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In all cases the dose regimen is adjusted individually by your doctor, in particular according to the pulse rate and therapeutic success.

The maximum recommended dose is 20mg bisoprolol fumarate once daily.

Treatment of stable chronic heart failure
The initiation of treatment of stable chronic heart failure with Safcor necessitates a special titration phase and requires regular monitoring by the doctor.

Preconditions for treatment with bisoprolol fumarate are:
- Stable chronic heart failure without acute failure during the past six weeks,
- Mainly unchanged basic therapy during the past two weeks,
- Treatment at optimal dose with an ACE inhibitor (or other vasodilator in case of intolerance to ACE inhibitors) and a diuretic, and optionally cardiac glycosides.

It is recommended that the treating physician be experienced in the management of chronic heart failure.

The treatment of stable chronic heart failure with bisoprolol fumarate is initiated according to the following titration scheme, individual adaptation may be necessary depending on how well the patient tolerates each dose, i.e. the dose is to be increased only, if the previous dose is well tolerated.

1st week : 1.25mg bisoprolol fumarate once daily (Safcor 2.5mg half (□) a tablet).
2nd week : 2.5mg bisoprolol fumarate (Safcor 2.5mg one (1) tablet) once daily.
3rd week : 3.75mg bisoprolol fumarate (Safcor 2.5mg one and a half (1□) tablets) once daily.
4th - 7th week : 5mg bisoprolol fumarate (Safcor 5mg one (1) tablet) once daily.
8th - 11th week : 7.5mg bisoprolol fumarate (Safcor 5mg one and a half (1□) tablets) once daily.
12th week and beyond : 10mg bisoprolol fumarate (Safcor 10mg one (1) tablet) once daily as maintenance treatment.

The maximum recommended dose is 10mg bisoprolol fumarate once daily. Patients should be titrated to and maintained at this dose unless prevented by adverse effects.
After initiation of treatment with 1.25mg bisoprolol fumarate once daily. Patients should be observed over a period of approximately 4 hours (especially as regards blood pressure, heart rate, conduction disturbances, signs of worsening of heart failure).
During the titration phase or thereafter, transient worsening of heart failure, fluid retention, hypotension or bradycardia may occur. In this case it is recommended first to reduce the dose of bisoprolol fumarate. Bisoprolol fumarate should be discontinued only if clearly necessary, but its reintroduction and/or uptitration should always be considered when the patient becomes stable again.

Duration of treatment for all indications
Treatment with Safcor is generally a long-term therapy.
The treatment may be interrupted if necessary and reintroduced as appropriate.
Do not stop treatment abruptly or change the recommended dose without talking to your doctor first since this might lead to a transitory worsening of heart condition. Especially in patients with ischaemic heart disease, treatment must not be discontinued suddenly. If discontinuation is necessary, the dose is gradually decreased.

Special populations
Renal or hepatic impairment:
- 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 renal impairment (creatinine clearance < 20 ml/min) and in patients with severe hepatic impairment a daily dose of 10mg bisoprolol fumarate must not be exceeded.

- Treatment of stable chronic heart failure: There is no information regarding pharmacokinetics of bisoprolol fumarate in patients with chronic heart failure and concomitant hepatic or renal impairment. Titration of the dose in these populations must therefore be made with particular caution.

Elderly:
No dosage adjustment is required.

Administration
Safcor tablets are taken in the morning with or without food. They are swallowed with some liquid and not to be chewed.

Overdose
The most frequent signs of Safcor overdose include slow heart rate (bradycardia), marked drop in blood pressure, acute heart failure, hypoglycaemia and bronchospasm. In the case of suspected Safcor overdose, please inform your doctor immediately. Depending on the degree of overdose your doctor can then decide which measures to take. In general, if overdose occurs, bisoprolol fumarate treatment is stopped and supportive and symptomatic treatment is provided. Limited data suggest that bisoprolol fumarate is hardly dialysable.

Storage and Stability
Store below 30ºC.
Protect from light and moisture.
Keep out of the reach of children.

How Supplied
Safcor Tablets 2.5mg are available in Alu Alu pack of 14 Tablets.
Safcor Tablets 5mg are available in Alu Alu pack of 14 Tablets.
Safcor Tablets 10mg are available in Alu Alu pack of 14 Tablets.

ہدایات:
دوا ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
روشنی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے پر ہی فروخت کریں۔

Saffron
Pharmaceuticals (Pvt.) Ltd.
19 Km. Sheikhupura Road, Faisalabad-Pakistan.
Tel: +92-41-2423914-18, Fax: +92-41-2423919
E-mail: info@saffronpharma.com
www.saffronpharma.com

Safcor

Tablets
2.5mg
5mg
10mg

(Bisoprolol Fumarate B.P)

سیف کور

۲.۵ ملی گرام
۵ ملی گرام
۱۰ ملی گرام

(بِسوپرولول فیوماریٹ بی۔پی)

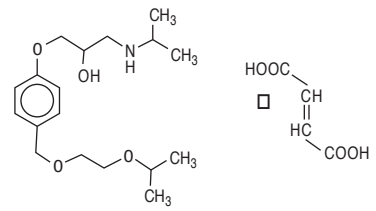
Composition:

SAFCOR Tablets 2.5 mg
Each film coated tablet contains:
Bisoprolol fumarate B.P……. 2.5 mg

SAFCOR Tablets 5 mg
Each film coated tablet contains:
Bisoprolol fumarate B.P……. 5 mg

SAFCOR Tablets 10 mg
Each film coated tablet contains:
Bisoprolol fumarate B.P……. 10 mg

Description:
Bisoprolol fumarate is the INN for (±)-1-{[**α**-(2-isopropoxyethoxy)-p-tolyl] oxy]-3-(isopropylamino)-2- propanol fumarate. It is a recemate and as a derivative of phenoxyaminopropanol, it belongs to the class of therapeutic substances, which are known as the Beta-blockers. The structural formula is as follows:



The molecular weight is 383.48; the white crystalline substance melts at 101°C. Bisoprolol fumarate is very freely soluble in water and methanol and freely soluble in ethanol and chloroform. Bisoprolol is less lipophilic than propranolol but more lipophilic than atenolol. This middle position is the determinant factor for the virtually ideal pharmacokinetic profile of bisoprolol.

Pharmacological Properties:
Pharmacodynamics
Bisoprolol Fumarate, the active ingredient of SAFCOR, is a beta 1-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilizing activity. It only shows very low affinity to the beta2-receptor of the smooth muscles of bronchi and vessels as well as to the beta2-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and beta2-mediated metabolic effects. Its beta 1-selectivity extends beyond the therapeutic dose range.

Pharmacokinetics
Absorption: Bisoprolol Fumarate is almost completely (>90%) absorbed from the gastrointestinal tract and, because of its small first pass metabolism of approximately 10%, has a bioavailability of approximately 90% after oral administration. The bioavailability is not affected by food intake. Bisoprolol shows linear kinetics and the plasma concentrations are proportional to the administered dose over the dose range 5 to 20 mg. Peak plasma concentrations occur within 2-3 hours.
Distribution: Bisoprolol Fumarate is extensively distributed. The volume of distribution is 3.5 L/kg. Binding to plasma proteins is approximately 30%.

Metabolism: Bisoprolol Fumarate is metabolized via oxidative pathways with no subsequent conjugation. All metabolites, being very polar, are renally eliminated. The major metabolites in human plasma and urine were found to be without pharmacological activity. In vitro data from studies in human liver microsomes show that bisoprolol fumarate is primarily metabolized via CYP3A4 (~95%) with CYP2D6 having only a minor role.

Elimination: The clearance of bisoprolol fumarate is 'balanced' between renal elimination of the unchanged molecule (~50%) and hepatic metabolism (~50%) to metabolites, which are also renally excreted. The total clearance of bisoprolol is approximately 15 l/h. Bisoprolol Fumarate has an elimination half-life of 10-12 hours.

Indication:
SAFCOR Tablets 5 mg, SAFCOR Tablets 10mg
- Treatment of high blood pressure (hypertension).
- Treatment of Coronary Heart disease (angina Pectoris).

SAFCOR Tablets 2.5 mg, Safcor Tablets 5 mg, Safcor Tablets 10 mg
- Treatment of stable chronic moderate to severe heart failure with reduced systolic ventricular function (ejection fraction 35%, based on echocardiography) in addition to ACE inhibitors, and diuretics, and optionally cardiac glycoside.

Contraindications:
SAFCOR must not be used in patients with:
- Acute heart failure or during episodes of heart failure decompensation requiring intravenous therapy with substances increasing the contractility of the heart,
- Shock induced by disorders of cardiac function (cardiogenic shock),
- Severe disturbances of atrioventricular conduction (second or third degree AV block) without a pacemaker,
- Sick sinus syndrome,
- Sinoatrial block,
- Slowed heart rate, causing symptoms
- Decreased blood pressure, causing symptoms
- Severe bronchial asthma or severe chronic obstructive pulmonary disease,
- Severe forms of peripheral arterial occlusive disease or Raynaud's syndrome,
- Untreated tumours of the adrenal gland (Phaeochromocytoma),
- Metabolic acidosis,

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- Hypersensitivity to bisoprolol fumarate or to any of the excipients (see composition).

Special warnings and precautions:
The following section describes when SAFCOR must be used with special caution:
- Diabetes mellitus with extremely fluctuating blood glucose level: symptoms of markedly reduced blood glucose (hypoglycaemia) such as tachycardia, palpitations or sweating can be masked,
- Strict fasting,
- Ongoing desensitization therapy,
- Mild disturbances of atrioventricular conduction (first degree AV block),
- Disturbed blood flow in the coronary vessels due to vasospasms (Prinzmetal's angina),
- Peripheral arterial occlusive disease (intensification of complaints may occur especially when starting therapy),
- Patients with a personal or family history of psoriasis.

Respiratory system: In bronchial asthma or other symptomatic chronic obstructive pulmonary diseases concomitant bronchodilator therapy is indicated. An increase in airway resistance may occasionally occur in patients with asthma, requiring a higher dose of beta2-sympathomimetics.

Allergic reactions: Beta-blockers, including SAFCOR, may increase the sensitivity to allergens and the severity of anaphylactic reactions because the adrenergic counter regulation under beta-blockade may be alleviated. Treatment with adrenaline may not always give the expected therapeutic effect.

General anaesthesia: In patients undergoing general anaesthesia the anaesthetist must be aware of beta-blockade. If it is thought necessary to withdraw SAFCOR before surgery, this should be done gradually and completed about 48 hours prior to anaesthesia.

Phaeochromocytoma: In patients with a tumour of the adrenal gland phaeochromocytoma) SAFCOR may only be administered after previous alpha-receptor blockade.

Thyrotoxicosis: Under treatment with SAFCOR the symptoms of a thyroid hyperfunction (thyrotoxicosis) may be masked.

Special Populations
So far no sufficient therapeutic experience is available for SAFCOR in patients with heart failure and concomitant insulin dependent type I diabetes mellitus, impaired kidney function (serum creatinine >3.4 mg/dl), impaired liver function, restrictive cardiomyopathy, congenital heart diseases or haemodynamically relevant organic valvular heart disease. No sufficient therapeutic experience is available either in patients with mild heart failure (NYHA II) as well as heart failure and myocardial infarction within the last 3 months.

There is insufficient experience with bisoprolol fumarate in children, therefore the use of SAFCOR recommended for children.

Effects on the ability to drive and use machines
In a study with patients suffering from coronary heart disease bisoprolol fumarate did affect the driving performance of the patients. However, due to individually different reactions, the ability to drive a vehicle or to operate machinery may be impaired. This needs to be considered particularly at the start of treatment, after change of dose, as well as in conjunction with alcohol.

Pregnancy and lactation
During pregnancy SAFCOR should only recommended following careful assessment of benefit-to-risk ratio by the doctor. In general, beta-blockers reduce placental blood flow and may affect the development of unborn child. Placental and uterine blood flow as well as the growth of the unborn child must be monitored and, in case of harmful effects on pregnancy or the foetus, alternative therapeutic measures considered.

The newborn infant must be monitored closely after delivery. Symptoms of reduced blood glucose and slowed pulse rate generally may occur within the first 3 days of life.

There are no data on the excretion of bisoprolol fumarate in human breast milk or the safety of bisoprolol fumarate exposure in infants. Therefore administration of SAFCOR is not recommended during breastfeeding.

Adverse effects:
The adverse effects described below are sorted according to system organ classes. Frequencies are classified as follows:
Very common (affects more than 1 person in 10)
Common (affects less than 1 person in 10)
Uncommon (affects less than 1 person in 100)
Rare (affects less than 1person in 1,000)
Very rare (affects less than 1 person in 10,000)

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

Cardiac disorders
Very common: bradycardia (in patients with chronic heart failure).
Common: worsening of pre-existing heart failure (in patients with hypertension or angina pectoris); worsening of pre-existing heart failure (in patients with hypertension or angina pectoris).
Nervous system disorders
Common: dizziness*, headache*.
Eye disorders
Rare: reduced tear flow (to be considered if the patient uses contact lenses).
Very rare: conjunctivitis.

Ear and labyrinth disorders
Rare: hearing disorders

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, diarrhea, constipation.

Skin and subcutaneous tissue disorders
Rare: hypersensitivity reactions such as itching, flush, rash.
Very rare: alopecia. Beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash.

Musculoskeletal and connective tissue disorders
Uncommon: muscle weakness, muscle cramps.

Vascular disorders
Common: feeling of coldness or numbness in the extremities, hypotension especially in patients with heart failure.
Uncommon: orthostatic hypotension.

General disorders
Common: asthenia (in patients with in patients with chronic heart failure), fatigue*
Uncommon: asthenia (in patients with hypertension or angina pectoris)

Hepatobilary disorders
Rare: hepatitis

Reproductive system and breast disorders
Rare: potency disorders

Psychiatric disorders
Uncommon: depression, sleep disorders
Rare: nightmares, hallucinations

Applies only to patients with hypertension or angina pectoris:

*These symptoms especially occur at the beginning of the therapy. They are generally mild and usually disappear within 1-2 weeks.

Tell your doctor if you notice any of the side effects listed above or any other unwanted or unexpected effects. To prevent serious reaction, speak to a doctor immediately if a side effect is severe, occurred suddenly or gets worse rapidly.

Interactions:
The effect and tolerability of medicines can be influenced by simultaneous intake of other medication. Such interactions can also occur if a short time has elapsed since the use of the other medication. Tell your doctor if you are taking any other medicine – even those not prescribed to you by a doctor.

Combinations not recommended
Treatment of stable chronic heart failure
Class-I antiarrhythmic medicines (e.g. quinidine, disopyramide, lidocaine, phenytoin; flecainide, propafenone) may increase the depressant effect of SAFCOR on atrio-ventricular impulse conduction and the contractility of the heart.

All indications
Calcium antagonists of the verapamil type to a lesser extent of the diltiazem type may lead to reduced contractility of the heart muscle and delayed atrio-ventricular impulse conduction when used concomitantly with SAFCOR. Especially intravenous administration of verapamil in patients on ß'df-blocker treatment may lead to profound hypotension and atrioventricular block.

Centrally acting blood pressure-lowering medicines (such as clonidine, methyldopa, moxonodine, rilmenidine) may lead to a reduction of heart rate and cardiac output, as well as to vasodilation due to a decrease in the central sympathetic tonus. Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of "rebound hypertension".

Combinations to be used with caution
Treatment of hypertension or coronary heart disease (angina pectoris)
Class-I antiarrhythmic medicines (e.g. quinidine, disopyramide, lidocaine, phenytoin; flecainide, propafenone) may increase the depressant effect of SAFCOR on atrio-ventricular impulse conduction and the contractility of the heart.

All indications
Calcium antagonists of the dihydropyridine type (e.g. nifedipine) may increase the risk of hypotension when used concomitantly with SAFCOR. An increased risk of further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

Class-III antiarrhythmic medicines (e.g. amiodarone) may increase the inhibitory effect of SAFCOR on atrio-ventricular impulse conduction.

Topical ß-blockers (e.g. eye drops for glaucoma treatment) may add to the systemic effects of SAFCOR.

Parasympathomimetic medicine may increase the inhibitory effect on atrio-ventricular impulse conduction and the risk of bradycardia when used concomitantly with SAFCOR.

The blood sugar lowering effect of insulin or oral antidiabetic medicines may be intensified. Warning signs of reduced blood glucose (hypoglycemia) – especially accelerated heart rate (tachycardia) – may be masked or suppressed. Such interactions are considered to be more likely with nonselective ß-blockers.

Anaesthetic agents may increase the risk of cardiodepressive actions of SAFCOR leading to hypotension (for further information on general anaesthesia see also section special warnings and precautions).

Cardiac glycosides (digitalis) may lead to an increase in impulse conduction time and thus reduction in heart rate when used concomitantly with SAFCOR.

Non-steroidal ant-inflammatory medicines (NSAIDs) may reduced the blood pressure-lowering effect of SAFCOR.

ß-Sympathomimetics (e.g. isoprenaline, dobutamine) used in combination with SAFCOR may lead to a reduced effect of both agents.

A combination of SAFCOR with sympathomimetics that activate both – and – adrenoceptor (e.g. noradrenaline, adrenaline) may intensify the – adrenoceptor-mediated vasoconstrictor effects of these agents leading to blood pressure increase and exacerbated intermittent claudication. Such interactions are considered to be more likely with nonselective-blockers.

Antihypertensive agents as well as other medicines with blood pressure lowering potential (e.g. tricyclic antidepressants, barbiturates, phenothiazines) may increase the blood pressure lowering effect of SAFCOR

Combinations to be considered
Mefloquine may increase the risk of decelerating the heart rate (bradycardia), if used in combination with Safcor.

Monoamine oxidase inhibitors (except MAO-ß inhibitors) may enhance the hypotensive effect of the beta-blockers. Concomitant use may also be a risk for hypertensive crisis.

Dosage and Administration
Treatment hypertension or angina pectoris