Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

ESMOCARD 100 mg/10 ml solution for injection

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

ESMOCARD 100 mg/10 ml is indicated for supraventricular tachycardia (except for pre-excitation syndromes) and for the rapid control of the ventricular rate in 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.

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

ESMOCARD 100 mg/10 ml is not indicated for use in children aged up to 18 years (see section 4.2).

ESMOCARD 100 mg/10 ml is not intended for use in chronic settings.

4.2 Posology and method of administration

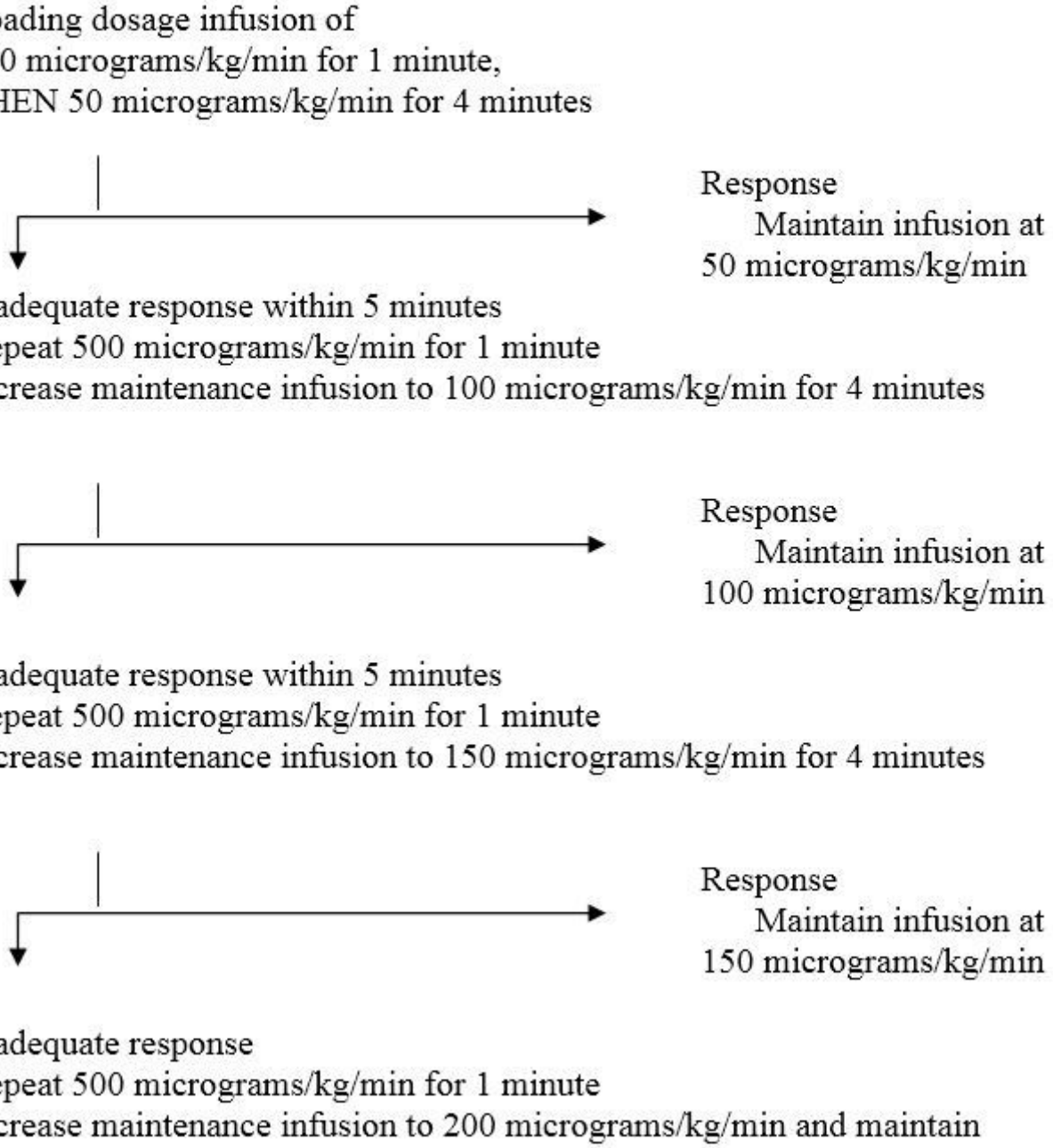
ESMOCARD 100 mg/10 ml solution for injection in a vial with 10 ml is a clear solution ready for intravenous use. The concentration of this product is 10 mg/ml esmolol hydrochloride.

SUPRAVENTRICULAR TACHYARRHYTHMIA

The dosage of ESMOCARD 100 mg/10 ml should be titrated individually. A starting dose is required, followed by a maintenance dosage.

The effective dose of ESMOCARD 100 mg/10 ml 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 5to 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 ESMOCARD 100 mg/10 ml 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 ESMOCARD 100 mg/10 ml 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 minute 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 minute 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 ESMOCARD 100 mg/10 ml 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 ESMOCARD 100 mg/10 ml infusions abruptly in CAD patients.

PERIOPERATIVE TACHYCARDIA AND HYPERTENSION

For perioperative tachycardia and hypertension the dosing regimen may vary as follows:
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/mingiven over four minutes, stopping at the desired therapeutic effect.

Replacement of ESMOCARD 100 mg/10 ml therapy by alternative drugs
After patients achieve an adequate control of the heart rate and a stable clinical status, transition to alternative drugs (such as antiarrhytmics or calcium antagonists) may be accomplished.

Reducing the dosage:
When ESMOCARD 100 mg/10 ml is to be replaced by alternative drugs, the physician should carefully consider the labelling of the alternative drug selected and reduce the dosage of ESMOCARD 100 mg/10 ml as follows:
1) Within the first hour after the first dose of the alternative drug, reduce the ESMOCARD 100 mg/10 mlinfusion rate by one-half (50%).

2) After administration of the second dose of the other alternative drug, monitor the patient's response and if satisfactory control is maintained for the first hour, discontinue theESMOCARD 100 mg/10 ml 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.

ESMOCARD 100 mg/10 ml 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.

Special populations

Elderly
The elderly should be treated with caution, starting with a lower dosage. Special studies in the elderly have not been conducted. However, analysis of data of 252 patients over 65 years indicated that no variations in pharmacodynamic effects occurred as compared with data from patients under 65.

Patients with kidney insufficiency
In patients with renal insufficiency caution is needed when ESMOCARD 100 mg/10 ml is administered by infusion, since the acid metabolite of ESMOCARD 100 mg/10 ml 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 have a main role in the ESMOCARD 100 mg/10 ml metabolism.

Paediatric population (age under 18 years)
Thesafetyandefficacyof ESMOCARD 100 mg/10 ml in children aged up to 18 years have not yet been established. Therefore, ESMOCARD 100 mg/10 ml isnotindicatedforuseinthepaediatricpopulation(see section 4.1).
Currently available data are described in section 5.1 and 5.2 but no recommendation on a posology can be made.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- Severe sinus bradycardia (less than 50 beats per minute);
- "Sicksinus" -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. ESMOCARD 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 ESMOCARD 100 mg/10 ml. In the event of a hypotensive episode, the infusion rate should be reduced or, when necessary, be discontinued.

The use of ESMOCARD 100 mg/10 ml 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 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 ESMOCARD 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 ESMOCARD 100 mg/10 ml was presumably being used to control the ventricular rate.

The most frequently observed side effect is hypotension, which is dose related but can occur at any dose. This can be severe. n 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 ESMOCARD 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 ESMOCARD 100 mg/10 ml. ESMOCARD 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.

ESMOCARD 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.

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

The elderly should betreated with caution, starting with a lower dosage, but tolerance is usually good in theelderly.

Sympathetic stimulation is necessary in supporting circulatory function in congestiveheart failure. Beta- blockade carries thepotential hazard offurther depressing myocardial contractility and precipitating more severe failure.
Continued depression of the myocardium with beta blocking agents over a period of time can, in somecases, lead to cardiac failure.

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

ESMOCARD 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 ESMOCARD 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 beta1 selectivity and titratability, ESMOCARD 100 mg/10 ml should be used with caution in patients with bronchospastic diseases. However, since beta1 selectivity is not absolute, ESMOCARD 100 mg/10 ml should be carefully titrated to obtain the lowest possible effective dose. In the event ofbronchospasm, theinfusion should beterminated immediately and a beta2 agonist should be administered ifnecessary.

If the patient already uses a beta2 receptorstimulating agent, it can benecessary to re-evaluate the dose of this agent. ESMOCARD 100 mg/10 ml should be used with caution in patients with ahistory of wheezing and asthma.

Precautions
ESMOCARD 100 mg/10 ml should be used with caution in diabetics or in case of suspected of actual hypoglycaemia.
The severity of hypoglycaemia is less than the one observed with less cardio-selective beta-blockers. Beta-blockers may mask the prodromal symptoms of hypoglycaemia such as tachycardia. However, dizziness and sweating, however, 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).

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 to a serious local reaction and possible skin necrosis.

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

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 should only be used with the utmost care.

In hypovolemic patients, ESMOCARD 100mg/10 ml can attenuate reflex tachycardia and increase the risk of circulatory collapse. Therefore, ESMOCARD 100mg/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 ESMOCARD 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.

Use in thepaediatric population (age under 18 years)
The safety and efficacy of ESMOCARD 100 mg/10 ml in children have not been established.

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 interactions

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

Concomitant use of ESMOCARD 100 mg/10 ml and C lass I anti-arrhythmic - agents (e.g. disopyramide , quinidine) and amiodarone may have potentiating effect on atrial-conduction time and induce negative inotropic effect.

Concomitant use of ESMOCARD 100 mg/10 mland insulin or oral antidiabetic drugs may intensify the blood sugar lowering effect (especially non-selective beta-blockers). Beta-adrenergic blockade may prevent the appearance of signs of hypoglycemia (tachycardia), but other manifestations such as dizziness and sweating may not be masked.

Anaesthetic drugs: insituations where the patient's volume status is uncertain or concomitant antihypertensive drugs are utilized, there may beattenuation of thereflex tachycardia and an increase of therisk ofhypotension.

Continuation of beta-blockade reduces the risk of arrhythmia during induction and intubation. The anaesthesist should be informed when the patient is receiving a beta-blocking agent in addition to ESMOCARD 100 mg/10 ml . The hypotensive effects of inhalation anaesthetic agents may be increased in the presence of ESMOCARD 100 mg/10 ml . The dosage of either agent may be modified as needed to maintain thedesired haemodynamics.

The combination of ESMOCARD 100 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 oramisulpride concomitantly with beta-blockers.

Concomitant administration of tricyclic antidepressants (such as imipramine and amitriptyline), barbiturates and phenothiazines (such as chlorpromazine), as well as other antihypertensive agents (such as clozapine) may increase the blood pressure lowering effect. Dosing of ESMOCARD 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 ESMOCARD 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 ESMOCARD 100 mg/10 ml and a catecholamine depletor should therefore be closely observed for evidence ofhypotension 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 ESMOCARD 100 mg/10 mland warfarin showed that concomitant administration of ESMOCARD 100 mg/10 mland warfarin does not alter warfarin plasma levels. ESMOCARD 100 mg/10 mlconcentrations, however, were equivocally higher when given with warfarin.

When digoxin and ESMOCARD 100 mg/10 mlwere 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 ESMOCARD 100 mg/10 ml may increase AV conduction time. Digoxin did not affect ESMOCARD 100 mg/10 mlpharmacokinetics.

When intravenous morphine and ESMOCARD 100 mg/10 mlinteraction was studied in normal subjects, no effect on morphine blood levels was seen. The ESMOCARD 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 ESMOCARD 100 mg/10 mlon the duration of suxamethonium chloride-induced or mivacurium-induced neuromuscular blockade has been studied in patients undergoing surgery. ESMOCARD 100 mg/10 ml did not affect the onset of neuromuscular blockade by suxamethonium chloride , but the duration ofneuromuscular blockade was prolonged from 5 minutes to 8 minutes. ESMOCARD 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 mivacuriumare not of major clinical importance, ESMOCARD 100 mg/10 ml should be titrated with caution in patients being treated concurrently with warfarin, digoxin, morphine or suxamethoniumchloride 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.
There are insufficient data to determine the possible harmful effects of esmolol hydrochloride during pregnancy. To date, there are no indications for an increased risk on birth defect in humans. Animal studies have shown reproductive toxicity (see section 5.3.).
The potential risk for humans is unknown. Based on thepharmacological action, in the later period of pregnancy, sideeffects on thefoetus and neonate(especially hypoglycemia, hypotension and bradycardia) should be taken into account.
If treatment with esmolol hydrochlorideis considered necessary, theuteroplacental blood flow and foetal growth should be monitored. The newborn infant must be closely monitored.

Lactation
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 hydrochloride on fertility.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

In case ofundesirable effects, the dose of ESMOCARD 100 mg/10 ml can be reduced ordiscontinued.

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 (≥1/1,000 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)

System Organ Class	**Frequency**				
	Very common	**Common**	**Uncommon**	**Very rare**	**Not known**
Metabolism andnutrition disorders		Anorexia			Hyperkalemia Metabolic acidosis
Psychiatric disorders		Depression Anxiety	Thinking abnormal		
Nervous systemdisorders		Dizziness **1**Somnolence Headache Paraesthesiae Disturbance in attention Confusional state Agitation	Syncope Convulsion Speech disorder		
Eye disorders			Visualimpairment		
Cardiac disorders			Bradycardia Atrioventricular block Pulmonary arterial pressureincreased Cardiac Failure Ventricular extrasystoles Nodal rhythmAngina 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**		Skindiscolouration **2** Erythema **2**	Skin necrosis **2** (due to extra vasation)	Psoriasis [3] AngioedemUrticaria
Musculoskeletal andconnective tissue disorders			Musculoskeletal pain 4		
Renal and urinarydisorders			Urinary retention		
General disorders andadministration siteconditions		Asthenia Fatigue Injection site reaction Infusion sitereaction Infusion siteinflammation Infusion siteinduration	Chills Pyrexia Oedema 2 Pain 2 Infusion siteburning Infusion siteecchymosis Chest pain		Infusion site phlebitisInfusion site vesicles Blistering 2

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

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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517. Website: www.hpra.ie. E-mail: medsafety@hpra.ie.

4.9 Overdose

Cases ofmassive accidental overdoses with concentrated solutions of ESMOCARD 100 mg/10 mlhave occurred. Some of these overdoses have been fatal while others resulted in permanent disability. Loading 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, cardiacarrest, bronchospasm, respiratory insufficiency, loss of consciousness to coma, convulsions, nausea, vomiting, hypoglycemia and hyperkalemia.

Treatment
Because of the short elimination half-life of ESMOCARD 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 ESMOCARD 100 mg/10 ml administered. This may take longer than the 30 minutes seen with discontinuation at therapeutic dose levels of ESMOCARD 100 mg/10 ml. Artificial respiration may be necessary. Based on the observed clinical effects, the following general measuresshould also be considered:

Bradycardia:atropine or another anticholinergic drug should begiven i.v.. When thebradycardia cannot betreated sufficiently apacemaker may benecessary.

Bronchospasm:nebulised beta-2-sympathomimetics should be given. If this is not sufficient intravenous beta-2-sympathomimetics oraminophylline can be considered.

Symptomatic hypotension: fluids and/orpressor agents should be given i.v..

Cardiovascular depression orcardiac shock: diuretics orsympathomimetics can beadministered. The dose of sympathomimetics (depending on the symptoms: dobutamine, dopamine, noradrenaline, isoprenaline, etc.) depends on the therapeutic effect.

In casefurther treatment is necessary, thefollowing agents can begiven i.v. based on the clinical situation and judgment of the treating healthcare professional:
- 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 hydrochlorideis a beta-selective (cardioselective) adrenergic receptor blocking agent.

At therapeutic doses esmolol hydrochloridehas no significant intrinsic sympathicomimetic activity (ISA) or membrane stabilising activity.

Esmolol hydrochloride, the active ingredient of ESMOCARD 100 mg/10 ml, is chemically related to the phenoxy propanolamine class of beta-blockers.

Based on thepharmacological properties esmolol hydrochloride 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, thetherapeutic effect is achieved sooner than the stabile plasma concentration. The infusion rate can then beadjusted to obtain thedesired pharmacological effect.

esmolol hydrochloridehas the known hemodynamic and electrophysiologic effect of beta-blockers:
- Reduction of theheart frequency during rest and exercise;
- Reduction of theisoprenaline caused increase of theheart frequency;
- Increase of therecovering time of the SA-node;
- Delay of the AV-conductance;
- Prolonging theAV-interval with normal sinus rhythm and during atrium stimulation without delay in theHis-Purkinje tissue;
- Prolonging of PQtime, induction of AVblock grade II;
- Prolonging thefunctional refractory period of atriaand ventricles;
- Negative inotrope effect with decreased ejection fraction;
- Decrease in blood pressure;

Children
An uncontrolled pharmacokinetic/efficacystudy was undertaken in 26 paediatric patients aged 2-16 years with supraventricular tachycardia (SVT). A loading dose of 1000 micrograms/kgof esmolol hydrochloridewas administered followed by a continuous infusion of 300 micrograms/kg/min.SVT was terminated in 65% of patients within 5 minutes of the commencement ofesmolol.

In a randomised but uncontrolled dose comparison study, efficacy was assessed in 116 paediatric patients aged 1 week to – 7 years with hypertension following repair of coarctation of the aorta. Patients received an initial infusion of either 125 micrograms/kg, 250 micrograms/kg, or 500 micrograms/kg,followed by a continuous infusion of 125 micrograms/kg/min, 250 micrograms/kg/min, or 500 micrograms/kg /min respectively. There was no significant difference in hypotensive effect between the 3 dosage groups. 54% of patients overall required medication other than esmolol hydrochlorideto achieve satisfactory blood pressure control. No difference was apparent in this regard between thedifferent dose groups.

5.2 Pharmacokinetic properties

The kinetics of esmolol hydrochloride 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 perminute.

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 theester 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.
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 ahalf-life of about 3.7 hours.

Children
A pharmacokinetic study was undertaken in 22 paediatric patients aged 3-16 years. A loading dose of 1000 micrograms/kg of esmolol hydrochloridewas administered followed by a continuous infusion of 300 micrograms/kg/min. The observed mean total body clearance was 119 mL/kg/min, the mean volume of distribution 283 mL/kg, and the mean terminal elimination half-life 6.9 min, indicating that esmolol hydrochloridekinetics in children are similar to those in adults. However, largeinter-individual variability was observed.

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 hydrochloride . This effect was observed at doses at least 10 times higher than the therapeutic dose. No studies have been done on the effect of ESMOCARD 100 mg/10 ml on the fertility and on peri- and postnatal effects. Esmolol hydrochloridewas found to be not mutagenic in several in vitro and in vivo test systems. The safety of esmolol hydrochloridehas not been examined in long-term studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate
Acetic acid 99%
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

ESMOCARD 100 mg/10 ml solution for injection **MUST NOT** beused in combination with sodium bicarbonate solutions or other medicinal products (e.g. furosemide, diazepam and thiopental) that arechemically incompatible with esmolol.

6.3 Shelf life

24 months.
The opened product is physicochemically stable for 24 hours at 2 to 8 °C.
From a microbiological point ofview, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of theuser 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

Do not store above 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 with a chlorobutyl rubber stopper, 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 bevisually inspected forparticulate matter and discoloration prior to administration. Only a clear and colourless solution should be used.
Any unused solution and thecontainers should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Orpha-Devel Handels und Vertriebs GmbH
Wintergasse 85/1B
A-3002 Purkersdorf
Austria

8 MARKETING AUTHORISATION NUMBER

PA1353/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 7th March 2008
Date of last renewal: 31st August 2010

10 DATE OF REVISION OF THE TEXT

October 2020