SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Multiflex ERMOLOC Premix 10 mg/mL IV Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Drug substance:

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

Excipients:

This medicinal product contains approximately 30.45 mmol (or 700 mg) sodium in each bag. For excipients see 6.1.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Clear, colorless to light yellow solution.

The solution has a pH between 4.5 to 5.5 and osmolarity of approximately 300 mOsm/L.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Supraventricular tachycardia or non-compensatory sinus tachycardia

ERMOLOC is indicated in cases of atrial fibrillation or atrial flutter that occur in perioperative, postoperative or other emergency situations where rapid control of the ventricular rate with a short-acting preparation is desired.

ERMOLOC is also indicated in the case of uncompensated sinus tachycardia if the physician has decided to correct the accelerated heart rate with a special intervention.

ERMOLOC is intended for short-term use.

Intraoperative and postoperative tachycardia and / or hypertension

ERMOLOC is indicated for tachycardia and hypertension seen during endotracheal intubation, anesthesia induction, surgical procedure, on exiting anesthesia, and in the postoperative period, if the physician has decided to correct such a special intervention.

It is not recommended to use ERMOLOC in order to prevent such situations from occurring.

4.2. Posology and method of administration

Posology/administrationfrequency and duration

Dosing in the treatment of supraventricular tachycardia or uncompensated sinus tachycardia

ERMOLOC is administered by continuous intravenous infusion with or without a loading dose. Additional loading doses and/or titration of the maintenance infusion (stepwise dosing) may be required, depending on the desired ventricular response.

Table 1-Stepwise Dosing

Step	Operation
1	Optional loading dose (500 mcg / kg within 1 min), then 50 mcg / kg / min for 4 min
2	Optional loading dose if required, 100 mcg / kg / min for 4 min.
3	Optional loading dose if required, 150 mcg / kg / min for 4 min.
4	If required, increase the dose to 200 mcg / kg / min.

In cases where the loading dose is not administered, pharmacokinetically and pharmacodynamically fixed concentrations of esmolol administered at a fixed concentration are reached in about 30 minutes.

The effective maintenance dose is 50 to 200 micrograms/kg/min, although doses as low as 25 micrograms/kg/min are sufficient for continuous and stepwise dosing. Doses higher than 200 micrograms/kg/min decrease the effect and cause a small increase in heart rate and increase the rate of adverse reactions.

The maintenance infusion can be continued for up to 48 hours.

Intraoperative and postoperative tachycardia and / or hypertension

It is not always recommended to titrate slowly for therapeutic effect in this use. Therefore, two dosing options are offered: Immediate control and step control.

1. Dose recommendation for immediate control

- It is administered as bolus dose 1 mg/kg within 30 seconds, followed by 150 microgram/kg/min infusion if necessary.
- The infusion rate as needed to maintain the desired heart rate and blood pressure is adjusted. See Maximum Recommended Doses below.

2. Dose recommendation for step titration

- It is administered as a bolus dose of 500 microgram/kg within 1 minute, followed by a maintenance infusion of 50 microgram/kg/minute within 4 minutes.
- Depending on the response achieved, the dosing determined for supraventricular tachycardia is continued. See Maximum Recommended Doses below.

Maximum recommended doses

- Maintenance doses higher than 200 micrograms/kg/min are not recommended for the treatment of tachycardia. Doses higher than 200 micrograms/kg/min decrease the effect, causing a small increase in heart rate and increasing the rate of adverse reactions.
- Higher maintenance infusion doses (250-300 micrograms/kg/min) may be required for

the treatment of hypertension. The reliability of doses above 300 micrograms/kg/min has not been studied.

Transition from ERMOLOC treatment to alternative drugs

Patients can be switched to alternative antiarrhythmic drugs after providing adequate control of heart rate and a stable clinical picture.

When switching from ERMOLOC treatment to alternative drugs, the physician should carefully examine the instructions for use of the selected alternative drug and reduce the dose of ERMOLOC as follows:

- Within 30 minutes after the first dose of the alternative medicine, ERMOLOC infusion rate is reduced in half (50%).
- After the administration of the second dose of the alternative medicine, the patient's response is monitored and if adequate control is achieved in the first hour, ERMOLOC infusion is discontinued.

Method of Administration:

Since ERMOLOC is a ready-to-use solution, it is used intravenously without dilution.

Additional information on special populations:

Renal failure:

Since ERMOLOC acid metabolite is excreted in an unchanged form by the kidneys in patients with renal failure, caution should be exercised when ERMOLOC is administered by infusion. Excretion of the acid metabolite is significantly reduced in individuals with end-stage renal disease, the elimination half-life has increased to approximately ten times normal, and plasma levels are significantly increased.

Hepatic failure:

Since esterases in red blood cells play a fundamental role in ERMOLOC metabolism, special precautions are not required in case of hepatic failure.

Pediatric population:

The efficacy or safety of ERMOLOC in use in children under the age of 18 has not yet been proven. Existing data are described in sections 5.1 and 5.2, but no recommendation on a posology can be made from these data.

Geriatric population:

In the elderly, the treatment should be started with a low dose and the administration should be done carefully.

Special studies have not been conducted in the elderly. However, analysis of data from 252 patients over 65 years of age shows that there is no difference with those under 65 years of age in terms of pharmacodynamic effects.

4.3. Contraindications

Hypersensitivity to the active substance, to any of the excipients, to other substances or to other beta-blockers (cross-sensitivity between beta-blockers is possible),

- Severe sinus bradycardia (less than 50 beats per minute),
- Sick sinus syndrome; severe AV node conduction disturbances (non-pacemaker); second or third degree heart blocks,
- Cardiogenic shock,
- Severe hypotension,
- Decompensated heart failure,
- Simultaneous or recent use of verapamil intravenously. ERMOLOC should not be administered within 48 hours after verapamil discontinuation (see section 4.4).
- Untreated pheochromocytoma,
- Pulmonary hypertension,
- Acute asthma attack,
- Metabolic acidosis.

4.4. Special warnings and special precautions for use

It is recommended to continuously monitor the blood pressure and the ECG in all patients treated with ERMOLOC.

The use of ERMOLOC for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised haemodynamically 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 the effects of ERMOLOC, severe reactions may occur, including loss of consciousness, cardiogenic shock, cardiac arrest. Several deaths have been reported in complex clinical states where ERMOLOC was presumably being used to control ventricular rate.

The most frequently observed side effect is hypotension, which is dose related but can occur at any dose. This can be severe. In the event of a hypotensive episode the infusion rate should be lowered or, if necessary, be discontinued. Hypotension is usually reversible (within 30 minutes after discontinuation of administration of ERMOLOC). In some cases, additional interventions may be necessary to restore blood pressure. In patients with a low systolic blood pressure, extra caution is needed when adjusting the dosage and during the maintenance infusion.

Bradycardia, including severe bradycardia, and cardiac arrest has occurred with the use of ERMOLOC. ERMOLOC should be used with special caution in patients with low pretreatment heart rates and only when the potential benefits are considered to outweigh the risk.

ERMOLOC is contraindicated in patients with pre-existing severe sinus bradycardia (see section 4.3). If the pulse rate decreases to less than 50-55 beats per minute at rest and the patient experiences symptoms related to bradycardia, the dosage should be reduced or administration stopped.

Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure. 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.

Caution should be exercised when using ERMOLOC in patients with compromised cardiac function. At the first sign or symptom of impending cardiac failure, ERMOLOC should be withdrawn. Although withdrawal may be sufficient because of the short elimination half-life of ERMOLOC, specific treatment may also be considered (see section 4.9). ERMOLOC is contraindicated in patients with decompensated heart failure (see section 4.3).

Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block or other cardiac conduction disturbances (see section 4.3).

ERMOLOC should be used with caution and only after pre-treatment with alpha-receptor blockers in patients with pheochromocytoma (see section 4.3).

Caution is required when ERMOLOC is used to treat hypertension following induced hypothermia.

Patients with bronchospastic disease should, in general, not receive beta-blockers. Because of its relative beta-1 selectivity and titratability, ERMOLOC should be used with caution in patients with bronchospastic diseases. However, since beta-1 selectivity is not absolute, ERMOLOC should be carefully titrated to obtain the lowest possible effective dose. In the event of bronchospasm, the infusion should be terminated immediately and a beta-2-agonist should be administered if necessary.

If the patient already uses a beta-2-receptor stimulating agent, it may be necessary to re-evaluate the dose of this agent.

ERMOLOC should be used with caution in patients with a history of wheezing or asthma.

ERMOLOC should be used with caution in diabetics or in case of suspected or actual hypoglycaemia. Beta-blockers may mask the prodromal symptoms of a hypoglycaemia such as tachycardia. However, dizziness and sweating may not be affected. Concomitant use of beta-blockers and antidiabetic agents can increase the effect of the antidiabetic agents (see section 4.5).

Infusion site reactions have occurred with the use of ERMOLOC. These reactions have included infusion site irritation and inflammation as well as more severe reactions such as thrombophlebitis, necrosis, and blistering, in particular when associated with extravasation (see section 4.8). Infusions into small veins or through a butterfly catheter should be avoided. If a local infusion site reaction develops, an alternative infusion site should be used.

Beta-blockers may increase the number and the duration of anginal attacks in patients with Prinzemetal's angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Non-selective beta-blockers should not be used for these patients and beta-1 selective blockers should only be used with the utmost care.

In hypovolemic patients, ERMOLOC can attenuate reflex tachycardia and increase the risk of circulatory collapse. Therefore, ERMOLOC should be used with caution in such patients.

In patients with peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication), beta-blockers should be used with great caution as aggravation of these disorders may occur.

Some beta-blockers, especially those administered intravenously, including ERMOLOC, have been associated with increases in serum potassium levels and hyperkalemia. The risk is increased in patients with risk factors such as renal impairment and those on haemodialysis.

Beta-blockers may increase both the sensitivity toward allergens and the seriousness of anaphylactic reactions. Patients using beta-blockers may be unresponsive to the usual doses of epinephrine used to treat anaphylactic or anaphylactoid reactions (see section 4.5).

Beta-blockers have been associated with the development of psoriasis or psoriasiform eruptions and with aggravation of psoriasis. Patients with a personal or family history of psoriasis should be administered beta-blockers only after careful consideration of expected benefits and risks.

Beta-blockers, such as propranolol and metoprolol, may mask certain clinical signs of hyperthyroidism (such as tachycardia). Abrupt withdrawal of existing therapy with beta-blockers in patients at risk or suspected of developing thyrotoxicosis may precipitate

thyroid storm and these patients must be monitored closely.

This medicinal product contains approximately 30.45 mmol (700 mg) of sodium per 250 mL bag. To be taken into consideration by patients on a controlled sodium diet.

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

Care should always be exercised whenever ERMOLOC is used with other antihypertensive agents or other drugs that may cause hypotension or bradycardia: the effects of ERMOLOC may be enhanced or the side-effects of hypotension or bradycardia may be exacerbated.

Calcium antagonists such as verapamil and to a lesser extent diltiazem have a negative influence on contractility and AV conduction. The combination should not be given to patients with conduction abnormalities and ERMOLOC should not be administered within 48 hours of discontinuing verapamil (see section 4.3).

Calcium antagonists such as dihydropyridine derivatives (e.g., nifedipine) may increase the risk of hypotension. In patients with cardiac insufficiency and who are being treated with a calcium antagonist, treatment with beta-blocking agents may lead to cardiac failure. Careful titration of ERMOLOC and appropriate haemodynamic monitoring is recommended.

Concomitant use of ERMOLOC and Class I anti-arrhythmic drugs (e.g., disopyramide, quinidine) and amiodarone may have potentiating effect on atrial-conduction time and induce negative inotropic effect.

Concomitant use of ERMOLOC and insulin or oral anti-diabetic drugs may intensify the blood sugar lowering effect (especially non-selective beta-blockers). Beta-adrenergic blockade may prevent the appearance of signs of hypoglycaemia (tachycardia), but other manifestations such as dizziness and sweating may not be masked.

Anaesthetic drugs: in situations where the patient's volume status is uncertain or concomitant antihypertensive drugs are utilized, there may be attenuation of the reflex tachycardia and an increased the risk of hypotension. Continuation of beta-blockade reduces the risk of arrhythmia during induction and intubation. The anaesthetist should be informed when the patient is receiving a beta-blocking agent in addition to ERMOLOC. The hypotensive effects of inhalation anaesthetic agents may be increased in the presence of ERMOLOC. The dosage of either agent may be modified as needed to maintain the desired haemodynamics.

The combination of ERMOLOC with ganglion blocking agents can enhance the hypotensive effect.

NSAIDs may decrease the hypotensive effects of beta-blockers.

Special caution must be taken when using floctafenine or amisulpride concomitantly with beta-blockers.

Concomitant administration of tricyclic antidepressants (such as imipramine and amitriptyline), barbiturates or phenothiazines (such as chlorpromazine), as well as other antipsychotic agents (such as clozapine) may increase the blood pressure lowering effect. Dosing of ERMOLOC should be adjusted downward to avoid unexpected hypotension.

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 reactions (see section 4.4).

The effects of ERMOLOC may be counteracted by sympathomimetic drugs having beta-adrenergic agonist activity with concomitant administration. The dose of either agent may need to be adjusted based on patient response, or use of alternate therapeutic agents considered.

Catecholamine-depleting agents, e.g., reserpine, may have an additive effect when given with beta-blocking agents. Patients treated concurrently with ERMOLOC 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.

Use of beta-blockers with moxonidine or alpha-2-agonists (such as clonidine), increases the risk of withdrawal rebound hypertension. If clonidine or moxonidine are used in combination with a beta-blocker and both treatments have to be discontinued, the beta blocker should be discontinued first and then the clonidine or moxonidine after a few days.

The use of beta-blockers with ergot derivatives may result in severe peripheral vasoconstriction and hypertension.

Data from an interaction study between ERMOLOC and warfarin showed that concomitant administration of ERMOLOC and warfarin does not alter warfarin plasma levels. ERMOLOC concentrations, however, were equivocally higher when given with warfarin.

When digoxin and ERMOLOC were concomitantly administered intravenously to healthy volunteers, there was a 10-20% increase in digoxin blood levels at some time points. The combination of digitalis glycosides and ERMOLOC may increase AV conduction time. Digoxin did not affect ERMOLOC pharmacokinetics.

When intravenous morphine and ERMOLOC interaction was studied in healthy subjects, no effect on morphine blood levels was seen. The ERMOLOC steady-state blood levels

were increased by 46% in the presence of morphine, but no other pharmacokinetic parameters were changed.

The effect of ERMOLOC on the duration of suxamethonium chloride-induced or mivacurium-induced neuromuscular blockade has been studied in patients undergoing surgery. ERMOLOC did not affect the onset of neuromuscular blockade by suxamethonium chloride, but the duration of neuromuscular blockade was prolonged from 5 minutes to 8 minutes. ERMOLOC moderately prolonged the clinical duration (18.6%) and recovery index (6.7%) of mivacurium.

Although the interactions observed in studies of warfarin, digoxin, morphine, suxamethonium chloride or mivacurium are not of major clinical importance, ERMOLOC should be titrated with caution in patients being treated concurrently with warfarin, digoxin, morphine, suxamethonium chloride or mivacurium.

4.6. Pregnancy and lactation

General advice

Pregnancy category: C / D (2. and 3. trimester)

Women with child-bearing potential/Contraception

Women of childbearing potential must use effective contraception during treatment.

Pregnancy

Animal studies are insufficient in terms of effects on pregnancy/and/or/embryonal/fetal development/and-or/birth/and-or/postnatal development. Studies with ERMOLOC in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Esmolol hydrochloride is **not recommended during pregnancy.**

Based on the pharmacological action, in the later period of pregnancy, side effects on the foetus and neonate (especially hypoglycemia, hypotension and bradycardia) should be taken into account.

It should be used if ERMOLOC treatment is necessary during pregnancy, but if the potential benefit exceeds the toxicity to the fetus, the uteroplacental blood flow and foetal growth should be monitored. The newborn infant must be closely monitored.

Breastfeeding

Esmolol hydrochloride should not be used during breast-feeding.

It is not known whether esmolol hydrochloride/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded.

Fertility

There are no studies investigating the effect of esmolol on reproductive ability / fertility in

humans.

4.7. Effects on ability to drive and use machines

Since it is not possible to use ERMOLOC while driving and using machines, its effect on this issue is unknown.

4.8. Undesirable effects

In case of undesirable effects, the dose of ERMOLOC can be reduced or discontinued.

Most of the undesirable effects observed have been mild and transient. The most important one has been hypotension.

The frequency of occurrence of adverse events is classified as follows: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1000 to < 1/100), Very rare (<1/10000), Not known (Cannot be estimated from the available data)

Metabolism and nutrition disorders

Common : Anorexia

Not known : Hyperkalaemia, metabolic acidosis

Psychiatric disorders

Common : Depression, anxiety

Uncommon : Thinking abnormal

Nervous system disorders

Common : Dizziness/lightheadedness[1], somnolence, headache, paraesthesia, disturbance in attention, confusional state, agitation

Uncommon : Syncope, convulsion, speech disorder.

Eye disorders

Uncommon : Visual impairment

Cardiac disorders

Uncommon : Bradycardia, atrioventricular block, pulmonary arterial pressure increase, cardiac failure, ventricular extrasystoles, nodal rhythm, angina pectoris.

Very rare : Sinus arrest, asystole.

Unknown : Accelerated idioventricular rhythm, coronary arteriospasm, cardiac arrest.

Vascular disorders

Very common : Hypotension

Uncommon : Peripheral ischemia, pallor, facial and neck flushing

Very rare : Thrombophlebitis[2]

Respiratory, thoracic and mediastinal disorders

Uncommon : Dyspnoea, pulmonary edema, bronchospasm, wheezing, nasal congestion, rhonchi and rales in lung sounds

Gastrointestinal disorders

Common : Nausea, vomiting

Uncommon : Dysgeusia, dyspepsia, constipation, dry mouth, abdominal pain

Skin and subcutaneous tissue disorders

Very common : Diaphoresis[1]

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

Very rare : Skin necrosis (due to extravasation) 2

Not known : Psoriasis[3], angioedema, urticaria

Musculoskeletal, connective tissue and skeletal disorders

Uncommon : Musculoskeletal pain[4]

Renal and urinary tract disorders

Uncommon : Urinary retention

General disorders and administration site conditions:

Common : Asthenia, fatigue, injection site reaction, infusion site reaction, infusion site inflammation, infusion site induration

Uncommon : Chills, fever, edema[2], pain[2], infusion site burning, infusion site ecchymosis

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

1. Dizziness and diaphoresis are in association with symptomatic hypotension.
2. In association with Injection and Infusion site reactions.
3. Beta-blockers as a drug class can cause psoriasis in some situations, or worsen it.
4. Including midscapular pain and costochondritis

<u>Reporting of suspected adverse reactions</u>

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9. Overdose

Cases of massive accidental overdoses with concentrated solutions of ERMOLOC have occurred. Some of these overdoses have been fatal while others have resulted in permanent disability. Bolus doses in the range of 625 mg to 2.5 g (12.5 to 50 mg/kg) have been fatal.

Overdose Symptoms

In case of overdose the following symptoms can occur: severe hypotension, sinus bradycardia, atrioventricular block, heart insufficiency, cardiogenic shock, cardiac arrest, bronchospasm, respiratory insufficiency, loss of consciousness to coma, convulsions, nausea, vomiting, hypoglycaemia and hyperkalaemia.

Overdose Treatment

Because of the short elimination half-life of ERMOLOC (approximately 9 minutes), the first step in the management of toxicity should be to discontinue the administration of the drug. The time taken for symptoms to disappear following overdosing will depend on the amount of ERMOLOC administered. This may take longer than the 30 minutes seen with discontinuation at therapeutic dose levels of ERMOLOC. Artificial respiration may be necessary. Based on the observed clinical effects, the following general measures should also be considered:

- ***Bradycardia:*** Atropine or another anticholinergic drug should be given i.v. When the bradycardia cannot be treated sufficiently a pacemaker may be necessary.
- ***Bronchospasm:*** Nebulised beta-2-sympathomimetics should be given. If this is not sufficient intravenous beta-2-sympathomimetics or aminophylline can be considered.
- ***Symptomatic hypotension:*** Fluids and/or pressor agents should be given i.v.
- ***Cardiovascular depression or cardiac shock:*** Diuretics or sympathomimetics can be administered. The dose of sympathomimetics (depending on the symptoms: dobutamine, dopamine, noradrenaline, isoprenaline, etc.) depends on the therapeutic effect.

In case further treatment is necessary, the following agents can be administered intravenously based on the clinical situation and judgement of the treating healthcare professional:

- Atropine
- Inotropic agents
- Calcium ions

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-blocking agents, selective.

ATC code: C07AB09

ERMOLOC is a beta-selective (cardioselective) adrenergic receptor blocking agent. At therapeutic doses ERMOLOC has no significant intrinsic sympathomimetic activity (ISA) or membrane stabilising activity.

Esmolol hydrochloride, the active ingredient of ERMOLOC, is chemically related to the phenoxy propanolamine class of beta-blockers.

Based on the pharmacological properties ERMOLOC has a rapid onset and a very short duration of action by which the dose can be quickly adjusted.

When an appropriate loading dose is used, steady state blood levels are obtained within 5 minutes. However, the therapeutic effect is achieved sooner than the stable plasma concentration. The infusion rate can then be adjusted to obtain the desired pharmacological effect.

ERMOLOC has the known haemodynamic and electrophysiologic effect of beta-blockers:

- Reduction of the heart frequency during rest and exercise;
- Reduction of the isoprenaline caused increase of the heart frequency;
- Increase of the recovering time of the SA-node;
- Delay of the Atrioventricular (AV) conductance;
- Prolonging the Atrioventricular (AV) interval with normal sinus rhythm and during atrium stimulation without delay in the His-Purkinje tissue;
- Prolonging of PQ time, induction of AV block grade II;
- Prolonging the functional refractory period of atria and ventricles;
- Negative inotropic effect with decreased ejection fraction;
- Decrease in blood pressure.

Pediatric Population

An uncontrolled pharmacokinetic/efficacy study was undertaken in 26 paediatric patients aged 2 to 16 years with supraventricular tachycardia (SVT). A loading dose of 1000 micrograms/kg of ERMOLOC was administered followed by a continuous infusion of 300 micrograms/kg/minute. SVT was terminated in 65% of patients within 5 minutes of the commencement of esmolol.

In a randomised but uncontrolled dose comparison study, efficacy was assigned in 116 paediatric patients aged 1 week to 7 years with hypertension following repair of coarctation of the aorta. Patients receiving an initial infusion of either 125 micrograms/kg, 250 micrograms/kg, or 500 micrograms/kg, followed by a continuous infusion of 125 micrograms/kg/minute, 250 micrograms/kg/minute, or 500 micrograms/kg/minute respectively. There was no significant difference in hypotensive effect between the 3

dosage groups. 54% of patients overall required medication other than ERMOLOC to achieve satisfactory blood pressure control. No difference was apparent in this regard between the different dose groups.

5.2 Pharmacokinetic properties

Absorption

After intravenous administration, the maximum plasma concentration is reached rapidly.

Distribution

The distribution half-life of esmolol hydrochloride is very short, about 2 minutes. The volume of distribution is 3.4 L/kg.

Biotransformation

Esmolol hydrochloride is metabolised by esterases into an acid metabolite (ASL-8123) and methanol. This occurs through hydrolysis of the ester group by esterases in the red blood cells.

The metabolism of esmolol hydrochloride is independent when the dose is between 50 and 300 micrograms/kg/minute.

Esmolol hydrochloride is 55% bound to human plasma protein compared with only 10% for the acid metabolite.

Elimination

The elimination half-life after intravenous administration is approximately 9 minutes.

The total clearance is 285 mL/kg/minute; this is independent of the circulation of the liver or any other organ. Esmolol hydrochloride is excreted by the kidneys, partly unchanged (less than 2% of the administered amount), partly as acid metabolite that has a weak (less than 0.1% of esmolol) beta-blocking activity. The acid metabolite is excreted in the urine and has a half-life of about 3.7 hours.

Linearity/Nonlinearity case:

Esmolol kinetics is linear in healthy adults. When a loading dose is not administered, the time to reach plasma fixed levels is linear with dose when administered at doses of 50-300 micrograms/kg/min.

Characteristics in patients

Pediatric population:

A pharmacokinetic study was undertaken in 22 paediatric patients aged 3 to 16 years. A loading dose of 1000 micrograms/kg of ERMOLOC was administered, followed by a continuous infusion of 300 micrograms/kg/minute. The observed mean total body clearance was 119 ml/kg/minute, the mean volume of distribution 283 mL/kg and the mean terminal elimination half-life 6.9 minutes, indicating that ERMOLOC kinetics in children

are similar to those in adults. However, large inter-individual variability was observed.

5.3 Preclinical safety data

No teratogenic effect has been observed in animal studies. In rabbits an embryo toxic effect has been observed (increase in fetal resorption) which was probably caused by Esmolol. This effect was observed at doses at least 10 times higher than the therapeutic dose.
No studies have been done on the effect of ERMOLOC on the fertility and on peri- and postnatal effects. Esmolol was found to be not mutagenic in several in vitro and in vivo test systems. The safety of esmolol has not been examined in 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

This drug should not be mixed with other drugs or sodium bicarbonate solution, as there are no compatibility studies available.
Avoid contact with alkaline substances.

6.3 Shelf life

24 months.
Opened product is physicochemically stable for 24 hours when stored at 2-8°C. Microbiologically, the product bag should be used immediately after opening.
If not used immediately, in-use storage times and conditions are the responsibility of the user. This period cannot normally be longer than 24 hours between 2-8 °C when the bag is not opened under controlled and validated aseptic conditions.

6.4 Special precautions for storage

It should be stored in its package at room temperature below 25 °C. It should not be stored in the refrigerator or frozen. For the storage conditions of the solution, see section 6.3.

6.5 Nature and contents of container

250 mL non-pvc bag with two outlets in an aluminum outer bag.

6.6 Instructions for use and handling and disposal

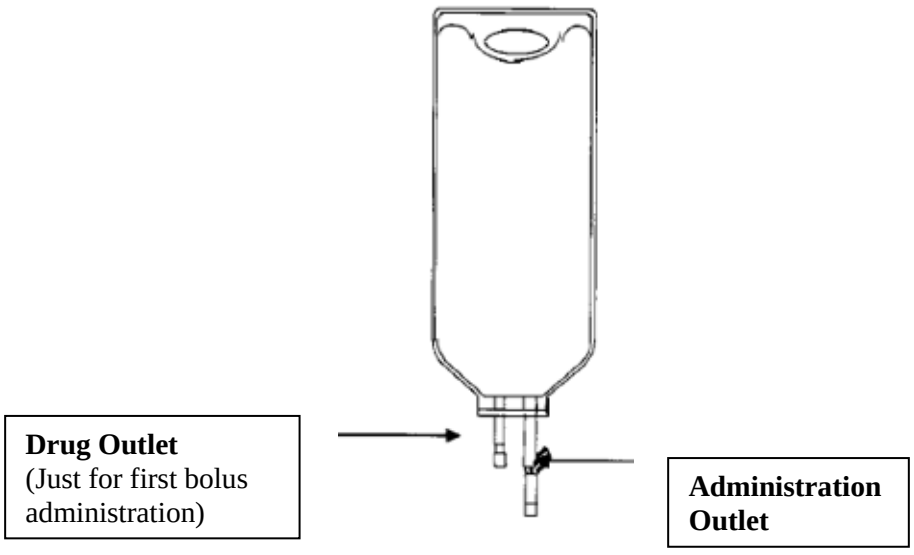
Unused products or waste materials must be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulation".

BAG USAGE INSTRUCTIONS

Ready-to-use solution for Multiflex ERMOLOC Premix 10 mg/mL IV Solution for Infusion is presented in 250 mL polyolefinic bags (two PVC-output non-latex polyolefinic bags, one for drug administration into the bag and the other for administration of the drug in the bag).

The drug delivery tip in the bag of the ready-to-use solution for Multiflex ERMOLOC Premix 10 mg/mL IV Solution for Infusion should only be used to withdraw the first bolus from the bag; not for repeated bolus administration. Aseptic technique should be used when taking the bolus dose. No additional medication should be added to the Multiflex ERMOLOC Premix 10 mg/mL IV Solution for Infusion ready-to-use solution. Each bag is for single patient use. The bag should be used within 24 hours after the seal of the drug administration outlet is broken and the drug is withdrawn from the bag. The unused portion and bag of the solution should be disposed of in accordance with local practice. Do not reuse partially used bags.

Figure 1. Double - outlet Multiflex bag



ATTENTION

Do not use plastic bags for serial connection. This type of use can cause embolism due to the drawing of residual air from the first container before the administration of the liquid in the second container is completed.

TO OPEN

It should not be removed from its outer packaging (outer bag) until just before use. The outer bag should not be used if it has been previously opened or damaged. The outer bag is intended to prevent moisture. The inner bag maintains the sterility of the solution.

The outer bag is opened from its notched place and the premix bag is removed. The opacities that can be seen on the plastic bag at this stage depend on the moisture absorption during the sterilization process and do not affect the quality or reliability of the solution. Opacity will gradually decrease.

The inner bag is squeezed and checked for small leaks. If there is a leak, the solution should be discarded as sterilization will be affected. Before application, the solution is inspected visually for particulate matter and discoloration. Only clear and colorless or light yellow solutions should be used.

No extra substance should be added to Multiflex ERMOLOC Premix 10 mg/mL.

PREPARATIONS FOR INTRAVENOUS ADMINISTRATION (aseptic technique should be used)

1. The premix bag is hung on a hanger from the hanging area.
2. The plastic cover is removed from the application outlet on the bottom of the bag.
3. Administration set is attached; the administration is started by following the instructions given with the set.

7. MARKETING AUTHORISATION HOLDER

MAGNA PHARMA İlaç A.Ş.
İncirköy Mah. Köyönü Cad.
No.:85 Beykoz / İstanbul
Phone: 0216 413 50 66
Fax: 0216 413 50 99

8. MARKETING AUTHORISATION NUMBER

2017/809

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20.10.2017

Date of renewal of the authorisation:

10. DATE OF REVISION OF THE TEXT