For the use of a Registered Medical Practitioner only

CILACAR® C

℞ Cilnidipine and Chlorthalidone Tablets

COMPOSITION

Each film coated tablet contains :

Cilnidipine IP ..... 10 mg

Chlorthalidone IP ..... 12.5 mg

Excipients ..... q.s.

Colours: Brilliant Blue FCF & Titanium Dioxide IP

PHARMACEUTICAL FORM

Film coated tablet

THERAPEUTIC INDICATION

Treatment of essential hypertension,

Cilacar C 12.5 may be administered in patients whose Blood Pressure (BP) is not adequately controlled with monotherapy of Cilnidipine or Chlorthalidone or dual therapy of lower doses.

POSOLOGY AND METHOD OF ADMINISTRATION

The recommended adult oral dosage of Cilacar C 12.5 mg is one tablet per day.

CONTRAINDICATIONS

FDC of Cilnidipine and Chlorthalidone is contraindicated in:

- Cardiogenic shock,
- recent MI or acute unstable angina,
- severe aortic stenosis,
- Anuria, Known hypersensitivity to Chlorthalidone or any of the excipients. Anuria, severe hepatic or renal failure (creatinine clearance <30ml/min),
- hypersensitivity to Chlorthalidone and other sulphonamide derivatives,
- refractory hypokalaemia, hyponatraemia and hypercalcaemia, symptomatic hyperuricaemia
- (History of gout or uric acid calculi),
- hypertension during pregnancy,
- untreated Addison's disease,
- Concomitant lithium therapy.

SPECIAL WARNINGS & 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- If Cilnidipine is withdrawn from a daily dose of 5 mg, appropriate measures, such as replacement with other antihypertensive agents, should be taken.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.

Effects on Ability to Drive and Operate Machine:

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.

Chlorthalidone

- Plasma electrolyte should be periodically determined in appropriate intervals to detect possible electrolyte imbalance especially hypokalaemia and hyponatraemia. Hypokalaemia and hyponatraemia may occur.
- Measurement of electrolytes is recommended, especially in the older patient, those receiving digitalis preparations for cardiac failure, those taking an abnormal (low in potassium) diet or those suffering from gastrointestinal complaints. Hypokalaemia may predispose to arrhythmias in patients receiving digitalis.
- Impaired glucose tolerance may occur and diabetic patients should be aware of the potential for increased glucose levels. Close monitoring of glycaemia is recommended in the initial phase of therapy and in prolonged therapy test for glucosuria should be carried out at regular intervals.
- In patients with impaired hepatic function or progressive liver disease, minor alterations in fluid and electrolyte balance may precipitate hepatic coma.
- Hyperuricaemia may occur. Only a minor increase in serum uric acid usually occurs but in cases of prolonged elevation, the concurrent use of a uricosuric agent will reverse the hyperuricaemia.

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 coadministered 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 measured 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 extrarenal clearances.
Cimetidine	It has been reported that the effect of other Ca Antagonist (eg: Nifedipine etc) were enhanced.	It is thought that cimetidine decreases the hepatic blood flow with the consequent suppression of the enzymatic metabolism of calcium antagonists in liver microsomes, and at the same time, cimetidine lowers gastric acid output and thus increases absorption of calcium antagonists
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.
Antifungal azoles: Itraconazole, Miconazole etc	The blood concentration of Cilnidipine may be elevated.	Antimycotic azoles are thought to inhibit CYP3A4, a drug metabolizing enzyme for Cilnidipine.
Grape Fruit Juice	It has been demonstrated that the plasma concentration of Cilnidipine is elevated.	Details of the underlying mechanism remain to be elucidated, but some constituents in grape fruit juice may inhibit CYP3A4, a drug metabolizing enzyme for Cilnidipine.

Chlorthalidone

Chlorthalidone may be combined with all medicinal products used for the treatment of hypertension, the action of which is potentiated by Chlorthalidone. It can also be combined with medicinal products used for the treatment of heart failure.

The administration of Chlorthalidone may affect the action of the following drugs:

Diuretics may reduce lithium excretion and thus increase its plasma levels. Since diuretics raise blood lithium levels, the latter must be monitored in patients under lithium therapy who are taking Chlorthalidone at the same time. Where lithium has induced polyuria, diuretics may exert a paradoxical antidiuretic effect.

Diuretics potentiate the action of curare derivatives.

Antihypertensive drugs action may be potentiated by diuretics (e.g. guanethidine, methyldopa, ß blockers, vasodilators, calcium antagonists, ACE inhibitors). The combination of diuretics and ACE inhibitors may lead to severe hypotension. It is recommended that the dosage of Chlorthalidone be reduced or administration interrupted 2 to 3 days prior to starting treatment with an ACE inhibitor and/or that this treatment be started with a low dose of the ACE inhibitor.

It may prove necessary to readjust the dosage of insulin and of oral antidiabetic agents due to the risk of reduction of the hypoglycaemic effect, caused by the possible reduction of insulin release by the pancreas due to the hypokalaemic effect.

Thiazide-induced hypokalaemia or hypomagnesaemia may favour the occurrence of digitalis induced cardiac arrhythmias.

Concurrent administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol, increase the risk of adverse effects caused by amantadine, enhance the hyperglycaemic effect of diazoxide, and reduce renal excretion of cytotoxic agents (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

Administration of thiazide diuretics with vitamin D or with calcium salts may potentiate the increase in serum calcium, due to an inhibition of urinary excretion.

The action of Chlorthalidone may be affected by the administration of the following drugs:

The hypokalaemic effect of diuretics may be increased by corticosteroids, ACTH, ß 2 –agonists, amphotericin, and carbenoxolone with risk of heart and/or muscle disorders.

Concomitant administration of certain non-steroidal anti-inflammatory drugs (e.g. indomethacin) may weaken the diuretic and antihypertensive activity of diuretics, and there have been isolated reports of a deterioration in renal function in predisposed patients.

The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and stomach-emptying rate.

Absorption of thiazide diuretics is impaired in the presence of anionic exchange resins such as cholestyramine. A decrease in the pharmacological effect may be expected.

Concomitant treatment with cyclosporine may increase the risk of hyperuricaemia and gout-type complications.

By analogy with all the other diuretics, it is noted that there is a decrease in the anticoagulant effect of oral anticoagulants when combined with Chlorthalidone.

Concomitant administration of ketanserin increases the risk of hypokalaemia and a prolonged QT interval.

USE IN SPECIAL POPULATIONS

Pregnancy and Lactation

The FDC of Cilacar C 12.5 should not be given to pregnant ladies and expecting women. It is advisable to avoid the administration of FDC of Cilacar C 12.5 in nursing mothers.

Renal impairment

No dose adjustment is required for use of FDC of Cilacar C 12.5 in patients with impaired renal function. FDC of Cilacar C is contraindicated in severe renal failure.

Hepatic impairment

FDC of Cilacar C 12.5 is contraindicated in patients with severe hepatic failure. Caution should be used in patients with impaired hepatic function.

Pediatric population

The safety and efficacy of FDC of Cilnidipine and Chlorthalidone in pediatric patients has not been established (no clinical experience).

Elderly (age 65 years or over)

Close medical observation is needed when treating patients of advanced age with FDC of Cilacar C 12.5.

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	
Psychoneurological	Headache, Headache dull, Dizziness, Dizziness on standing up, Shoulder muscle stiffness	Sleepiness, Insomnia, Tremor finger, Forgetfulness	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	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.

Chlorthalidone:

The following adverse drug reactions which have been derived from multiple sources, including post-marketing experience with Chlorthalidone are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. Frequency estimate: very rare < 0.01%; rare ≥ 0.01% to < 0.1%; uncommon ≥ 0.1% to < 1%; common ≥1% to < 10%; very common ≥10%, not known: cannot be estimated from the available data.

Blood and lymphatic system disorders

Rare: thrombocytopenia, leukopenia, agranulocytosis, and eosinophilia.

Immune system disorders

Not Known: Hypersensitivity to Chlorthalidone, other sulphonamide derivatives or any of the excipients.

Metabolism and nutrition disorders

Very common: mainly at higher doses, hypokalaemia, hyperuricaemia, and hyperlipidaemia.

Common: hyponatraemia, hypomagnesaemia, hyperglycaemia and decreased appetite.

Rare: hypercalcaemia, worsening of diabetic metabolic state, and gout.

Very rare: alkalosis hypochloraemic, alkalosis hypokalaemic.

Nervous system disorders

Common: dizziness, vertigo, weakness.

Rare: paraesthesia, headache.

Eye disorders

Rare: disturbances of vision.

Cardiac disorders

Rare: arrhythmia.

Vascular disorders

Common: orthostatic hypotension, which may be aggravated by alcohol, anaesthetics or sedatives.

Very rare: vasculitis.

Respiratory, thoracic and mediastinal disorders

Very rare: idiosyncratic/ non-cardiogenic pulmonary oedema.

Gastrointestinal disorders

Common: minor gastrointestinal distress.

Rare: mild nausea and vomiting, abdominal pain upper, constipation, and diarrhoea.

Very rare: pancreatitis.

Hepatobiliary disorders

Rare: cholestasis or jaundice.

Skin and subcutaneous tissue disorders

Common: urticaria and other forms of skin rash.

Rare: photosensitivity reaction.

Renal and urinary disorders

Rare: glycosuria.

Very rare: allergic tubulointerstitial nephritis.

Reproductive system and breast disorders

Common: erectile dysfunction.

Investigations

Very rare: blood cholesterol increased.

Interference with the results of diagnostic tests:

The concomitant administration of thiazide diuretics during the bentiromide test period will invalidate the results of it as thiazide diuretics are also metabolised to arylamines and therefore will increase the percentage of para amino benzoic acid (PABA) recovered.

And with physiological/laboratory values:

- Bilirubin
- Calcium
- Cholesterol, low-density lipoproteins and triglycerides
- Creatinine (serum concentrations may increase)
- Glucose in blood and urine
- Magnesium, potassium and sodium
- Protein-bound iodine (serum concentrations may decrease)
- Uric acid Calcium concentrations in urine (may decrease)

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 + Chlorthalidone. 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 no effective because of its high rate of protein-binding.

Chlorthalidone

Symptoms

In poisoning due to an overdosage the following signs and symptoms may occur: dizziness, nausea, somnolence, hypovolaemia, hypotension, and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.

Treatment

There is no specific antidote. Induction of vomiting or gastric lavage and administration of activated charcoal should be employed to reduce absorption if the patient is conscious. Blood pressure and fluid and electrolyte balance should be monitored and appropriate corrective measures taken. Intravenous fluid and electrolyte replacement may be indicated. Supplementation with artificial plasma may be required.

CLINICAL PHARMACOLOGY

Pharmacodynamic Properties

Mechanism of action

Cilnidipine

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.

Chlorthalidone

Pharmacotherapeutic group, ATC Code: Thiazide-type diuretic, C03BA04.

Chlorthalidone is a benzothiadiazine (thiazide)-related diuretic, chemically related to the sulphonamides, with a long duration of action. Thiazide and thiazide-like diuretics act primarily on the distal renal *tubule* (early convoluted part), inhibiting NaCl reabsorption (by antagonising the Na+-Cl- cotransporter) and promoting Ca++ reabsorption (by an unknown mechanism). The enhanced delivery of Na+ and water to the cortical collecting tubule and/or the increased flow rate leads to increased secretion and excretion of K+ and H+.

In persons with normal renal function, diuresis is induced after the administration of 12.5 mg Chlorthalidone. The resulting increase in urinary excretion of sodium and chloride and the less prominent increase in urinary potassium are dose dependent and occur both in normal and in oedematous patients. The diuretic effect sets in after 2-3 hours, reaches its maximum after 4-24 hours, and may persist for 2-3 days.

Thiazide-induced diuresis initially leads to decreases in plasma volume, cardiac output, and systemic blood pressure. The renin-angiotensin-aldosterone system may possibly become activated.

In hypertensive individuals, Chlorthalidone gently reduces blood pressure. On continued administration, the hypotensive effect is maintained, probably due to the fall in peripheral resistance; cardiac output returns to pre-treatment values, plasma volume remains somewhat reduced and plasma renin activity may be elevated.

On chronic administration, the antihypertensive effect of Chlorthalidone is dose dependent between 12.5 and 50 mg/day. Raising the dose above 50 mg increases metabolic complications and is rarely of therapeutic benefit.

As with other diuretics, when Chlorthalidone is given as monotherapy, blood pressure control is achieved in about half of patients with mild to moderate hypertension. In general, elderly and black patients are found to respond well to diuretics given as primary therapy. Randomised clinical trials in the elderly have shown that treatment of hypertension or predominant systolic hypertension in older persons with low-dose thiazide diuretics, including Chlorthalidone, reduces cerebrovascular (stroke), coronary heart and total cardiovascular morbidity and mortality. Combined treatment with other anti-hypertensives potentiates the blood-pressure- lowering effects.

In a large proportion of patients failing to respond adequately to monotherapy, a further decrease in blood pressure can thus be achieved. Because thiazide diuretics including Chlorthalidone reduce Ca++ excretion, they have been used to prevent the formation of recurrent renal calcium oxalate stones. In addition, bone loss in elderly women was reduced. Thiazide diuretics have been found to be useful in nephrogenic diabetes insipidus. The mechanism of action has not been elucidated.

Pharmacokinetic 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 4.7 ng/mL, 5.4 ng/mL and 15.7 ng/mL, respectively and the $AUC_{0\text{-}24}$ to be 23.7 ng•hr/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)**	**$T_{1/2}$ (α) (hr)**	**T1/2 (ß) (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.

Chlorthalidone

Chlorthalidone is administered orally. The drug is 75% bound to plasma proteins and is also highly bound to red blood cells (blood to plasma ratio 72.5), with carbonic anhydrase as the binding site. Chlorthalidone crosses the placenta and is distributed into human breast milk. The onset of action is about 2 hours, with peak effects occurring in 2—6 hours and the duration of action lasting 48-72 hours. The majority of the drug is excreted unchanged in the urine (50-74%), with some potential biliary excretion. The mean half-life of Chlorthalidone is approximately 40 to 60 hours.

Chlorthalidone is absorbed from the GI tract following oral administration, with a bioavailability of about 65%.

INCOMPATIBILITIES

Not Applicable.

PACKAGING INFORMATION

Blister of 4 tablets and 10 tablets

STORAGE AND HANDLING INSTRUCTIONS

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

Marketed by & ® Regd. Trade Mark of :
J. B. CHEMICALS & PHARMACEUTICALS LTD.
Neelam Centre, 'B' Wing, Hind Cycle Road,
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Note: This prescribing information is applicable for India Market only.