SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

ESMOCARD 100 mg/10 mL (Solution for infusion)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ESMOCARD 100 mg/10 mL contains 10 mg esmolol hydrochloride per 1 mL.

Each single dose vial of 10 mL contains 100 mg esmolol hydrochloride.

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

A clear and colourless solution free of visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- **Supraventricular tachycardia:**

ESMOCARD is indicated for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in peri-operative, post-operative, or other emergent circumstances where short-term control of ventricular rate with a short-acting medicine is desirable.

ESMOCARD is also indicated in non-compensatory sinus tachycardia where, in the clinician's judgement, the rapid heart rate requires specific intervention.

ESMOCARD is not intended for use in chronic settings where transfer to another medicine is anticipated.

- **Intra-operative and post-operative tachycardia and/or hypertension:**

ESMOCARD is indicated for the treatment of tachycardia and hypertension that occur during induction and tracheal intubation, during surgery, on emergence from anaesthesia, and in the post-operative period, when in the clinician's judgement such specific intervention is considered indicated. Use of ESMOCARD to prevent such events is not recommended.

4.2 Posology and method of administration

Posology

Supraventricular tachycardia:

In the treatment of supraventricular tachycardia, responses to ESMOCARD usually (over 95 %) occur within the range of 50 to 200 µg/kg/min (0,05 to 0,2 mg/kg/min). The average effective dosage is approximately 100 µg/kg/min (0,1 mg/kg/min) even though dosages as low as 25 µg/kg/min (0,025 mg/kg/min) have been adequate in some patients. Dosages as high as 300 µg/kg/min (0,3 mg/kg/min) have been used, but these high dosages provide little additional effect and has an increased rate of adverse effects and are therefore not recommended.

The dosage of ESMOCARD in supraventricular tachycardia must be individualised by titration in which each step consists of a loading dose followed by a maintenance dose.

To start treatment of a patient with supraventricular tachycardia, administer a loading infusion of 500 µg/kg/min (0,5 mg/kg/min) over one minute followed by a four-minute maintenance infusion of 50 µg/kg/min (0,05 mg/kg/min). If an adequate therapeutic effect is observed over the five minutes of medicine administration, maintain the maintenance infusion dosage with periodic adjustments up or down as required. If an adequate

therapeutic effect is not observed, the same loading dose is repeated over one minute followed by an increased maintenance infusion rate of 100 µg/kg/min (0,1 mg/kg/min).

Continue the titration procedure as above, repeating the original loading infusion of 500 µg/kg/min (0,5 mg/kg/min) over one minute, but increasing the maintenance infusion rate over the subsequent four minutes by 50 µg/kg/min (0,05 mg/kg/min) increments. As the desired heart rate or blood pressure is approached, omit the subsequent loading doses and titrate the maintenance dosage up or down to the endpoint. Also, if required, increase the interval between steps from 5 to 10 minutes.

This specific dosage regimen has not been studied intra-operatively and due to the time required for titration it may not be optimal for intra-operative use.

The safety of dosages above 300 µg/kg/min (0,3 mg/kg/min) has not been studied. In the event of an adverse reaction, the dosage of ESMOCARD may be reduced or discontinued. If a local infusion site reaction develops, an alternative infusion site should be used, and caution should be taken to prevent extravasation. The use of butterfly needles should be avoided.

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

After achieving an adequate control of the heart rate and a stable clinical status in patients with supraventricular tachycardia, transition to alternative anti-dysrhythmic medicines such as propranolol or digoxin may be accomplished. A recommended guideline for such transition is provided below but the physician should carefully consider the labelling instructions for the alternative medicine selected:

Alternative medicine: Propranolol hydrochloride at a dosage of 10 - 20 mg four to six hourly.

Alternative medicine: Digoxin at a dosage of 0,125 – 0,5 mg six hourly (PO or IV)

The dosage of ESMOCARD should be reduced as follows:

1. Thirty minutes after the first dose of the alternative medicine, reduce the infusion rate of ESMOCARD by one half (50 %).
2. After the second dose of the alternative medicine, monitor the patient's response and if satisfactory control is maintained for the first hour, discontinue ESMOCARD.

The use of infusions of ESMOCARD up to 24 hours has been well documented, in addition, limited data from 24 to 48 hours (N = 48) indicate that ESMOCARD is well-tolerated up to 48 hours.

Intra-operative and post-operative tachycardia and/or hypertension:

During intra-operative and post-operative situations, it is not always advisable to slow titrate the dose of ESMOCARD to a therapeutic effect. Therefore, two dosing options are presented: immediate control dosing and; a gradual control when the physician has time to titrate.

- Immediate control during anaesthesia: For intra-operative treatment of tachycardia and/or hypertension give an 80 mg (approximately 1 mg/kg) bolus dose over 30 seconds followed by a 150 µg/kg/min (0,15 mg/kg/min) infusion, if required. Adjust the infusion rate as needed up to 300 µg/kg/min (0,3 mg/kg/min) to maintain desired heart rate and/or blood pressure.

- Gradual control: For post-operative tachycardia and hypertension, the dosing schedule is the same as that used in supraventricular tachycardia. To start treatment, administer a loading dosage infusion of 500 µg/kg/min (0,5 mg/kg/min) of ESMOCARD for one minute followed by a four-minute maintenance infusion of 50 µg/kg/min (0,05 mg/kg/min). If an adequate therapeutic effect is not observed within five minutes, repeat the same loading dosage and follow with a maintenance infusion increased to 100 µg/kg/min (0,1 mg/kg/min). (See 'Supraventricular tachycardia")

Note

Higher dosages (250 – 300 µg/kg/min (0,25 – 0,3 mg/kg/min)) may be required for adequate control of blood pressure than those required for the treatment of atrial fibrillation, flutter and sinus tachycardia. One third of the post-operative hypertensive patients required these higher dosages.

Method of administration

ESMOCARD 100 mg/10 mL *(Single dose vial for infusion):*

The single dose vial is pre-diluted to provide a ready-to-use 10 mg/mL concentration solution recommended for intravenous administration. It may be used to administer the appropriate ESMOCARD loading dose infusions by hand-held syringe while the maintenance dose infusion is being prepared.

When using the 10 mg/mL solution a loading dose of 0,5 mg/kg/min for a 70 kg patient would be 3,5 mL.

Any unused portion should be discarded.

See section 6.6 for disposal and other handling.

4.3 Contraindications

ESMOCARD is contraindicated in patients with:

- hypersensitivity to esmolol or to any of the excipients listed in section 6.1 or other beta-blockers (cross sensitivity between beta-blockers is possible)
- severe sinus bradycardia (heart rate less than 50 beats per minute)
- sick sinus syndrome; severe AV-nodal conductance disorders (without pacemaker); second- or third-degree heart block
- cardiogenic shock
- severe hypotension
- decompensated heart failure

- concomitant or recent intravenous administration of verapamil. ESMOCARD must not be administered within 48 hours of discontinuing verapamil (see section 4.5)
- non-treated pheochromocytoma (see section 4.4)
- pulmonary hypertension
- acute asthmatic attack, bronchoconstriction or patients with a history of chronic respiratory diseases such as bronchitis (see section 4.4)
- metabolic acidosis
- late phase peripheral vascular disease or Raynaud's phenomenon.

The normal dose should be reduced in elderly patients, or in patients suffering from renal dysfunction. Particular caution should be taken in this regard.

In the peri-operative period, it is generally unwise to reduce the dosage to which the patient is accustomed, as there may be danger of aggravation of angina pectoris or hypertension.

A patient's normal tachycardic response to hypovolaemia or blood loss may be obscured during or after surgery. Particular caution should be taken in this regard (see section 4.4).

4.4 Special warnings and precautions for use

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

The use of ESMOCARD for control of ventricular response in patients with supraventricular dysrhythmias should be undertaken with caution when the patient is compromised haemodynamically or is taking other medicines 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, severe reactions may occur, including loss of consciousness, cardiogenic shock, cardiac arrest. Several deaths have been reported in complex clinical states where esmolol as contained in ESMOCARD 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 ESMOCARD). In some cases, additional interventions may be necessary to restore blood pressure. In patients with 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. ESMOCARD should be used with special caution in patients with low pretreatment heart rates.

ESMOCARD is contraindicated in patients with pre-existing severe sinus bradycardia (see section 4.3). If the pulse rate decreases to less than 50 to 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 medicines over a period of time can lead to cardiac failure.

Caution should be exercised when using ESMOCARD in patients with compromised cardiac function. At the first sign or symptom of impending cardiac failure, ESMOCARD should be withdrawn. Although withdrawal may be sufficient because of the short elimination half-life of ESMOCARD, specific treatment may also be

considered (see section 4.9).

ESMOCARD is contraindicated in patients with decompensated heart failure (see section 4.3).

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

ESMOCARD 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 is used to treat hypertension following induced hypothermia.

Patients with bronchospastic disease should, in general, not receive beta-blockers (i.e., ESMOCARD). Because of its relative beta-1 selectivity and titratability, ESMOCARD should be used with caution in patients with bronchospastic diseases. However, since beta-1 selectivity is not absolute, ESMOCARD 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 medicine, it may be necessary to re-evaluate the dose of this medicine.
ESMOCARD should be used with caution in patients with a history of wheezing or asthma.

ESMOCARD should be used with caution in patients suffering from diabetes mellitus or in case of suspected or actual hypoglycaemia. Beta-blockers, such as ESMOCARD may mask the prodromal symptoms of hypoglycaemia such as tachycardia. However, dizziness and sweating may not be affected.
Concomitant use of beta-blockers, such as ESMOCARD, and antidiabetic medicines can increase the effect of

the antidiabetic medicines (blood glucose–lowering) (see section 4.5).

Infusion site reactions have occurred with the use of ESMOCARD 10 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.

During intravenous administration of ESMOCARD special care should be taken since sloughing of the skin and necrosis have been reported in association with infiltration and extravasation of intravenous infusions.

The use of ESMOCARD in patients already on beta-blocker therapy is not recommended as it may compromise the myocardial function.

Beta-blockers, such as ESMOCARD, may increase the number and the duration of anginal attacks in patients with Prinzmetal 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 can attenuate reflex tachycardia and increase the risk of circulatory collapse. Therefore, ESMOCARD should be used with caution in such patients (see section 4.3).

Treatment with beta-blockers such as ESMOCARD may be associated with exacerbation of peripheral vascular disease, or the development of Raynaud’s phenomenon (due to the unopposed arteriolar alpha-sympathetic activation) (see section 4.3).

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

ESMOCARD should be used with caution in patients with renal function impairment as ESMOCARD or the acid metabolite is primarily excreted unchanged by the kidneys.

Beta-blockers (i.e., ESMOCARD) 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, such as ESMOCARD, 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 including ESMOCARD 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, such as ESMOCARD, in patients at risk or suspected of developing thyrotoxicosis may precipitate thyroid storm and these patients must be monitored closely.

ESMOCARD may exacerbate skeletal muscle weakness and should be used with caution in patients with myasthenia gravis.

Severe peripheral vascular disease and even peripheral gangrene may be precipitated. ESMOCARD may exacerbate sexual impotence and gastrointestinal disturbances.

It is dangerous to administer ESMOCARD concomitantly with the following medicines: hypoglycaemic medicines, phenothiazines and various anti-dysrhythmic medicines Such medicine interactions can have life-threatening consequences (see section 4.5).

Note: Digitalisation of patients receiving long-term beta-blocker therapy such as ESMOCARD, may be necessary if congestive cardiac failure is likely to develop. This combination can be considered despite the potentiation of the negative chronotropic effect of the two medicines. Careful control of dosages, and of the individual patient's response (and notably pulse rate), is essential in this situation.

Abrupt discontinuation of therapy may cause exacerbation of angina pectoris in patients suffering from ischaemic heart disease. Discontinuation of therapy should be gradual, and patients should be advised to limit the extent of their physical activity during the period that the medicine is being discontinued (see section 4.8).

Administration to pregnant mothers shortly before giving birth or during labour may result in the newborn infants being born hypotonic, collapsed and hypoglycaemic (see section 4.6).

Special populations

Adverse reactions to beta-blockers such as ESMOCARD are more frequent in elderly patients, in patients with renal decompensation, and in patients who receive beta-blockers intravenously (see section 4.8).

Paediatric population

Safety and efficacy in children have not been established.

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Due to the short duration of action and the short periods of time over which ESMOCARD is used, many of the medicine interactions associated with beta-blockers do not apply.

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

Verapamil: In patients with depressed myocardial function the concurrent use of calcium-channel blockers such as verapamil and ESMOCARD has led to fatal cardiac arrests and caution should be exercised when considering co-administration.
Calcium antagonists e.g., verapamil and diltiazem (to a lesser extent) have a negative influence on contractility and AV conduction. The combination should not be given to patients with conduction abnormalities and ESMOCARD should not be administered within 48 hours of discontinuing verapamil (see section 4.3).

Dihydropyridine derivatives (e.g., nifedipine): Such calcium antagonists may increase the risk of hypotension. In patients with cardiac insufficiency and who are being treated with a calcium antagonist, treatment with beta-blocking medicines may lead to cardiac failure. Careful titration of ESMOCARD and appropriate haemodynamic monitoring is recommended.

Quinidine: The metabolism of beta-blockers such as ESMOCARD may be decreased by quinidine and worsen

the interaction between antidysrhythmic medicines and ESMOCARD which affect cardiac conduction and causing bradycardia and heart block.

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

Antidiabetic medicines, sulfonylurea or insulin: Concomitant use of ESMOCARD and insulin or oral anti-diabetic medicines may intensify the blood sugar lowering effect (especially non-selective beta-blockers). ESMOCARD may mask some symptoms of developing hypoglycaemia such as an increase in pulse rate and blood pressure (tachycardia), but other manifestations such as dizziness and sweating may not be masked.

Anaesthetics: The use of ESMOCARD in combination with general anaesthetics causing myocardial depression such as ether, cyclopropane and trichloroethylene should be avoided.

In situations where the patient's volume status is uncertain or concomitant antihypertensive medicines 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 dysrhythmia during induction and intubation.

The anaesthetist should be informed when the patient is receiving a beta-blocking medicine in addition to ESMOCARD.

The hypotensive effects of inhalation anaesthetic medicines may be increased in the presence of ESMOCARD. The dosage of either medicine may be modified as needed to maintain the desired haemodynamics.

Ganglion blocking medicines: The combination of ESMOCARD with ganglion blocking medicines can enhance the hypotensive effect.

Nonsteroidal Anti-Inflammatory Drugs (NSAID): NSAIDs may decrease the hypotensive effects of

ESMOCARD.

Floctafenine or amisulpride: Special caution must be taken when using floctafenine or amisulpride concomitantly with beta-blockers, such as ESMOCARD.

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

Dopamine, epinephrine (adrenaline) & norepinephrine: Patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic while treated with ESMOCARD. Such patients may not respond to the usual doses of epinephrine (adrenaline) used to treat these allergic reactions (see section 4.4).
ESMOCARD should not be used to control supraventricular tachycardia in the presence of medicines which are vasoconstrictive and inotropic such as dopamine, epinephrine (adrenaline) and norepinephrine because of the danger of blocking cardiac contractility when systemic vascular resistance is high.

Aminophylline or theophylline: Concurrent use with ESMOCARD may result in mutual inhibition of therapeutic effects and the clearance of theophylline may be decreased.
The effects of ESMOCARD may be counteracted by sympathomimetic medicines having beta-adrenergic agonist activity with concomitant administration. The dose of either medicine may need to be adjusted based on patient response, or use of alternate therapeutic medicines considered.

Catecholamine-depleting medicines (e.g., reserpine): Concurrent use with ESMOCARD may result in additive and possibly excessive beta-adrenergic blockade; close observation is recommended since bradycardia and hypotension may occur, which may result in vertigo, syncope, or postural hypotension.

Moxonidine or alpha-2-agonists (e.g., clonidine): Caution should be exercised when transferring a patient from moxonidine or alpha-2-agonists (e.g., clonidine). The withdrawal of clonidine or moxonidine may result in the release of large amounts of catecholamines that may give rise to a hypertensive crisis. If beta-blockers, such as ESMOCARD, are administered in these circumstances, the unopposed alpha receptor stimulation may potentiate this effect.

If ESMOCARD, and clonidine or moxonidine are given concurrently, and both treatments have to be discontinued, ESMOCARD should be discontinued first and then clonidine or moxonidine after a few days, as severe rebound hypertension may occur.

Ergot derivatives: The use of beta-blockers (e.g., ESMOCARD) with ergot derivatives may result in severe peripheral vasoconstriction and hypertension.

Warfarin: ESMOCARD concentrations are higher when given concurrently with warfarin, but it is unlikely to be of clinical importance.

Digoxin: When administered with ESMOCARD the blood levels of digoxin increase by 10 – 20 %. The combination of digitalis glycosides and ESMOCARD may increase AV conduction time. Digoxin does not affect the pharmacokinetics of ESMOCARD.

Morphine: In the presence of morphine, ESMOCARD steady-state blood levels were increased by 46 % but no other pharmacokinetic parameters were changed.

Succinylcholine (i.e., suxamethonium chloride): The effect of beta-blockers (i.e., ESMOCARD) on the duration of suxamethonium chloride-induced and mivacurium induced neuromuscular blockade has been studied in patients undergoing surgery. Beta-blockers (i.e., ESMOCARD) did not affect the onset of neuromuscular blockade by succinylcholine (suxamethonium chloride), but the duration of neuromuscular blockade was prolonged. Beta-blockers (i.e., ESMOCARD) moderately prolonged the clinical duration and recovery index of mivacurium.

Although the interactions observed in studies of warfarin, digoxin, morphine, suxamethonium chloride or mivacurium are not of major clinical importance, ESMOCARD 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

ESMOCARD should not be used in pregnancy, as the safety and efficacy of ESMOCARD during pregnancy has not been established.

Although there are no adequate and well-controlled studies in pregnant women, use of ESMOCARD in the last trimester of pregnancy (shortly before giving birth) or during labour or delivery has been reported to cause foetal bradycardia, which continued after termination of medicine infusion, and/or the newborn infants being born hypotonic, collapsed and hypoglycaemic (see section 4.4).

Breastfeeding

ESMOCARD should not be used during breastfeeding, as the safety and efficacy of ESMOCARD during breastfeeding has not been established.

Fertility

There are no human data on the effects of ESMOCARD on fertility.

4.7 Effects on the ability to drive and use machines

ESMOCARD may cause dizziness. Do not drive or operate machinery if you experience dizziness.

4.8 Undesirable effects

a. Summary of the safety profile

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

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

Adverse reactions to beta-blockers such as ESMOCARD are more frequent in elderly patients, in patients with renal decompensation, and in patients who receive beta-blockers intravenously (see section 4.8).

b. Tabulated list of adverse reactions

MedDRA System Organ Class (SOC)	**Frequent**	**Less frequent**	**Frequency unknown**
Immune system disorders		Hypersensitivity reactions.	
Metabolism and	Anorexia.		Hyperkalaemia, metabolic acidosis.

nutrition disorders			
Psychiatric disorders	Depression, anxiety or nervousness.	Abnormal thinking.	Vivid dreams and nightmares.
Nervous system disorders	Dizziness[1], somnolence, headache, paraesthesia, disturbance in attention, confusional state, agitation.	Syncope (fainting), convulsion, speech disorder.	Generalised tonic-clonic seizures.
Eye disorders		Visual impairment.	Abnormal vision, dry eye.
Cardiac disorders		Bradycardia (heart rate less than 50 beats per minute), chest pain, heart (atrioventricular) block, pulmonary arterial pressure increased, congestive heart failure (cardiac failure), ventricular	Accelerated idioventricular rhythm, coronary arteriospasm, cardiac arrest, asymptomatic hypotension.

		extrasystoles, nodal rhythm, angina pectoris, sinus arrest, asystole.	
Vascular disorders	Hypotension.	Peripheral ischaemia, reduced peripheral circulation (cold hands and feet), pale skin (pallor), flushing, thrombophlebitis[2].	Oedema.
Respiratory, thoracic and mediastinal disorders		Dyspnoea, pulmonary oedema, bronchospasm, wheezing, nasal congestion, rhonchi, rales.	
Gastrointestinal disorders	Nausea, vomiting.	Dysgeusia (taste perversion), dyspepsia, constipation, dry mouth, abdominal	Abdominal discomfort.

		pain.	
Skin and subcutaneous tissue disorders	Diaphoresis[1].	Skin discolouration[2], erythema[2], local skin necrosis [2] (due to extravasation).	Psoriasis[3], angioedema, urticaria.
Musculoskeletal and connective tissue disorders		Musculoskeletal pain[4], skeletal muscle weakness.	
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 (fever), redness, pain[2] and swelling (oedema[2]**)** at the injection site, burning at infusion site, 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 medicine class, including ESMOCARD, can cause psoriasis in some situations, or worsen it.
4. Including midscapular pain and costochondritis.

c. Description of selected adverse reactions

Bronchoconstriction may occur in patients suffering from asthma, bronchitis and other chronic pulmonary diseases (see section 4.3). Congestive cardiac failure and marked bradycardia may also manifest. A variety of neuropsychiatric disorders, ranging from vague fatigue and nightmares to overt psychosis, have been observed.

Abrupt discontinuation of therapy may cause exacerbation of angina pectoris in patients suffering from ischaemic heart disease. Discontinuation of therapy should be gradual, and patients should be advised to limit the extent of their physical activity during the period that the medicine is being discontinued (see sections 4.2 and 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms

In case of overdose the following symptoms can occur: severe hypotension, bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, electro-mechanical dissociation, respiratory

insufficiency, loss of consciousness to coma, convulsions, nausea, vomiting, hypoglycaemia and hyperkalaemia.

Massive accidental overdose can occur due to dilution errors.

Treatment

The first step in the management of toxicity should be to discontinue the ESMOCARD infusion as it has an elimination half-life of approximately 9 minutes.

The time taken for symptoms to disappear following overdosing will depend on the amount of ESMOCARD administered. This may take longer than the 30 minutes seen with discontinuation at therapeutic dose levels of ESMOCARD. Artificial respiration may be necessary.

Cases of mild overdose should be observed for at least four hours, as apnoea and cardiovascular collapse may appear suddenly.

Based on the observed clinical effects, the following general measures should be considered:

Bradycardia: Intravenous administration of atropine or other anticholinergic medicines. If the response is inadequate, glucagon may be given intravenously.

The use of glucagon has been successful to counteract the cardiovascular effects (bradycardia, hypotension) resulting from overdose with ESMOCARD. An intravenous dose of 2 to 3 mg should be administered over a period of 30 seconds and repeated, if necessary, followed by an intravenous glucagon infusion at the rate of 5 mg per hour until the patient has been stabilised.

Alternatively, dobutamine or isoprenaline may be required to reverse beta-blockade. When the bradycardia cannot be treated sufficiently a pacemaker may be necessary.

Bronchospasm: Intravenous administration or inhalation of aminophylline and/or intravenous administration of a beta-2-agonist e.g., salbutamol.

Cardiovascular depression or cardiac shock (cardiac failure): Intravenous administration of a diuretic, digitalis glycoside and/or sympathomimetics. In shock resulting from inadequate cardiac contractility intravenous administration of sympathomimetics may be considered. The dose of sympathomimetics (depending on the symptoms: dobutamine, dopamine, isoproterenol (i.e., isoprenaline), amrinone or noradrenaline etc.) depends on the therapeutic effect.

Symptomatic hypotension: Intravenous administration of fluids and/or pressor medicines.

In case further treatment is necessary, atropine, inotropic medicines or calcium ions can be given intravenously based on the clinical situation and judgment of the treating healthcare provider.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 5.2 Adrenolytics (Sympatholytics)

Pharmacotherapeutic group: Beta-blocking medicines, selective.

ATC code: C07AB09

Esmolol hydrochloride is a beta-1 cardio selective antagonist with rapid onset and a very short duration of action.

It has little if any intrinsic sympathomimetic activity, and it lacks membrane-stabilising actions. Esmolol hydrochloride inhibits the beta-1 receptors mainly located in cardiac tissue, but this cardio selective effect is not absolute.

Antidysrhythmic activity is due to blockade of adrenergic stimulation of cardiac pacemaker potentials.

5.2 Pharmacokinetic properties

After intravenous doses esmolol is hydrolysed by esterase's in the red blood cells to a free acid metabolite (with 1/1500 the activity of esmolol) and methanol.

Steady-state blood concentrations are reached within 30 minutes with doses of 50 to 300 micrograms/kg per minute. The time to steady state may be reduced to 5 minutes by giving an appropriate loading dose. Blood concentrations of esmolol decline in a biphasic manner with a distribution half-life of about 2 minutes and an elimination half-life of about 9 minutes. The free acid metabolite has a half-life of approximately 3,7 hours (increased up to tenfold in renal failure).

Esmolol has low lipid solubility and is about 55 % bound to plasma proteins. It is excreted in the urine, almost entirely as the de-esterified metabolite.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid

Hydrochloric acid

Sodium acetate trihydrate

Water for injection.

6.2 Incompatibilities

ESMOCARD injection is not compatible with Sodium bicarbonate (5 %) injection.

Compatible intravenous solutions:

Dextrose (5 %) and Sodium chloride (0,45 %)

Sodium chloride (0,9 %) injection

Dextrose (5 %) injection

Dextrose (5 %) in Lactate Ringers' injection

Lactate Ringers' injection

Dextrose 5 % in sodium chloride (0,9 %) injection

Sodium chloride (0,45 %) injection

Potassium chloride (40 mEq/litre) in Dextrose (5 %).

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 ° C. Do not freeze.

6.5 Nature and contents of container

ESMOCARD 100 mg/10 mL: The solution is contained in a clear and colourless Type 1 glass vial closed with a grey serum rubber stopper, sealed with transparent ring flip-off seal packed into PVC tray or packed into blisters placed into cardboard box.

5 vials are placed together in one PVC tray or blister.

1 PVC tray or blister, containing 5 vials, per outer cardboard box.

6.6 Special precautions for disposal and other handling

ESMOCARD is a parenteral medicine which should be inspected visually for particulate matter and discolouration before administration, whenever the solution and container permit.

ESMOCARD 100 mg/10 mL is pre-diluted. Discard any unused portion after use.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd.

100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive, Irene

Pretoria

8 REGISTRATION NUMBER(S)

45/5.2/0806

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of registration: 11 June 2018

10 DATE OF REVISION OF THE TEXT

06 August 2024