

1.3.1 Summary of product characteristics (SPC)

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1. NAME OF THE MEDICINAL PRODUCT

Cardex 5 mg film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains: Bisoprolol Fumarate 5 mg.
For a full list of excipients see Section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.

Beige colored heart shaped film coated tablets engraved with "HU" on one side and plain on the other side with break line on both sides.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of Hypertension

Treatment of stable chronic angina

Treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides (for additional information see section 5.1)

4.2 Posology and method of administration

Administration:

For oral use.

Cardex tablet should be taken in morning and can be taken with food in morning. They should be swallowed in liquid and should not be chewed.

Treatment of hypertension and chronic stable angina pectoris

Adults

The dosage should be individually adjusted. It is recommended to start with 5 mg per day. The usual dose is 10 mg once daily with a maximum recommended dose of 20 mg per day.

Patients with renal impairment

In patients with severe renal impairment (creatinine clearance < 20 ml/min) the dose should not exceed 10 mg once daily. This dosage may eventually be divided into halves.

Patients with severe liver impairment

No dosage adjustment is required, however careful monitoring is advised.

Elderly

No dosage adjustment is normally required. It is recommended to start with the lowest possible dose.

Children

There is no experience with bisoprolol in children, therefore its use cannot be recommended for children.

Discontinuation of treatment

Treatment should not be stopped abruptly (see section 4.4). The dosage should be diminished slowly by a weekly halving of the dose.

Treatment of stable chronic heart failure

Adults

Standard treatment of CHF consists of an ACE inhibitor (or an angiotensin receptor blocker in case of intolerance to ACE inhibitors), a beta-blocker, diuretics, and when appropriate cardiac glycosides. Patients should be stable (without acute failure) when bisoprolol treatment is initiated.

It is recommended that the treating physician 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 bisoprolol requires a titration phase

The treatment with bisoprolol is to be started with a gradual uptitration according to the following steps:

- 1.25 mg once daily for 1 week, if well tolerated increase to
- 2.5 mg once daily for a further week, if well tolerated increase to
- 3.75 mg once daily for a further week, if well tolerated increase to
- 5 mg once daily for the 4 following weeks, if well tolerated increase to
- 7.5 mg once daily for the 4 following weeks, if well tolerated increase to
- 10 mg once daily for the maintenance therapy.

The maximum recommended dose is 10 mg once daily.

Close monitoring of vital signs (heart rate, blood pressure) and symptoms of worsening heart failure is recommended during the titration phase. Symptoms may already occur within the first day 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, hypotension, or bradycardia reconsideration of the dosage of the concomitant medication is recommended. It may also be necessary to temporarily lower the dose of bisoprolol or to consider discontinuation.

The reintroduction and/or uptitration of bisoprolol should always be considered when the patient becomes stable again.

If discontinuation is considered, gradual dose decrease is recommended, since abrupt withdrawal may lead to acute deterioration of the patient's condition.

Treatment of stable chronic heart failure with bisoprolol is generally a long-term treatment.

Special population

Renal or hepatic impairment

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

Elderly

No dosage adjustment is normally required.

Children

There is no paediatric experience with bisoprolol, therefore its use cannot be recommended for children.

4.3 Contraindications

Cardex is contraindicated in chronic heart failure patients with:

- acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
- cardiogenic shock
- second or third degree AV block (without a pacemaker)
- sick sinus syndrome
- sinoatrial block
- Symptomatic bradycardia
- Symptomatic hypotension
- severe bronchial asthma or severe chronic obstructive pulmonary disease
- late stages of peripheral arterial occlusive disease and Raynaud's syndrome
- untreated phaeochromocytoma (see section 4.4)
- metabolic acidosis
- hypersensitivity to bisoprolol or to any of the excipients (See section 6.1)

4.4 Special warnings and precautions for use

Special warnings:

Applies only to chronic heart failure:

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

Applies to all indications:

Especially in patients with ischemic heart disease the cessation of therapy with bisoprolol must not be done abruptly unless clearly indicated, because this may lead to transition worsening of heart condition (See section 4.2).

Precautions:

Applies only to hypertension or angina pectoris:

Bisoprolol must be used with caution in patients with hypertension or angina pectoris and accompanying heart failure.

Applies only to chronic heart failure:

The initiation of treatment with bisoprolol necessitates regular monitoring. For posology and method of administration please (See section 4.2).

There is no therapeutic experience of bisoprolol treatment of 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

Applies to all indications:

Bisoprolol must be used with caution in:

- bronchospasm (bronchial asthma, obstructive airways diseases).

In bronchial asthma or other chronic obstructive lung diseases, which may cause symptoms, bronchodilating therapy is recommended to be given concomitantly. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of beta2-stimulants may have to be increased.

- diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia (e.g. tachycardia, palpitations or sweating) can be masked.
- strict fasting
- ongoing desensitisation therapy

As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Adrenaline treatment does not always give the expected therapeutic effect.

- first degree AV block
- Prinzmetal's angina
- peripheral arterial occlusive disease (intensification of complaints might happen especially during the start of therapy)
- general anaesthesia

In patients undergoing general anaesthesia beta-blockade reduces the incidence of arrhythmias and myocardial ischemia during induction and intubation, and the post-operative period. It is currently 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 drugs, resulting in bradyarrhythmias, attenuation of the 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.

Patients with psoriasis or with a history of psoriasis should only be given beta-blockers (e.g. bisoprolol) after carefully balancing the benefits against the risks.

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

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

4.5 Interactions with other medicinal products and other forms of interaction

Combinations not recommended

Applies only to chronic heart failure:

- Class I antiarrhythmic drugs (e.g. quinidine, disopyramide; lidocaine, phenytoin; flecainide, propafenone): Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

Applies to all indications:

- Calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type: Negative influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients on β -blocker treatment may lead to profound hypotension and atrioventricular block.
- Centrally acting antihypertensive drugs such as clonidine and others (e.g. methyldopa, moxonidine, rilmenidine): Concomitant use of centrally acting antihypertensive drugs may worsen heart failure by a decrease in the central sympathetic tonus (reduction of

heart rate and cardiac output, vasodilation). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of “rebound hypertension”.

Combinations to be used with caution

Applies only to hypertension or angina pectoris:

Class-I antiarrhythmic drugs (e.g. quinidine, disopyramide; lidocaine, phenytoin; flecainide propafenone): Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

Applies to all indications

- Calcium antagonists of the dihydropyridine type such as felodipine and 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 antiarrhythmic drugs (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 bisoprolol.
- Parasympathomimetic drugs: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.
- Insulin and oral antidiabetic drugs: Increase of blood sugar lowering effect. Blockade of beta-adrenoreceptors may mask symptoms of hypoglycaemia.
- Anaesthetic agents: Attenuation of the reflex tachycardia and increase of the risk of hypotension (for further information on general anaesthesia see also section 4.4.).
- Digitalis glycosides: Reduction of heart rate, increase of atrio-ventricular conduction time.
- Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs may reduce the hypotensive effect of bisoprolol.
- β -Sympathomimetic agents (e.g. isoprenaline, dobutamine): Combination with bisoprolol may reduce the effect of both agents.
- Sympathomimetics that activate both β - and α -adrenoceptors (e.g. noradrenaline, adrenaline): Combination with bisoprolol may unmask the α -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 β -blockers.

- Concomitant use with antihypertensive agents as well as with other drugs 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 for hypertensive crisis.
- Rifampicin: Slight reduction of the half-life of bisoprolol due to the induction of hepatic drugmetabolising enzymes. Normally no dosage adjustment is necessary.
- Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

4.6 Fertility, pregnancy and lactation

Pregnancy Category C

Pregnancy:

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/newborn. In general, beta-adrenoceptor blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g. hypoglycaemia and bradycardia) may occur in the fetus and newborn infant. If treatment with beta-adrenoceptor blockers is necessary, beta1-selective adrenoceptor blockers are preferable.

Bisoprolol is not recommended during pregnancy unless clearly necessary. If treatment with bisoprolol is considered necessary, the uteroplacental blood flow and the fetal growth should be monitored. In case of harmful effects on pregnancy or the fetus alternative treatment should be recommended. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.

Lactation:

There are no data on the excretion of bisoprolol excreted in human milk. Therefore, breastfeeding is not recommended during administration of bisoprolol.

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, due to individual variations in reactions to the drug, the ability to drive a vehicle or to operate machinery may be impaired. This should be considered particularly at start of treatment and upon change of medication as well as in conjunction with alcohol.

4.8 Undesirable effects

The following definitions apply to the frequency terminology used hereafter:

Very common ($\geq 1/10$)

Common ($\geq 1/100, < 1/10$)

Uncommon ($\geq 1/1,000, < 1/100$)

Rare ($\geq 1/10,000, < 1/1,000$)

Very rare ($< 1/10,000$)

Psychiatric disorders:

Uncommon: sleep disorders, depression.

Rare: nightmares, hallucinations.

Nervous system disorders:

Common: dizziness*, headache*

Rare: syncope

Eye disorders:

Rare: reduced tear flow (to be considered if the patient uses lenses).

Very rare: conjunctivitis.

Ear and labyrinth disorders:

Rare: hearing disorders.

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 especially in patient with heart failure.

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 (such as itching, flush, rash).

Very rare: beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash, alopecia.

Musculoskeletal and connective tissue disorders:

Uncommon: muscular weakness and cramps.

Reproductive system and breast disorders:

Rare: potency disorders

General disorders:

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

Uncommon: asthenia (in patients with hypertension or angina pectoris)

Investigations:

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

Applies only to 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.

To report any side effect(s)

• Saudi Arabia:

National Pharmacovigilance and Drug Safety Center (NPC)

Fax: +966-11-205-7662

Call NPC at +966-11-2038222

Exts: 2317-2356-2353-2354-2334-2340

Toll free phone: 8002490000

E-mail: npc.drug@sfd.gov.sa

Website: www.sfda.gov.sa/npc

• Other GCC States:

Please contact the relevant competent authority.

4.9 Overdose

The most common signs expected with overdose of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. There is limited experience with overdose of bisoprolol, only a few cases of overdose with bisoprolol have been reported. Bradycardia and/or hypotension were noted. All patients recovered. There is a wide inter-individual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive.

In general, if overdose occurs, discontinuation of bisoprolol treatment and supportive and symptomatic treatment is recommended.

Based on the expected pharmacologic actions and recommendations for other beta-blockers, the following general measures may be considered when clinically warranted.

Bradycardia: Administer intravenous atropine. If the response is inadequate, isoprenaline or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transvenous pacemaker insertion may be necessary.

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 temporary pacing.

Acute worsening of heart failure: Administer i.v. diuretics, inotropic agents, vasodilating agents.

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, beta2-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

Limited data suggest that bisoprolol is hardly dialysable.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective

ATC Code: C07AB07

Cardex is a potent highly beta₁-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and without relevant membrane stabilising activity. It only shows 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 beta₁-selectivity extends beyond the therapeutic dose range.

Chronic heart failure:

In total 2647 patients were included in the CIBIS II trial. 83% (n = 2202) were in NYHA class III and 17% (n = 445) were in NYHA class IV. They had stable symptomatic systolic heart failure (ejection fraction $\leq 35\%$, based on echocardiography). Total mortality was reduced from 17.3% to 11.8% (relative reduction 34%). A decrease in sudden death (3.6% vs 6.3%, relative reduction 44%) and a reduced number of heart failure episodes requiring hospital admission (12% vs 17.6%, relative reduction 36%) was observed. Finally, a significant improvement of the functional status according to NYHA classification has been shown. During the initiation and titration of bisoprolol hospital admission due to bradycardia (0.53%), hypotension (0.23%), and acute decompensation (4.97%) were observed, but they were not more frequent than in the placebo-group (0%, 0.3% and 6.74%). The numbers of fatal and disabling strokes during the total study period were 20 in the bisoprolol group and 15 in the placebo group.

The CIBIS III trial investigated 1010 patients aged ≥ 65 years with mild to moderate chronic heart failure (CHF; NYHA class II or III) and left ventricular ejection fraction $\leq 35\%$, who had not been treated previously with ACE inhibitors, beta-blockers, or angiotensin receptor blockers. Patients were treated with a combination of bisoprolol and enalapril for 6 to 24 months after an initial 6 months treatment with either bisoprolol or enalapril.

There was a trend toward higher frequency of chronic heart failure worsening when bisoprolol was used as the initial 6 months treatment. Non inferiority of bisoprolol-first versus enalapril-first treatment was not proven in the per-protocol analysis, although the two strategies for initiation of CHF treatment showed a similar rate of the primary combined endpoint death and hospitalization at study end (32.4% in the bisoprolol-first group vs. 33.1% in the enalapril-first group, per-protocol population). The study shows that bisoprolol can also be used in elderly chronic heart failure patients with mild to moderate disease.

Hypertension or angina pectoris:

Bisoprolol is used for the treatment of hypertension and angina pectoris. As with other Beta-1-blocking agents, the method of acting in hypertension is unclear. However, it is known that Bisoprolol reduces plasma renin activity markedly.

Antianginal mechanism: Bisoprolol by inhibiting the cardiac beta receptors inhibits the response given to sympathetic activation. That results in the decrease of heart rate and contractility this way decreasing the oxygen demand of the cardiac muscle.

In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases.

5.2 Pharmacokinetic properties

Bisoprolol is absorbed almost completely from the gastrointestinal tract. Together with the very small first pass effect in the liver, this results in a high bioavailability of approximately 90%. The plasma protein binding of bisoprolol is about 30 %. The distribution volume is 3.5 l/kg. The total clearance is approximately 15 l/h.

The plasma elimination half-life (10-12 hours) provides 24 hours efficacy following a once daily dosage.

Bisoprolol is excreted from the body by two routes, 50 % is metabolised by the liver to inactive metabolites which are then excreted by the kidneys. The remaining 50 % is excreted by the kidneys in an unmetabolised form. Since elimination takes place in the kidneys and the liver to the same extent a dosage adjustment is not required for patients with impaired liver function or renal insufficiency.

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.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenicity..

Like other beta-blockers, bisoprolol caused maternal (decreased food intake and decreased body weight) and embryo/fetal toxicity (increased incidence of resorptions, reduced birth weight of the offspring, retarded physical development) at high doses but was not teratogenic.

6. Pharmaceutical particulars

6.1 List of excipients

- Microcrystalline Cellulose
- Starch
- Talc
- Colloidal Silicone Dioxide
- Magnesium Stearate
- Opadry
- Simethicone Emulsion
- Ferric Oxide Yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30 °C.

6.5 Nature and contents of container

Three Aluminum-PVC/PVDC blisters of 10 film coated tablets each, packed in a printed carton with folded leaflet.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. Marketing authorisation holder

Acino Pharma AG, Birsweg 2, 4253 Liesberg, Switzerland.

8. Marketing authorisation number(s)

9. Date of first authorisation/renewal of the authorisation

10. Date of revision of the text

August 2016