rapidly reversible with decreased infusion rate or after discontinuation of therapy with BREVIBLOC. For both BREVIBLOC and propranolol, hypotension was reported less frequently in patients receiving concomitant digoxin.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

BREVIBLOC PREMIXED Injection

- NDC 10019-055-61, 2500 mg / 250 mL (10 mg/mL) Ready-to-use INTRAVIA Bags
- NDC 10019-075-87, 2000 mg / 100 mL (20 mg/mL) Ready-to-use INTRAVIA Bags

BREVIBLOC Double Strength Premixed Injection

- NDC 10019-115-01, 100 mcg / 10 mL (10 mcg/mL) Ready-to-use Vials, Package of 25

16.2 Storage


Each bag contains no preservative. Once drug has been withdrawn from ready-to-use bag, the bag should be used within 24 hours, with any unused portion discarded.

Visually inspect the container. If the administration port protector is damaged, detached, or not present, discard container as solution path sterility may be impaired.

Do not use plastic containers in series connections. Such use could result in an embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Do not remove unit from overwrap until ready to use. Do not use if overwrap has been previously opened or damaged. The overwrap is a moisture barrier. The inner bag maintains sterility of the solution. Tear overwrap at notch and remove premixed bag. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

Check for minute leaks by squeezing the inner bag firmly. If leaks are found, discard solution, as sterility may be impaired. Do not use unless the solution is clear (colorless to light yellow) and the seal is intact.

17 PATIENT COUNSELING INFORMATION

Physicians should inform patients of the risks associated with BREVIBLOC injection:

- The most common adverse reactions are symptomatic hypotension (hypershuddorosis, dizziness) and asymptomatic hypotension.