Professional Information

SCHEDULING STATUS:

S3

1 NAME OF THE MEDICINE

EMCOR 2,5 film-coated tablets

EMCOR 5 film-coated tablets

EMCOR 10 film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each EMCOR 2,5 tablet contains 2,5 mg bisoprolol fumarate.

Each EMCOR 5 tablet contains 5 mg bisoprolol fumarate.

Each EMCOR 10 tablet contains 10 mg bisoprolol fumarate.

Sugar free.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

EMCOR 2,5 mg: White, heart-shaped biconvex film-coated tablets, scored on both sides.

EMCOR 5 mg: Yellowish-white, heart-shaped biconvex film coated tablets, scored on both sides.

EMCOR 10 mg: Pale orange-light orange, heart-shaped biconvex film coated tablets, scored on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

EMCOR 2,5; 5 and 10 mg

EMCOR is indicated for the treatment of stable chronic heart failure with reduced systolic ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides. The patients should have stable chronic heart failure without acute failure during the previous six weeks and an unchanged basic therapy during the previous two weeks. They should be treated at optimal dose with an ACE inhibitor (or other vasodilator in case of intolerance to ACE inhibitors) and a diuretic and, optionally, cardiac glycosides, prior to the administration of EMCOR.

EMCOR 5 and 10 mg:
EMCOR is indicated for the management of mild to moderate essential hypertension and angina pectoris. It may be used alone or in combination with other antihypertensive medicines.

4.2 Posology and method of administration

Posology

Treatment of stable chronic heart failure

Patients should be stable (without acute failure) when bisoprolol treatment with EMCOR is initiated. It is recommended that the treating medical practitioner should be experienced in the management of chronic heart failure.
Transient worsening of heart failure, hypotension, or bradycardia may occur during the titration period and thereafter.

Titration phase

The treatment of stable chronic heart failure with EMCOR requires a titration phase.
The treatment with EMCOR should be started with a gradual uptitration according to the following steps:
The recommended starting dose is

- 1,25 mg once daily

Depending on individual tolerance the dose is increased in intervals of two weeks or longer to

- 2,5 mg once daily, 3,75 mg once daily, 5 mg once daily, 7.5 mg once daily, 10 mg once daily.

If a dose increase is not well tolerated treatment may be maintained at a lower dose.

The maximum recommended dose is 10 mg once daily.

Close monitoring of vital and other signs (heart rate, blood pressure, conduction disturbances) and symptoms of worsening heart failure is recommended during the titration phase. Symptoms may already occur within the first 4 hours after initiating the therapy.

Treatment modification

If the maximum recommended dose is not well tolerated, gradual dose reduction may be considered.

In case of transient worsening of heart failure, with acute pulmonary oedema, hypotension, cardiogenic shock, symptomatic bradycardia or AV block reconsideration of the dosage of the concomitant medication is recommended. It may also be necessary to temporarily lower the dose of EMCOR or to consider discontinuation. The reintroduction and/or uptitration of EMCOR should be considered when the patient becomes stable again.

Treatment of hypertension or angina pectoris

The dose must be individualised according to response and tolerance.

Hypertension

The recommended dosage is 5 mg EMCOR once daily.

If necessary, the dosage may be increased to 10 mg once daily. Individual patients may benefit from a dose of 20 mg once daily.

The maximum recommended dosage is 20 mg once daily.

Angina pectoris

The recommended dosage is 5 mg EMCOR once daily.

If necessary, the dosage may be increased to 10 mg once daily.

No benefit was shown by increasing the dose to 20 mg once daily.

The maximum recommended dosage is 20 mg once daily.

Method of administration

EMCOR tablets should be taken in the morning and can be taken with food. They should be swallowed with liquid and should not be chewed.

Duration of therapy:

The duration of treatment is not limited. It depends upon the nature and severity of the disease. The treatment with EMCOR must not be stopped abruptly since this might lead to a transitory worsening of the condition. Especially in patients with ischaemic heart disease, treatment must not be discontinued suddenly. Gradual reduction of the daily dose if recommended.

Special populations

Renal or hepatic impairment

Treatment of stable chronic heart failure

There is no information regarding pharmacokinetics of bisoprolol in patients with both chronic heart failure and impaired hepatic or renal function. Uptitration of the dose in these populations should therefore be made with additional caution.

Treatment of hypertension or angina pectoris

In patients with liver or kidney function disorders of mild to moderate severity, no dosage adjustment is normally required. In patients with severe kidney function disorders (creatinine clearance < 30 ml/min) and in patients with severely impaired liver function a daily dose of 10 mg EMCOR should not be exceeded.

There is only limited experience with the use of EMCOR in dialysis patients. There are no indications of the necessity to alter the dose regimen.

Elderly

No dosage adjustment is required in elderly patients.

Children

There is no paediatric experience with EMCOR Therefore, its use cannot be recommended for children below 18 years, (see section 4.3).

4.3 Contraindications

Bisoprolol is contra-indicated in patients with:

- hypersensitivity to bisoprolol or to any of the excipients of EMCOR (see section 6.1)
- acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
- cardiogenic shock
- AV block of second or third degree (without a pacemaker)
- sick sinus syndrome
- sinoatrial block
- symptomatic bradycardia
- symptomatic hypotension
- severe bronchial asthma
- peripheral arterial occlusive disease and Raynaud's syndrome
- phaeochromocytoma before full alpha blockade is achieved (see section 4.4)
- metabolic acidosis
- pregnancy (see Pregnancy and lactation.)
- children below 18 years (see section 4.2).

4.4 Special warnings and precautions for use

Applies only to chronic heart failure

The treatment of stable chronic heart failure with bisoprolol has to be initiated with a special titration phase (see section 4.2).

Applies only to angina pectoris and hypertension

Especially in patients with ischaemic heart disease the cessation of therapy with bisoprolol must not be done abruptly unless clearly indicated, because this may lead to transitional worsening of heart conditions including angina pectoris, and/or rebound hypertension (see section 4.2.).

Applies to all indications

Discontinuation of therapy should be gradual, and patients should be advised to limit the extent of their physical activity during the period in which the medicine is being discontinued.
EMCOR must be used with caution in patients with hypertension or angina pectoris and accompanying heart failure.

EMCOR must be used with caution in:

- Concomitant treatment with inhalation anaesthetics.
- Diabetes mellitus with large fluctuations in blood glucose values, as symptoms and signs of hypoglycaemia can be masked, as well as the body’s reaction to hypoglycaemia may be reduced.
- Strict fasting.
- Ongoing desensitisation therapy. As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Epinephrine (adrenaline) treatment may not always yield the expected therapeutic effect.
- First degree AV block.
- Prinzmetal’s angina; Cases of coronary vasospasm have been observed. Despite its high $beta_1$-selectivity, angina attacks cannot be completely excluded when bisoprolol is administered to patients with Prinzmetal's angina. Utmost caution must be exercised.
- Peripheral arterial occlusive disease (intensification of complaints might occur especially during the start of therapy)

EMCOR may aggravate the symptoms of peripheral arterial occlusive disease (PAOD) or Raynaud's syndrome (due to unopposed arteriolar alpha-sympathetic activation). Severe peripheral vascular disease and even peripheral gangrene may be precipitated.

- General anaesthesia

  In patients undergoing general anaesthesia, beta-blockade reduces the incidence of dysrhythmias and myocardial ischaemia during induction and intubation, and in the post-operative period. It is recommended that maintenance beta-blockade be continued peri-operatively. The anaesthetist must be aware of beta-blockade, because of the potential for interactions with other medicines, resulting in bradydysrhythmias, attenuation of reflex tachycardia and the decreased reflex ability to compensate for blood loss. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

Applies only to chronic heart failure

The initiation of treatment of stable chronic heart failure with bisoprolol necessitates regular monitoring.

There is no therapeutic experience of bisoprolol treatment in heart failure in patients with the following diseases and conditions:

- insulin-dependent diabetes mellitus (type I)
- severely impaired renal function
- severely impaired hepatic function
- restrictive cardiomyopathy
- congenital heart disease
- haemodynamically-significant organic valvular disease
- myocardial infarction within 3 months

Digitalisation of patients receiving long-term EMCOR therapy 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.

Applies only to all indications

Asthma and Chronic Obstructive Pulmonary Disease

Although cardioselective (beta$_1$) beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers, these should be avoided in patients with obstructive airways diseases, unless there are compelling clinical reasons for their use. Where such reasons exist, EMCOR may be used with caution. In bronchial asthma or other chronic obstructive lung diseases, which may cause symptoms, bronchodilating therapy should be given concomitantly. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of β_2-stimulants may have to be increased.

Psoriasis

Patients with psoriasis or with a history of psoriasis should only be given bisoprolol after carefully balancing the benefits against the risks.

Phaeochromocytoma

In patients with phaeochromocytoma, bisoprolol must not be administered until after alpha-receptor blockade.

Thyrotoxicosis

Under treatment with bisoprolol, the symptoms of a thyrotoxicosis may be masked.

Clonidine

Caution should be exercised when transferring a patient from clonidine. The withdrawal of clonidine

may result in the release of large amounts of catecholamines, which may give rise to a hypertensive crisis.

If beta-blockers are administered in these circumstances, the unopposed alpha receptor stimulation may potentiate this effect.

If a beta-blocker and clonidine are given concurrently, the clonidine should not be discontinued until several days after the withdrawal of the beta-blocker, as severe rebound hypertension may occur.

4.5 Interaction with other medicines and other forms of interaction

Combinations not recommended

- *Calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type:* Negative effect on contractility and atrio ventricular conduction. Intravenous administration of verapamil in patients on EMCOR treatment may lead to profound hypotension and atrio-ventricular block.
- *Class I antidysrhythmic medicines (e.g. quinidine, disopyramide; lidocaine, phenytoin; flecainide, propafenone):* Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased. (In patients with chronic heart failure)
- Centrally acting antihypertensive medicines (e.g. clonidine, methyldopa, moxonodine): Concomitant use of centrally acting antihypertensive medicines may lead to a further reduction in heart rate and cardiac output and to vasodilation. Abrupt withdrawal may increase the risk of “rebound hypertension”.

Combinations to be used with caution

- *Calcium antagonists of the dihydropyridine type (e.g. nifedipine, amlodipine):*
- Concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.
- *Class-III antidysrhythmic medicines (e.g. amiodarone):*

  Effect on atrio-ventricular conduction time may be potentiated.

- *Topical beta-blockers* (e.g. eye drops for glaucoma treatment) may add to the systemic effects of EMCOR.
- *Parasympathomimetic medicines*: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.
- *Insulin and oral antidiabetic medicines:* Increase of blood sugar lowering effect. Blockade of beta-adrenoceptors may mask symptoms of hypoglycaemia (see section 4.4).
- *Anaesthesia:* Attenuation of the reflex tachycardia and increase of the risk of hypotension.
- *Digoxin:* Decrease in heart rate, lengthening of atrio-ventricular conduction time.
- *Non-steroidal anti-inflammatory drugs (NSAIDs):* NSAIDs may reduce the hypotensive effect of EMCOR
- *Beta-sympathomimetics medicines (e.g. isoprenaline, dobumamine):* Combination with EMCOR may reduce the effect of both agents. Higher doses of epinephrine (adrenaline) may be necessary for treatment of allergic reactions.
- Sympathomimetics that activate both beta- and alpha-adrenoceptors [e.g. norepinephrine (noradrenaline), epinephrine (adrenaline)]:
- Combination with EMCOR may unmask the alpha-adrenoceptor-mediated vasoconstrictor effect of these medicines leading to blood pressure increase and exacerbated intermittent claudication.
- Concomitant use with other antihypertensive medicines or with other medicinal products with blood pressure lowering potential (e.g. tricyclic antidepressants, barbiturates, phenothiazines) may increase the risk of hypotension.

Combinations to be considered

- *Mefloquine:* Increased risk of bradycardia.
- *Monoamine oxidase inhibitors (except MAO-B inhibitors):* Enhanced hypotensive effect of the beta-blockers but also risk of hypertensive crisis.

- *Rifampicin:* Slight reduction of the half-life of bisoprolol possible due to the induction of hepatic drug-metabolising enzymes. Normally no dosage adjustment is necessary.
- *Ergotamine derivatives:* Exacerbation of peripheral circulatory disturbances.

  In high-dose salicylate administration the toxic effect of salicylates on the central nervous system may be enhanced.

4.6 Fertility, pregnancy and lactation

Pregnancy

EMCOR should not be used in pregnancy.

Safety in pregnancy has not been established (see section 4.3).

EMCOR has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn.

Beta-adrenoceptor blockers such as EMCOR reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour.

Adverse effects (e.g. hypoglycaemia, hypotonia, bradycardia and cardiovascular collapse) may occur in the foetus and newborn infant.

Lactation

EMCOR may be excreted in human milk. Therefore, mothers on treatment with EMCOR should not breastfeed their infants.

Fertility

No human data on fertility are known for the combination product.

4.7 Effects on ability to drive and use machines

In a study with coronary heart disease patients, bisoprolol did not impair driving performance. However, depending on the individual patients' response to treatment, the ability to drive a vehicle

or to use machines may be impaired. This needs to be considered particularly at the start of treatment, upon change in medication, or in conjunction with alcohol.

4.8 Undesirable effects

Tabulated summary of adverse reactions

Frequencies are defined as follows: very common: > 1/10; common ≥ 1/100, < 1/10; uncommon: ≥ 1/1000, < 1/100; rare: ≥ 1/10 000, < 1/1000; very rare: < 1/10 000

Investigations

Rare increased triglycerides, increased liver enzymes (ALAT, ASAT).

Psychiatric disorders

Uncommon sleep disorders, depression, restlessness

Rare nightmares, hallucinations

Nervous system disorders

Common dizziness, headache

Eye disorders

Rare reduced tear flow (to be taken into consideration in patients wearing contact lenses)

Very rare conjunctivitis

Ear and labyrinth disorders

Rare hearing impairment

Cardiac disorders

Very common bradycardia (in patients with chronic heart failure)

Common worsening of pre-existing heart failure (in patients with chronic heart failure)

Uncommon AV-conduction disturbances, worsening of pre-existing heart failure (in patients with hypertension or angina pectoris), bradycardia (in patients with hypertension or angina pectoris)

Vascular disorders

Common feeling of coldness or numbness in the extremities, hypotension

Uncommon orthostatic hypotension, Raynaud's phenomenon, peripheral gangrene.

Frequency not known syncope

Respiratory, thoracic and mediastinal disorders

Uncommon bronchospasm in patients with bronchial asthma or a history of obstructive airways disease

Rare allergic rhinitis

Gastrointestinal disorders

Common gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation

Hepatobiliary disorders

Rare hepatitis

Skin and subcutaneous tissue disorders

Rare hypersensitivity reactions (pruritis, flush, rash and angioedema)

Very rare activation or worsening of psoriasis or inducing a psoriasis-like rash, alopecia

Musculoskeletal and connective tissue disorders

Uncommon muscle weakness, muscle cramps, myopathy

Reproductive system and breast disorders

Rare erectile dysfunction

General disorders and administration site conditions

Common asthenia (in patients with chronic heart failure), fatigue

Uncommon asthenia (in patients with hypertension or angina pectoris)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit /risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reaction to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) & eReporting platform (who-umc.org) found on SAHRPA website.

4.9 Overdose

Symptoms

In overdose, side effects will be exacerbated and exaggerated (see section 4.8).

With overdose third degree AV-block, bradycardia, hypotension and dizziness have been reported**.**

The most common signs expected with overdosage of a beta-blocker such as EMCOR are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia.

Treatment

There is a wide interindividual variation in sensitivity to one single high dose of EMCOR and patients with heart failure are very sensitive. It is mandatory to initiate the treatment of these patients with a gradual uptitration according to the scheme given in the dosage and directions for use.

Cases of mild overdose should be observed for at least four hours, as apnoea and cardiovascular collapse may appear suddenly. Repeated activated charcoal is necessary in severe overdose.

If overdose occurs, treatment with EMCOR should be stopped and supportive and symptomatic treatment should be provided. Limited data suggest that bisoprolol is hardly dialysable. Based on the expected pharmacologic actions and recommendations for other beta-blockers, the following general measures should be considered when clinically warranted:

- *Bradycardia:* Atropine may be used to treat severe bradycardia. If the response is inadequate, glucagon may be given intravenously. Alternatively, dobutamine or isoprenaline may be required to reverse beta-blockade. Transvenous cardiac pacing may be required for severe bradycardia.
- *Hypotension:* Intravenous fluids and vasopressors should be administered. Intravenous glucagon may be useful.
- *AV block (second or third degree):* Patients should be carefully monitored and treated with isoprenaline infusion or transvenous cardiac pacemaker insertion.
- *Acute worsening of heart failure*: Administer i.v. diuretics, inotropic agents, vasodilating agents.
- *Bronchospasm:* Bronchospasm should be treated with IV aminophylline or inhaled, or IV beta-agonist, e.g. salbutamol.
- *Hypoglycaemia:* Administer i.v. glucose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 6.1 Cardiac Stimulants

Bisoprolol is a $ß_1$-selective beta-adrenoceptor antagonist with low $ß_2$-receptor affinity. It has no intrinsic sympathomimetic activity nor membrane-stabilising properties. It reduces blood pressure, and by blockade of the cardiac $ß_1$-receptors, reduces heart rate and depresses plasma renin levels.

5.2 Pharmacokinetic properties

The kinetics of bisoprolol are linear and independent of age.

Absorption

Because of its moderate hepatic metabolism, it is subject only to a very small hepatic first pass metabolism. Therefore, bisoprolol displays a high bioavailability of 90 % after an oral dose and absorption is not affected by food. Tmax varies from 1 – 4 hours.

Distribution

The plasma protein binding of bisoprolol is about 30 %. The distribution volume is 3,5 l/kg. Total clearance is approximately 15 l/h.

Biotransformation

In man, 50 % of a dose is metabolised in the liver while the other 50 % is eliminated unchanged via the kidneys. None of the metabolites have $ß_1$-receptor blocking action.

Elimination:

Bisoprolol is absorbed after oral administration in man and excreted predominantly via the urine as unaltered substance and metabolites. The plasma elimination half-life is 10-12 hours, resulting in a duration of action of 24 hours.

Pharmacokinetics in special populations

In patients with chronic heart failure (NYHA stage III) the plasma levels of bisoprolol are higher and the half-life is prolonged compared to healthy volunteers. Maximum plasma concentration at steady state is 64±21 ng/ml at a daily dose of 10 mg and the half-life is 17± 5 hours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

anhydrous calcium hydrogen phosphate; crospovidone, maize starch, magnesium stearate, microcrystalline cellulose, anhydrous silica colloidal.

Film coating

dimethicone 100, hypromellose, iron oxide, macrogol 400, titanium dioxide.

6.2 Incompatibilities

None

6.3 Shelf life

EMCOR 2,5 tablets: 3 years

EMCOR 5 tablets: 5 years

EMCOR 10 tablets: 5 years

6.4 Special precautions for storage

Store at or below 25 °C in airtight containers and protect from light.

Blisters should not be removed from the carton until they are required for use.

6.5 Nature and contents of container

PVC/Aluminium blisters containing 30 tablets.

6.6 Special precautions for disposal and other handling

Any unused (including expired) product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Merck (Pty) Ltd

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8 REGISTRATION NUMBERS

EMCOR 2,5 tablets: 51/6.1/1021

EMCOR 5 tablets: 51/6.1/1022

EMCOR 10 tablets: 51/6.1/1023

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 February 2020

10 DATE OF REVISION OF THE TEXT

17 October 2025