Cilnidipine 10 mg and Bisoprolol Fumarate 5 mg Tablets

CILACAR-B 5

NAME OF THE MEDICINAL PRODUCT
Cilnidipine 10 mg and Bisoprolol Fumarate 5 mg Tablets

DOSAGE FORMS AND STRENGTHS
Film coated tablets

COMPOSITION
Each film coated tablet contains:
Cilnidipine IP ..... 10 mg
Bisoprolol Fumarate IP ..... 5 mg
Excipients ..... q.s.
Colours: Red Oxide of Iron, Black Oxide of Iron & Titanium Dioxide IP

CLINICAL PARTICULARS-
THERAPEUTIC INDICATION
The FDC of Clinidipine & Bisoprolol is indicated for the treatment of essential hypertension associated with Coronary Artery Disease (CAD).

POSOLOGY AND METHOD OF ADMINISTRATION
The recommended dose is 1 tablet daily.
The dose can be increased upto 2 tablets per day to control blood pressure.

CONTRAINDICATIONS
Cilnidipine
Cilnidipine is contraindicated in the following patients:
- Patients with hypersensitivity to the active substance or to any of the excipients.
- Pregnant women or women having possibilities of being pregnant.

Bisoprolol fumarate
Bisoprolol is contraindicated in:
- hypersensitivity to the active substance or to any of the excipients.
- acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
- cardiogenic shock
- AV block of second or third degree
- sick sinus syndrome
- sinoatrial block
- symptomatic bradycardia
- symptomatic hypotension
- severe bronchial asthma or severe chronic obstructive pulmonary disease
- severe forms of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome
- untreated phaeochromocytoma
- metabolic acidosis.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Cilnidipine
Careful Administration (Cilnidipine should be administered with care in the following patients.): Patients with serious hepatic dysfunction [The plasma concentration may become elevated.] Patients with a history of serious adverse reactions to calcium antagonists.
Important Precautions:
- As it has been reported that sudden withdrawal of a calcium antagonist caused aggravation of certain symptoms. Therefore, if the discontinuation of cilnidipine is necessary, the dosage should be gradually decreased under close observation.
- If Cilnidipine is withdrawn from a daily dose of 5 mg, appropriate measures, such as replacement with other antihypertensive agents, should be taken.
- Direct the patient not to discontinue this drug without physician's instructions.

Bisoprolol fumarate
Special warnings:
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 condition.
Precautions:
Bisoprolol must be used with caution in patients with hypertension or angina pectoris and accompanying heart failure.
There is a risk of myocardial infarction and sudden death if the treatment is suddenly discontinued in patients with coronary heart disease.
Bisoprolol must be used with caution in:
- bronchospasm (bronchial asthma, chronic obstructive pulmonary disease (COPD))
  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, this medicinal product may be used with caution. In patients with obstructive airways diseases, the treatment with bisoprolol should be started at the lowest possible dose and patients should be carefully monitored for new symptoms (e.g. dyspnoea, exercise intolerance, cough). 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 beta$_2$-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. Epinephrine treatment may not always yield the expected therapeutic effect.
- AV block of first degree
- 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.
- peripheral arterial occlusive disease. Aggravation of symptoms may occur especially when starting therapy.
- General anaesthesia.

In patients undergoing general anaesthesia beta-blockade reduces the incidence of arrhythmias and myocardial ischaemia during induction and intubation, and the post-operative period. It is currently recommended that maintenance of beta-blockade should be continued peri-operatively. The anaesthetist must be aware of beta-blockade because of the potential for interactions with other medicinal products, 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-blocking agent 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-blocking agents (e.g. bisoprolol) after carefully balancing the benefits against the risks.
In patients with phaeochromocytoma bisoprolol must not be administered until after alpha-receptor blockade.
Under treatment with bisoprolol the symptoms of a thyrotoxicosis may be masked.
Combination of bisoprolol with calcium antagonists of the verapamil or diltiazem type, with Class I antiarrhythmic medicinal products and with centrally acting antihypertensive medicinal products is generally not recommended.

DRUG INTERATIONS
Cilnidipine
Cilnidipine is chiefly metabolized by the drug-metabolizing enzyme CYP3A4 and in part by CYP2C19.
Precautions for co-administration (Cilnidipine and the following drugs should be co-administered with care):
Other anti-hypertensive drugs, Digoxin, Cimetidine, Rifampicin, Antifungal azoles (Itraconazole, Miconazole etc), Grape fruit juice.

Bisoprolol fumarate
Combinations not recommended
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 medicinal products such as clonidine and others (e.g. methyldopa, moxonodine, rilmenidine): Concomitant use of centrally acting antihypertensive medicinal products 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-blocking agent discontinuation, may increase the risk of " rebound hypertension" .
Combinations to be used with caution
Class I antiarrhythmic medicinal products (e.g. quinidine, disopyramide; lidocaine, phenytoin; flecainide, propafenone): Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.
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 medicinal product (e.g. amiodarone): Effect on atrio-ventricular conduction time may be potentiated.
Topical beta-blocking agents (e.g. eye drops for glaucoma treatment) may add to the systemic effects of bisoprolol.
Parasympathomimetic medicinal products: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.
Insulin and oral antidiabetic medicinal products: Increase of blood sugar lowering effect. Blockade of beta-adrenoceptors may mask symptoms of hypoglycaemia.
Anaesthetic agents: Attenuation of the reflex tachycardia and increase of the risk of hypotension.
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 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-blocking agents, but also risk for 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.

USE IN SPECIAL POPULATIONS
Cilnidipine
Pregnancy-
Dosage should not be given to pregnant ladies or Expecting women. It is reported that on the Experiments on animals (Rats), Fetal Toxicity and postponement of pregnancy period & Delivery was observed.
Lactation-
It is advisable to avoid dosage to feeding mothers, in case of unavoidable reason, feeding to babies should be stopped. In case of Experiments on animals, it is observed that the dosage transfers to feeding milk.
Renal Impairment:
Repeated oral administration of Cilnidipine at a dose of 10 mg once a day for 7 days in patients with impaired renal function caused no differences in the pharmacokinetic profile compared with that in patients with normal renal function.
Pediatric use:
The safety of Cilnidipine in pediatric patients has not been established (no clinical experience).
Elderly patients:
Cilnidipine should be administered carefully under close observation of the patient's condition, taking such measures as starting with a lower dose (e.g. 5 mg). Use in the Elderly is generally acknowledged that the excessive hypotensive action should be avoided in the elderly.

Bisoprolol fumarate
Pregnancy
Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn. In general, beta-adrenoceptor blocking agents 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 foetus and newborn infant. If treatment with beta-adrenoceptor blocking agents is necessary, beta$_1$-selective adrenoceptor blocking agents are preferable.
Bisoprolol is not recommended during pregnancy unless clearly necessary. If treatment with bisoprolol is considered necessary, monitoring of the uteroplacental blood flow and the foetal growth is recommended. In case of harmful effects on pregnancy or the foetus consideration of alternative treatment is recommended.The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.
Breastfeeding
It is not known whether this medicinal product is excreted in human milk. Therefore, breastfeeding is not recommended during administration of bisoprolol.
Renal or hepatic impairment
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 liver function disorders it is recommended that a daily dose of 10 mg is not exceeded.
Experience with the use of bisoprolol in renal dialysis patients is limited. However, there is no evidence that the dosage regime needs to be altered.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Cilnidipine
The symptoms, such as dizziness may occur because of the hypotensive action from this drug.
Give warning against engaging in hazardous activities requiring alertness, such as working at a height, operating machinery or driving motor vehicles.

Bisoprolol fumarate
In a study with coronary heart disease patients bisoprolol did not impair driving performance. Depending on the individual patient's response the ability to drive a vehicle or to use machines may be impaired. This needs to be considered particularly at start of treatment, upon change of medication, or in conjunction with alcohol.

UMDESIRABLE EFFECTS
Cilnidipine
(1) Clinical significant adverse reactions:
- Hepatic function disorder and jaundice accompanied with increased AST (GOT), ALT (GPT) and γ-GTP may occur. Therefore, close observation should be made, and if any abnormality is observed, appropriate measures, such as discontinuation of cilnidipine, should be taken.
- Thrombocytopenia (incidence: <0.1 %): Since thrombocytopenia may occur, close observation should be made, and if any abnormality is observed, appropriate measures, such as discontinuation of cilnidipine, should be taken.

(2) Other adverse reactions –
If any of the following adverse reactions occur, appropriate measures should be taken depending on the symptoms.

	Less than 0.1 ~ 5%	**Less than 0.1%**	**Frequency unknown**
Hepatic	Increase in AST(GOT), ALT(GPT), LDH etc	ALP increased	
Renal	Increase in Creatinine or Urea Nitrogen, Urinary Protein positive	Urine Sediment present	
Psychoneurological	Headache, Headache dull, Dizziness, Dizziness on standing up, Shoulder muscle stiffness	Sleepiness, Insomnia, Tremor finger, Amnesia	Numbness
Cardiovascular	Flushed face, Palpitation, Feeling hot, ECG abnormal (ST depressed, inverted T waves), Decrease in blood pressure	Chest pain, cardiothoracic ratio increased, tachycardia, AV block, feeling cold	Extrasystole
Gastrointestinal	Nausea, Vomiting, Abdominal pain	Constipation, bloating, thirst, gingival hypertrophy, heartburn, diarrhea	
Hypersensitivity	Rash	Redness, Itching	Photosensitivity
Hematologic	Increase or decrease in WBC, Neutrophil, Hemoglobin	Increase or decrease in RBC, Hematocrit, Eosinophil, Lymphocytes	
Other	Oedema (Face, Lower leg etc), General Malaise, pollakiuria, Increase in serum cholesterol, Increase or decrease in CK (CPK), Uric acid, Serum potassium, and Serum phosphorus	Feeling of weakness, gastrocnemius muscle cramps, periophthalmic dryness, ocular hyperemia and feeling of irritation, dysgeusia, urine sugar positive, increase or decrease in fasting blood sugar, total protein, serum Ca and CRP, cough	Tinnitus

Bisoprolol fumarate
The following definitions apply to the frequency terminology used hereafter:
Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), Not known (cannot be estimated from the available data).
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 patients with heart failure)
Uncommon: Orthostatic hypotension
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 and angioedema
Very rare: beta-blocking agents may provoke or worsen psoriasis or induce psoriasis-like rash, alopecia
Musculoskeletal and connective tissue disorders
Uncommon: muscular weakness, muscle cramps
Reproductive system and breast disorders
Rare: erectile dysfunction
General disorders and administration site conditions
Common: fatigue*, asthenia (patients with chronic heart failure)
Uncommon: asthenia (in patients with hypertension or angina pectoris)
Investigations
Rare: increased triglycerides, increased liver enzymes (ALAT, ASAT)
* These symptoms especially occur at the beginning of the therapy in patients with hypertension or angina pectoris. They are generally mild and usually disappear within 1– 2 weeks.
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. Kindly report any suspected adverse reactions to pharmavigil@jbpharma.com

OVERDOSE
Cilnidipine
Overdosage of Cilnidipine may cause excessive reduction in blood pressure. If reduction in blood pressure is remarkable, appropriate measures such as lifting lower extremities, fluid therapy and administration of vasopressors should be taken. Hemodialytical removal of cilnidipine is not effective because of its high rate of protein-binding.

Bisoprolol fumarate
Symptoms
With overdose (e.g. daily dose of 15 mg instead of 7.5 mg) third degree AV-block, bradycardia, and dizziness have been reported. In general, the most common signs expected with overdose of a beta-blocking agent are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. To date a few cases of overdose (maximum: 2000 mg) with bisoprolol have been reported in patients suffering from hypertension and/or coronary heart disease showing bradycardia and/or hypotension; 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. Therefore, it is mandatory to initiate the treatment of these patients with a gradual uptitration.
Management
In general, if overdose occurs, bisoprolol treatment 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-blocking agents, the following general measures should 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 transvenous cardiac pacemaker insertion.
Acute worsening of heart failure: Administer i.v. diuretics, inotropic agents, vasodilating agents.
Bronchospasm: Administer bronchodilator therapy such as isoprenaline, beta$_2$-sympathomimetic medicinal products and/or aminophylline.
Hypoglycaemia: Administer i.v. glucose.

CLINICAL PHARMACOLOGY
PHARMACODYNAMICS
Cilnidipine
Antihypertensive Effect: In various hypertensive animal models (spontaneously hypertensive rats, renal hypertensive rats and dogs, DOCA salt hypertensive rats, and stroke-prone spontaneously hypertensive rats, a single oral dose of cilnidipine showed a gradual and long-lasting hypotensive action that was dose-dependent at 1 mg/kg or more. In contrast, it showed a weak hypotensive action in normotensive rats. The duration of the action was not prolonged by an excessive dosage. In renal hypertensive dogs, cilnidipine showed an additive effect when co-administered with a β-blocker or an angiotensin-converting enzyme (ACE) inhibitor.
In stroke-prone spontaneously hypertensive rats and renally hypertensive dogs, repeated oral doses of cilnidipine had a stable hypotensive action which did not show attenuation. Discontinuation of cilnidipine did not cause a rebound in blood pressure.
In conscious and unrestrained spontaneously hypertensive rats, cilnidipine did not increase the heart rate during hypotension. Cilnidipine did not increase the plasma noradrenaline level during hypotension, nor did it cause a significant decrease, which an adrenergic blocker (guanethidine sulfate) did. Cilnidipine did not cause orthostatic hypotension, although a ganglion blocker (pentolinium) did in a tilt test using rabbits.
In patients with essential hypertension, a single daily dose of cilnidipine showed an hypotensive action that maintained for 24 hours and was still evident early in the next morning. Power spectral analysis of the R-R intervals of 24 hours electrocardiogram revealed that cilnidipine did not increase sympathetic activity or the heart rate as a reflex response to the reduction of blood pressure.
Inhibitory Action on Stress-Induced Pressor Response: In conscious and unrestrained spontaneously hypertensive rats, cilnidipine inhibited the elevation of blood pressure and plasma norepinephrine levels induced by cold stress. Cilnidipine also inhibited the elevation of blood pressure induced by air jet stress (mental stress) in rats.
In healthy adult male volunteers whose blood pressure was elevated by ≥20% in cold stress test, cilnidipine suppressed the elevation of blood pressure induced by cold stress.
Inhibitory Action on Sympathetic Stimulation-Induced Pressor Response: In pithed spontaneously hypertensive rats, cilnidipine suppressed the elevation of blood pressure induced by electrical sympathetic stimulation.
In isolated and perfused mesenteric arterial vascular preparation in spontaneously hypertensive rats, cilnidipine also inhibited the release of norepinephrine induced by electrical sympathetic stimulation.
Effect on Cerebral Circulation: In spontaneously hypertensive rats, cilnidipine did not decrease cerebral blood flow even if the dose which decreases blood pressure by 30-40% in rats was administered. The auto-regulation of cerebral blood flow was satisfactorily maintained while the blood pressure was decreased.
In hypertensive patients complicated by cerebrovascular disease, the cerebral blood flow was maintained while blood pressure was lowered.
Effects on Cardiac Function: In dogs, cilnidipine decreased heart rate and myocardial contractility at a higher dose than that inducing an increased flow of arterial blood.
In anesthetized open chest dogs, cilnidipine decreased the myocardial oxygen consumption at dose inducing hypotension. At the time, it neither caused tachycardia nor affected cardiac contractility.
In patients with essential hypertension, cilnidipine did not affect heart rate while the blood pressure was decreased and in patients with abnormal cardiothoracic ratio (CTR), it improved the CTR.
Effects on Renal Function: In anesthetized spontaneously hypertensive rats, cilnidipine increased the urinary volume, renal blood flow and glomerular filtration rate at the dose inducing hypotension. Cilnidipine also increased the urinary volume, renal blood flow and glomerular filtration rate, when the renal function was depressed by endothelin.
In patients with essential hypertension, cilnidipine did not affect renal function while the blood pressure was decreased.
Effect on Cardiovascular Disturbance Associated with Hypertension: In stroke-prone spontaneously hypertensive rats, a single daily dose of cilnidipine suppressed the appearance of stroke and improved the survival rate. In addition, it lessened cardiac hypertrophy (increased heart weight), thickening of the ventricular wall, myocardial fibrosis and lesions in the kidney. Moreover, it depressed medial thickening in the coronary arterial wall and decreased calcium content in the aorta.
In patients with essential hypertension, cilnidipine decreased the atherosclerotic index and serum lipid peroxide.
Mechanism of Action:
Experimental data suggest that cilnidipine binds to the dihydropyridine binding sites of the L-type voltage dependent calcium channel and inhibits Ca^{2+} influx across the cell membranes of vascular smooth muscle cells via this channel (rabbits in vitro).
Consequently, vascular smooth muscle is relaxed, causing vasodilation. Through this mechanism, cilnidipine is considered to have a hypotensive action.
Cilnidipine inhibits Ca^{2+} influx via N-type voltage dependent calcium channels in the sympathetic nerve cell membrane. The inhibition of Ca^{2+} influx via N-type voltage dependent calcium channel was observed over a similar range of drug concentrations to those inhibiting L-type voltage dependent Ca^{2+} channels (rats in vitro).
Consequently, release of norepinephrine from sympathetic nerve terminals would be inhibited. Cilnidipine is considered to suppress the reflex increase in heart rate which may be mediated by sympathetic activation after blood pressure reduction and to inhibit stress-related hypertension through this mechanism

Bisoprolol fumarate
Mechanism of action
Bisoprolol is a highly beta$_1$-selective-adrenoceptor blocking agent, lacking intrinsic sympathomimetic and relevant membrane stabilising activity. It only shows low affinity to the beta$_2$-receptor of the smooth muscles of bronchi and vessels as well as to the beta$_2$-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and beta$_2$-mediated metabolic effects. Its beta$_1$-selectivity extends beyond the therapeutic dose range.
Bisoprolol is used for the treatment of hypertension, angina pectoris and heart failure. 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.
The indication heart failure was investigated in the CIBIS II trial. In total 2647 patients were included, 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 <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 ≤ 35%, who had not been treated previously with ACE inhibitors, beta-blocking agents, 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 a 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.
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.

PHARMACOKINETICS
Cilnidipine
Plasma Drug Levels:
When a single dose of cilnidipine 5 mg, 10 mg or 20 mg cilnidipine was orally administered to 6 healthy male volunteers, the C_{max} was found to be 4.7 ng/mL, 5.4 ng/mL and 15.7 ng/mL, respectively and the AUC_{0-24} to be 23.7ng·hr/mL, 27.5ng·hr/mL and 60.1ng·hr/mL, respectively. Thus, both parameters increased in a dose dependent manner.
When a single dose of cilnidipine 10 mg was repeatedly administered once a day to 6 healthy male volunteers, pharmacokinetic parameters of cilnidipine were indicated as follows.
The plasma concentration reached a steady-state from Day 4 of the administration and there was no evidence of the accumulation.
Metabolism and Excretion:
From the metabolites identified in the plasma and urine of healthy male volunteers, it is considered that the major route of cilnidipine metabolism is demethylation of the methoxyethyl group followed by hydrolysis of the cinnamyl ester and oxidation of the dihydropyridine ring. It is considered that CYP3A4 is mainly involved and CYP2C19 is partly involved in the demethylation of the methoxyethyl group (in vitro).
The calcium channel blocking action of the metabolite with the demethylated methoxyethyl group was only 1/00 of that of the parent compound (in rabbits).
When a single oral dose of cilnidipine 10 mg was repeatedly administered to healthy male volunteers once a day for 7 days, no unchanged compound of cilnidipine but 5.2% of the dose was excreted in the urine as metabolites. (The approved administration of cilnidipine is orally once a day after breakfast.)
An *in vitro* experiment showed that cilnidipine was 99.3% bound to human serum protein.

Bisoprolol fumarate
Absorption
Bisoprolol is absorbed and has a biological availability of about 90% after oral administration.
Distribution
The plasma protein binding of bisoprolol is about 30%. The distribution volume is 3.5 l/kg.
Biotransformation and elimination
Total clearance is approximately 15 l/h. The half-life in plasma of 10-12 hours gives a 24 hour effect after dosing once daily.
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.
Linearity/non-linearity
The kinetics of bisoprolol are linear and independent of age.
Special population
Since the 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. The pharmacokinetics in patients with stable chronic heart failure and with impaired liver or renal function has not been studied. 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.

NONCLINICAL TOXICOLOGY
Cilnidipine
No data available.

Bisoprolol fumarate
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenicity. Like other beta-blocking agents, bisoprolol caused maternal (decreased food intake and decreased body weight) and embryo/foetal toxicity (increased incidence of resorptions, reduced birth weight of the offspring, retarded physical development) at high doses, but was not teratogenic.

STORAGE AND HANDLING INSTRUCTIONS
Store at a temperature not exceeding 30°C. Protected from light and moisture.
Keep out of reach of children.

SHELF LIFE:
24 Months

PACKAGING INFORMATION
Blister of 10 & 4 Tablets

Marketed by & ® Regd. Trade Mark of:
J. B. CHEMICALS & PHARMACEUTICALS LTD.
Neelam Centre, 'B' Wing, Hind Cycle Road, Worli, Mumbai - 400 030, India.

Note: This prescribing information is applicable for India Market only

Date: April 2026