Esmolol Hydrochloride

CATEGORIES:

Ingredients: Esmolol Hydrochloride.
Indications: Tachycardia, supraventricular; Tachycardia, intraoperative; Tachycardia, postoperative; Hypertension, perioperative.
Off-label Indications: Not clinically relevant: Ischemia, Myocardial; Tachyarrhythmia.
Pregnancy Category C.
FDA Approved 1986-12-01.
DRUG CLASS: Antiadrenergics, beta blocking; Antiarrhythmics, class II.

Brand Names: Brevibloc (US, Argentina, Austria, Belgium, Brazil, Canada, Czech-republic, Denmark, England, Hungary, Israel, Italy, Korea, Mexico, Netherlands, Philippines, Poland, South-africa, Switzerland, Taiwan, Uruguay); Miniblock (India). (International brand names outside U.S. in italics).

DESCRIPTION:

NOT FOR DIRECT INTRAVENOUS INJECTION. AMPUL MUST BE DILUTED PRIOR TO ITS INFUSION. (SEE DOSAGE AND ADMINISTRATION)

Esmolol hydrochloride is a beta<sub>1</sub>-selective (cardioselective) adrenergic receptor blocking agent with a very short duration of action (elimination half-life is approximately 9 minutes). The chemical name for esmolol hydrochloride is (±)-methyl p-[2-hydroxy-3-(isopropylamino)propoxy]hydrocinnamate hydrochloride. Esmolol hydrochloride has the empirical formula C<sub>16</sub>H<sub>26</sub>NO<sub>4</sub>Cl and a molecular weight of 331.8. It has one asymmetric center and exists as an enantiomeric pair. Esmolol hydrochloride is a white to off-white crystalline powder. It is a relatively hydrophilic compound which is very soluble in water and freely soluble in alcohol. Its partition coefficient (octanol/water) at pH 7.0 is 0.42 compared to 17.0 for propranolol. Brevibloc injection is a clear, colorless to light yellow, sterile, nonpyrogenic solution.

2.5 g, 10 ml ampul: Each ml contains 250 mg esmolol hydrochloride in 25% propylene glycol, 25% alcohol and water for injection; buffered with 17.0 mg sodium acetate, and 0.00715 ml glacial acetic acid. Sodium hydroxide and/or hydrochloric acid added, as necessary, to adjust pH to 3.5-5.5.

100 mg, 10 ml single dose vial: Each ml contains 10 mg esmolol hydrochloride and water for injection, buffered with 2.8 mg Sodium Acetate, and 0.546 mg glacial acetic acid. Sodium hydroxide and/or hydrochloric acid added, as necessary, to adjust pH to 4.5-5.5.

Storage: Store at controlled room temperature 15-30°C (59-86°F). Freezing does not adversely affect the product, but exposure to elevated temperatures should be avoided.

CLINICAL PHARMACOLOGY:

Esmolol HCl is a beta<sub>1</sub>-selective (cardioselective) adrenergic receptor blocking agent with rapid onset, a very short duration of action, and no significant intrinsic sympathomimetic or membrane stabilizing activity at therapeutic dosages. Its elimination half-life after intravenous infusion is approximately 9 minutes. Esmolol HCl inhibits the beta<sub>1</sub> receptors located chiefly in cardiac muscle, but this preferential effect is not absolute and at higher doses it begins to inhibit beta<sub>2</sub> receptors located chiefly in the bronchial and vascular musculature.

Pharmacokinetics and Metabolism

Esmolol HCl 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/kg/h, which is greater than cardiac output; thus the metabolism of esmolol HCl 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 HCl 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 esmolol HCl for dosages from 50-300 μg/kg/min (0.05-0.3 mg/kg/min) are obtained within 5 minutes. (Steady-state is reached in about 30 minutes without the loading dose.) Steady-state blood levels of esmolol HCl 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 HCl 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 HCl, 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 esmolol HCl.

Metabolism of esmolol HCl results in the formation of the corresponding free acid and methanol. The acid metabolite has been shown in animals to have about 1/1500th the activity of esmolol and in normal volunteers its blood levels do not correspond to the level of beta-blockade. The acid metabolite has an elimination half-life of about 3.7 hours and is excreted in the urine with a clearance approximately equivalent to the glomerular filtration rate. Excretion of the acid metabolite is significantly decreased in patients with renal disease, with the elimination half-life increased to about 10-fold that of normals, and plasma levels considerably elevated.

Methanol blood levels, monitored in subjects receiving esmolol HCl for up to 6 hours at 300 μg/kg/min (0.3 mg/kg/min) and 24 hours at 150 μg/kg/min (0.15 mg/kg/min), approximated endogenous levels and were less than 2% of levels usually associated with methanol toxicity. Esmolol HCl has been shown to be 55% bound to human plasma protein, while the acid metabolite is only 10% bound.

**Pharmacodynamics**

Clinical pharmacology studies in normal volunteers have confirmed the beta blocking activity of esmolol HCl, showing reduction in heart rate at rest and during exercise, and attenuation of isoproterenol-induced increases in heart rate. Blood levels of esmolol HCl 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 electrophysiology studies, esmolol HCl 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, esmolol HCl, at dosages of 200 μg/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, esmolol HCl 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 catheterization, the maximum therapeutic dose of 300 μg/kg/min (0.3 mg/kg/min) of esmolol HCl 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 esmolol HCl infusion, all of the hemodynamic parameters had returned to pretreatment levels.

The relative cardioselectivity of esmolol HCl was demonstrated in 10 mildly asthmatic patients. Infusions of esmolol HCl [100, 200 and 300 μg/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 μg/kg/min (0.3 mg/kg/min), esmolol HCl produced slightly enhanced bronchomotor sensitivity to dry air stimulus. These effects were not clinically significant, and esmolol HCl was well tolerated by all patients. Six (6) 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 COPD who received therapeutic dosages of esmolol HCl for treatment of supraventricular tachycardia (51 patients) or in perioperative settings (32 patients).

**Supraventricular Tachycardia**

In two multicenter, randomized, double-blind, controlled comparisons of esmolol HCl with placebo and propranolol, maintenance doses of 50 to 300 μg/kg/min (0.05 to 0.3 mg/kg/min) of esmolol HCl 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 60-70% of the patients treated with esmolol HCl had a desired therapeutic effect (either a 20% reduction in heart rate, a decrease in heart rate to less than 100 bpm, or, rarely, conversion to NSR) and about 95% of those who responded did so at a dosage of 200 μg/kg/min (0.2 mg/kg/min) or less. The average effective dosage of esmolol HCl was approximately 100-115 μg/kg/min (0.1-0.115 mg/kg/min) in the two studies. Other multicenter baseline-controlled studies gave essentially similar results. In the comparison with propranolol, about 50% of patients in both the esmolol HCl 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 diaphoresis or dizziness) in about 12% of patients, and therapy was discontinued in about 11% of patients, about half of whom were symptomatic. In comparison to propranolol, hypotension was about three times as frequent with esmolol HCl, 53% vs. 17%. The hypotension was rapidly reversible with decreased infusion rate or after discontinuation of therapy with esmolol HCl. For both esmolol HCl and propranolol, hypotension was reported less frequently in patients receiving concomitant digoxin.

INDICATIONS AND USAGE:

**Supraventricular Tachycardia**

Esmolol HCl is indicated for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other emergent circumstances where short term control of ventricular rate with a short-acting agent is desirable. Esmolol HCl is also indicated in noncompensatory sinus tachycardia where, in the physician's judgement, the rapid heart rate requires specific intervention. Esmolol HCl is not intended for use in chronic settings where transfer to another agent is anticipated.

**Intraoperative and Postoperative Tachycardia and/or Hypertension**

Esmolol HCl is indicated for the treatment of tachycardia and hypertension that occur during induction 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. Use of esmolol HCl to prevent such events is not recommended.

**CONTRAINDICATIONS:**

Esmolol HCl is contraindicated in patients with sinus bradycardia, heart block greater than first degree, cardiogenic shock or overt heart failure (see WARNINGS).

**WARNINGS:**

**Hypotension**

In clinical trials 20-50% of patients treated with esmolol HCl have experienced 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 diaphoresis or dizziness). Hypotension can occur at any dose but is dose-related so that doses beyond 200 μg/kg/min (0.2 mg/kg/min) are not recommended. Patients should be closely monitored, especially if pretreatment blood pressure is low. Decrease of dose or termination of infusion reverses hypotension, usually within 30 minutes.

**Cardiac Failure**

Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. Continued depression of the myocardium with beta blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, esmolol HCl should be withdrawn. Although withdrawal may be sufficient because of the short elimination half-life of esmolol HCl, specific treatment may also be considered (see OVERDOSAGE). The use of esmolol HCl for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically 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 esmolol HCl's effects, several cases of death have been reported in complex clinical states where esmolol HCl was presumably being used to control ventricular rate.

**Intraoperative and Postoperative Tachycardia and/or Hypertension**

Esmolol HCl should not be used as the treatment for hypertension in patients in whom the increased blood pressure is primarily due to the vasoconstriction associated with hypothermia.

**Bronchospastic Diseases**

**PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS.**

Because of its relative beta₁ selectivity and titratability, esmolol HCl may be used with caution in patients with bronchospastic diseases. However, since beta₁ selectivity is not absolute, esmolol HCl should be carefully titrated to obtain the lowest possible effective dose. In the event of bronchospasm, the infusion should be terminated immediately; a beta₂ stimulating agent may be administered if conditions warrant but should be used with particular caution as patients already have rapid ventricular rates.

**Diabetes Mellitus and Hypoglycemia**

Esmolol HCl should be used with caution in diabetic patients requiring a beta blocking agent. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

**PRECAUTIONS:**

**General**

Infusion concentrations of 20 mg/ml were associated with more serious venous irritation, including thrombophlebitis, than concentrations of 10 mg/ml. Extravasation of 20 mg/ml may lead to a serious local reaction and possible skin necrosis. Concentrations greater than 10 mg/ml or infusion into small veins or through a butterfly catheter should be avoided.

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

Care should be taken in the intravenous administration of esmolol HCl as sloughing of the skin and necrosis have been reported in association with infiltration and extravasation of intravenous infusions.

**Carcinogenesis, Mutagenesis, and Impairment of Fertility**

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

**Pregnancy Category C**

Teratogenicity studies in rats at intravenous dosages of esmolol HCl up to 3000 µg/kg/min (3 mg/kg/min) (10 times the maximum human maintenance dosage) for 30 minutes daily produced no evidence of maternal toxicity, embroyotoxicity or teratogenicity, while a dosage of 10,000 µg/kg/min (10 mg/kg/min) produced maternal toxicity and lethality. In rabbits, intravenous dosages up to 1000 µg/kg/min (1 mg/kg/min) for 30 minutes daily produced no evidence of maternal toxicity, embroyotoxicity or teratogenicity, while 2500 µg/kg/min (2.5 mg/kg/min) produced minimal maternal toxicity and increased fetal resorptions.

Although there are no adequate and well-controlled studies in pregnant women. Esmolol HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers

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

Pediatric Use

The safety and effectiveness of esmolol HCl in children have not been established.

INTERACTIONS:

Catecholamine-depleting drugs, (e.g., reserpine), may have an additive effect when given with beta blocking agents. Patients treated concurrently with esmolol HCl 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 esmolol HCl and warfarin showed that concomitant administration of esmolol HCl and warfarin does not alter warfarin plasma levels. Esmolol HCl concentrations were equivocally higher when given with warfarin, but this is not likely to be clinically important.

When digoxin and esmolol HCl were concomitantly administered intravenously to normal volunteers, there was a 10-20% increase in digoxin blood levels at some time points. Digoxin did not affect esmolol HCl pharmacokinetics. When intravenous morphine and esmolol HCl were concomitantly administered in normal subjects, no effect on morphine blood levels was seen, but esmolol HCl steady-state blood levels were increased by 46% in the presence of morphine. No other pharmacokinetic parameters were changed.

The effect of esmolol HCl on the duration of succinylcholine-induced neuromuscular blockade was studied in patients undergoing surgery. The onset of neuromuscular blockade by succinylcholine was unaffected by esmolol HCl, 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, esmolol HCl should be titrated with caution in patients being treated concurrently with digoxin, morphine, succinylcholine or warfarin.

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 epinephrine used to treat allergic reaction.

Caution should be exercised when considering the use of esmolol HCl and Verapamil in patients with depressed myocardial function. Fatal cardiac arrests have occurred in patients receiving both drugs. Additionally, esmolol HCl should not be used to control supraventricular tachycardia in the presence of agents which are vasoconstrictive and inotropic such as dopamine, epinephrine, and norepinephrine because of the danger of blocking cardiac contractility when systemic vascular resistance is high.

ADVERSE REACTIONS:

The following adverse reaction rates are based on use of esmolol HCl 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 WARNINGS). Deaths have been reported in post-marketing experience occurring during complex clinical states where esmolol HCl was presumably being used simply to control ventricular rate (see WARNINGS, Cardiac Failure).

**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 esmolol HCl infusion in 63% of these patients and within 30 minutes after discontinuation of infusion in 80% of the remaining patients. Diaphoresis accompanied hypotension in 10% of patients. Peripheral ischemia occurred in approximately 1% of patients. Pallor, flushing, bradycardia (heart rate less than 50 beats per minute), chest pain, syncope, pulmonary edema and heart block have each been reported in less than 1% 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.

**Central Nervous System:** Dizziness has occurred in 3% of patients; somnolence in 3%, confusion, headache, and agitation in about 2%, and fatigue in about 1% of patients. Paresthesia, asthenia, depression, abnormal thinking, anxiety, anorexia, and lightheadedness were reported in less than 1% of patients. Seizures were also reported in less than 1% of patients with one death.

**Respiratory:** Bronchospasm, wheezing, dyspnea, nasal congestion, rhonchi, and rales have each been reported in less than 1% of patients.

**Gastrointestinal:** Nausea was reported in 7% of patients. Vomiting has occurred in about 1% of patients. Dyspepsia, constipation, dry mouth, and abdominal discomfort have each occurred in less than 1% of patients. Taste perversion has also been reported.

**Skin (infusion site):** Infusion site reactions including inflammation and induration were reported in about 8% of patients. Edema, erythema, skin discoloration, burning at the infusion site, thrombophlebitis, and local skin necrosis from extravasation have each occurred in less than 1% of patients.

**Miscellaneous:** Each of the following has been reported in less than 1% of patients: Urinary retention, speech disorder, abnormal vision, midscapular pain, rigors, and fever.

**OVERDOSAGE:**

**Acute Toxicity:** A few cases of massive accidental overdosage of esmolol HCl have occurred due to errors in dilution. These intravenous bolus doses of esmolol HCl of 5000-6250 μg/kg (5-6.25 mg/kg) over 1-2 minutes have produced hypotension, bradycardia, drowsiness and loss of consciousness. The effects have resolved within 10 minutes, in some cases with administration of a pressor agent.

Because of its approximately 9-minute elimination half-life, the first step in the management of toxicity should be to discontinue the esmolol HCl infusion. Then, based on the observed clinical effects, the following general measures should also be considered:

**Bradycardia:** Intravenous administration of atropine or another anticholinergic drug.

**Bronchospasm:** Intravenous administration of a beta₂ stimulating agent and/or a theophylline derivative.

**Cardiac Failure:** Intravenous administration of a diuretic and/or digitalis glycoside. In shock resulting from inadequate cardiac contractility, intravenous administration of dopamine, dobutamine, isoproterenol, or amrinone may be considered.

**Symptomatic Hypotension:** Intravenous administration of fluids and/or pressor agents.

**DOSAGE AND ADMINISTRATION:**

**2.5 g Ampul**

THE 2.5 g AMPUL IS NOT FOR DIRECT INTRAVENOUS INJECTION. THIS DOSAGE FORM IS A CONCENTRATED, POTENT DRUG WHICH MUST BE DILUTED PRIOR TO ITS INFUSION. ESMOLOL HCl SHOULD NOT BE ADMIXED WITH SODIUM BICARBONATE. ESMOLOL HCl SHOULD NOT BE MIXED WITH OTHER DRUGS PRIOR TO DILUTION IN A SUITABLE INTRAVENOUS FLUID. (See Compatibility With Commonly Used Intravenous Fluids)

**Dilution:** Aseptically prepare a 10 mg/ml infusion, by adding two 2.5 g ampuls to a 500 ml container, or one 2.5 g ampul to a 250 ml container, of a compatible intravenous solution listed below. (Remove overage prior to dilution as appropriate.) This yields a final concentration of 10 mg/ml. The diluted solution is stable for at least 24 hours at room temperature. Note: Concentrations of esmolol HCl greater than 10 mg/ml are likely to produce irritation on continued infusion (see PRECAUTIONS). Esmolol HCl has, however, been well tolerated when administered via a central vein.

**100 mg Vial**

This dosage form is prediluted to provide a ready-to-use 10 mg/ml concentration recommended for esmolol HCl intravenous administration. It may be used to administer the appropriate esmolol HCl 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/min for a 70 kg patient would be 3.5 ml.
**Supraventricular Tachycardia**

In the treatment of supraventricular tachycardia, responses to esmolol HCl usually (over 95%) occur within the range of 50 to 200 μg/kg/min (0.05 to 0.2 mg/kg/min). The average effective dosage is approximately 100 μg/kg/min (0.1 mg/kg/min) although dosages as low as 25 μg/kg/min (0.025 mg/kg/min) have been adequate in some patients. Dosages as high as 300 μg/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 esmolol HCl in supraventricular tachycardia must be individualized 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 μg/kg/min (0.5 mg/kg/min) over 1 minute followed by a 4 minute maintenance infusion of 50 μg/kg/min (0.05 mg/kg/min). If an adequate therapeutic effect is observed over the 5 minutes of drug administration, maintain the maintenance infusion dosage with periodic adjustments up or down as needed. If an adequate therapeutic effect is not observed, the same loading dosage is repeated over 1 minute followed by an increased maintenance rate infusion of 100 μg/kg/min (0.1 mg/kg/min).

Continue titration procedure as above, repeating the original loading infusion of 500 μg/kg/min (0.5 mg/kg/min) over 1 minute, but increasing the maintenance infusion rate over the subsequent 4 minutes by 50 μg/kg/min (0.05 mg/kg/min) increments. As the desired heart rate or blood pressure is approached, omit subsequent loading doses and titrate the maintenance dosage up or down to endpoint. Also, if desired, increase the interval between steps from 5-10 minutes (see TABLE 1).

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Loading Dose (over 1 minute)</th>
<th>Maintenance Dosage (over 4 minutes)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>μg/kg/min</td>
<td>mg/kg/min</td>
</tr>
<tr>
<td>0-1</td>
<td>500</td>
<td>0.5</td>
</tr>
<tr>
<td>1-5</td>
<td>500</td>
<td>0.5</td>
</tr>
<tr>
<td>5-6</td>
<td>500</td>
<td>0.5</td>
</tr>
<tr>
<td>6-10</td>
<td>500</td>
<td>0.5</td>
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<td>10-11</td>
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<td>11-15</td>
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<td>15-16</td>
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<tr>
<td>16-20</td>
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<tr>
<td>20-(24 hr)</td>
<td>Maintenance dose titrated to heart rate or other clinical endpoint.</td>
<td></td>
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</tbody>
</table>

* As the desired heart rate or endpoint is approached, the loading infusion may be omitted and the maintenance infusion titrated to 300 μg/kg/min (0.3 mg/kg/min) or downward as appropriate. Maintenance dosages above 200 μg/kg/min (0.2 mg/kg/min) have not been shown to have significantly increased benefits. The interval between titration steps may be increased.

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

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

In the event of an adverse reaction, the dosage of esmolol HCl may be reduced or discontinued. If a local infusion site reaction develops, an alternate infusion site should be used and caution should be taken to prevent extravasation. The use of butterfly needles should be avoided.

Abrupt cessation of esmolol HCl 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 esmolol HCl 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, digoxin, or verapamil, may be
accomplished. A recommended guideline for such a transition is given below but the physician should carefully consider the labeling instructions for the alternative agent selected (see TABLE 2).

<table>
<thead>
<tr>
<th>Alternative Agent</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol HCl</td>
<td>10-20 mg q 4-6 h</td>
</tr>
<tr>
<td>Digoxin</td>
<td>0.125-0.5 mg q 6 h (po or IV)</td>
</tr>
<tr>
<td>Verapamil</td>
<td>80 mg q 6 h</td>
</tr>
</tbody>
</table>

The dosage of esmolol HCl should be reduced as follows:

1. Thirty minutes following the first dose of the alternative agent, reduce the infusion rate of esmolol HCl 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 esmolol HCl.

The use of infusions of esmolol HCl up to 24 hours has been well documented; in addition, limited data from 24-48 hours (n=48) indicate that esmolol HCl is well tolerated up to 48 hours.

Intraoperative and Postoperative Tachycardia and/or Hypertension

In the intraoperative and postoperative settings it is not always advisable to slowly titrate the dose of esmolol HCl to a therapeutic effect. Therefore, two dosing options are presented: immediate control dosing and a gradual control when the physician has time to titrate.

1. Immediate Control: For intraoperative treatment of tachycardia and/or hypertension give an 80 mg approximately 1 mg/kg) bolus dose over 30 seconds followed by a 150 μg/kg/min infusion, if necessary. Adjust the infusion rate as required up to 300 μg/kg/min to maintain desired heart rate and/or blood pressure.

2. Gradual Control: For postoperative tachycardia and hypertension, the dosing schedule is the same as that used in supraventricular tachycardia. To initiate treatment, administer a loading dosage infusion of 500 μg/kg/min of esmolol HCl for 1 minute followed by a 4 minute maintenance infusion of 50 μg/kg/min. If an adequate therapeutic effect is not observed within 5 minutes, repeat the same loading dosage and follow with a maintenance infusion increased to 100 μg/kg/min (see CLINICAL PHARMACOLOGY, Supraventricular Tachycardia).

Note: Higher doses (250-300 μg/kg/min) may be required for adequate control of blood pressure than those required for the treatment of atrial fibrillation, flutter and sinus tachycardia. One third of the postoperative hypertensive patients required these higher doses.

Compatibility With Commonly Used Intravenous Fluids

Esmolol HCl injection was tested for compatibility with 10 commonly used intravenous fluids at a final concentration of 10 mg esmolol HCl per ml.

Esmolol HCl injection was found to be compatible with the following solutions and was stable for at least 24 hours at controlled room temperature or under refrigeration:

Dextrose (5%) injection.
Dextrose (5%) in lactated Ringer's injection.
Dextrose (5%) in Ringer's injection.
Dextrose (5%) and sodium chloride (0.45%) injection.
Dextrose (5%) and sodium chloride (0.9%) injection.
Lactated Ringer's injection.
Potassium chloride (40 mEq/L) in dextrose (5%) injection.
Sodium chloride (0.45%) injection.
Sodium chloride (0.9%) injection.
Esmolol HCl injection was NOT compatible with sodium bicarbonate (5%) injection.

**Note:** Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.