SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

ESMOLOL HYDROCHLORIDE 2500 mg powder for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

A vial of 50 ml contains 2500 mg esmolol hydrochloride.

Each ml of reconstituted concentrate for solution for infusion contains 50 mg esmolol hydrochloride (50 mg/ml).

Each ml of the diluted solution for infusion contains 10 mg esmolol hydrochloride (10 mg/ml).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion

The powder is white to almost white.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ESMOLOL HYDROCHLORIDE 2500 mg powder is indicated for supraventricular tachycardia (except for pre- excitation syndromes), and for the rapid control of 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.

ESMOLOL HYDROCHLORIDE 2500 mg powder is also indicated for tachycardia and hypertension occurring in the perioperative phase and non-compensatory sinus tachycardia where, in physician’s judgement the rapid heart rate requires specific intervention.

ESMOLOL HYDROCHLORIDE 2500 mg powder is not indicated for use in children aged up to 18 years (see section 4.2).

ESMOLOL HYDROCHLORIDE 2500 mg powder is not intended for use in chronic settings.

4.2 Posology and method of administration

ESMOLOL HYDROCHLORIDE 2500 mg powder for concentrate for solution for infusion MUST NOT BE ADMINISTERED WITHOUT RECONSTITUTION/DILUTION.

The reconstituted/diluted solution for infusion must be used immediately after opening (see sections 4.4 and 6).
The administration of incorrect reconstituted/diluted ESMOLOL HYDROCHLORIDE 2500 mg powder may result in death (see section 4.4).

Posology

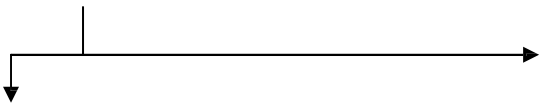
SUPRAVENTRICULAR TACHYARRHYTHMIA

The dosage of ESMOLOL HYDROCHLORIDE 2500 mg powder should be titrated individually. A starting dose is required, followed by a maintenance dosage.

The effective dose of ESMOLOL HYDROCHLORIDE 2500 mg powder 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.

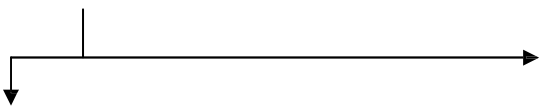
Flow Chart for Initiation and Maintenance of Treatment

Loading dosage infusion of
500 micrograms/kg/min for 1 minute,
THEN 50 micrograms/kg/min for 4 minutes



Respon
se
Maintain infusion at
50
micrograms/kg/min

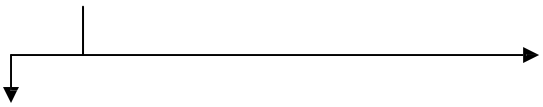
Inadequate response within 5 minutes
Repeat 500 micrograms/kg/min for 1
minute
Increase maintenance infusion to 100 micrograms/kg/min for 4 minutes



Respon
se
Maintain infusion at
100
micrograms/kg/min

Inadequate response within 5 minutes
Repeat 500 micrograms/kg/min for 1

minute
Increase maintenance infusion to 150 micrograms/kg/min for 4 minutes



Respon
se
Maintain infusion at
150
micrograms/kg/min

Inadequate response
Repeat 500 micrograms/kg/min for 1 minute
Increase maintenance infusion to 200 micrograms/kg/min and maintain

As the desired heart rate or safety end-point (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 HYDROCHLORIDE 2500 mg powder 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 HYDROCHLORIDE 2500 mg powder infusions for longer than 24 hours has not been thoroughly evaluated. Infusion durations greater than 24 hours should only be used with caution.

Abrupt discontinuation of ESMOLOL HYDROCHLORIDE 2500 mg powder 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 HYDROCHLORIDE 2500 mg powder 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/min given over four minutes, stopping at the desired therapeutic effect.

Replacement of ESMOLOL HYDROCHLORIDE 2500 mg powder 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 ESMOLOL HYDROCHLORIDE 2500 mg powder is to be replaced by alternative drugs, the physician should carefully consider the labelling of the alternative drug selected and reduce the dosage of ESMOLOL HYDROCHLORIDE 2500 mg powder as follows:

1) Within the first hour after the first dose of the alternative drug, reduce the ESMOLOL HYDROCHLORIDE 2500 mg powder infusion 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 the ESMOLOL HYDROCHLORIDE 2500 mg powder 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 HYDROCHLORIDE 2500 mg powder 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 of patients under 65.

Patients with kidney insufficiency
In patients with renal insufficiency caution is needed when ESMOLOL HYDROCHLORIDE 2500 mg powder is administered by infusion, since the acid metabolite of ESMOLOL HYDROCHLORIDE 2500 mg powder 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 ESMOLOL HYDROCHLORIDE 2500 mg powder metabolism.

Paediatric population (age under 18 years):
The safety and efficacy of ESMOLOL HYDROCHLORIDE 2500 mg powder in children aged up to 18 years have not yet been established. Therefore, ESMOLOL HYDROCHLORIDE 2500 mg powder is not indicated for use in the paediatric population (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.

Method of Administration

The powder must be reconstituted/diluted before use. The reconstituted/diluted powder can be administered in two different concentrations in two different volumes:

i. The standard concentration is 10 mg/ml, using a final volume of 250 ml

ii. In some cases where a lower volume is considered necessary, a higher concentration (50 mg/ml) can be prepared by diluting the powder in a final volume of 50 ml and administered with a PERFUSOR/MOTOR PUMP. There is limited clinical experience with the use of this higher concentration. This higher concentration should be infused only through a large vein or a central catheter using a perfusor pump (see section 4.4).

See section 6.6 for method of preparation.

INFUSION RATE CONVERSION TABLES (microgram/kg/min -> ml/min) for a **diluted** solution for infusion **(10 mg/ml)** administered through **STANDARD INFUSION**:

Conversion table : microgram/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: microgram/kg/min → ml/hour (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/hour**	**ml/hour**	**ml/hour**	**ml/hour**	**ml/hour**	**ml/hour**	**ml/hour**
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

INFUSION RATE CONVERSION TABLES (microgram/kg/min -> ml/min) for a **<u>concentrated</u>** solution for infusion **(50 mg/ml)** administered with a **PERFUSOR/MOTOR PUMP**:

Conversion table : microgram/kg/min → ml/min (esmolol diluted to 50 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	0.4	0.04	0.08	0.12	0.16	0.2	0.24
45	0.45	0.045	0.09	0.135	0.18	0.225	0.27
50	0.5	0.05	0.1	0.15	0.2	0.25	0.3
55	0.55	0.055	0.11	0.165	0.22	0.275	0.33
60	0.6	0.06	0.12	0.18	0.24	0.3	0.36
65	0.65	0.065	0.13	0.195	0.26	0.325	0.39
70	0.7	0.07	0.14	0.21	0.28	0.35	0.42
75	0.75	0.075	0.15	0.225	0.3	0.375	0.45
80	0.8	0.08	0.16	0.24	0.32	0.4	0.48
85	0.85	0.085	0.17	0.255	0.34	0.425	0.51
90	0.9	0.09	0.18	0.27	0.36	0.45	0.54
95	0.95	0.095	0.19	0.285	0.38	0.475	0.57

Conversion table : microgram/kg/min → ml/hour (esmolol diluted to 50 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/hour**	**ml/hour**	**ml/hour**	**ml/hour**	**ml/hour**	**ml/hour**	**ml/hour**
40	24	2.4	4.8	7.2	9.6	12	14.4
45	27	2.7	5.4	8.1	10.8	13.5	16.2
50	30	3	6	9	12	15	18
55	33	3.3	6.6	9.9	13.2	16.5	19.8
60	36	3.6	7.2	10.8	14.4	18	21.6
65	39	3.9	7.8	11.7	15.6	19.5	23.4
70	42	4.2	8.4	12.6	16.8	21	25.2
75	45	4.5	9	13.5	18	22.5	27
80	48	4.8	9.6	14.4	19.2	24	28.8
85	51	5.1	10.2	15.3	20.4	25.5	30.6
90	54	5.4	10.8	16.2	21.6	27	32.4
95	57	5.7	11.4	17.1	22.8	28.5	34.2
100	60	6	12	18	24	30	36
105	63	6.3	12.6	18.9	25.2	31.5	37.8
110	66	6.6	13.2	19.8	26.4	33	39.6
115	69	6.9	13.8	20.7	27.6	34.5	41.4
120	72	7.2	14.4	21.6	28.8	36	43.2

4.3 Contraindications

- Hypersensitivity to the active substance;
- 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 HYDROCHLORIDE 2500 mg powder 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

ESMOLOL HYDROCHLORIDE 2500 mg powder for concentrate for solution for infusion must be reconstituted/diluted and used immediately after opening (see section 6).

Incorrect dilutions of ESMOLOL HYDROCHLORIDE 2500 mg powder may result in severe overdoses. These overdoses may result in death or in permanent disability (see section 4.9).

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

It is recommended to continuously monitor the blood pressure and the ECG in all patients treated with ESMOLOL HYDROCHLORIDE 2500 mg powder. In the event of a hypotensive episode, the infusion rate should be reduced or, when necessary, be discontinued.

The use of ESMOLOL HYDROCHLORIDE 2500 mg powder 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 ESMOLOL HYDROCHLORIDE 2500 mg powder, severe reactions may occur, including loss of consciousness, cardiogenic shock, cardiac arrest. Several deaths have been reported in complex clinical states where ESMOLOL HYDROCHLORIDE 2500 mg powder 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. 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

HYDROCHLORIDE 2500 mg powder). 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 HYDROCHLORIDE. ESMOLOL HYDROCHLORIDE 2500 mg powder 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 HYDROCHLORIDE 2500 mg powder 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.

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

Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and Betablockade 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 HYDROCHLORIDE 2500 mg powder in patients with compromised cardiac function. At the first sign or symptom of impending cardiac failure, ESMOLOL HYDROCHLORIDE 2500 mg powder should be withdrawn. Although withdrawal may be sufficient because of the short elimination half-life of ESMOLOL HYDROCHLORIDE 2500 mg powder , specific treatment may also be considered (see section 4.9). ESMOLOL HYDROCHLORIDE 2500 mg powder 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 HYDROCHLORIDE 2500 mg powder 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 HYDROCHLORIDE 2500 mg powder 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, ESMOLOL HYDROCHLORIDE 2500 mg powder should be used with caution in patients with bronchospastic diseases. However, since beta1 selectivity is not absolute, ESMOLOL HYDROCHLORIDE 2500 mg powder should be carefully titrated to obtain the lowest possible effective dose. In the event of bronchospasm, the infusion should be

terminated immediately and a beta2 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 HYDROCHLORIDE 2500 mg powder should be used with caution in patients with a history of wheezing and asthma.

Precautions
ESMOLOL HYDROCHLORIDE 2500 mg powder 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. The administration of the 50 mg/ml solution should be strictly done in a large vein or in a central catheter only using a perfusor pump.

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, ESMOLOL HYDROCHLORIDE 2500 mg powder can attenuate reflex tachycardia and increase the risk of circulatory collapse. Therefore, ESMOLOL HYDROCHLORIDE 2500 mg powder 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 HYDROCHLORIDE 2500 mg powder, 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 the paediatric population (age under 18 years)
The safety and efficacy of ESMOLOL HYDROCHLORIDE 2500 mg powder ESMOLOL HYDROCHLORIDE 2500 mg powder in children have not been established.

4.5 Interaction with other medicinal products and other forms of interaction

Care should always be exercised whenever ESMOLOL HYDROCHLORIDE 2500 mg powder is used with other antihypertensive agents or other drugs that may cause hypotension or bradycardia: the effects of ESMOLOL HYDROCHLORIDE 2500 mg powder 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 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 HYDROCHLORIDE 2500 mg powder and appropriate haemodynamic monitoring is recommended.

Concomitant use of ESMOLOL HYDROCHLORIDE 2500 mg powder and Class 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 ESMOLOL HYDROCHLORIDE 2500 mg powder and 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: 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 increase of the risk of hypotension.

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 ESMOLOL HYDROCHLORIDE 2500 mg powder. The hypotensive effects of inhalation anaesthetic agents may be increased in the presence of ESMOLOL HYDROCHLORIDE 2500 mg powder. The dosage of either agent may be modified as needed to maintain the desired haemodynamics.

The combination of ESMOLOL HYDROCHLORIDE 2500 mg powder 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 and phenothiazines (such as chlorpromazine), as well as other antipsychotic agents (such as clozapine) may increase the blood pressure lowering effect. Dosing of ESMOLOL HYDROCHLORIDE 2500 mg powder 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 HYDROCHLORIDE 2500 mg powder 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 HYDROCHLORIDE 2500 mg powder 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 HYDROCHLORIDE 2500 mg powder and warfarin showed that concomitant administration of ESMOLOL HYDROCHLORIDE 2500 mg powder and warfarin does not alter warfarin plasma levels. ESMOLOL HYDROCHLORIDE 2500 mg powder concentrations, however, were equivocally higher when given with warfarin.

When digoxin and ESMOLOL HYDROCHLORIDE 2500 mg powder 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 HYDROCHLORIDE 2500 mg powder may increase AV conduction time. Digoxin did not affect ESMOLOL HYDROCHLORIDE 2500 mg powder pharmacokinetics.

When intravenous morphine and ESMOLOL HYDROCHLORIDE 2500 mg powder interaction was studied in normal subjects, no effect on morphine blood levels was seen. The ESMOLOL HYDROCHLORIDE 2500 mg powder steady-state blood levels were increased by 46% in the presence of morphine, but no other pharmacokinetic parameters were changed.

The effect of ESMOLOL HYDROCHLORIDE 2500 mg powder on the duration of suxamethonium chloride-induced or mivacurium-induced neuromuscular blockade has been studied in patients undergoing surgery. ESMOLOL HYDROCHLORIDE 2500 mg powder 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 HYDROCHLORIDE 2500 mg powder 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 HYDROCHLORIDE 2500 mg powder should be titrated with caution in patients being treated concurrently with warfarin, digoxin, morphine or 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 in 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 defects in humans. 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.

If treatment with esmolol hydrochloride is considered necessary, the uteroplacental 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 of undesirable effects, the dose of ESMOLOL HYDROCHLORIDE 2500 mg powder can be reduced or discontinued.
Most of the undersirable 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 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] Angioedem a 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 Chest Pain		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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Cases of massive accidental overdoses with concentrated solutions of ESMOLOL HYDROCHLORIDE 2500 mg powder have 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, cardiac arrest, bronchospasm, respiratory insufficiency, loss of consciousness to coma, convulsions, nausea, vomiting, hypoglycemia and hyperkalemia.

Treatment
Because of the short elimination half-life of ESMOLOL HYDROCHLORIDE 2500 mg powder powder for concentrate for solution for infusion (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 HYDROCHLORIDE 2500 mg powder administered. This may take longer than the 30 minutes seen with discontinuation at therapeutic dose levels of ESMOLOL HYDROCHLORIDE 2500 mg powder. 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: 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 hydrochloride is a beta-selective (cardioselective) receptor blocking agent.

At therapeutic doses esmolol hydrochloride has no significant intrinsic sympathicomimetic activity (ISA) or membrane stabilising activity. Esmolol hydrochloride, the active ingredient of ESMOLOL HYDROCHLORIDE 2500 mg powder, is chemically related to the phenoxy propanolamine class of beta-blockers.

Based on the pharmacological 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, the therapeutic effect is achieved sooner than the stabile plasma concentration. The infusion rate can then be adjusted to obtain the desired pharmacological effect.

Esmolol hydrochloride has the known hemodynamic 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 inotrope effect with decreased ejection fraction;
- Decrease in blood pressure.

<u>Children</u>

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

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 hydrochloride to achieve satisfactory blood pressure control. No difference was apparent in this regard between the different 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 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 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 a half-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 hydrochloride was 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 hydrochloride kinetics in children are similar to those in adults. However, large inter-individual variability was observed.

5.3 Preclinical safety data

No teratogenic effect has been observed in animal studies. In rabbits an embryo toxic effect has been observed (increase in fetal resorption) which was probably caused by esmolol 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 esmolol hydrochloride on the fertility and on peri- and postnatal effects. Esmolol hydrochloride was found to be not mutagenic in several in vitro and in vivo test systems. The safety of esmolol hydrochloride has not been examined in long-term studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

60 months
The in-use storage condition is 25°C.

The opened, reconstituted and diluted product is physicochemically stabile during 24 hours at 25 °C. From microbiological point of view the product must be used immediately after opening and dilution. In case this is not done, the user is responsible for use and administration. Normally, the period of use is not more than 24 hours at 2-8 °C, unless opening, reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions of the reconstituted solution see section 6.3.

6.5 Nature and contents of container

A clear, colourless, 50 ml glass vial with a bromobutyl rubber stopper and a flip off seal containing 2500 mg powder for concentrate for solution for infusion. The vial is packed in an outer cardboard carton.

Pack size: 1 vial per carton

6.6 Special precautions for disposal and other handling

ESMOCARD LYO 2500 mg powder for concentrate for solution for infusion **MUST NOT BE ADMINISTERED WITHOUT RECONSTITUTION/DILUTION.**

The powder must be reconstituted/diluted before use. The reconstituted/diluted powder can be administered in two different concentrations in two different volumes (see section 4.2):

1. The powder can be administered as a diluted solution for infusion **(10 mg/ml)**
   with a volume of 250 ml through STANDARD INFUSION

OR

2. The powder can be administered as a concentrated solution for infusion **(50 mg/ml**) with a volume of 50 ml with a PERFUSOR/MOTOR PUMP. There is limited clinical experience with the use of this higher concentration. This higher concentration should be infused only through a large vein or a central catheter using a perfusor pump (see section 4.4).

I. INSTRUCTION FOR USE for a diluted solution for infusion **(10 mg/ml)**
administered through STANDARD INFUSION:

Presentation	***Volume of diluent to be added***	***Final concentration of the reconstituted /diluted solution***	***Final volume of the reconstituted /diluted solution***	***Administration***
2500 mg Esmolol powder	**Step 1** Reconstitute one vial with 50ml of one of below mentioned solutions. **Step 2**	**10 mg/ml**	250 ml	Standard infusion with a volume of 250 ml
	Dilute immediately the reconstituted content of the vial (50 ml) to 250 ml with one of below mentioned solutions.			

II. INSTRUCTION FOR USE for a concentrated solution for infusion **(50 mg/ml)** administered with a PERFUSOR/MOTOR PUMP:

Presentation	***Volume of diluent to be added***	***Final concentration of the reconstituted solution***	***Final volume of the reconstituted solution***	***Administration***
2500 mg Esmolol powder	Reconstitute one vial with 50ml of one of below mentioned solutions. No further dilution is necessary.	**50 mg/ml**	50 ml	Use a perfusor/motor pump which takes syringes with a 50 ml volume

Appropriate solutions for reconstitution and dilution are:
NaCl 9 mg / ml (0.9%) solution
Glucose 50 mg / ml (5%) solution
Glucose 50 mg / ml (5%) in Ringer's solution
Glucose 50 mg / ml (5%) in NaCl 9 mg / ml (0.9%) solution
Glucose 50 mg / ml (5%) in Ringer-lactate solution
Ringer-lactate solution

Diluents for the final solution for infusion are commonly used for intravenously administered liquids, in glass as well as in PVC bottles.

The white to almost white lyophilised powder will dissolve completely after reconstitution. Mix gently until a clear solution is obtained.
Reconstituted solutions should be visually examined for particulate matter and discoloration. Only a clear and colourless solution should be used.

The opened, reconstituted and diluted product is physicochemically stable during 24 hours at 25°C. From microbiological point of view **the product must be used immediately**. In case this is not done, the user is responsible for use and administration. Normally, the period of use is not more than 24 hours at 2-8 °C, unless opening, reconstitution/dilution has taken place in controlled and validated aseptic conditions.

Any unused solution and the containers 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(S)

PL 30414/0008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04/10/2010

10 DATE OF REVISION OF THE TEXT

22/11/2018