SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE HUMAN MEDICINAL PRODUCT

ESMOBLOC 10 mg/ml Solution for I.V. Infusion

Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

Esmolol hydrochloride: 10 mg/mL (Each 250 mL bag contains 2500 mg esmolol hydrochloride).

Excipients:

100 mL solution includes;

Sodium Chloride	0.59 g
Sodium Acetate Trihydrate	0.28 g

This medicinal product contains approximately 30.45 mmol (or 700 mg) of sodium in each bag.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Clear and colorless solution with a shade of yellow.

pH value of the solution is 4.5 - 5.5, and its osmolarity is approximately 312 mOsm/l.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Supraventricular tachycardia or non-compensated sinus tachycardia

ESMOBLOC is indicated for atrival fibrillation or atrial flutter cases that occur perioperatively, postoperatively or in cases which require immediate intervention to quickly control ventricle speed using an effective preparation.

ESMOBLOC is also indicated for cases of non-compensated sinus tachycardia if the physician decides to restore the heart rate with a special intervention.

ESMOBLOC is for short-term use.

Intraoperative or postoperative tachycardia and/or hypertension

ESMOBLOC is indicated for cases where the physician decides to heal tachycardia and hypertension observed during endotracheal intubation, anesthesia induction, surgical procedure,

anesthesia recovery and postoperative period, with a special intervention.

Use of ESMOBLOC for the prevention of such cases is not recommended.

4.2. Posology and method of administration

Posology/administration frequency and duration

Dosage in the treatment of supraventricular tachycardia or non-compensated sinus tachycardia

ESMOBLOC is administered with or without a loading dosage through continued intravenous infusion. Depending on the desired ventricular response, additional loading dosage and/or sustainment infusion (gradual dosing) titration may be necessary.

Table 1-Gradual Dosing

Step	Procedure
1	Optional loading dosage (500 micrograms/kg in 1 min), then 50 micrograms/kg/min for 4 min
2	If necessary, the optional loading dosage, 100 micrograms/kg/min for 4 min
3	If necessary, the optional loading dosage, 150 micrograms/kg/min for 4 min
4	If necessary, dosage is increased to 200 micrograms/kg/min

In cases where loading dosage is not administered, the pharmacokinetically and pharmacodynamically stabilized concentrations of esmolol which is administered in a fixed concentration, is achieved in roughly 30 minutes.

While low dosages such as 25 micrograms/kg/min are sufficient for the effective sustainment dosage, continued and gradual dosing, they range from 50 to 200 micrograms/kg/min. High doses over 200 micrograms/kg/min have a lower effect, cause a small increase in the heart rate, and increase the rate of adverse reactions.

Sustainment infusion may be carried out for up to 48 hours.

Intraoperative or postoperative tachycardia and/or hypertension

Gradual titration is not always recommended for therapeutic effect in this usage. Therefore, there are two dosage options: instant control and gradual control.

1. Dosage recommendation for instant control

- As bolus dosage, 1 mg/kg is administered in the first 30 seconds, and if necessary, 150 micrograms/kg/min is administered through infusion.
- Infusion rate is adjusted as necessary in order to sustain the desired heart rate and

blood pressure. Please see the Maximum Recommended Doses section below

2. Dosage recommendation for gradual titration

- As bolus dosage, 500 micrograms/kg is administered in the first 1 minute, and then 4 micrograms/kg/min is administered through sustainment infusion in 4 minutes.
- Depending on the resulting response, dosage indicated for supraventricular tachycardia is continued. Please see the Maximum Recommended Doses section below

Maximum recommended doses

- Sustainment doses over 200 micrograms/kg/min is recommended for the treatment of tachycardia. High doses over 200 micrograms/kg/min have a lower effect, cause a small increase in the heart rate, and increase the rate of adverse reactions.

- Higher sustainment infusion doses (250-300 micrograms/kg/min) may be required for the treatment of hypertension. The safety of doses over 300 micrograms/kg/min has not been studied.

Transitioning from ESMOBLOC treatment to alternative drugs

Once sufficient control and stabilized clinical picture have been achieved, alternative anti-arrhythmic drugs may be used.

When transitioning from ESMOBLOC treatment to alternative drugs, the physician should carefully read the user instructions and decrease the dose of ESMOBLOC as follows:

- In 30 minutes after the first dose of the alternative drugs, ESMOBLOC infusion rate is halved (50%).

- After the second dose of the alternative medication, the patient's response is monitored and if sufficient control is achieved in the first hour, ESMOBLOC infusion is discontinued.

Method of administration:

As ESMOBLOC is a ready-to-use solution, it is administered intravenously without dilution.

Additional information on special populations:
Renal failure:
As the acidic metabolite of ESMOBLOC is discharged through the kidneys without undergoing any transformation in patients with renal failure, administration of ESMOBLOC through infusion requires caution. In individuals with final stage kidney disease, the discharge of acidic metabolite is severely decreased, the elimination half-file is ten times the normal, and the plasma levels are significantly increased.

Hepatic failure:

As esterase in red blood cells play a vital role in the metabolism of ESMOBLOC, hetapic failure does not require special measures.

Pediatric population:

The effect or safety of ESMOBLOC with children under 18 has not been proven. Currently available data is specified under sections 5.1 and 5.2; however, this data may not constitute any recommendations about the posology.

Geriatric population:

In older patients, the treatment should start with small doses and carefully administered.
There are no studies available specific to the elderly. However, the analysis of the data obtained from 252 patients over 65 demonstrate no difference compared to patients under 65 in terms of pharmacodynamics effects.

4.3. Contraindications

- Hypersensitivity to the active substance, any of the excipients, other substances or other beta blockers (cross sensitivity among beta blockers is possible),
- Severe sinus bradycardia (less than 50 beats per minute),
- Sick sinus syndrome; severe AV bond conduction disorders (no pacemaker); second or third degree heart blocks,
- Cardiogenic shock,
- Severe hypotension,
- Decompensated heart failure,
- Concurrent or recent use of verapamil intravenously. ESMOBLOC should not be used for 48 hours after the final dose of verapamil (see section 4.4),
- Non-treated pheochromocytoma,
- Pulmonary hypertension,
- Acute asthma attack,
- Metabolic acidosis.

4.4. Special warnings and precautions for use

It is recommended to constantly monitor the blood pressure and EKG of all patients receiving ESMOBLOC treatment.

If the patient has a hemodynamic disorder or is taking other drugs that decrease one or all of

the parameters below, extreme caution is necessary for the use of ESMOBLOC to control the ventricle response of patients with supraventricular arrhythmia. Peripheral resistance, myocardial filling, myocardial contractility or electrical impulse propagation in myocardium. When the effects of ESMOBLOC start or go away too quickly, severe reactions such as loss of consciousness, cardiogenetic shock, and cardiac arrest may occur.

Several fatalities were reported in complex clinical circumstances where Esmolol Hydrochloride is assumed to be used for the control of ventricle speed.

The most common side-effect is hypotension which is dose-dependent, but can be seen in all dosages. Hypotension may be severe. In case of a hypotension episode, infusion rate should be decreased or, if necessary, infusion should be stopped. Hypotension generally can be remedies (in 30 minutes after the conclusion of ESMOBLOC treatment). In some cases, additional interventions may be required to restore the blood pressure to the normal values. Dose adjustment and sustainment infusion require special care in patients with low systolic blood pressure.

Bradycardia, including severe bradycardia, and cardiac arrest has occurred during the administration of Esmolol Hydrochloride. ESMOBLOC should be used in patients with a low heart rate before treatment, only if its benefit outweighs its risks.

ESMOBLOC is contraindicated for patients with a history of severe sinus bradycardia (see section 4.3). If pulse is below 50-55 beats per minute while at rest, and if there are symptoms of bradycardia, either the dosage should be decreased or the treatment should be concluded.

Sympathetic activity is required in order to support the circulation functionalities in cases of congestive heart failure. Beta blockage has a risk of aggravating the failure by increasing myocardial depression. If myocardial depression is maintained with beta blocker for a significant period of time, it may cause heart failure in some cases.

The use of ESMOBLOC requires caution in patients with cardiac dysfunction. As soon as the first signs and symptoms of heart failure are observed, ESMOBLOC treatment should be discontinued. Even though discontinuing ESMOBLOC treatment is enough thanks to its short elimination half-life, specific treatment procedures may be considered as well (see section 4.9). ESMOBLOC is contraindicated for patients with decompensated heart failure (see section 4.3).

Due to their negative effects on the duration of conduction at the heart, beta blockers should be given to patients with first degree heart block or other heart conduction disorders with extreme caution (see section 4.3).

ESMOBLOC should be used for patients with pheochromocytoma with extreme caution and only if they received a preliminary treatment with alpha-receptor blockers (see section 4.3).

The use of ESMOBLOC for the treatment of hypothermia induced hypertension requires

caution.
In general, patients with bronchospastic disorders should not use beta blockers. ESMOBLOC may be used in these patients with caution as they are selective compared to Beta-1 receptors, and can be titrated during use. However, as the selectivity of beta-1 is not absolute, ESMOBLOC should be carefully titrated to obtain the smallest, effective dose. In case of bronchospasm, infusion should be discontinued immediately and, if necessary, a beta-2 agonist preparation should be administered.

If the patient is already using a beta-2-receptor stimulant agent, the dose of this agent may need to be re-adjusted.

ESMOBLOC should be used with extreme caution in patients with a history of noisy breathing or asthma.

ESMOBLOC should be used with extreme caution in diabetic patients or patients with suspicion of acquired hypoglycemia. Beta blockers may hide prodromal symptoms of hypoglycemia such as tachycardia. However, dizziness and sweating may remain unaffected. Concurrent of beta blockers and anti-diabetic agents, may lead to an increase in the hypoglycemic effect of the anti-diabetic agents (see section 4.5).

Reactions occurred in the infusion site as a result of Esmolol Hydrochloride use. These reactions may include not only irritation and inflammation, but also more severe reactions such as thrombophlebitis, necrosis and blistering that are specifically related to extravasation (see section 4.8). Administrations through small veins or butterfly catheter should be avoided. When a local infusion site reaction occurs, an alternative infusion site should be used.

Beta blockers may increase the incidence and duration of angina attacks in patients with Prinzmetal angina that is connected with non-compensated alpha-receptor induced coronary artery vasoconstriction. In these patients, non-selective beta blockers should not be used; beta-1 selective blockers should be used with extreme caution.

ESMOBLOC may weaken the reflex tachycardia in hypovolemic patients and increase the risk of circulation collapse. Therefore ESMOBLOC should be used with caution when these patients are concerned.

Beta blockers should be used for patients with peripheral circulation disorders (Raynaud disease or syndrome, intermittent claudication).

Some beta blockers, including ESMOBLOC, that are administered intravenously, have been correlated with an increase in the levels of serum potassium, and hyperkalemia. This risk is increased for patients with risk factors such as renal failure or hemodialysis treatment.

Beta blockers increase both the sensitivity to allergens and the severity of anaphylactic reactions. Patients using beta blockers may not respond to epinephrine in regular doses used for

the treatment of anaphylactic or anaphylactoid reactions (see section 4.5).

It has been reported that beta blockers may lead to psoriasis or rashes resembling psoriasis, and aggregate an existing case of psoriasis. For patients with a personal or family history of psoriasis, beta blockers should only be used after the possible benefits and risks of treatment have been carefully assessed.

Beta blockers such as propranolol and metoprolol may mask certain clinical signs of hyperthyroid (such as tachycardia). For patients with the risk or suspicion of thyrotoxicosis development, suddenly discontinuing the beta blocker treatment may expedite the thyroid crisis, and such diseases should be closely monitored.

This product is offered in a 250 ml bag and contains 30.45 mmol sodium. This fact should be taken into consideration for the patients subjected to controlled sodium diet.

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

When ESMOBLOC is used together with other anti-hypertensive agents or other drugs that may cause bradycardia, extreme caution is required. Effects of ESMOBLOC or the side-effects of hypotension or bradycardia may be aggravated.

Calcium antagonist such as Verapamil has a negative effect in lower levels on diltiasem contractility and AV conduction. This combination should not be used for patients with conduction abnormalities, and ESMOBLOC should not be administered for 48 hours after the last dose of verapamil (see section 4.3).

Dihydropyridine derivative (e.g. nifedipine) calcium antagonists may increase the risk of hypotension. Giving patients being treated with calcium antagonists for heart failure, beta blockers, may cause heart failure. Careful titration of ESMOBLOC and proper hemodynamic monitoring is recommended.

Concurrent use of ESMOBLOC with Class I anti-arrhythmic drugs (e.g. disopyramide, quinidine) and amiodarone may have a reinforcement effect on atrial-conduction and cause a negative, inotropic effect.

Concurrent use of ESMOBLOC with insulin or oral anti-diabetic drugs may increase the blood sugar lowering effect (especially the non-selective beta-blockers).Beta-adrenergic blockage may hinder the observation of the signs of hypoglycemia (tachycardia); however, other signs such as headache / dizziness and sweating may not be masked.

Anesthesia drugs: In cases where the volume status of the patients is not clear, or where concurrent antihypertensive drugs are used, the risk of decrease in reflex tachycardia, or hypotension may increase.Continuing beta-blockage decreases the risk of arrhythmia during induction and intubation. The anesthetist should be informed when the patient is given a beta-

blocker agent in addition to ESMOBLOC. Hypotensive effects of inhalation anesthesia may be amplified in the presence of ESMOBLOC. The dosage of each agent may be adjusted to maintain the desired hemodynamic parameters.

Combination of ESMOBLOC with ganglion blocking drugs, may increase the hypotensive effect.

When co-administered with non-steroidal anti-inflammatory drugs (NSAII), hypotensive effects of beta blockers decrease.

Using floctafenine or amisulpiride concurrently with beta-blockers require extreme caution.

Using other antipsychotic agents (such as clozapine) together with Tricyclic anti-depressants (such as imipramine and amitriptiline), barbiturates or phenothiazine (such as chlorpromazine) may increase the blood pressure decreasing effect. In order to avoid an unexpected case of hypotension, ESMOBLOC dosage should be lowered in concurrent use.

While taking beta-blockers, patients under the risk of anaphylactic reactions may react to (accidental, diagnostic or therapeutic) exposure to allergens. Patients using beta blockers may not respond to the doses of mutate epinephrine used in the treatment of anaphylactic reactions (see section 4.4).

When used concurrently, the effects of ESMOBLOC may decrease due to sympathicomimetic drugs with beta-adrenergic, agonist activity. The dosage of each agent should be adjusted to the patient's response, or alternative therapeutic agents should be considered.

Drugs causing a catecholamine discharge (e.g. reserpine) may exhibit additive effects when given together with beta blockers. Patients that concurrently take ESMOBLOC and drug treatment that causes catecholamine discharge may be closely monitored for signs of hypotension and significant bradycardia that may lead to vertigo, syncope or postural hypotension.

The use of beta blockers together with moxonidine or alpha-2-agonists (such as clonidine) increases the risk of withdrawal induced rebound hypertension. If clonidine or moxonidine will be used together with a beta blocker, and both drugs are to be discontinued afterwards, firstly beta blocker should be discontinued and clonidine or moxonidine should be discontinued several days afterwards.

Concurrent use of beta blockers with ergo derivatives may result in severe peripheral vasoconstriction and hypertension.

Data obtained from a study that was carried out to determine the existence of an interaction between Esmolol Hydrochloride and varfarin, indicated that the concurrent use of Esmolol Hydrochloride and varfarin did not change the plasma levels of varfarin. Nevertheless, the

concentration of Esmolol Hydrochloride used together with varfarin was seen to be higher.
The levels of digoxin in the blood reportedly increased by 10-20% at certain times when Esmolol Hydrochloride and digoxin are administered intravenously to healthy volunteers. Esmolol Hydrochloride combination AV transfer duration may be extended with digital glycoside. Digoxin did not affect the pharmacokinetic characteristics of Esmolol Hydrochloride.

When intravenous morphine and Esmolol Hydrochloride was concurrently administered to healthy volunteers, no change was observed in the levels of morphine in the blood. It was determined that the stabilized blood levels of Esmolol Hydrochloride rose by 46% but none of the other pharmacokinetic parameters changed in the presence of morphine.

The effects of Esmolol Hydrochloride on the duration of neuromuscular blockage stimulated with suxamentonium chloride and mivacurium. Esmolol Hydrochloride does not affect the initiation of neuromuscular blockage induced with suxamentonium chloride; however, the duration of the neuromuscular blockage rose from 5 minutes to 8 minutes. Esmolol Hydrochloride partially extended the clinic duration of mivaurium (18.6%) and recovery index (6.7%).

The interactions observed in studies carried out with varfarin, digoxin, morphine, suxamentonium chloride or mivacurium are clinically insignificant, while titration must be carried out with caution for cases where ESMOBLOC is concurrently administered with varfarin, digoxin, morphine, suxamentonium chloride or mivacurium.

4.6. Pregnancy and lactation

General recommendations

Pregnancy Category: C/D (2^{nd} and 3^{rd} trimester)

Women with childbearing potential/Contraception

Women with the potential to bare children must use an effective method of birth control during the treatment.

Pregnancy

Studies on animals are limited in terms of effects on pregnancy and/or embryo/fetal development and/or birth and/or after-birth development. Procreation toxicity was observed in the animal studies of Esmolol Hydrochloride (see section 5.3). Potential risk towards humans is unknown.
Esmolol hydrochloride is **not recommended during pregnancy**.

Due to its pharmaceutical effects, its delayed side effects on the fetus and the newborn (especially hypoglycemia, hypotension and bradycardia) should be monitored.

If ESMOBLOC treatment is necessary during pregnancy, it should be administered only if its potential benefits outweigh its toxicity for the fetus, and the uteroplacental blood circulation and fetal development should be monitored. Newborns should be closely monitored.

Lactation

Esmolol hydrochloride is should not be used while breastfeeding.

It is not known whether esmolol hydrochloride passes into mother's milk. Potential risks cannot be neglected when newborn babies/babies are concerned.

Fertility

There are no studies available on the effects of esmolol on the fertility of humans.

4.7. Effects on ability to drive and use machines

As it is not possible to use ESMOBLOC while driving, or operating machinery, its effects are not known.

4.8. Undesirable effects

In case of undesirable effects, the dosage of ESMOBLOC may be decreased or the administration may be terminated.

Most of the side-effects are reported to be mild and temporary. And the most important one is hypotension.

The incidence of adverse reactions are assessed with the criteria below: Very common (≥1/10), common (≥1/100 , <1/10); uncommon (≥1/1.000 , <1/100); rare (≥1/10.000 , <1/1.000); very rare (<1/10.000), not known (it cannot be estimated from the available data).

Metabolism and nutrition disorders

Common:	Anorexia.
Unknown:	Hyperkalemia, metabolic acidosis.

Psychiatric disorders

Common:	Depression, anxiety
Uncommon:	Abnormal thoughts

Nervous system disorders

Common:	Light-headedness / dizziness[1], sleepiness, headache, paresthaesia, distraction, confusion, agitation
Uncommon:	Syncope, convulsions, speech disorders

Ophthalmic disorders

Uncommon: Disoriented vision.

Cardiac disorders

Uncommon: Bradycardia, atrioventricular block, increased pulmonary arterial pressure, heart failure, ventricular extrasystole, nodal rhythm, angina pectoris.

Very rare: Sinus stopping, asystole

Unknown: Accelerated idioventricular rhythm, coronary arteriospasm, cardiac arrest

Vascular disorders

Very common: Hypotension.

Uncommon: Peripheral ischemia, shortness of breath, redness around the face and the neck.

Very rare: Trombophilebite[2]

Respiratory, chest and mediastinal disorders

Uncommon: Dyspnea, pulmonary edema, bronchospasm, noisy breathing, nasal congestion, rhonchus and ralls in the rhythm of the lungs

Gastrointestinal disorders

Common: Nausea, vomiting.

Uncommon: Dysgeusia, dyspepsia, constipation, dry mouth, stomachache

Cutaneous and subcutaneous tissue disorders :

Very common: Diaphoresis[1]

Uncommon: Skin discoloring[2], erythema[2]

Very rare: Cutaneous necrosis (due to extravasation).[2]

Unknown: Psoriasis[3], angio-edema, urticaria.

Musculoskeletal disorders, ligament and skeletal disorders

Uncommon: Musco-skeletal pain[4]

Renal and urinary tract disorders

Uncommon: Urinary retention

General disorders and administration site diseases:

Common: Asthenia, fatigue, injection site reaction, infusion site reaction, infusion site inflammation, infusion site indurations.

Uncommon: Shivering, high fever, edema[2], pain[2], infusion site inflammation, infusion site ecchymosis.

Unknown: Infusion site phlebitis, infusion site vesicles, infusion site blistering.[2]

1. Light-headedness/dizziness and diaphoresis were observed together with symptomatic hypotension.
2. These reactions are related to the injection and infusion site reactions.
3. Beta blockers may, as a class reaction, cause or aggregate psoriasis.
4. Including midscapular pain and costochondritis.

4.9 Overdose and therapy

There are cases of accidental overdose with concentrated Esmolol Hydrochloride solutions. While some these cases were fatal, others caused temporary loss of functions. Bolus doses of the preparation between 625 mg and 2.5 g (12.5 – 50 mg/kg) resulted in fatality.

Symptoms of overdosing

Overdosing may lead to the following symptoms: Severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, shortness of breath, loss of consciousness with the possibility of coma, stroke, nausea, vomiting, hypoglycemia and hyperkalemia.

Treatment of overdosing

Due to a short elimination half-life (approximately 9 minutes), the first step of the toxicity treatment is stopping the ESMOBLOC infusion. The time it takes the symptoms of overdosing to go away, depends on the amount of ESMOBLOC administered. This period may be over 30 minutes after the final dose when ESMOBLOC is administered in the therapeutic dose. Artificial respiration may be necessary. Afterwards, depending on the observed clinical effects, the treatments below may be implemented:

- ***Bradycardia:*** Atropine or another anticholinergic drug is administered intravenously. A pacemaker may be necessary if bradycardia cannot be treated well enough.

- ***Bronchospasm:*** Nebulize beta-2-sempatomimeticles should be administered. If this is not enough, an intravenous administration of beta-2-sempatomimeticles or aminophylline should be considered.

- ***Symptomatic hypotension:*** Fluids and/or pressor agents should be administered ıntravenously.

- ***Cardiovascular depression or cardiac shock:*** Diuretics or sympathicomimetics may be administered. The dose of the sympathicomimetics (dobutamin, dopamine, noradrenalin or isoprenaline depending on the symptoms) to be administered depend on the therapeutic effect.

When a more advanced treatment is necessary, the following drugs may be administered intravenously depending on the clinical situation and the decision to be made by the physician implementing the treatment.
- Atropine;
- Inotropic agents;
- Calcium ions.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Selective beta blocker drugs

ATC code: C07AB09
Esmolol hydrochloride is a beta selective (cardioselective) adrenergic receptor blockage agent. Therapeutic doses do not contain a significant intersect sympathomimetic activity (ISA) or membrane stabilizing activity.

The active substance of ESMOBLOC, esmolol hydrochloride, in terms of chemistry, belongs to the phenoxy propanolamine class of beta blockers.

Depending on pharmacological characteristics, esmolol hydrochloride shows its effects right away, and lasts short enough for the dosage to be adjusted quickly.

With the suitable loading dose, stabilized status levels are achieved in 5 minutes in the blood. However, therapeutic effect is achieved in a shorter time than stabilized plasma concentration. The infusion rate may be adjusted to obtain the desired pharmacological effect.

Esmolol hydrochloride possessed the known hemodynamic and electrophysiological effects of beta blockers:

- Decreased heart rate when resting and exercising;
- Increased heart rate after decreasing isoprenaline;
- Increased recovery time of sinoatrial (SA) knot;
- Delayed atrioventricular (AV) conduction;
- Atrioventricular (AV) range being extended during atrium stimulation with normal sinus rhythm and without delays in His-Purkinje tissue;
- Extended PQ duration, stage II atrioventricular block induction;
- Extended atrium and ventricular functional refractor period;
- Decreased ejection fraction and negative inotropic effect;
- Decreased blood pressure.

Pediatric population:

A controlled pharmacokinetic/activity study was carried out with 26 pediatric patients with supraventricular tachycardia between the ages 2 and 16. After a 1000 microgram/kg esmolol hydrochloride loading dose is administered, 300 microgram/kg/min dose was administered with sustainment infusion. In 5 minutes after starting to administer esmolol, supraventricular tachycardia was ended in 65% of the patients.
In a randomized, non-controlled, dose comparison study involving 116 pediatric patients between the ages 1 and 7, activity in hypertension developing after the aorta coarctation was fixed, was investigated. The patients who were administered esmolol hydrochloride loading doses of 125 microgram/kg, 250 microgram/ks and 500 microgram/kg, were than administered sustainment treatment with 125 microgram/kg, 250 microgram/kg and 500 microgram/kg. The three dosage groups did not demonstrate a significant difference in terms of hypotensive effect. In 54% of the patients, a drug other than esmolol hydrochloride was necessary to achieve sufficient control over the blood pressure. In this regard, there weren't any significant differences between the various dosage groups.

5.2. Pharmacokinetic properties

Absorption:
Maximum plasma concentration is quickly achieved after intravenous administration.

Distribution:
The distribution half-life of esmolol hydrochloride is approximately 2 minutes, which is very short. Its distribution volume is 3.4 L/kg.

Biotransformation:
Esmolol hydrochloride is metabolized by esterases to an acid metabolite (ASL-8123) and methanol. This metabolism is actualized through hydrolysis by the esterases in the erythrocyte of the ester bonds.

The metabolism of esmolol hydrochloride is not dosage dependent when the dosage is between 50 and 300 microgram/kg/minute.

It was demonstrated that esmolol hydrochloride bonded with human plasma protein at a rate of 55%, and that acid metabolite bonded at a rate of 10% only.

Elimination:
Elimination half-life intravenous administration is approximately 9 minutes.

Its total clearance is 285 ml/kg/minute; total clearance does not depend on the circulation of the liver or other organs. Esmolol hydrochloride is discharged through the kidneys partially without transformation (less than 2% of the administered amount) and partially as an acid metabolite with the activity of a weak beta blocker. Acid metabolite is discharged through urine, and has an elimination half-life of approximately 3.7 hours.

Linearity/Non-linearity:
Esmolol kinetics is linear in healthy adults. If a loading dose is not administered, when a dosage of 50-300 microgram/kg/minute is administered, the time it takes to achieve plasma stabilized levels is proportional to the dosage.

Characteristic features of patients

Pediatric population:

A pharmaceutical study was carried out involving 22 pediatric patients between the ages of 3 and 16. After a 1000 microgram/kg esmolol hydrochloride loading dose is administered, 300 microgram/kg/min dose was administered with sustainment infusion. The study demonstrated a total body clearance of 119 ml/kg/minute, average distribution volume of 283 ml/kg, and average terminal elimination half-lie of 6.9 minutes, which pointed out that the kinetics of esmolol hydrochloride in the children involved in the study was not different that those of adults.However, significant individual differences were observed in the children.

5.3. Pre-clinic safety data

No teratogenic effect was observed in animal studies. An embryotoxic effect (increased fetal resorption) was observed, which was probably caused by esmolol hydrochloride. This effect was observed in dosages 10 times and higher than the therapeutic dosage.

There are no studies available regarding the perinatal and postnatal effects of esmolol hydrochloride on fertility. Esmolol hydrochloride was found to be not mutagenic in *in vitro* and *in vivo* test systems. The reliability of esmolol hydrochloride was not investigated with long-term studies.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium acetate trihydrate
Glacial acetic acid
Sodium chloride
Sodium hydroxide and/or hydrochloric acid –for pH adjustment
Water for injection

6.2. Incompatibilities

As there are no incompatibility studies, this drug should not be mixed with other drugs or sodium bicarbonate solutions.

6.3. Shelf life

24 months.

Once opened, the product remains physio-chemically stabilized for 24 hours, provided that it is kept at 2-8°C.

In terms of microbiology, the product must be used immediately once opened. If it cannot be used immediately, the duration and conditions of storage before starting to use is the responsibility of the user. This period may not be over 24 hours provided that the bag remains at 2-8°C, controlled and aseptic conditions, and unopened.

6.4. Special precautions for storage

It should be stored at room temperatures under 25°C. It should not be kept in a fridge or be frozen. See section 6.3 for the storage conditions of the solution.

6.5. Nature and contents of container

1 unit of 250 ml PP bag with two ports placed in an external aluminum bag. The product is offered with and without its set.

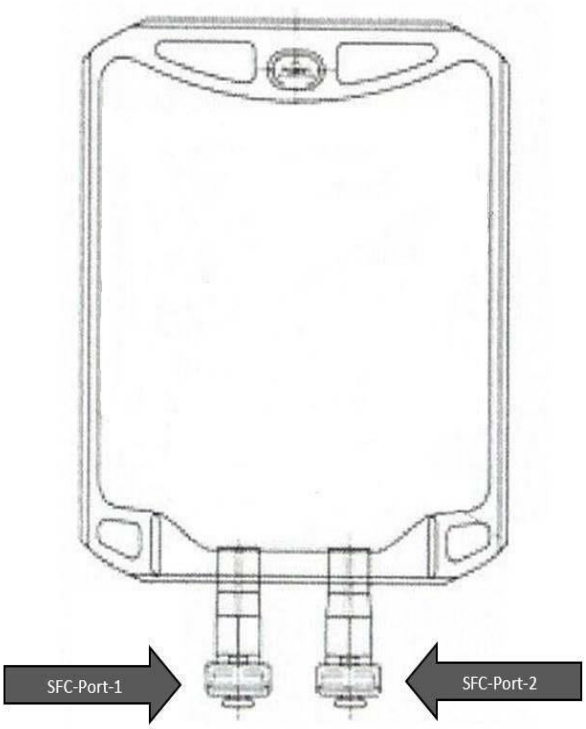
6.6. Special precautions for disposal and other handling

Unused products or waste materials should be disposed of according to the regulations on “Medicinal Product Control", and "Packaging and Packaging Waste Control".

INSTRUCTIONS FOR THE BAG
ESMOBLOC 10 mg/ml I.V. infusion solution is offered in PP-6280 bags of 250 ml (non-latex polypropylene bags with two SFC exits with one bag for the administration of drugs into the bag, the other for the drug in the bag to be given to the patient).

The tip chosen for the administration of the drug in the bag for ESMOBLOC 10 mg/ml I.V. infusion should only be used for the first bolus administration from the bag, and is not for repeated bolus administration. While drawing the bolus dosage, an aseptic technique should be used. ESMOBLOC 10 mg/ml I.V. solution for infusion should not be added any additional drugs. Each bag is for use with a single patient. Once the drug administration exit seal is broken and the drug is drawn from the bag, the bag must be used completely in 24 hours. Any remaining solution or the bag should be disposed of according to the local regulations. Do not re-use partially used bags.

Figure 1: Polypropylene bag with two SFC ports



WARNING

Do not use the plastic bags for connection in series. Such usage may cause emboli as a result of the residual air being suck out from the first container once the liquid administration in the second container has been completed.

OPENING THE BAG

The bag should not be removed from its external packaging (external bag) until it is used. It should not be used if the external bag is damaged or was previously opened. The purpose of the external bag is to prevent moisture. The inner bag safeguards the sterility of the solution.

Open the external bag from the notched edge and remove the premixed bag. The opacity seen on the plastic bag at this stage, is related to the humidity absorption during the sterilization process, and does not affect the quality or reliability of the solution. Opacity will gradually fade away.

Squeeze the inner bag to check for small leaks. If there are any leaks, the solution must be disposed of due to contamination. Before administration, carefully perform a visual check of the solution for particle matter and change of color. Only the clear, colorless or light yellow solutions should be used.

No extra substances should be added to ESMOBLOC 10 mg/ml I.V. solution for infusion.

PREPARATION FOR INTRAVENOUS ADMINISTRATION (aseptic technique should be applied)

1. Hang the premixed bag.
2. Remove the plastic cover on the administration exits at the bottom of the bag.
3. Insert the administration set, and start the procedure according to the instructions provided with the set.

7. MARKETING AUHTORISATION HOLDER

Name : POLİFARMA İlaç San. ve Tic. A.Ş.
Address : Vakıflar OSB Mahallesi, Sanayi Caddesi, No:22/1 Ergene/Tekirdağ/TURKEY
Phone : +90 282 675 14 04
Fax : +90 282 675 14 05

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10. DATE OF REVISION OF THE TEXT

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