For the use of a Registered Medical Practitioner or a Hospital or a Laboratory

TORCILIN

Cilnidipine Tablets IP

COMPOSITION

TORCILIN 5

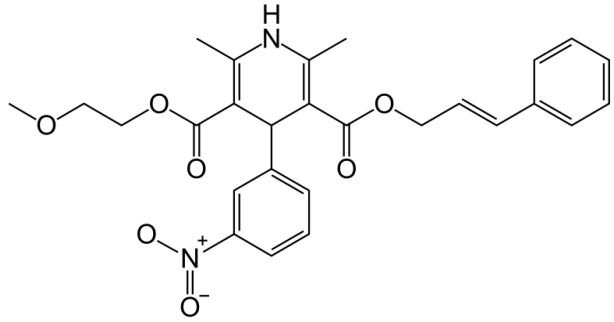
Each film coated tablet contains:
Cilnidipine IP…….5 mg
Excipients q.s.
Color: Titanium Dioxide I.P.

TORCILIN 10

Each film coated tablet contains:
Cilnidipine IP…….10 mg
Excipients q.s.
Color: Titanium Dioxide I.P.

DESCRIPTION:

Clinidipine is the novel calcium antagonist accompanied with L-type and N-type calcium channel blocking function and belonging to the chemical class O3-(2-methoxyethyl) O5-[(E)-3-phenylprop-2-enyl] 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine- 3,5-dicarboxylate. Clinidipine is crystalline powder of pale yellow which has not taste and smell. Its molecular formula is $C_{27}H_{28}N_2O_7$ and its molecular weight is 492.52. The structural formula is:



CLINICAL PHARMACOLOGY

Mechanism of Action

Unlike other calcium channel antagonists, cilnidipine blocks the influx of Ca2+ ions into both vascular smooth muscle at the level of L-type Ca^{2+} channels and neuronal cells at the level of N-type Ca2+ channels. The L-type Ca^{2+} channel blockade by cilnidipine affects predominantly vascular smooth muscle, thereby producing vasodilation of peripheral resistance vessels and coronary arteries. The blockade of N-type Ca^{2+} channels affect predominantly peripheral nerve endings of sympathetic neurons, thereby dilating blood vessels by lowering plasma catecholamine levels. Cilnidipine produced greater reductions in blood pressure in patients with hypertension than in healthy volunteers. Although increases in heart rate were noted in studies

with conventional L-type selective DHPs, the changes in heart rate with cilnidipine were negligible, even in patients with rapid blood pressure reduction. Thus, it appears that the hypotension-induced baroreflex sympathetic stimulation is attenuated by this inhibitory action on N-type Ca^{2+} channels and that even greater blood pressure-lowering effects are achieved with cilnidipine. Furthermore, cilnidipine antagonized the increase in blood pressure in response to acute cold stress, which is not usually depressed by L-type Ca2+ channel antagonists. Direct negative inotropic effects were not, however, detected in hypertensive patients who received cilnidipine.

Cilnidipine is a dihydropyridine calcium-channel blocker. It inhibits cellular influx of calcium, thus causing vasodilatation. It has greater selectivity for vascular smooth muscle. It has little or no action at the SA or AV nodes and -ve inotropic activity is rarely seen at therapeutic doses.

Pharmacokinetics

After oral administration, large amount of the drug could be detected in the gallbladder, bladder, liver and kidney. Approximately 18 %-29 % and 80 % of the dose was excreted in urine and feces, respectively within 72 h in dogs. The purpose of this experiment was to investigate the metabolism of cilnidipine in human liver microsomes *in vitro* and the effects of selective CYP450 inhibitors on the metabolism of cilnidipine in human liver microsomes and the major CYP450 isoform involved in the metabolism of cilnidipine.

INDICATION

Cilnidipine used for the treatment of mild to moderate hypertension.

DOSAGE:

Adult: 5-10 mg once daily, increase to 20 mg once daily if necessary.
Cilnidipine usually administered orally after breakfast 5 - 10mg once a day in adults.

CONTRAINDICATIONS

- Cilnidipine should not be administered in pregnant women and women suspected of being pregnant.

- Cardiogenic shock, recent MI or acute unstable angina and severe aortic stenosis.

- Cilnidipine should carefully administration in following patients: There is a possibility that the blood concentration raises patients with severe hepatic dysfunction and patients with a history of adverse reactions suffered from calcium antagonist.

- Special attention required when administered to patients with serious liver dysfunction because this agent is metabolized in the liver.

- Administration of calcium antagonists suddenly stop, the patients develop the symptoms have been reported. Hence, it was reduced gradually and requiring withdrawal of the agent is performed carefully monitored.

SPECIAL PRECAUTIONS

Sudden withdrawal may exacerbate angina. Discontinue in patients who experience ischemic pain, hypotension, poor cardiac reserve and heart failure following administration. Patient may feel dizziness due to decrease the pressure. So, do not work at height, drive a car or operate heavy machinery while taking this medicine. An ingredient in grapefruit juice may intensify the medicine's effect so avoid drinking grape fruit juice as much as possible.

DRUG INTERACTIONS

Other antihypertensives and antipsychotics that cause hypotension may modify insulin and glucose responses. Quinidine, carbamazepine, phenytoin, rifampicin, cimetidine and erythromycin are also interacted with the Cilnidipine.

ADVERSE DRUG REACTIONS

Skin, skin appendages failure: Desquamation, Quincke's edema, Hair loss, Hives, Pruritus**,** Erythema multiforme**,** Papule**,** Rash, Cutaneous dryness and Drying periocular.

Central-peripheral nervous system disorders: Stiff neck, Stiffness of muscle, Dizziness**,** Cool feeling, Disorientation, Headache, Sluggishness, Musculus gastrocnemius spasticity, Difficulty walking, Vertigo, Lightheadedness and Sense to hand vibration.

Impaired vision: Eye abnormalities and Hyperemia, irritation of eyes.

Special sensory impairment of other: Reduced sense of taste and Dysgeusia (bitter).

Mental disorder: Vaguely, Somnolence, Forget things and Insomnia.

Digestive tract disorders: Gastritis, Gastric ulcer, Gastrointestinal hemorrhage, Nausea and vomiting, Diarrhea, Stomatitis, Dry mouth, Gingival hypertrophy**,** Hemorrhagic gastritis**,** Brash, Anorexia, Stomach discomfort, Epigastric pain, Constipation, Sense of fullness in the abdomen and Periodontitis.

Liver and bile duct disorders: Liver dysfunction, Hepatocyte damage, Rise of AST, Elevation of ALT and Increase in serum bilirubin.

Metabolism and nutrition disorders: LDH rise, Serum inorganic phosphorus rise, Serum inorganic phosphorus reduction**,** CPK raise, CPK decline, Serum potassium rise, Decrease in serum potassium**,** Serum calcium rise, Fasting blood glucose level rise, Blood sugar levels**,** Serum cholesterol rise, Hyperlipidemia, Blood uric acid increased, Hyponatremia, Serum total protein rise, Urine sugar positive and Triglyceride rise.

Cardiovascular disorders (general): Heart failure, Reduction in blood pressure, ST depression, abnormal electrocardiogram, ST segment elevation, CRP rise, cardiothoracic ratio increase, Myocardial infarction, Heart rate, heart rhythm disorder, Atrioventricular block, Atrial tachycardia, Palpitation, Ventricular tachycardia, Atrial fibrillation, Tachycardia, T-wave

inversion, Blood vessels (cardiac) failure, Facial redness, Generalized redness and Transient ischemic stroke.

Respiratory Disorder: Respiratory failure, Pharynx different feeling, Sore throat, Throat burning sensation, Dyspnea, Cough and Epistaxis.

Blood disorder: Red blood cell disorder, Hemoglobin increase**,** Polycythemia, Anemia Erythropenia, Decreased hemoglobin, Hematocrit value decrease, Hematocrit increase, White blood cell-reticuloendothelial disorder, Variation of eosinophils, Eosinophilia, Leukopenia, Leukocytosis, Changes in neutrophil, Change (rod) neutrophil, Change (segmental) neutrophil, Changes in lymphocyte, Platelet-bleeding coagulopathy, Thrombocytopenia.

Urological disorder: Blood creatinine increased, renal function deterioration, renal failure, Uric protein rise, Urea nitrogen rise, Decrease in urinary volume, frequent urination, Urinary sediment (red blood cells) and Urine sediment (white blood cell).

General: Facial edema, Facial puffiness, Chest pain, Chest distress sense, Tightness of the chest, Bad mood**,** General malaise (feeling), Edema, glow of the face, Hot flushes, Face heat sensation, Weakness, Lower leg edema, Worsening heart failure, Feeling of warmth. Dizziness, flushing, headache, hypotension, peripheral oedema, tachycardia, palpitations, GI disturbances, increased micturition frequency, lethargy, eye pain, depression, ischaemic chest pain, cerebral or myocardial ischaemia, transient blindness, rashes, fever, abnormal liver function, gingival hyperplasia, myalgia, tremor and impotence.

EXPIRY DATE:
Do not use later than the date of expiry.

STORAGE:
Store Protected from light and moisture at a temperature not exceeding 30°C.

PRESENTATION
TORCILIN 5 and TORCILIN 10 are available in strip of 10 Tablets

MARKETED BY

TORRENT PHARMACEUTICALS LTD.
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IN/ TORCILIN 5,10mg/OCT-2018/02/PI