1 NAME OF THE MEDICINAL PRODUCT

Esmolol Amomed 100 mg/10 ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of 10 ml solution for injection contains 100 mgEsmolol hydrochloride.
1 ml aqueous solution contains 10 mg Esmolol hydrochloride(10 mg/ml).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
The solution is clear and colourless.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Esmolol Amomed 100 mg/10 ml is indicated for supraventricular tachycardia (except for pre-excitationsyndromes) and for the rapid control of the ventricular rate in adult patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other circumstances where short-term control of the ventricular rate with a short-actingagent is desirable.

Esmolol Amomed 100 mg/10 ml is also indicated for tachycardia and hypertension occuring in the perioperative phase and non-compensatory sinus tachycardia in adult patients where, in the physician's judgement the rapid heartrate requires specific intervention.

Esmolol Amomed 100 mg/10 ml is not intended for use inchronic settings.

4.2 Posology and method of administration

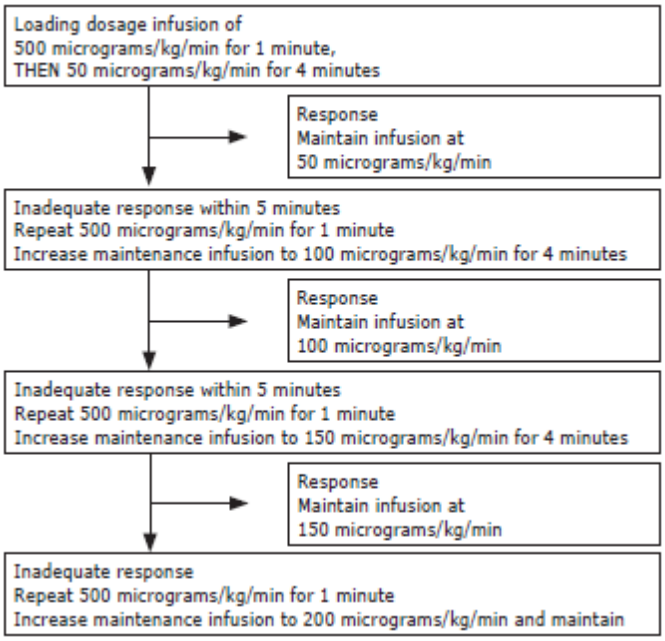
Esmolol Amomed 100 mg/10 ml solution for injection isa clear solution ready for intravenous use. The concentrationof this product is 10 mg/ml Esmolol hydrochloride.

SUPRAVENTRICULAR TACHYARRHYTHMIA

The dosage of Esmolol should be titrated individually.A starting dose is required, followed by a maintenance dosage.

The effective dose of Esmolol hydrochloride is within the range of 50 to 200 micrograms/kg/min, although doses as high as 300 micrograms/kg/min have been used. In a fewpatients the average effective dosage of 25 micrograms/ kg/min has been adequate.

Flow Chart for Initiation and Maintenance of Treatment



As the desired heart rate or safety endpoint (e.g. loweredblood pressure) is approached, OMIT the loading infusion and reduce the incremental dose in the maintenance infusion from 50 micrograms/kg/min to 25 micrograms/kg/min or lower.

If necessary, the interval between the titration steps may beincreased from 5 to 10 minutes.

NB: Maintenance doses above 200 micrograms/kg/min havenot been shown to have significantly increased benefits, andthe safety of doses above 300 micrograms/kg/min has not been studied.

In the event of an adverse reaction, the dosage of Esmolol may be reduced or discontinued. Pharmacological adverse reactions should resolve within 30 minutes.

If a local infusion site reaction develops, an alternative infusion site should be used and caution should be taken to prevent extravasation.

The administration of Esmolol infusions for longer than
24 hours has not been thoroughly evaluated. Infusion durations greater than 24 hours should only be used with caution.

Conversion table: **microg/kg/min → ml/min** (Esmolol diluted to 10 mg/ml strength)							
	500 µg/kg/min	50 µg/kg/min	100 µg/kg/min	150 µg/kg/min	200 µg/kg/min	250 µg/kg/min	300 µg/kg/min
	1 min only						
kg	**ml/min**	**ml/min**	**ml/min**	**ml/min**	**ml/min**	**ml/min**	**ml/min**
40	2	0,2	0,4	0,6	0,8	1	1,2
45	2,25	0,225	0,45	0,675	0,9	1,125	1,35
50	2,5	0,25	0,5	0,75	1	1,25	1,5
55	2,75	0,275	0,55	0,825	1,1	1,375	1,65
60	3	0,3	0,6	0,9	1,2	1,5	1,8
65	3,25	0,325	0,65	0,975	1,3	1,625	1,95
70	3,5	0,35	0,7	1,05	1,4	1,75	2,1
75	3,75	0,375	0,75	1,125	1,5	1,875	2,25
80	4	0,4	0,8	1,2	1,6	2	2,4
85	4,25	0,425	0,85	1,275	1,7	2,125	2,55
90	4,5	0,45	0,9	1,35	1,8	2,25	2,7
95	4,75	0,475	0,95	1,425	1,9	2,375	2,85
100	5	0,5	1	1,5	2	2,5	3
105	5,25	0,525	1,05	1,575	2,1	2,625	3,15
110	5,5	0,55	1,1	1,65	2,2	2,75	3,3
115	5,75	0,575	1,15	1,725	2,3	2,875	3,45
120	6	0,6	1,2	1,8	2,4	3	3,6

Conversion table: **microg/kg/min → ml/h** (Esmolol diluted to 10 mg/ml strength)							
	500 µg/kg/min	50 µg/kg/min	100 µg/kg/min	150 µg/kg/min	200 µg/kg/min	250 µg/kg/min	300 µg/kg/min
	1 min only						
kg	**ml/h**	**ml/h**	**ml/h**	**ml/h**	**ml/h**	**ml/h**	**ml/h**
40	120	12	24	36	48	60	72
45	135	13,5	27	40,5	54	67,5	81
50	150	15	30	45	60	75	90
55	165	16,5	33	49,5	66	82,5	99
60	180	18	36	54	72	90	108
65	195	19,5	39	58,5	78	97,5	117
70	210	21	42	63	84	105	126
75	225	22,5	45	67,5	90	112,5	135
80	240	24	48	72	96	120	144
85	255	25,5	51	76,5	102	127,5	153
90	270	27	54	81	108	135	162
95	285	28,5	57	85,5	114	142,5	171
100	300	30	60	90	120	150	180
105	315	31,5	63	94,5	126	157,5	189
110	330	33	66	99	132	165	198
115	345	34,5	69	103,5	138	172,5	207
120	360	36	72	108	144	180	216

Abrupt discontinuation of Esmolol in patients has not been reported to produce the withdrawal effects which may occur with abrupt withdrawal of beta-blockers following chronic use in coronary artery disease (CAD) patients. However, caution should still be used in discontinuing Esmolol infusions abruptly in CAD patients.

PERIOPERATIVE TACHYCARDIA AND HYPERTENSION

When treating tachycardia and/or hypertension in the perioperative setting, the following dose regimens may be used.

a) For the intraoperative treatment – during anaesthesia when immediate control is required, a bolus injection of

80 mg is given over 15 to 30 seconds, followed by a 150 micrograms/kg/min infusion. Titrate the infusion rate as required up to 300 micrograms/kg/min.
b) Upon awakening from anaesthesia administer an infusion of 500 micrograms/kg/min for up to 4 minutes followed by an infusion of 300 micrograms/kg/min.
c) For postoperative situations when time for titration is available, give the 500 micrograms/kg/min loading dose over one minute before each titration step to produce a rapid onset of action. Use titration steps of 50, 100, 150, 200, 250 and 300 micrograms/kg/min given over four minutes, stopping at the desired therapeutic effect.

Replacement of Esmolol therapy by alternative drugs Afternachieving an adequate control of the heart rate anda stable clinical status, transition to alternative drugs(antiarrhytmics or calcium antagonists) may be accomplished.

When Esmolol is replaced by alternative drugs, the physicianshould carefully consider the labelling of the alternative drugand the dosage of Esmolol should be reduced as follows:

1) Within the first hour after the first dose of the alternative drug, the infusion rate of Esmolol should be reduced byone-half (50%).

2) After administration of the second dose of the other alternative drug, the patient response should besupervised and if satisfactory control is maintained for the first hour, discontinue the Esmolol infusion.

Additional dosing information: as the desired therapeuticeffect or a safety endpoint (e.g. lowered blood pressure) is approached, omit the loading dose and reduce the incremental infusion to 12.5–25 micrograms/kg/min. Also, if desired, increase the interval between titration steps from five to tenminutes.

Esmolol Amomed 100 mg/10 ml solution for injection shouldbe discontinued when heart rate or blood pressure rapidly approach or exceed a safety limit, and then restarted without a loading infusion at a lower dose after the heart rate or blood pressure has returned to an acceptable level.

Elderly
Special studies of elderly have not been performed yet. However, an analysis of data of 252 patients over 65 years indicated that no variations in pharmacodynamic effectsoccurred as compared with data of patients younger than65 years.

Patients with kidney insufficiency
In patients with renal insufficiency caution is needed when Esmolol is administered by infusion, since the acid metabolite is excreted through the kidneys. Excretion of the acid metabolite is significantly decreased in patients with renal disease, with the elimination half-life increased to about tenfold that of normals, and plasma levels considerably elevated.

Patients with liver insufficiency
In case of liver insufficiency no special precautions are necessary since the esterases in the red blood cells havea main role in the Esmolol metabolism.

Paediatric population (age under 18 years)
There are limited data available on the use of Esmolol hydrochloride in children. The safety and effectiveness of Esmolol hydrochloride in children have not been established.

4.3 Contraindications

- hypersensitivity to the active substance or to any of theexcipients listed in section 6.1
- severe bradycardia (less than 50 beats per minute)
- "sick sinus"-syndrome; severe AV-nodal conductancedisorders (without pacemaker); 2nd or 3rd degree AV-block
- cardiogenic shock
- severe hypotension
- overt heart failure
- non-treated phaeochromocytoma
- pulmonary hypertension
- acute asthmatic attack
- metabolic acidosis

4.4 Special warnings and precautions for use

It is advised to terminate the infusion gradually because of the risk of rebound tachycardia.

Esmolol hydrochloride should be used with caution in diabetics or in case of hypoglycaemia:
The severity of hypoglycaemia is less than the one observedwith less cardio-selective beta-blockers. The beta-blockers can mask the prodromal symptoms of hypoglycaemia such as tachycardia. Dizziness and sweating, however, may not be affected.

The most frequently observed side effect is hypotension which is rapidly reversible with dosage reduction or discontinuation. In patients with a low systolic blood pressure, extra caution is needed when adjusting the dosage and during maintenance infusion.

It is advised to continuously monitor the blood pressure andECG in all patients treated with Esmolol. In the event of a hypotensive episode, the infusion rate should be reduced or, when necessary, be discontinued.

Due to its negative effect on conduction time, beta-blockersshould only be given with caution to patients with first degree heart block.

The elderly should be treated with caution, starting witha lower dosage, but tolerance is usually good in the elderly.

Beta-blockers may increase the number and the duration of anginal attacks in patients with Prinzmetal'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 only with the utmost care.

Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta-blockade carries the potential hazard of further depressing myocardialcontractility and precipitating more severe failure. Continueddepression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, Esmolol should be withdrawn. Although withdrawal may be sufficient because of the short elimination half-life of Esmolol, specific treatment may also be considered (see section 4.9).

The use of Esmolol for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease anyor all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium. Despite the rapid onset andoffset of the effects of Esmolol, several cases of death have been reported in complex clinical states where Esmolol was presumably being used to control the ventricular rate.

Patients with bronchospastic disease should, in general, not receive beta-blockers. Because of its relative $beta_1$-selectivity and titratability, Esmolol should be used with caution in patients with bronchospastic diseases. However, since $beta_1$-selectivity is not absolute, Esmolol 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 $beta_2$-receptorstimulating agent, it can be necessary to re-evaluate the dose of this agent.

Esmolol should be used with caution in patients with a history of wheezing and asthma.

In patients with psoriasis or a history of psoriasis, the administration of Esmolol hydrochloride should be carefully weighed as it should be done in any event.

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

Beta-blockers may induce bradycardia. 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.

Beta-blockers may increase both the sensitivity toward allergens and the seriousness of anaphylactic reactions.

Infusions of concentrations of 20 mg/ml have been associated with significant venous irritation and thrombophlebitis in animals and man. Extravasation of 20 mg/ml may lead toa serious local reaction and possible skin necrosis.

Local reactions have also been reported following infusion ofconcentrations of 10 mg/ml. Infusion into small veins or through a butterfly catheter should therefore be avoided.

Use in the paediatric population (age under 18 years)
The safety and effectiveness of Esmolol hydrochloride in children have not been established.

4.5 Interaction with other medicinal products and other forms of interaction

Calcium antagonists such as verapamil and to a lesser extent diltiazem have a negative influence on contractility and AV-conduction. As with other beta-blocking agents Esmolol should be used with caution in combination with verapamil inpatients with impaired ventricular function. The combinationshould not be given to patients with conduction abnormalities and Esmolol should not be administered within 48 hours of discontinuing verapamil.

Calcium antagonists such as dihydropyridine derivatives (e.g. nifedipine) may increase the risk of hypotension. In patients with cardiac insufficiency and who are being treatedwith a calcium antagonist, treatment with beta-blockingagents may lead to cardiac failure. Careful titration of Esmolol hydrochloride 10 mg/ml solution for injection and appropriate haemodynamic monitoring is recommended

Concomitant use of Esmolol and class I antiarrhythmic agents (such as disopyramide and quinidine) and also amiodarone can increase the action of both on the AV-conductance time and induce negative inotropic effect.

Concomitant use of Esmolol and insulin or oral antidiabetic drugs may intensify the blood sugar lowering effect (especially non-selective beta-blockers). Beta-adrenergic blockade mayprevent the appearance of signs of hypoglycemia (tachycardia).

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

The combination of Esmolol hydrochloride 10 mg/ml solutionfor injection 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 oramisulpride concomitantly with beta-blockers.

Concomitant administration of tricyclic antidepressants, barbiturates and phenothiazines as well as other antihypertensive agents may increase the blood pressure lowering effect. Dosing of Esmolol hydrochloride 10 mg/ml solution for injection should be adjusted downward to avoid unexpected hypotension.

Sympathomimetic agents may counteract the effect of beta-adrenergic blocking agents.

Catecholamine-depleting agents, e.g. reserpine, may have an additive effect when given with beta-blocking agents. Patients treated concurrently with Esmolol Amomed 100 mg/10 ml solution for injection and a catecholamine depletor should therefore be closely observed for evidence of hypotension ormarked bradycardia, which may result in vertigo, syncope orpostural hypotension.

Concomitant use of clonidine and beta-blockers increase therisk of "rebound" hypertension. When clonidine is used inconjunction with non-selective beta-blockers, such aspropranolol, treatment with clonidine should be continued for some time after treatment, when the beta-blocker has beendiscontinued.

Data from an interaction study between Esmolol Amomed 100 mg/10 ml solution for infusion and warfarin showed thatconcomitant administration of Esmolol Amomed
100 mg/10 ml solution for injection and warfarin does notalter warfarin plasma levels. Esmolol Amomed 100 mg/10 ml solution for injection concentrations, however, were equivocally higher when given with warfarin.

When digoxin and Esmolol Amomed 100 mg/10 ml solution for injection were concomitantly administered intravenouslyto normal volunteers, there was a 10–20% increase in digoxin blood levels at some time points. The combination of digitalisglycosides and Esmolol Amomed 100 mg/10 ml solution for injection may increase AV conduction time. Digoxin did not affect Esmolol Amomed 100 mg/10 ml solution for injection pharmacokinetics.

When intravenous morphine and Esmolol Amomed 100 mg/10 ml solution for injection interaction was studied in normal subjects, no effect on morphine blood levels was seen. The Esmolol Amomed 100 mg/10 ml solution for injection steady- state blood levels were increased by 46% in the presence of morphine, but no other pharmacokinetic parameters were changed.

The effect of Esmolol Amomed 100 mg/10 ml solution forinjection on the duration of suxamethonium chloride-induced neuromuscular blockade has been studied in patients undergoing surgery. The onset of neuromuscular blockade by suxamethonium chloride was unaffected by Esmolol Amomed
100 mg/10 ml solution for injection, but the duration of neuromuscular blockade was prolonged from 5 minutes to 8 minutes.
Although the interactions observed in studies of warfarin, digoxin, morphine or suxamethonium chloride are not of major clinical importance, Esmolol Amomed 100 mg/10 ml solution for injection should be titrated with caution in patients being treated concurrently with warfarin, digoxin, morphine or suxamethonium chloride.

4.6 Pregnancy and lactation

Pregnancy
Esmolol is not recommended during pregnancy.
There are insufficient data to determine the possible harmfuleffects of Esmolol during pregnancy. To date, there are no indications for an increased risk on birth defect in humans. Animal studies have shown reproductive toxicity (see section5.3). The potential risk for humans is unknown. 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. Beta-blockers reduce the placenta circulation.
If treatment with Esmolol is considered necessary, the uteroplacental blood flow and foetal growth should be monitored. The newborn infant must be closely monitored.

Lactation
It is unknown whether Esmolol is excreted in breast milk. Lactation is not advised during the use of Esmolol.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

In case of an adverse reaction, the dose of Esmolol can bereduced or discontinued.

Most of the adverse reactions observed have been mild and transient. The most important adverse reaction is hypotension.

The following terminologies have been used in order to classify the occurrence of undesirable effects:

Very common (≥1/10)
Common (≥1/100 to <1/10) Uncommon (≥1/1.000 to <1/100) Rare (≥1/10.000 to <1/1.000)
Very rare (<1/10.000)
Not known (cannot be estimated from the available data)

Nervous system disorders
- Common: paraesthesiae, disturbance in attention, dizziness[1], somnolence, headache
- Uncommon: convulsions, syncope, dysgeusia, speech disorder

Cardiac disorders
- Uncommon: bradycardia, atrioventricular block
- Very rare: sinus arrest, asystole

Eye disorders
- Uncommon: visual impairment

Respiratory, thoracic and mediastinal disorders
- Uncommon: bronchospasm, wheezing, dyspnoea, nasal congestion, pulmonary oedema, rhonchi, rales

Gastrointestinal disorders
- Common: nausea, vomiting
- Uncommon: dyspepsia, constipation, mouth dryness, abdominal pain

Renal and urinary disorders
- Uncommon: urinary retention

Skin and subcutaneous tissue disorders
- Very common: diaphoresis
- Uncommon: erythema[2], skin discolouration[2]
- Very rare: skin necrosis due to extravasation[2]
- Not known: psoriasis[3]

Musculoskeletal and connective tissue disorders
- Uncommon: musculoskeletal pain

Metabolism and nutrition disorders
- Common: anorexia

Vascular disorders
- Very common: hypotension
- Uncommon: peripheral ischaemia, pallor, flushing
- Very rare: thrombophlebitis[2]

General disorders and administration site conditions
- Common: asthenia, fatigue, injection site reaction, infusion site reaction, infusion site inflammation, infusion site induration
- Uncommon: chest pain, oedema[2], pain[2], infusion site burning, fever and chills

Psychiatric disorders:
- Common: depression, anxiety, confusional state, agitation
- Uncommon: thinking abnormal

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

Cases of massive accidental overdoses of Esmolol have occurred. 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.

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, hypoglycemia and hyperkalemia.

Because of the short elimination half-life of Esmolol Amomed 100 mg/10 ml solution for injection (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 Esmolol Amomed 100 mg/10 ml solution for injection administered. This may take longer than the
30 minutes seen with discontinuation at therapeutic dose levels. 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 given i.v.:
- Atropine: 0.5–2 mg
- Inotropic agents
- Calcium ions

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-blocking agents, selective ATC code: C07AB09

Esmolol is a parenteral administered, cardioselective beta- inhibitor.

In therapeutic doses Esmolol does not have intrinsic sympathicomimetic activity (ISA) of importance and no membrane stabilising (local anaesthetic) properties.

Based on the pharmacological properties Esmolol has a fast and short action by which the dose can be quickly adjusted:

After a high starting dose a steady state plasma concentrationis reached within 5 minutes (without starting dose in 30 minutes). However, the therapeutic effect is sooner obtained than the stabile plasma concentration. The infusionrate can then be adjusted to obtain the desired pharmacological effect.

Esmolol hydrochloride has the known hemodynamic andelectrophysiologic effect of beta-blockers:

- Reduction of the heart frequency during rest andexercise
- Reduction of the isoprenaline caused increase of theheart frequency
- Increase of the recovering time of the SA-node
- Delay of the AV-conductance
- Prolonging the 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 inotrope effect with decreased ejection fraction Decrease in blood pressure

5.2 Pharmacokinetic properties

The kinetics of Esmolol are linear in healthy adults, the plasma concentration is proportional to the dose. If a loading dose is not used then steady-state blood concentrations arereached within 30 minutes with doses of 50 to 300 micro-grams/kg per minute.

The distribution half-life of Esmolol hydrochloride is very fast, about 2 minutes. The volume of distribution is 3.4 l/kg.

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 redblood cells.

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

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

The elimination half-life after intravenous administrationis approximately 9 minutes. The total clearance is285 ml/kg/min; 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 theadministered amount), partly as acid metabolite that hasa 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.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients Sodium acetate trihydrateAcetic acid
Hydrochloric acid 10% (for pH adjustment)Water for injection

6.2 Incompatibilities

Esmolol Amomed 100 mg/10 ml solution for injection **must not** be used in combination with sodium carbonate solutionsor other medicinal products (e.g. furosemide, diazepam andthiopental) that are chemically incompatible with Esmolol.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.The product should be used immediately after first opening.

6.4 Special precautions for storage

Store below 25°C.

Keep the vial in the outer carton in order to protect from light. For storage conditions of the solution see section 6.3.

6.5 Nature and contents of container

Each vial of 10 ml solution contains 100 mg Esmolol hydrochloride (10 mg/ml).

A clear, colourless glass vial, a rubber stopper with a flip-offseal, containing 10 ml solution for injection. The vials arepacked in an outer cardboard carton.

Pack size: 5 vials per carton.

6.6 Special precautions for disposal and otherhandling

The solution should be examined visually for particulate matter and discoloration prior to administration. Only clear and colourless solution should be used.

Any unused solution and the containers should be disposed of in accordance with local requirements.

7 MANUFACTURER

Amomed Pharma GmbH
STORCHENGASSE 1,1150 VIENNA AUSTRIA

8 MARKETING AUTHORISATION HOLDER

AOP ORPHAN PHARMACEUTICALS ISRAEL LTD., 10 Riza St. Aseret 7685800
Israel

9 REGISTRATION NUMBER

159-69-34872

Revised in July 2021 according to MOHs guidelines