ESMOLOL HYDROCHLORIDE- esmolol hydrochloride injection
Baxter Healthcare Corporation

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Esmolol Hydrochloride injection safely and effectively. See full prescribing information for Esmolol Hydrochloride injection.
Esmolol Hydrochloride injection, for intravenous use
Initial U.S. Approval: 1986

RECENT MAJOR CHANGES

Warnings and Precautions, Hypoglycemia (5.6) 06/2023

INDICATIONS AND USAGE

Esmolol hydrochloride injection is a beta adrenergic blocker indicated for the short-term treatment of:

- Control of ventricular rate in supraventricular tachycardia including atrial fibrillation and atrial flutter and control of heart rate in noncompensatory sinus tachycardia (1.1)
- Control of perioperative tachycardia and hypertension (1.2)

DOSAGE AND ADMINISTRATION

- Administer intravenously (2.1, 2.2)
- Titrate using ventricular rate or blood pressure at ≥4-minute intervals. (2.1, 2.2)
- Supraventricular tachycardia (SVT) or noncompensatory sinus tachycardia (2.1)
    - Optional loading dose: 500 mcg per kg infused over one minute
    - Then 50 mcg per kg per minute for the next 4 minutes
    - Adjust dose as needed to a maximum of 200 mcg per kg per minute.
    - Additional loading doses may be administered
- Perioperative tachycardia and hypertension (2.2)
    - Loading dose: 500 mcg per kg over 1 minute for gradual control (1 mg per kg over 30 seconds for immediate control)
    - 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)

DOSAGE FORMS AND STRENGTHS

- Injection: 100 mg/10 mL (10 mg/mL) in 10 mL vial (3)

CONTRAINDICATIONS

- Severe sinus bradycardia (4)
- Heart block greater than first degree (4)
- Sick sinus syndrome (4)
- Decompensated heart failure (4)
- Cardiogenic shock (4)
- Coadministration of IV cardiodepressant calcium-channel antagonists (e.g. verapamil) in close proximity to esmolol hydrochloride injection (4, 7)
- Pulmonary hypertension (4)
- Known hypersensitivity to esmolol (4)

WARNINGS AND PRECAUTIONS

- Risk of hypotension, bradycardia, and cardiac failure: Monitor for signs and symptoms of cardiovascular adverse effects. Reduce or discontinue use (5.1, 5.2, 5.3, 5.10)
- Risk of exacerbating reactive airway disease (5.5)
- Diabetes: May mask symptoms of hypoglycemia and alter glucose levels; monitor (5.6)
- Risk of unopposed alpha-agonism and severe hypertension in untreated pheochromocytoma (5.9)

- Risk of myocardial ischemia when abruptly discontinued in patients with coronary artery disease (5.12, 5.15)

ADVERSE REACTIONS

Most common adverse reactions (incidence> 10%) are symptomatic hypotension (hyperhidrosis, dizziness) and asymptomatic hypotension (6)
To report SUSPECTED ADVERSE REACTIONS, contact Baxter Healthcare Corporation at 1-866-888-2472 or FDA at 1-800-FDA-1088 or ***www.fda.gov/medwatch***.

DRUG INTERACTIONS

- Digitalis glycosides: Risk of bradycardia (7)
- Anticholinesterases: Prolongs neuromuscular blockade (7)
- Antihypertensive agents: Risk of rebound hypertension (7)
- Sympathomimetic drugs: Dose adjustment needed (7)
- Vasoconstrictive and positive inotropic effect substances: Avoid concomitant use (7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2023

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Supraventricular Tachycardia or Noncompensatory Sinus Tachycardia

Esmolol hydrochloride injection 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 hydrochloride injection is also indicated in noncompensatory sinus tachycardia where, in the physician’s judgment, the rapid heart rate requires specific intervention. Esmolol hydrochloride injection is intended for short-term use.

1.2 Intraoperative and Postoperative Tachycardia and/or Hypertension

Esmolol hydrochloride injection is indicated for the short-term 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 hydrochloride injection to prevent such events is not recommended.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing for the Treatment of Supraventricular Tachycardia or Noncompensatory Sinus Tachycardia

Esmolol hydrochloride injection is administered by continuous intravenous infusion with or without a loading dose. Additional loading doses and/or titration of the maintenance infusion (step-wise dosing) may be necessary based on desired ventricular response.

Table 1 Step-Wise Dosing

Step	Action
1	Optional loading dose (500 mcg per kg over 1 minute), then 50 mcg per kg per min for 4 min
2	Optional loading dose if necessary, then 100 mcg per kg per min for 4 min
3	Optional loading dose if necessary, then 150 mcg per kg per min for 4 min
4	If necessary, increase dose to 200 mcg per kg per min

In the absence of loading doses, continuous infusion of a single concentration of esmolol reaches pharmacokinetic and pharmacodynamic steady-state in about 30 minutes.

The effective maintenance dose for continuous and step-wise dosing is 50 to 200 mcg per kg per minute, although doses as low as 25 mcg per kg per minute have been adequate. Dosages greater than 200 mcg per kg per minute provide little added heart rate lowering effect, and the rate of adverse reactions increases.

Maintenance infusions may be continued for up to 48 hours.

2.2 Intraoperative and Postoperative Tachycardia and Hypertension

In this setting it is not always advisable to slowly titrate to a therapeutic effect. Therefore two dosing options are presented: immediate control and gradual control.

Immediate Control

- Administer 1 mg per kg as a bolus dose over 30 seconds followed by an infusion of 150 mcg per kg per min if necessary.
- Adjust the infusion rate as required to maintain desired heart rate and blood pressure. Refer to Maximum Recommended Doses below.

Gradual Control

- Administer 500 mcg per kg as a bolus dose over 1 minute followed by a maintenance infusion of 50 mcg per kg per min for 4 minutes.
- Depending on the response obtained, continue dosing as outlined for supraventricular tachycardia. Refer to Maximum Recommended Doses below.

Maximum Recommended Doses

- For the treatment of tachycardia, maintenance infusion dosages greater than 200 mcg per kg per min are not recommended; dosages greater than 200 mcg per kg per min provide little additional heart rate-lowering effect, and the rate of adverse reactions increases.
- For the treatment of hypertension, higher maintenance infusion dosages (250-300 mcg per kg per min) may be required. The safety of doses above 300 mcg per kg per minute has not been studied.

2.3 Transition from Esmolol Hydrochloride Injection Therapy to Alternative Drugs

After patients achieve adequate control of the heart rate and a stable clinical status, transition to alternative antiarrhythmic drugs may be accomplished.

When transitioning from esmolol hydrochloride injection to alternative drugs, the physician should carefully consider the labeling instructions of the alternative drug selected and reduce the dosage of esmolol hydrochloride injection as follows:

1. Thirty minutes following the first dose of the alternative drug, reduce the esmolol hydrochloride infusion rate by one-half (50%).
2. 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 esmolol hydrochloride infusion.

2.4 Directions for Use

This dosage form is prediluted to provide a ready-to-use, iso-osmotic solution of 10 mg/mL esmolol hydrochloride in sodium chloride recommended for esmolol hydrochloride intravenous administration. The ready-to-use vial may be used to administer a loading dosage by hand-held syringe while the maintenance infusion is being prepared. When using a 10 mg/mL concentration, a loading dose of 0.5 mg/kg infused over 1 minute, for a 70 kg patient is 3.5 mL.

Esmolol hydrochloride injection is not compatible with Sodium Bicarbonate (5%) solution (limited stability) or furosemide (precipitation).

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

Compatibility with Commonly Used Intravenous Fluids

Esmolol hydrochloride injection was tested for compatibility with ten commonly used intravenous fluids at a final concentration of 10 mg esmolol hydrochloride per mL. Esmolol hydrochloride 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, USP
- Dextrose (5%) in Lactated Ringer’s Injection
- Dextrose (5%) in Ringer’s Injection
- Dextrose (5%) and Sodium Chloride (0.45%) Injection, USP

- Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
- Lactated Ringer's Injection, USP
- Potassium Chloride (40 mEq/liter) in Dextrose (5%) Injection, USP
- Sodium Chloride (0.45%) Injection, USP
- Sodium Chloride (0.9%) Injection, USP

3 DOSAGE FORMS AND STRENGTHS

Esmolol hydrochloride injection is an iso-osmotic solution of esmolol hydrochloride in sodium chloride.

Table 2 Esmolol Hydrochloride Injection Presentations

Product Name	Esmolol Hydrochloride Injection
Total Dose	100 mg / 10 mL
Esmolol Hydrochloride Concentration	10 mg/mL
Packaging	10 mL Vial

4 CONTRAINDICATIONS

Esmolol hydrochloride injection 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)].*
- Decompensated heart failure: May worsen heart failure.
- Cardiogenic shock: May precipitate further cardiovascular collapse and cause cardiac arrest.
- IV administration of cardiodepressant calcium-channel antagonists (e.g., verapamil) and esmolol hydrochloride injection in close proximity (i.e., while cardiac effects from the other are still present); fatal cardiac arrests have occurred in patients receiving esmolol hydrochloride injection and intravenous verapamil.
- Pulmonary hypertension: May precipitate cardiorespiratory 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 heart rate, maintenance doses greater than 200 mcg per kg per min are not recommended. Monitor patients closely, especially if pretreatment blood pressure is low. In case of an

unacceptable drop in blood pressure, reduce or stop esmolol hydrochloride injection. Decrease of dose or termination of infusion reverses 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 esmolol hydrochloride injection. Patients with first-degree atrioventricular block, sinus node dysfunction, or conduction disorders may be at increased risk. Monitor heart rate and rhythm in patients receiving esmolol hydrochloride injection *[see Contraindications (4)]*.

If severe bradycardia develops, reduce or stop esmolol hydrochloride injection.

5.3 Cardiac Failure

Beta blockers, like esmolol hydrochloride 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 esmolol hydrochloride injection and start supportive therapy *[see Overdosage (10)]*.

5.4 Intraoperative and Postoperative Tachycardia and/or Hypertension

Monitor vital signs closely and titrate esmolol hydrochloride injection slowly in the treatment of patients whose blood pressure is primarily driven by vasoconstriction associated with hypothermia.

5.5 Reactive Airways Disease

Patients with reactive airways disease should, in general, not receive beta blockers. Because of its relative $beta_1$ selectivity and titratability, titrate esmolol hydrochloride injection to the lowest possible effective dose. In the event of bronchospasm, stop the infusion immediately; a $beta_2$ stimulating agent may be administered with appropriate monitoring of ventricular rates.

5.6 Hypoglycemia

Beta-blockers may prevent early warning signs of hypoglycemia, such as tachycardia, and increase the risk for severe or prolonged hypoglycemia at any time during treatment, especially in patients with diabetes mellitus or children and patients who are fasting (i.e., surgery, not eating regularly, or are vomiting). If severe hypoglycemia occurs, patients should be instructed to seek emergency treatment.

5.7 Infusion Site Reactions

Infusion site reactions have occurred with the use of esmolol hydrochloride 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 vasoconstriction. Do not use nonselective beta blockers.

5.9 Use in Patients with Pheochromocytoma

If esmolol hydrochloride injection is used in the setting of pheochromocytoma, give it in combination with an alpha-blocker, and only after the alpha-blocker has been initiated. Administration of beta-blockers alone in the setting of pheochromocytoma has been associated with a paradoxical increase in blood pressure from the attenuation of beta-mediated vasodilation in skeletal muscle.

5.10 Use in Hypovolemic Patients

In hypovolemic patients, esmolol hydrochloride 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), esmolol hydrochloride injection may aggravate peripheral circulatory disorders.

5.12 Abrupt Discontinuation of Esmolol Hydrochloride 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 esmolol hydrochloride injection.

Heart rate increases moderately above pretreatment levels 30 minutes after esmolol hydrochloride injection discontinuation.

5.13 Hyperkalemia

Beta blockers, including esmolol hydrochloride injection, 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 esmolol hydrochloride injection.

5.14 Use in Patients with Metabolic Acidosis

Beta blockers, including esmolol hydrochloride injection, 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 Hyperthyroidism

Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, monitor patients for signs of thyrotoxicosis when withdrawing beta blocking therapy.

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 esmolol hydrochloride injection 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 and common adverse effect has been hypotension *[see Warnings and Precautions (5.1)].* Deaths have been reported in post-marketing experience occurring during complex clinical states where esmolol hydrochloride injection was presumably being used simply to control ventricular rate *[see Warnings and Precautions (5.5)]*.

Table 3 Clinical Trial Adverse Reactions (Frequency ≥3%)

System Organ Class (SOC)	Preferred MedDRA Term	Frequency
VASCULAR DISORDERS	Hypotension*	
	Asymptomatic hypotension	25%
	Symptomatic hypotension (hyperhidrosis, dizziness)	12%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Infusion site reactions (inflammation and induration)	8%
GASTROINTESTINAL DISORDERS	Nausea	7%
NERVOUS SYSTEM DISORDERS	Dizziness	3%
	Somnolence	3%
* Hypotension resolved during esmolol hydrochloride infusion in 63% of patients. In 80% of the remaining patients, hypotension resolved within 30 minutes following discontinuation of infusion.		

Clinical Trial Adverse Reactions (Frequency <3%)

Psychiatric Disorders

Confusional state and agitation (~2%)
Anxiety, depression and abnormal thinking (<1%)

Nervous System Disorders

Headache (~ 2%)
Paresthesia, syncope, speech disorder, and lightheadedness (<1%)
Convulsions (<1%), with one death

Vascular Disorders

Peripheral ischemia (~1%)
Pallor and flushing (<1%)

Gastrointestinal Disorders

Vomiting (~1%)
Dyspepsia, constipation, dry mouth, and abdominal discomfort (<1%)

Renal and Urinary Disorders

Urinary retention (<1%)

6.2 Post-Marketing Experience

In addition to the adverse reactions reported in clinical trials, the following adverse reactions have been reported in the post-marketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or to establish a causal relationship to drug exposure.

Cardiac Disorders

Cardiac arrest, Coronary arteriospasm

Skin and Subcutaneous Tissue Disorders

Angioedema, Urticaria, Psoriasis

7 DRUG INTERACTIONS

Concomitant use of esmolol hydrochloride injection with other drugs that can lower blood pressure, reduce myocardial contractility, or interfere with sinus node function or electrical impulse propagation in the myocardium can exaggerate esmolol hydrochloride injection's effects on blood pressure, contractility, and impulse propagation. Severe interactions with such drugs can result in, for example, severe hypotension, cardiac failure, severe bradycardia, sinus pause, sinoatrial block, atrioventricular block, and/or cardiac arrest. In addition, with some drugs, beta blockade may precipitate increased withdrawal effects. (See clonidine, guanfacine, and moxonidine below.) Esmolol hydrochloride injection should therefore be used only after careful individual assessment of the risks and expected benefits in patients receiving drugs that can cause these types of pharmacodynamic interactions, including but not limited to:

- Digitalis glycosides: Concomitant administration of digoxin and esmolol hydrochloride injection leads to an approximate 10% to 20% increase of digoxin blood levels at some time points. Digoxin does not affect esmolol hydrochloride injection pharmacokinetics. Both digoxin and beta blockers slow atrioventricular conduction and decrease heart rate. Concomitant use increases the risk of

bradycardia.

- Anticholinesterases: Esmolol hydrochloride injection prolonged the duration of succinylcholine-induced neuromuscular blockade and moderately prolonged clinical duration and recovery index of mivacurium.
- Antihypertensive agents clonidine, guanfacine, or moxonidine: Beta blockers also increase the risk of clonidine-, guanfacine-, or moxonidine-withdrawal rebound hypertension. If, during concomitant use of a beta blocker, antihypertensive therapy needs to be interrupted or discontinued, discontinue the beta blocker first, and the discontinuation should be gradual.
- Calcium channel antagonists: In patients with depressed myocardial function, use of esmolol hydrochloride injection with cardiodepressant calcium channel antagonists (e.g., verapamil) can lead to fatal cardiac arrests.
- Sympathomimetic drugs: Sympathomimetic drugs having beta-adrenergic agonist activity will counteract effects of esmolol hydrochloride injection.
- Vasoconstrictive and positive inotropic agents: Because of the risk of reducing cardiac contractility in presence of high systemic vascular resistance, do not use esmolol hydrochloride injection to control tachycardia in patients receiving drugs that are vasoconstrictive and have positive inotropic effects, such as epinephrine, norepinephrine, and dopamine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Esmolol hydrochloride injection 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. Esmolol hydrochloride 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 dosage) for 30 minutes daily produced no evidence of maternal toxicity, embryotoxicity or teratogenicity, while a dosage of 10,000 mcg/kg/min produced maternal toxicity and lethality. In rabbits, intravenous 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 or delivery has been reported to cause fetal bradycardia, which continued after termination of drug infusion. Esmolol hydrochloride 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 esmolol hydrochloride injection, 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 esmolol hydrochloride injection in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of esmolol hydrochloride 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 responses between the elderly and younger patients. In general, dose selection for an elderly patient should usually start at the low end of the dosing range, reflecting greater frequency of decreased renal or cardiac function and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

No special precautions are necessary in patients with hepatic impairment because esmolol hydrochloride injection is metabolized by red-blood cell esterases *[see Clinical Pharmacology (12)].*

8.7 Renal Impairment

No dosage adjustment is required for esmolol in patients with renal impairment receiving a maintenance infusion of esmolol hydrochloride injection 150 mcg/kg for 4 hours. There is no information on the tolerability of maintenance infusions of esmolol hydrochloride injection using rates in excess of 150 mcg/kg or maintained longer than 4 hours *[see Clinical Pharmacology (12)].*

10 OVERDOSAGE

10.1 Signs and Symptoms of Overdose

Overdoses of esmolol hydrochloride injection can cause cardiac and central nervous system effects. These effects may precipitate severe signs, symptoms, sequelae, and complications (for example, severe cardiac and respiratory failure, including shock and coma), and may be fatal. Continuous monitoring of the patient is required.

- Cardiac effects include bradycardia, atrioventricular block (1^{st} -, 2^{nd} -, 3^{rd} degree), junctional rhythms, intraventricular conduction delays, decreased cardiac contractility, hypotension, cardiac failure (including cardiogenic shock), cardiac arrest/asystole, and pulseless electrical activity.
- Central nervous system effects include respiratory depression, seizures, sleep and mood disturbances, fatigue, lethargy, and coma.
- In addition, bronchospasm, mesenteric ischemia, peripheral cyanosis, hyperkalemia, and hypoglycemia (especially in children) may occur.

10.2 Treatment Recommendations

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

Bradycardia

Consider intravenous administration of atropine or another anticholinergic drug or cardiac pacing.

Cardiac Failure

Consider intravenous administration of a diuretic or digitalis glycoside. In shock resulting from inadequate cardiac contractility, consider intravenous administration of dopamine, dobutamine, isoproterenol, or inamrinone. Glucagon has been reported to be useful.

Symptomatic hypotension

Consider intravenous administration of fluids or vasopressor agents such as dopamine or norepinephrine.

Bronchospasm

Consider intravenous administration of a $beta_2$ stimulating agent or a theophylline derivative.

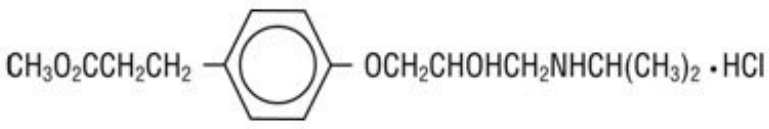
10.3 Dilution Errors

Massive accidental overdoses of esmolol hydrochloride injection have resulted from dilution errors. Use of BREVIBLOC PREMIXED Injection and BREVIBLOC PREMIXED Double Strength Injection may reduce the potential for dilution errors. Some of these overdoses have been fatal while others resulted in permanent disability. Bolus doses in the range of 625 mg to 2.5 g (12.5-50 mg/kg) have been fatal. Patients have recovered completely from overdoses as high as 1.75 g given over one minute or doses of 7.5 g given over one hour for cardiovascular surgery. The patients who survived appear to be those whose circulation could be supported until the effects of esmolol hydrochloride injection resolved.

11 DESCRIPTION

Esmolol hydrochloride injection is a beta adrenergic receptor blocker with a very short duration of action (elimination half-life is approximately 9 minutes). Esmolol hydrochloride is:

- (±)-Methyl p-[2-hydroxy-3-(isopropylamino) propoxy] hydrocinnamate hydrochloride and has the following structure:



- Esmolol hydrochloride has the empirical formula $C_{16}H_{26}NO_4Cl$ 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.

11.1 Esmolol Hydrochloride Injection Dosage Forms

Esmolol Hydrochloride Injection is a clear, colorless to light yellow, sterile, nonpyrogenic, iso-osmotic solution of esmolol hydrochloride in sodium chloride. The formulation is described in the table below:

Table 4 Formulation for Esmolol Hydrochloride Injection

Esmolol Hydrochloride, USP	10 mg/mL
Sodium Chloride, USP	5.9 mg/mL
Water for Injection, USP	Q.S. to volume of 10 mL
Sodium Acetate Trihydrate, USP	2.8 mg/mL
Glacial Acetic Acid, USP	0.546 mg/mL
Sodium Hydroxide	Q.S. to adjust pH to 4.5-5.5
Hydrochloric Acid	Q.S. to adjust pH to 4.5-5.5
Q.S. = Quantity sufficient	

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Esmolol hydrochloride injection is a $beta_1$-selective (cardioselective) adrenergic receptor blocking agent with rapid onset, a very short duration of action, and no significant intrinsic sympathomimetic or membrane stabilizing activity at therapeutic dosages. Its elimination half-life after intravenous infusion is approximately 9 minutes. Esmolol hydrochloride injection inhibits the $beta_1$ receptors located chiefly in cardiac muscle, but this preferential effect is not absolute and at higher doses it begins to inhibit $beta_2$ receptors located chiefly in the bronchial and vascular musculature.

12.2 Pharmacodynamics

Clinical pharmacology studies in normal volunteers have confirmed the beta blocking activity of esmolol hydrochloride injection, showing reduction in heart rate at rest and during exercise, and attenuation of isoproterenol-induced increases in heart rate. Blood levels of esmolol hydrochloride injection 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. The acid metabolite of esmolol exhibits negligible pharmacological activity.

In human electrophysiology studies, esmolol hydrochloride injection 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 hydrochloride injection, 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 mg). During exercise, esmolol hydrochloride injection produced reductions in heart rate, rate pressure product and cardiac index which were also similar to those produced by propranolol, but esmolol hydrochloride injection produced a significantly larger fall in systolic blood pressure. In patients undergoing cardiac catheterization, the maximum therapeutic dose of 300 mcg/kg/min of esmolol hydrochloride injection 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 hydrochloride infusion, all of the hemodynamic parameters had returned to pretreatment levels.

The relative cardioselectivity of esmolol hydrochloride injection was demonstrated in 10 mildly asthmatic patients. Infusions of esmolol hydrochloride injection 100, 200 and 300 mcg/kg/min produced no significant increases in specific airway resistance compared to placebo. At 300 mcg/kg/min, esmolol hydrochloride injection produced slightly enhanced bronchomotor sensitivity to dry air stimulus. These effects were not clinically significant, and esmolol hydrochloride injection was well tolerated by all patients. Six of the patients also received intravenous propranolol, and at a dosage of 1 mg, two experienced significant, symptomatic bronchospasm requiring bronchodilator treatment. One other propranolol-treated patient also experienced dry air-induced bronchospasm. No adverse pulmonary effects were observed in patients with COPD who received therapeutic dosages of esmolol hydrochloride injection for treatment of supraventricular tachycardia (51 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/kg/hr, 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 an elimination half-life of about 9 minutes.

Using an appropriate loading dose, steady-state blood levels of esmolol hydrochloride injection 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 esmolol hydrochloride injection, 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 esmolol hydrochloride injection 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.

Esmolol hydrochloride injection 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 esmolol hydrochloride injection with placebo and propranolol, maintenance doses of 50 to 300 mcg/kg/min of esmolol hydrochloride injection 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 hydrochloride injection 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 esmolol hydrochloride injection 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 esmolol hydrochloride injection 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 hyperhidrosis or dizziness) in about 12% of patients, and therapy was discontinued in about 11% of patients, about half of whom were symptomatic. Hypotension was more common with esmolol hydrochloride injection (53%) than with propranolol (17%). The hypotension was rapidly reversible with decreased infusion rate or after discontinuation of therapy with esmolol hydrochloride injection. For both esmolol hydrochloride injection and propranolol, hypotension was reported less frequently in patients receiving concomitant digoxin.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Esmolol Hydrochloride Injection

- NDC 10019-120-01, 100 mg / 10 mL (10 mg/mL) Ready-to-use Vials, Package of 25

16.2 Storage

Store at 25˚C (77˚F). Excursions permitted to 15˚-30˚C (59˚-86˚F) *[see USP Controlled Room Temperature].* Protect from freezing. Avoid excessive heat.

17 PATIENT COUNSELING INFORMATION

Physicians should inform patients of the risks associated with esmolol hydrochloride injection:

- The most common adverse reactions are symptomatic hypotension (hyperhidrosis, dizziness) and asymptomatic hypotension.
- Inform patients or caregivers that there is a risk of hypoglycemia when esmolol is given to patients who are fasting or who are vomiting. Monitor for symptoms of hypoglycemia. *[See Warnings and Precautions (5.6)]*.

Manufactured for

Baxter Healthcare Corporation

Deerfield, IL 60015 USA

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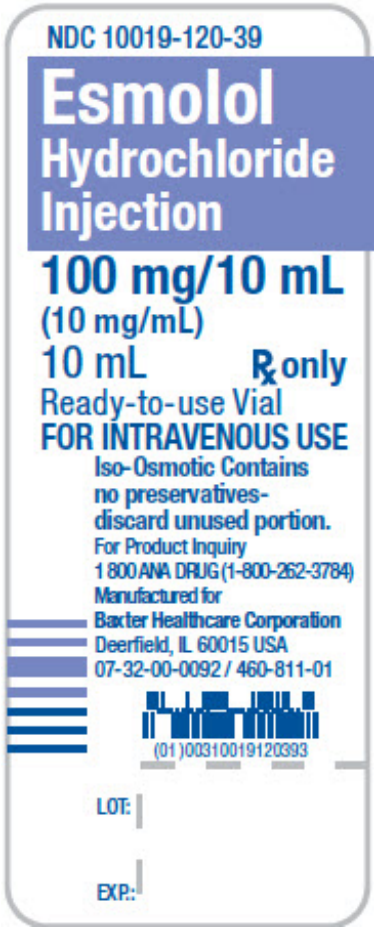
0719006352

PRINCIPAL DISPLAY PANEL - PACKAGING LABELING



Container Label

NDC 10019-120-39

Esmolol
Hydrochloride
Injection

100 mg/10 mL
(10 mg/mL)

10 mL
Rx only

Ready-to-use Vial

FOR INTRAVENOUS USE
Iso-Osmotic Contains
no preservatives-
discard unused portion.

For Product Inquiry
1 800 ANA DRUG (1-800-262-3784)

Manufactured for
Baxter Healthcare Corporation
Deerfield, IL 60015 USA

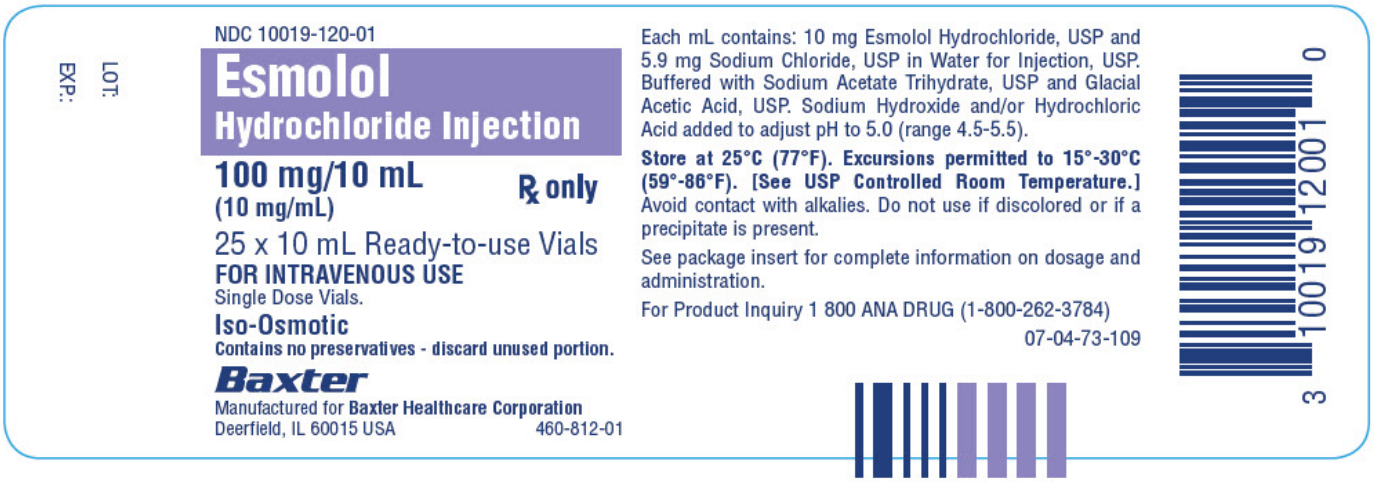
Barcode

07-32-00-0092 / 460-811-01

Barcode
(01)00310019120393

LOT:

EXP.:



Carton Label

LOT:

EXP:

NDC 10019-120-01
Esmolol
Hydrochloride Injection
100 mg/10 mL
(10 mg/mL) **Rx only**

25 x 10 mL Ready-to-use Vials
FOR INTRAVENOUS USE
Single Dose Vials.
Iso-Osmotic
Contains no preservatives - discard unused portion.

Baxter
Manufactured for Baxter Healthcare Corporation
Deerfield, IL 60015 USA 460-812-01

Each mL contains: 10 mg Esmolol Hydrochloride, USP and 5.9 mg Sodium Chloride, USP in Water for Injection, USP. Buffered with Sodium Acetate Trihydrate, USP and Glacial Acetic Acid, USP. Sodium Hydroxide and/or Hydrochloric Acid added to adjust pH to 5.0 (range 4.5-5.5).

Store at 25°C (77°F). Excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature.]
Avoid contact with alkalies. Do not use if discolored or if a

precipitate is present.

See package insert for complete information on dosage and administration.

For Product Inquiry 1 800 ANA DRUG (1-800-262-3784)

07-04-73-109

3 10019 12001 0

ESMOLOL HYDROCHLORIDE

esmolol hydrochloride injection

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:10019-120
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ESMOLOL HYDROCHLORIDE (UNII: V05260LC8D) (ESMOLOL - UNII:MDY902UXSR)	ESMOLOL HYDROCHLORIDE	10 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
SODIUM CHLORIDE (UNII: 451W47IQ8X)	5.9 mg in 1 mL
SODIUM ACETATE (UNII: 4550K0SC9B)	2.8 mg in 1 mL
ACETIC ACID (UNII: Q40Q9N063P)	0.546 mg in 1 mL
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
WATER (UNII: 059QF0KO0R)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:10019-120-01	25 in 1 CARTON	12/31/1986	
1	NDC:10019-120-39	10 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA019386	12/31/1986	

Labeler - Baxter Healthcare Corporation (005083209)

Registrant - Baxter Healthcare Corporation (005083209)

Establishment

Name	Address	ID/FEI	Business Operations
Baxter Healthcare Corporation		059140764	ANALYSIS(10019-120)

Establishment

Name	Address	ID/FEI	Business Operations
Baxter Healthcare Corporation		194684502	ANALYSIS(10019-120)

Revised: 6/2023 Baxter Healthcare Corporation