Professional Information

SCHEDULING STATUS

S3

APPROVED
Responsible Pharmacist
Sign: ..... Date: 08/03/2019

PROPRIETARY NAME AND DOSAGE FORM

ESMOCARD 100 mg/10 ml (Solution for infusion)

COMPOSITION

ESMOCARD 100 mg/10 ml: Each single dose vial contains as active ingredient 10 mg/ml esmolol hydrochloride i.e. 100 mg/10 ml single dose vial.

The following excipients are also included acetic acid, hydrochloric acid, sodium acetate trihydrate and water for injection.

Sugar free.

PHARMACOLOGICAL CLASSIFICATION

A 5.2 Adrenolytics (Sympatholytics)

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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.

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.

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 agent 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 agent 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.

CONTRAINDICATIONS

ESMOCARD is contraindicated in patients with:

- hypersensitivity to esmolol or any of the ingredients of ESMOCARD
- sinus bradycardia (heart rate less than 45 beats per minute)
- heart block greater than first degree
- cardiogenic shock
- heart failure
- pheochromocytoma (see WARNINGS AND SPECIAL PRECAUTIONS)

- asthma, bronchoconstriction or patients with a history of chronic respiratory diseases such as bronchitis (see WARNINGS AND SPECIAL PRECAUTIONS).
- late phase peripheral vascular disease or Raynaud's phenomenon.

WARNINGS AND SPECIAL PRECAUTIONS

Safety and efficacy in children have not been established.

Diabetes mellitus and hypoglycaemia

Particular caution should be exercised in patients suffering from diabetes mellitus, as ESMOCARD exacerbate hypoglycaemia and mask tachycardia occurring with hypoglycaemia. Other symptoms such as dizziness and sweating may not be significantly affected.

Impaired renal function

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.

Hypotension

Hypotension can occur at any dose and is generally defined as systolic pressure less than 90 mmHg and/or diastolic pressure less than 50 mmHg, but is dose related and therefore doses above 200 µg/kg/min (0,2 mg/kg/min) are not recommended. Patients should be closely monitored, especially if blood pressure is low before treatment. Hypotension usually resolves within 30 minutes once the dosage is reduced or the infusion is stopped.

Cardiac failure

Sympathetic stimulation is required in supporting circulatory function in congestive heart failure and beta-blockage has the potential hazard to further depress myocardial contractility and precipitating more severe failure. Continued depression of the myocardium with beta-blocking agents over a period of time can lead to cardiac failure. ESMOCARD should be withdrawn at the first sign or symptom of impending cardiac failure. Although withdrawal may be sufficient due to the short elimination half-life of ESMOCARD, specific treatment may also be considered (see KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT).

Caution should be taken when considering the use of ESMOCARD for control of ventricular response in patients with supraventricular dysrhythmias 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.

Treatment with beta-blockers

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

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

Adverse reactions to beta-blockers such as ESMOCARD are more common in elderly patients, in patients with renal decompensation, and in patients who receive beta-blockers intravenously.

ESMOCARD may obscure tachycardic responses due to hypovolaemia or blood loss during or after surgery.

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

ESMOCARD should never be given to patients with a pheochromocytoma without prior alpha-adrenergic blocker therapy.

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

ESMOCARD should not be used to treat hypertension in patients in whom the increased blood pressure is primarily due to vasoconstriction associated with hypothermia.

Bronchospastic diseases

Beta-blockers in general should not be used in patients with bronchospastic diseases. ESMOCARD may be used with caution in these patients due to its relative $beta_1$ selectivity and titratability. However, ESMOCARD should be carefully titrated to obtain the lowest possible effective dose, since $beta_1$ selectivity is not absolute. In case of bronchospasm the infusion should be terminated immediately and a $beta_2$ stimulating agent may be administered if conditions allow it but should be used with special caution as the patient already have rapid ventricular rates.

General administration precautions

Infusion concentrations of 20 mg/ml were associated with more severe venous irritation, which include thrombophlebitis, than concentrations of 10 mg/ml. Extravasation of 20 mg/ml may lead to more serious local reactions and possible skin necrosis. Concentrations of greater than 10 mg/ml or infusion into small veins or through a butterfly catheter should be avoided.

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.

Effect on the ability to drive and use machinery

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

INTERACTIONS

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.

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.

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 %. Digoxin does not affect the pharmacokinetics of ESMOCARD.

Morphine: In the presence of morphine ESMOCARD steady-state blood levels were increased by 46 %.

Succinylcholine: The duration of neuromuscular blockade induced by succinylcholine is prolonged by ESMOCARD.

Epinephrine (adrenaline): 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 beta-blockers. Such patients may not respond to the usual doses of epinephrine (adrenaline) used to treat these allergic reactions.

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.

Antidiabetic agents, sulfonylurea or insulin: ESMOCARD may mask some symptoms of developing hypoglycaemia such as an increase in pulse rate and blood pressure

Dopamine, epinephrine (adrenaline) & norepinephrine: ESMOCARD should not be used to control supraventricular tachycardia in the presence of agents 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 use of ESMOCARD in combination with general anaesthetics causing myocardial depression such as ether, cyclopropane and trichloroethylene should be avoided.

Quinidine: The metabolism of β-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.

HUMAN REPRODUCTION

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

Although there are no adequate and well-controlled studies in pregnant women, use of ESMOCARD in the last trimester of pregnancy or during labour or delivery has been reported to cause foetal bradycardia, which continued after termination of medicine infusion.

DOSAGE AND DIRECTIONS FOR USE

Note

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

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 ESMOCARD 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.

Dosage and directions for use in 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 agents 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 agent selected:

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

Alternative agent: 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 agent, reduce the infusion rate of ESMOCARD by one half (50 %).
2. After the second dose of the alternative agent, 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 – 48 hours (N=48) indicate that ESMOCARD is well-tolerated up to 48 hours.

Dosage and directions for use in 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.

Compatible intravenous solutions:

1. Dextrose (5 %) and Sodium chloride (0,45 %)
2. Sodium chloride (0,9 %) injection
3. Dextrose (5 %) injection
4. Dextrose (5 %) in Lactate Ringers' injection
5. Lactate Ringers' injection
6. Dextrose 5 % in sodium chloride (0,9 %) injection
7. Sodium chloride (0,45 %) injection
8. Potassium chloride (40 mEq/litre) in Dextrose (5 %)

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

SIDE EFFECTS

Adverse reactions are more common in patients with renal decompensation.

Cardiac disorders:

Less frequent: Bradycardia (heart rate less than 50 beats per minute), chest pain.

Frequency unknown: Peripheral ischaemia, pulmonary oedema, heart block, congestive heart failure, asymptomatic hypotension, symptomatic diaphoresis.

Vascular disorders:

Frequent: Hypotension.

Less frequent: Reduced peripheral circulation (cold hands and feet), flushing or pale skin, fainting.

Frequency unknown: Oedema.

Nervous system disorders:

Frequent: Dizziness.

Less frequent: Confusion, headache, fever.

Frequency unknown: Somnolence, fatigue, paraesthesia, generalised tonic-clonic seizures, agitation, speech disorder.

Psychiatric disorders:

Less frequent: Anxiety or nervousness.

Frequency unknown: Depression and abnormal thinking, vivid dreams and nightmares.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Bronchospasm, wheezing, dyspnoea.

Bronchoconstriction may occur in patients suffering from asthma, bronchitis and other chronic pulmonary diseases (see CONTRAINDICATIONS).

Gastrointestinal disorders:

Less frequent: Nausea or vomiting, anorexia.

Frequency unknown: Dyspepsia, constipation, dry mouth, abdominal discomfort and taste perversion.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Skeletal muscle weakness.

Skin and subcutaneous tissue disorders:

Frequency unknown: Erythema, skin discolouration.

Immune system disorders:

Less frequent: Hypersensitivity reactions.

Renal and urinary disorders:

Frequency unknown: Urinary retention.

Eye disorders:

Frequency unknown: Abnormal vision, dry eye.

General disorders and administrative site conditions:

Less frequent: Redness, pain and swelling at the injection site.

Frequency unknown: Asthenia, burning at infusion site, thrombophlebitis and local skin necrosis (from extravasation).

KNOWN SYMPTOMS OF OVERDOSAGES AND PARTICULARS OF ITS TREATMENT

Cardiac arrest can be caused by overdosage of ESMOCARD. It can also produce bradycardia, hypotension, bronchospasm, electro-mechanical dissociation and loss of consciousness.

Massive accidental overdose can occur due to dilution errors.

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. Then, based on the observed clinical effects, the following general measures should be considered:

Bradycardia: Intravenous administration of atropine or other anticholinergic medicines.

Bronchospasm: Intravenous administration of a $beta_2$-stimulating agent and/or a theophylline derivative.

Cardiac failure: Intravenous administration of a diuretic and/or digitalis glycoside. In shock resulting from inadequate cardiac contractility intravenous administration of dopamine, dobutamine, isoproterenol or amrinone may be considered.

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

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.

IDENTIFICATION

ESMOCARD 100 mg/10 ml: A clear and colourless solution free of visible particles.

PRESENTATION

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.

STORAGE INSTRUCTIONS

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

KEEP OUT OF REACH OF CHILDREN.

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

REGISTRATION NUMBER

45/5.2/0806

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION

Date of registration: 11 June 2018