BREVIBLOC PREMIXED INJECTION

(Esmolol Hydrochloride)

2,500 mg/250 mL (10 mg/mL) Ready-to-use Bags

250 mL Bags

Iso-Osmotic Solution of Esmolol Hydrochloride in Sodium Chloride

For Intravenous Use

Can be used for direct intravenous use.

Esmolol Hydrochloride concentration = 10 milligrams/mL (10,000 micrograms/mL)

Single Patient Use Only

No Preservatives Added

BREVIBLOC DOUBLE STRENGTH PREMIXED INJECTION

(Esmolol Hydrochloride)

2,000 mg/100 mL (20 mg/mL) Ready-to-use Bags

100 mL Bags

Iso-Osmotic Solution of Esmolol Hydrochloride in Sodium Chloride

For Intravenous Use

Can be used for direct intravenous use.

Esmolol Hydrochloride concentration = 20 milligrams/mL (20,000 micrograms/mL)

Single Patient Use Only

No Preservatives Added

BREVIBLOC INJECTION

(Esmolol Hydrochloride)

100 mg/10 mL (10 mg/mL) Ready-to-use Vials

10 mL Vials

Iso-Osmotic Solution of Esmolol Hydrochloride in Sodium Chloride

For Intravenous Use

Can be used for direct intravenous use.

Esmolol Hydrochloride concentration = 10 milligrams/mL (10,000 micrograms/mL)

Single Patient Use Only

No Preservatives Added

BREVIBLOC DOUBLE STRENGTH INJECTION

(Esmolol Hydrochloride)

100 mg/5 mL (20 mg/mL) Ready-to-use Vials

5 mL Vials

Iso-Osmotic Solution of Esmolol Hydrochloride in Sodium Chloride

For Intravenous Use

Can be used for direct intravenous use.

Esmolol Hydrochloride concentration = 20 milligrams/mL (20,000 micrograms/mL)

Single Patient Use Only

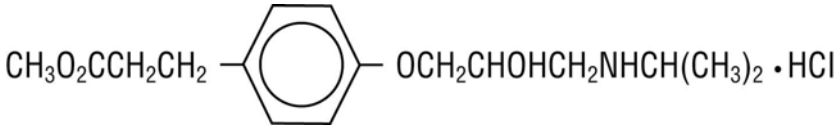
No Preservatives Added

R_x only

DESCRIPTION

BREVIBLOC (Esmolol Hydrochloride) is a $beta_1$-selective (cardioselective) adrenergic receptor blocking agent 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.

Brevibloc Premixed Injection

BREVIBLOC PREMIXED INJECTION is a clear, colorless to light yellow, sterile, nonpyrogenic, iso-osmotic solution of esmolol hydrochloride in sodium chloride.

2500 mg, 250 mL Single Use Premixed Bag – Each mL contains 10 mg Esmolol Hydrochloride, 5.9 mg Sodium Chloride, USP and Water for Injection, USP; buffered with 2.8 mg Sodium Acetate Trihydrate, USP and 0.546 mg Glacial Acetic Acid, USP. Sodium Hydroxide and/or Hydrochloric Acid added, as necessary, to adjust pH to 5.0 (4.5-5.5). The calculated osmolarity is 312 mOsmol/L. The 250 mL bag is a non-latex, non-PVC IntraVia bag with dual PVC ports. The IntraVia bag is manufactured from a specially designed multilayer plastic (PL 2408). Solutions in contact with the plastic container leach out certain chemical compounds from the plastic in very small amounts; however, biological testing was supportive of the safety of the plastic container materials. See **DOSAGE AND ADMINISTRATION**, **Directions for Use of the Premixed Bag** for additional information.

2000 mg, 100 mL Single Use Premixed Bag DOUBLE STRENGTH – Each mL contains 20 mg Esmolol Hydrochloride, 4.1 mg Sodium Chloride, USP and Water for Injection, USP; buffered with 2.8 mg Sodium Acetate Trihydrate, USP and 0.546 mg Glacial Acetic Acid, USP. Sodium Hydroxide and/or Hydrochloric Acid added, as

necessary, to adjust pH to 5.0 (4.5-5.5). The calculated osmolarity is 312 mOsmol/L. The 100 mL bag is a non-latex, non-PVC IntraVia bag with dual PVC ports. The IntraVia bag is manufactured from a specially designed multilayer plastic (PL 2408). Solutions in contact with the plastic container leach out certain chemical compounds from the plastic in very small amounts; however, biological testing was supportive of the safety of the plastic container materials. See **DOSAGE AND ADMINISTRATION**, **Directions for Use of the Premixed Bag** for additional information.

Brevibloc Injection

BREVIBLOC INJECTION is a clear, colorless to light yellow, sterile, nonpyrogenic, iso-osmotic solution of esmolol hydrochloride in sodium chloride.

100 mg, 10 mL Single Dose Vial – Each mL contains 10 mg Esmolol Hydrochloride, 5.9 mg Sodium Chloride, USP and Water for Injection, USP; buffered with 2.8 mg Sodium Acetate Trihydrate, USP and 0.546 mg Glacial Acetic Acid, USP. Sodium Hydroxide and/or Hydrochloric Acid added, as necessary to adjust pH to 5.0 (4.5-5.5).

100 mg, 5 mL DOUBLE STRENGTH Single Dose Vial – Each mL contains 20 mg Esmolol Hydrochloride, 4.1 mg Sodium Chloride, USP and Water for Injection, USP; buffered with 2.8 mg Sodium Acetate Trihydrate, USP and 0.546 mg Glacial Acetic Acid, USP. Sodium Hydroxide and/or Hydrochloric Acid added, as necessary to adjust pH to 5.0 (4.5-5.5).

CLINICAL PHARMACOLOGY

BREVIBLOC (Esmolol Hydrochloride) 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. BREVIBLOC 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.

Pharmacokinetics and Metabolism

BREVIBLOC (Esmolol Hydrochloride) 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 BREVIBLOC is not limited by the rate of blood flow to metabolizing tissues such as the liver or affected by hepatic or renal blood flow. BREVIBLOC 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 BREVIBLOC for dosages from 50-300 mcg/kg/min (0.05-0.3 mg/kg/min) are obtained within five minutes. (Steady-state is reached in about 30 minutes without the loading dose.) Steady-state blood levels of BREVIBLOC 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 BREVIBLOC 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 BREVIBLOC, 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 BREVIBLOC.

Metabolism of BREVIBLOC 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 ten-fold that of normals, and plasma levels considerably elevated.

Methanol blood levels, monitored in subjects receiving BREVIBLOC for up to 6 hours at 300 mcg/kg/min (0.3 mg/kg/min) and 24 hours at 150 mcg/kg/min (0.15 mg/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.

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