SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Esmolol Amomed 100 mg/10 ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of 10 ml solution for injection contains 100 mg esmolol hydrochloride.
1 ml aqueous solution contains 10 mg esmolol hydrochloride (10 mg/ml).
Excipients: This medicinal product contains approximately 0.34 mmol (or 7.88 mg) of sodium per vial.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
The solution is clear and colourless.
The solution has a pH between 4.5 to 5.5 and osmolarity of approximately 140 mOsm/l.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Esmolol Amomed 100 mg/10 ml is indicated for supraventricular tachycardia (except for pre-excitation syndromes) 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-acting agent is desirable.
Esmolol Amomed 100 mg/10 ml is also indicated for tachycardia and hypertension occurring in the perioperative phase and non-compensatory sinus tachycardia in adult patients where, in the physician's judgement the rapid heart rate requires specific intervention.
Esmolol Amomed 100 mg/10 ml is not intended for use in chronic settings.

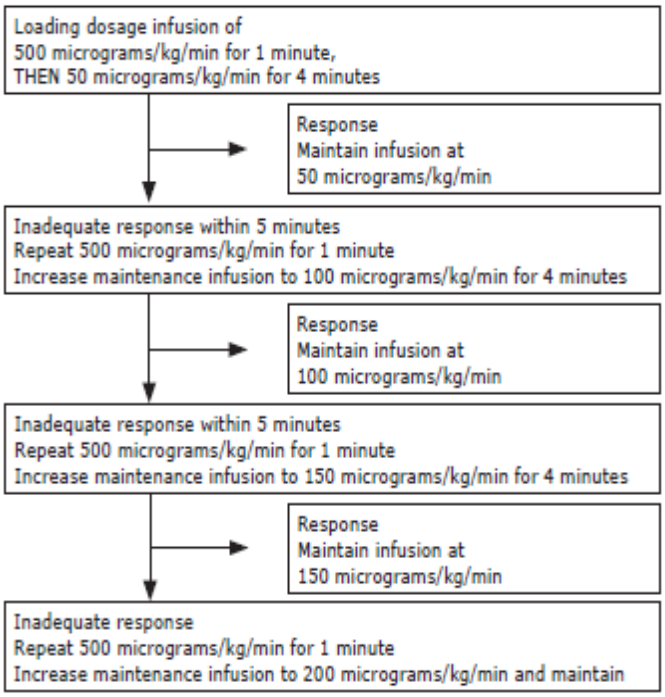
4.2 Posology and method of administration

Esmolol Amomed 100 mg/10 ml solution for injection is a clear solution ready for intravenous use. The concentration of 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 few patients 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. lowered blood 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 be increased from 5 to 10 minutes.

NB: Maintenance doses above 200 micrograms/kg/min have not been shown to have significantly increased benefits, and the 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

After achieving an adequate control of the heart rate and a stable clinical status, transition to alternative drugs (antiarrhythmics or calcium antagonists) may be accomplished.

When Esmolol is replaced by alternative drugs, the physician should carefully consider the labelling of the alternative drug and 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 by one-half (50%).

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

Additional dosing information: as the desired therapeutic effect 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 ten minutes.

Esmolol Amomed 100 mg/10 ml solution for injection should be 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 effects occurred as compared with data of patients younger than 65 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 normal, 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 have a 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, to any of the excipients listed in section 6.1 or other beta-blockers (cross sensitivity between beta-blockers is possible);
- Severe sinus bradycardia (less than 50 beats per minute);
- "Sick sinus" syndrome; severe AV-nodal conductance disorders (without pacemaker); 2nd or 3rd degree AV-block;
- Cardiogenic shock;
- Severe hypotension;
- Decompensated heart failure;
- Concomitant or recent intravenous administration of verapamil. Esmolol Amomed 100 mg/10 ml must not be administered within 48 hours of discontinuing verapamil (see section 4.5);
- Non-treated phaeochromocytoma;
- Pulmonary hypertension;
- Acute asthmatic attack;
- Metabolic acidosis.

4.4 Special warnings and precautions for use

Warnings

It is recommended to continuously monitor the blood pressure and the ECG in all patients treated with Esmolol Amomed 100 mg/10 ml.

The use of Esmolol Amomed 100 mg/10 ml 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 Esmolol Amomed 100 mg/10 ml, severe reactions may occur, including loss of consciousness, cardiogenic shock, cardiac arrest. Several deaths have been reported in complex clinical states where Esmolol Amomed 100 mg/10 ml 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 Esmolol Amomed 100 mg/10 ml). 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 Esmolol Amomed 100 mg/10 ml. Esmolol Amomed 100 mg/10 ml 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.

Esmolol Amomed 100 mg/10 ml 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 Esmolol Amomed 100 mg/10 ml in patients with compromised cardiac function. At the first sign or symptom of impending cardiac failure, Esmolol Amomed 100 mg/10 ml should be withdrawn. Although withdrawal may be sufficient because of the short elimination half-life of Esmolol Amomed 100 mg/10 ml, specific treatment may also be considered (see section 4.9). Esmolol Amomed 100 mg/10 ml 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).

Esmolol Amomed 100 mg/10 ml 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 Esmolol Amomed 100 mg/10 ml 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, Esmolol Amomed 100 mg/10 ml should be used with caution in patients with bronchospastic diseases. However, since beta-1 selectivity is not absolute, Esmolol Amomed 100 mg/10 ml 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.

Esmolol Amomed 100 mg/10 ml should be used with caution in patients with a history of wheezing or asthma.

Precautions

Esmolol Amomed 100 mg/10 ml 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 (blood glucose–lowering) (see section 4.5).

Infusion site reactions have occurred with the use of both esmolol hydrochloride 10 mg/ml and 20 mg/ml. 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, Esmolol Amomed 100 mg/10 ml can attenuate reflex tachycardia and increase the risk of circulatory collapse. Therefore, Esmolol Amomed 100 mg/10 ml 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 Esmolol Amomed 100 mg/10 ml, 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 medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Care should always be exercised whenever Esmolol Amomed 100 mg/10 ml is used with other antihypertensive agents or other drugs that may cause hypotension or bradycardia: the effects of Esmolol Amomed 100 mg/10 ml 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 Esmolol Amomed 100 mg/10 ml 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 Esmolol Amomed 100 mg/10 ml and appropriate haemodynamic monitoring is recommended.

Concomitant use of Esmolol Amomed 100 mg/10 ml 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 Esmolol Amomed 100 mg/10 ml 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 Esmolol Amomed 100 mg/10 ml. The hypotensive effects of inhalation anaesthetic agents may be increased in the presence of Esmolol Amomed 100 mg/10 ml. The dosage of either agent may be modified as needed to maintain the desired haemodynamics.

The combination of Esmolol Amomed 10 mg/10 ml 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 Esmolol Amomed 100 mg/10 ml 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 Esmolol Amomed 100 mg/10 ml 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 Esmolol Amomed 100 mg/10 ml 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 esmolol 100 mg/10 ml and warfarin showed that concomitant administration of esmolol 100 mg/10 ml and warfarin does not alter warfarin plasma levels. Esmolol 100 mg/10 ml concentrations, however, were equivocally higher when given with warfarin.

When digoxin and esmolol 100 mg/10 ml were concomitantly administered intravenously to normal volunteers, there was a 10-20% increase in digoxin blood levels at some time points. The combination of digitalis glycosides and Esmolol Amomed 100 mg/10 ml may increase AV conduction time. Digoxin did not affect esmolol 100 mg/10 ml pharmacokinetics.

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

The effect of esmolol 100 mg/10 ml on the duration of suxamethonium chloride-

induced or mivacurium-induced neuromuscular blockade has been studied in patients undergoing surgery. Esmolol 100 mg/10 ml 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. Esmolol 100 mg/10 ml 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, Esmolol Amomed 100 mg/10 ml should be titrated with caution in patients being treated concurrently with warfarin, digoxin, morphine, suxamethonium chloride or mivacurium.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are limited amount of data from the use of esmolol hydrochloride in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

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 hypoglycaemia, hypotension and bradycardia) should be taken into account.

If treatment with Esmolol Amomed 100 mg/10 ml is considered necessary, 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 human data on the effects of esmolol on fertility.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

In case of undesirable effects, the dose of Esmolol Amomed 100 mg/10 ml can be reduced or discontinued.
Most of the undesirable effects observed have been mild and transient. The most important one has been hypotension. The following undesirable effects are ranked according to MedDRA System Organ Class (SOC) and to their frequency.

Note: 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)

System Organ Class	**Frequency**				
	Very common	**Common**	**Uncommon**	**Very rare**	**Not known**
Metabolism and nutrition disorders		Anorexia			Hyperkalemia Metabolic acidosis
Psychiatric disorders		Depression Anxiety	Thinking abnormal		
Nervous system disorders		Dizziness [1] Somnolence Headache Paraesthesiae Disturbance in attention Confusional state Agitation	Syncope Convulsion Speech disorder		
Eye disorders			Visual impairment		
Cardiac disorders			Bradycardia Atrioventricular block Pulmonary arterial pressure increased Cardiac Failure Ventricular extrasystoles Nodal rhythm Angina pectoris	Sinus arrest Asystole	Accelerated idioventricular rhythm Coronary arteriospasm Cardiac arrest.
Vascular disorders	Hypotension		Peripheral ischaemia Pallor Flushing	Thrombophlebitis [2]	

[1] Dizziness and diaphoresis are in association with symptomatic hypotension. [2] In association with Injection and Infusion site reactions.

System Organ Class	Frequency				
	Very common	**Common**	**Uncommon**	**Very rare**	**Not known**
Respiratory, thoracic and mediastinal disorders			Dyspnoea Pulmonary oedema Bronchospasm Wheezing Nasal congestion Rhonchi Rales		
Gastrointestinal disorders		Nausea Vomiting	Dysgeusia Dyspepsia Constipation Dry mouth Abdominal pain		
Skin and subcutaneous tissue disorders	Diaphoresis[1]		Skin discolouration [2] Erythema [2]	Skin necrosis [2] (due to extravasation)	Psoriasis [3] Angioedema Urticaria
Musculoskeletal and connective tissue disorders			Musculoskeletal pain [4]		
Renal and urinary disorders			Urinary retention		
General disorders and administration site conditions		Asthenia Fatigue Injection site reaction Infusion site reaction Infusion site inflammation Infusion site induration	Chills Pyrexia Oedema [2] Pain [2] Infusion site burning Infusion site ecchymosis		Infusion site phlebitis Infusion site vesicles Blistering [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

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 have resulted in permanent disability. Loading doses in the range of 625 mg to 2.5 g (12.5 to 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, hypoglycaemia and hyperkalaemia.

Treatment

Because of the short elimination half-life of Esmolol Amomed 100 mg/10 ml (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 administered. This may take longer than the 30 minutes seen with discontinuation at therapeutic dose levels of Esmolol Amomed 100 mg/10 ml. 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. based on the clinical situation and judgment 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
Esmolol Amomed 100 mg/10 ml is a beta-selective (cardioselective) adrenergic receptor blocking agent. At therapeutic doses Esmolol Amomed 100 mg/10 mg has no significant intrinsic sympathomimetic activity (ISA) or membrane stabilising activity.
Esmolol hydrochloride, the active ingredient of Esmolol Amomed 100 mg/10 ml, is chemically related to the phenoxy propanolamine class of beta-blockers.
Based on the pharmacological properties Esmolol Amomed 100 mg/10 ml 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.
Esmolol hydrochloride 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 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 inotropic effect with decreased ejection fraction;
- Decrease in blood pressure.

5.2 Pharmacokinetic properties

Absorption
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 are reached within 30 minutes with doses of 50 to 300 micrograms/kg

per minute.

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

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

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.

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.

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 Esmolol 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
Acetic acid

Hydrochloric acid
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products or sodium bicarbonate solutions.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

The opened product is physicochemically stable for 24 hours at 2 to 8°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless opening has taken place in controlled and validated aseptic conditions.

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-off seal, containing 10 ml solution for injection. The vials are packed in an outer cardboard carton.
Pack size: 5 vials per carton.

6.6 Special precautions for disposal and other handling

Each vial is intended for single use only. Avoid contact with alkali.
The solution should be visually inspected for particulate matter and discoloration prior to administration. Only a clear and colourless solution should be used. Any unused solution and the containers should be disposed of in accordance with local requirements.

7 MANUFACTURER

AOP Orphan Pharmaceuticals GmbH Leopold-Ungar-Platz 2, Doebling 1190 Vienna, Austria

8 MARKETING AUTHORISATION HOLDER

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9 REGISTRATION NUMBER

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