For the use of a Registered Medical Practitioner only

CILACAR®-M 10/50

℞ Cilnidipine and Metoprolol Succinate (ER) Tablets

WARNING: ISCHEMIC HEART DISEASE:

Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Metoprolol Succinate Extended-Release Tablet, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1 - 2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Metoprolol succinate extended release tablet administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Warn patients against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Metoprolol succinate extended release tablet therapy abruptly even in patients treated only for hypertension.

COMPOSITION

Each film coated bilayered tablet contains:

Cilnidipine IP…….....10 mg

Metoprolol Succinate IP

eq. to Metoprolol Tartrate……...50 mg

(in extended release form)

Colour: Ponceau 4R Lake

PHARMACEUTICAL FORM

Tablet

THERAPEUTIC INDICATION

Treatment of essential hypertension in adults.

POSOLOGY AND METHOD OF ADMINISTRATION

The recommended adult oral dosage of Cilacar M (FDC of Cilnidipine and Metoprolol Succinate IP) is one tablet per day.

Cilacar M may be administered in patients whose Blood Pressure (BP) is not adequately controlled with monotherapy of cilnidipine or metoprolol succinate.

CONTRAINDICATIONS:

FDC of Cilnidipine and Metoprolol Succinate is contraindicated in

- Hypersensitivity to the active substance, other calcium channel antagonists or to any of the excipients listed.
- Advanced Aortic stenosis
- Severe bradycardia, second or third degree heart block, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place).
- Pregnancy.

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.

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.

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.

Metoprolol Succinate

Ischemic Heart Disease

Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred when discontinuing chronically administered Metoprolol Succinate, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of 1 - 2 weeks and monitor the patient. If angina markedly worsens or acute coronary ischemia develops, promptly reinstate Metoprolol Succinate, and take measures appropriate for the management of unstable angina. Warn patients not to interrupt therapy without their physician's advice. Because coronary artery disease is common and may be unrecognized, avoid abruptly discontinuing Metoprolol succinate in patients treated only for hypertension.

Heart Failure

Worsening cardiac failure may occur during up-titration of Metoprolol Succinate. If such symptoms occur, increase diuretics and restore clinical stability before advancing the dose of Metoprolol Succinate. It may be necessary to lower the dose of Metoprolol Succinate or temporarily discontinue it. Such episodes do notpreclude subsequent successful titration of Metoprolol Succinate.

Bronchospastic Disease

PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of its relative beta1 cardio-selectivity, however, Metoprolol Succinate may be used in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Because beta1-selectivity is not absolute, use the lowest possible dose of Metoprolol Succinate. Bronchodilators, including beta2-agonists, should be readily available or administered concomitantly.

Pheochromocytoma

If Metoprolol Succinate is used in the setting of pheochromocytoma, it should be given in combination with an alpha blocker, and only after the alpha blocker has been initiated. Administration of beta-blockers alone in the setting of pheochromocytoma has been associated a paradoxical increase in blood pressure due to the attenuation of beta-mediated vasodilatation in skeletal muscle.

Major Surgery

Avoid initiation of a high-dose regimen of Metoprolol Succinate in patients undergoing non cardiac surgery, since such use in patients with cardiovascular risk factors has been associated with bradycardia, hypotension, stroke and death. Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery; however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Diabetes and Hypoglycemia

Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Hepatic Impairment

Consider initiating Metoprolol Succinate therapy at doses lower than those recommended for a given indication; gradually increase dosage to optimize therapy, while monitoring closely for adverse events.

Thyrotoxicosis

Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of beta-blockade may precipitate a thyroid storm.

Anaphylactic Reaction

While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge and may be unresponsive to the usual doses of epinephrine used to treat an allergic reaction.

Peripheral Vascular Disease

Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease.

Calcium Channel Blockers

Because of significant inotropic and chronotropic effects in patients treated with beta-blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be exercised in patients treated with these agents concomitantly.

DRUG INTERACTIONS:

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)

Name of the drug	Signs, Symptoms and Treatment	Mechanism and Risk factor
Other antihypertensive drugs	Blood pressure may be excessively lowered.	Additive or synergistic potentiation of the effect has been implicated
Digoxin	It has been reported that some other calcium antagonists (eg: Nifedipine) increased the plasma concentration of digoxin. If any toxic signs/symptoms attributable to digoxin (eg: nausea, vomiting, headache, abnormal vision, arrhythmia) are observed. Appropriate measure should be instituted such as digoxin dose adjustment or discontinuation of cilnidipine, depending on patients condition.	The mechanism is not completely clarified yet, but is thought to lie in decreased renal and extra renal clearances.
Rifampicin	It has been reported that effects of other Ca Antagonist (like Nifedipine etc.) were reduced.	It is generally thought that hepatic drug metabolizing enzyme (Cytochrome P-450) induced by rifampicin facilitates metabolism of Ca antagonists and thus increases the clearances of these agents.

Metoprolol Succinate

Catecholamine Depleting Drugs

Catecholamine depleting drugs (eg, reserpine, monoamine oxidase (MAO) inhibitors) may have an additive effect when given with beta-blocking agents. Observe patients treated with Metoprolol succinate plus a catecholamine depletor for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

CYP2D6 Inhibitors

Drugs that inhibit CYP2D6 such as quinidine, fluoxetine, paroxetine, and propafenone are likely to increase Metoprolol concentration. In healthy subjects with CYP2D6 extensive metabolizer phenotype, coadministration of quinidine 100 mg and immediate-release metoprolol 200 mg tripled the concentration of S-metoprolol and doubled the Metoprolol elimination half-life. In four patients with cardiovascular disease, coadministration of propafenone 150 mg t.i.d. with immediate-release metoprolol 50 mg t.i.d. resulted in two- to five-fold increases in the steady-state concentration of metoprolol. These increases in plasma concentration would decrease the cardio-selectivity of metoprolol.

Digitalis, Clonidine, and Calcium Channel Blockers

Digitalis glycosides, clonidine, diltiazem and verapamil slow atrioventricular conduction and decrease heart rate. Concomitant use with beta blockers can increase the risk of bradycardia. If clonidine and a beta blocker, such as metoprolol are co administered, withdraw the beta-blocker several days before the gradual withdrawal of clonidine because beta-blockers may exacerbate the rebound hypertension that can follow the withdrawal of clonidine.

If replacing clonidine by beta-blocker therapy, delay the introduction of beta-blockers for several days after clonidine administration has stopped.

USE IN SPECIFIC POPULATIONS:

Pregnancy and Lactation

The FDC of Cilnidipine and Metoprolol Succinate should not be administered to pregnant women or women having possibilities of being pregnant. It is advisable to avoid the administration of FDC of Cilacar M in nursing mothers.

Renal impairment:

No dose adjustment is needed for use of FDC of Cilnidipine and Metoprolol Succinate in patients with Renal impairment.

Hepatic impairment

Caution should be taken while using FDC of Cilnidipine and Metoprolol Succinate in patients with impaired hepatic function.

Pediatric Use

The safety and efficacy of FDC of Cilnidipine and Metoprolol Succinate in children and adolescents aged below 18 years have not been established.

Geriatric Use

The FDC of Cilnidipine and Metoprolol Succinate should be administered carefully under close observation in elderly patients.

UNDESIRABLE 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	
Gastrointestinal	Nausea, Vomiting, Abdominal pain	Constipation, bloating, thirst, gingival hypertrophy, heartburn, diarrhea	
Hypersensitivity	Rash	Redness, Itching	Photosensitivity
Hematologic	Up or down in WBC, Neutrophil, Hemoglobin	Up or down in RBC, Hematocrit, Eosinophil, Lymphocytes	
Other	Oedema (Face, Lower leg etc), General Malaise, pollakiuria, Increase in serum cholesterol, Up or down in CK (CPK), Uric acid, Serum K, and Serum P	Feeling of weakness, gastrocnemius muscle cramps, periophthalmic dryness, ocular hyperemia and feeling of irritation, dysgeusia, urine sugar positive, up or down in fasting blood sugar, total protein, serum Ca and CRP, cough	Tinnitus

Note 1): The patient should be carefully monitored for these symptoms and if any abnormality is noted, cilnidipine should be discontinued.

Note 2): If any such symptoms appear, cilnidipine should be discontinued.

Metoprolol Succinate

The following adverse reactions have been reported:

- Worsening angina or myocardial infarction.
- Worsening heart failure.
- Worsening AV block.

The most adverse reactions with Metoprolol Succinate in reported Clinical Trials are mild and transient. The adverse reactions reported with Metoprolol are tiredness, dizziness, depression, diarrhea, shortness of breath, bradycardia and rash.

Post Marketing Experience:

Cardiovascular: Cold extremities, arterial insufficiency (usually of the Raynaud type), palpitations, peripheral edema, syncope, chest pain and hypotension.

Respiratory: Wheezing (bronchospasm), dyspnea. Central Nervous System: Confusion, short-term memory loss, headache, somnolence, nightmares, insomnia, anxiety/nervousness, hallucinations, paresthesia.

Gastrointestinal: Nausea, dry mouth, constipation, flatulence, heartburn, hepatitis, vomiting.

Hypersensitive Reactions: Pruritus.

Miscellaneous: Musculoskeletal pain, arthralgia, blurred vision, decreased libido, male impotence, tinnitus, reversible alopecia, agranulocytosis, dry eyes, worsening of psoriasis, Peyronie's disease, sweating, photosensitivity, taste disturbance.

Potential Adverse Reactions: In addition, there are adverse reactions not listed above that have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Metoprolol Succinate.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional liability, clouded sensorium, and decreased performance on neuropsychometrics.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

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@jbcpl.com

OVERDOSE:

There is no experience of overdose with Cilnidipine and Metoprolol Succinate. Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects of individual ingredient.

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.

Metoprolol Succinate

Signs and Symptoms - Overdosage of Metoprolol succinate may lead to severe bradycardia, hypotension, and cardiogenic shock. Clinical presentation can also include: atrioventricular block, heart failure, bronchospasm, hypoxia, impairment of consciousness/coma, nausea and vomiting.

Treatment

Consider treating the patient with intensive care. Patients with myocardial infarction or heart failure may be prone to significant hemodynamic instability. Seek consultation with a regional poison control center and a medical toxicologist as needed. Beta-blocker overdose may result in significant resistance to resuscitation with adrenergic agents, including beta-agonists.

On the basis of the pharmacologic actions of metoprolol, employ the following measures. There is very limited experience with the use of hemodialysis to remove metoprolol, however metoprolol is not highly protein bound.

Bradycardia: Evaluate the need for atropine, adrenergic-stimulating drugs or pacemaker to treat bradycardia and conduction disorders.

Hypotension: Treat underlying bradycardia. Consider intravenous vasopressor infusion, such as dopamine or norepinephrine. Heart failure and shock: May be treated when appropriate with suitable volume expansion, injection of glucagon (if necessary, followed by an intravenous infusion of glucagon), intravenous administration of adrenergic drugs such as dobutamine, with α1 receptor agonistic drugs added in presence of vasodilation.

Bronchospasm: Can usually be reversed by bronchodilators.

CLINICAL PHARMACOLOGY:

Pharmacodynamic properties:

Pharmacological class: Antihypertensive

Experimental data suggest that cilnidipine binds to the dihydropyridine binding sites of the L-type voltage dependent calcium channel and inhibits Ca2+ 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 Ca2+ influx via N-type voltage dependent calcium channels in the sympathetic nerve cell membrane.

The inhibition of Ca2+ influx via N-type voltage dependent calcium channel was observed over a similar range of drug concentrations to those inhibiting L-type voltage dependent Ca2+ 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.

Metoprolol Succinate

Clinical pharmacology studies have confirmed the beta-blocking activity of metoprolol in man, as shown by (1) reduction in heart rate and cardiac output at rest and upon exercise, (2) reduction of systolic blood pressure upon exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia. Metoprolol is a beta1-selective (cardioselective) adrenergic receptor blocking agent. This preferential effect is not absolute, however, and at higher plasma concentrations, metoprolol also inhibits beta2-adrenoreceptors, chiefly located in the bronchial and vascular musculature. Metoprolol has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for beta-blockade. Animal and human experiments indicate that metoprolol slows the sinus rate and decreases AV nodal conduction.

The relative beta1-selectivity of metoprolol has been confirmed by the following: (1) in normal subjects, Metoprolol is unable to reverse the beta2-mediated vasodilating effects of epinephrine.

This contrasts with the effect of nonselective beta-blockers, which completely reverse the vasodilating effects of epinephrine. (2) In asthmatic patients, Metoprolol reduces FEV1 and FVC significantly less than a nonselective beta-blocker, propranolol, at equivalent beta1-receptor blocking doses.

Pharmacokinetics properties:

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 4.7ng/mL, 5.4 ng/mL and 15.7 ng/mL, respectively and the $AUC_{0\text{-}24}$ to be 23.7 night/mL, 27.5 ng•hr/mL and 60.1 ng•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.

Parameter Day of closing	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2(\alpha)}$ (hr)	$T_{1/2(\beta)}$ (hr)	$AUC_{0\text{-}inf}$ (ng•hr/mL)
Day 1	9.5 ± 1.6	2.8 ± 1.0	1.0 ± 0.2	5.2 ± 2.0	51.4 ± 12.7
Day 4	13.5 ±5.0	3.7 ± 0.8	-	-	101.8 ±29.0
Day 7	16.5 ±7.9	3.0 ± 1.3	1.1 ± 0.6	8.1 ± 2.7	95.5 ± 34.5

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.

Metoprolol succinate:

Adults: In man, absorption of metoprolol is rapid and complete. Plasma levels following oral administration of conventional metoprolol tablets, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism.

Metoprolol crosses the blood-brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration. Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin. Metoprolol is a racemic mixture of R- and S- enantiomers, and is primarily metabolized by CYP2D6. When administered orally, it exhibits stereoselective metabolism that is dependent on oxidation phenotype. Elimination is mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3 to 7 hours. Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no beta-blocking activity.

Following intravenous administration of metoprolol, the urinary recovery of unchanged drug is approximately 10%. The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in metoprolol succinate dosage is usually needed in patients with chronic renal failure. Metoprolol is metabolized predominantly by CYP2D6, an enzyme that is absent in about 8% of Caucasians (poor metabolizers) and about 2% of most other populations. CYP2D6 can be inhibited by a number of drugs. Poor metabolizers and extensive metabolizers who Page concomitantly use CYP2D6 inhibiting drugs will have increased (several-fold) metoprolol blood levels, decreasing metoprolol cardioselectivity.

In comparison to conventional metoprolol, the plasma metoprolol levels following administration of Metoprolol succinate are characterized by lower peaks, longer time to peak and significantly lower peak to trough variation. The peak plasma levels following once-daily administration of Metoprolol succinate average one-fourth to one-half the peak plasma levels obtained following a corresponding dose of conventional metoprolol, administered once daily or in divided doses. At steady state the average bioavailability of metoprolol following administration of Metoprolol succinate, across the dosage range of 50 to 400 mg once daily, was 77% relative to the corresponding single or divided doses of conventional metoprolol.

Nevertheless, over the 24-hour dosing interval, β1-blockade is comparable and dose-related the bioavailability of metoprolol shows a dose-related, although not directly proportional, increase with dose and is not significantly affected by food following Metoprolol succinate administration.

INCOMPATIBILITIES:

Not Applicable.

PACKAGING INFORMATION

Blister of 4 Tablets & 10 Tablets.

STORAGE AND HANDLING INSTRUCTIONS

Store protected from light & moisture, at a temperature not exceeding 30°C.

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

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Note: This prescribing information is applicable for India Market only.