CILNIDIPINE

CILDINE®

10mg Film Coated Tablet
20mg Film Coated Tablet
CALCIUM CHANNEL BLOCKER

FORMULATION
Each film-coated tablet contains:
Cilnidipine 10mg
Cilnidipine 20mg

DESCRIPTION
10mg – Light orange to orange colored, circular, biconvex, film-coated tablets with break line on one side and plain on other side.
20mg – Light yellow to yellow colored, circular, biconvex, film-coated tablets with break line on one side and plain on other side.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamics
Mechanism of action
Cilnidipine is a dihydropyridine calcium-channel blocker. Cilnidipine binds to the dihydropyridine site of L-type voltage-dependent Ca channels present in vascular smooth muscle membranes and inhibits Ca^{2+} influx from L-type voltage-gated Ca channels. Inhibition of Ca^{2+} influx from L-type voltage-gated Ca channels in vascular smooth muscle induces vasorelaxation, a reduction in peripheral vascular resistance and a reduction in blood pressure.
Cilnidipine inhibits Ca^{2+} influx from N-type voltage-dependent Ca channels present in the cell membrane of the sympathetic nerves. In addition, Ca^{2+} influx from N-type and L-type voltage-gated Ca channel is suppressed almost equally in the same concentration range. Inhibition of Ca^{2+} influx from N-type voltage-gated Ca channels in sympathetic nerves inhibits release of noradrenaline from sympathetic nerve endings suppressing the increase in heart rate in response to lowering blood pressure (e.g., reflex tachycardia) and blood pressure increases during times of stress associated with elevated sympathetic nerve activity. Cilnidipine has little or no action at the SA or AV nodes and negative inotropic activity is rarely observed at the therapeutic doses.
Antihypertensive effect
The antihypertensive effects of Cilnidipine have been demonstrated in a number of hypertensive disease models including; spontaneously hypertensive rats, renal hypertensive rats and dogs, DOCA salt hypertensive rats, and spontaneously hypertensive rats with stroke. The antihypertensive effects of Cilnidipine were slow in onset, long lasting, and increased in a dose-dependent manner from 1mg/kg. The antihypertensive effect on normotensive rats was weak. Increased doing did not prolong blood pressure lowering effects of Cilnidipine. The blood pressure lowering effect of Cilnidipine is additive when combined with β-blockers, Angiotensin Converting Enzyme inhibitors, and Angiotensin II Receptor Blockers in renal hypertensive dogs.
Rebound hypertension was not observed upon withdrawal of treatment with Cilnidipine. Cilnidipine did not increase heart rate whilst lowering blood pressure after single dose tests in rats without spontaneous / unconstrained hypertension spontaneous syndrome.
In subjects with essential hypertension, Cilnidipine once daily by oral route, produced an antihypertensive effect lasting for 24 hours. Analysis of heartbeat frequency (RR interval) fluctuation over 24 hours showed no sympathetic nervous activity accompanying Cilnidipine associated blood pressure reduction and no increase in heart rate.
Inhibitory effect of pressurization by sympathetic nerve electrical stimulation
Cilnidipine suppressed blood pressure increases due to sympathetic stimulation in spontaneously hypertensive rats. Suppression of noradrenaline during sympathetic stimulation was suppressed in mesenteric arterial vascular perfusion specimens isolated from spontaneously hypertensive rats.
Effect on cerebral circulation
Cilnidipine did not reduce the cerebral blood flow even at doses showing a 30 to 40% reduction in blood pressure in spontaneously hypertensive rats.
In hypertensive patients with complications or cerebrovascular disease, cerebral blood flow was maintained despite reduction of blood pressure with Cilnidipine.
Effect on cardiac function
At doses, greater than usually employed for reducing blood pressure, Cilnidipine decreased heart rate and myocardial contraction force in dogs. Cilnidipine lowered myocardial oxygen consumption at antihypertensive doses in dogs but did not increase heart rate or suppress cardiac contractile force. In patients with essential hypertension, Cilnidipine did not affect pulse rate during blood pressure reduction and improves Cardiac Thoracic Ratio (CTR) in subjects with CTR abnormality.
Effect on kidney
Cilnidipine increased urine volume, the rate of renal blood flow and glomerular filtration rate at doses which reduce blood pressure in anesthetized spontaneously hypertensive rats. Furthermore, urine volume, the rate of renal blood flow and glomerular filtration rate were increased even when renal function was reduced with administration of endothelin. In patients with essential hypertension, Cilnidipine did worsen kidney function.
Effects on cardiovascular disorders associated with hypertension
Cilnidipine, administered orally once a day in rats with spontaneously stroke prone hypertension, delayed onset of cerebral hemorrhage and stroke, improved survival rate. Cilnidipine was also associated with a reduction in cardiac hypertrophy (increase in heart weight), thickening of the left ventricle wall, myocardium fibrosis, and improved pathology in the kidney. Furthermore, Cilnidipine inhibited thickening of coronary artery media and reduced the calcium content of the aorta. In patients with essential hypertension, Cilnidipine reduces arteriosclerosis index and serum lipid peroxidation.

Pharmacokinetics
Cilnidipine is absorbed from the small intestine. The time to maximum plasma concentration is 1.8 to 2.2 hours. It has a half-life of 7.5 hours. Cilnidipine is metabolized by the liver. 20% of the drug is eliminated in the urine and 80% in the feces.
Plasma concentration
After single oral administration of Cilnidipine 5mg, 10mg, and 20mg in 5 healthy adult male volunteers, C_{max} was 4.7 ng / mL, 5.4 ng / mL, and 15.7 ng / mL respectively. AUC 0 to 24 after single oral administration of Cilnidipine 5mg, 10mg, and 20mg, was 23.7 ng • hr / mL, 27.5 ng • hr / mL, and 60.1 ng • hr / mL, respectively. C_{max} and AUC 0 to 24 increased dose-dependently. The pharmacokinetic parameters with repeated administration of 10 mg Cilnidipine once a day in 6 healthy adult male patients is shown in Table 1. Steady State was achieved after day 4 of administration.
Table 1.

Number of days to be administered / parameter	C_{max} (ng / mL)	T_{max} (hr)	$T_{1/2}$ (β) (hr)	AUC $_{0-\infty}$ (ng • hr / mL)
Dosing Day 1	9.5 ± 1.6	2.8 ± 1.0	5.2 ± 2.0	51.4 ± 12.7
Day 4 of administration	13.5 ± 5.0	3.7 ± 0.8	-	101.8 ± 29.0
Dosing Day 7	16.5 ± 7.9	3.0 ± 1.3	8.1 ± 2.7	95.5 ± 34.5

(Mean ± standard deviation)

Plasma concentrations of Cilnidipine are increased in subjects with renal impairment (serum creatinine value: 1.5 to 3.1 mg / dL) relative to hypertensive subjects with normal renal function but are not clinically relevant.

Metabolism / Excretion
Cilnidipine undergoes demethylation of the methoxyethyl group, followed by hydrolysis of cinnamyl ester group and oxidation of dihydropyridine ring CYP3A4 is mainly involved in the demethylation reaction of the methoxyethyl group in the metabolic process, and CYP2C19 is involved in part (in vitro). The calcium antagonism of the demethylated form of the methoxyethyl group was 1/100 of that of Cilnidipine (rabbit). When 10 mg of Cilnidipine was repeatedly administered orally to healthy adult male for 7 days, no unchanged substance was detected in the urine, and 5.2% of the total dose was excreted as a metabolite. The human serum protein binding rate in vitro was 99.3%.
Impairment and Fertility
In animal experiments (rats), fetal toxicity and prolongation of gestation period and delivery time have been reported. Cilnidipine should not be administered to pregnant women. Cilnidipine was present in the milk of lactating rats. Cilnidipine is not recommended for use in whom are breast feeding children.

INDICATION
For the treatment of Essential Hypertension as monotherapy or in combination with other antihypertensive medications.

CONTRAINDICATIONS
Cilnidipine is contraindicated in patients with a history of hypersensitivity to Cilnidipine or any of the ingredients within tablets containing Cilnidipine.
Do not administer to pregnant women, lactating mothers or women who may be pregnant.

DOSAGE AND ADMINISTRATION
Adults: 10mg to 20mg of Cilnidipine tablet once daily after breakfast. Do not crush, chew, or dissolve this medication in water. Tablets should be taken whole with a glass of water. To achieve the best possible results, take the dose at the same time each day. Or as prescribed by the physician.
Elderly: Administration should be started at a low dose i.e., 5 mg and titrated upwards according to response.
Pregnant and Lactating women: Do not administer to pregnant women, women who may be pregnant or lactating women. In animal experiments (rats), fetal toxicity and prolongation of gestation period and delivery time have been reported. It is advisable to avoid administration to nursing women, but if it is inevitable to do so, breast feeding should be discontinued (Cilnidipine was present in the milk of lactating rats).
Children: Safety in low birth weight infants, neonates, infants, young children or children has not been established.

WARNINGS AND PRECAUTIONS
Caution should be observed when Cilnidipine is administered to patients with hypotension, poor cardiac reserve and heart failure, severe liver dysfunction, or history of severe adverse effects due to calcium antagonists. Sudden withdrawal of the drug may exacerbate angina. Cilnidipine must be discontinued in patients who experience ischemic pain following administration.

PREGNANCY AND LACTATION
Pregnancy Category C – Animal reproduction studies have shown adverse effects on the fetus and there are no adequate and well controlled studies in humans. Cilnidipine may be used in pregnancy only if the potential benefits justify the risk.
It is not known if Cilnidipine is secreted in human breast milk. A decision should be made to discontinue lactation, if the nursing mother needs to be prescribed Cilnidipine.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE
There are no data on the effects of Cilnidipine on the ability to drive or use machines. As with other calcium channel blockers, syncope, dizziness, hypotension, visual disturbances and blurred vision are known adverse reactions associated with the use of Cilnidipine. Patients should not drive a vehicle or operate a machine or perform tasks that require alertness if they experience these symptoms.

DRUG INTERACTIONS
Cilnidipine is mainly metabolized by drug metabolizing enzymes CYP3A4 and CYP2C19.
Laboratory interactions: False elevated spectrophotometric values of urinary vanillylmandelic acid may occur.
Cilnidipine may interact with other antihypertensive agents, aldesleukin, and antipsychotics which may cause hypotension. It may modify insulin and glucose responses. Interactions may occur with quinidine, carbamazepine, phenytoin, rifampicin, cimetidine, and erythromycin.

Drugs with Antihypertensive Action	Risk of Hypotension	Additive or synergistic action
Digoxin	It has been reported that other calcium antagonists (e.g., nifedipine) increase the concentration of digoxin in the blood. If digoxin intoxication symptoms (nausea vomiting, headache, visual abnormality, arrhythmia etc.) are observed, the dosage of digoxin should be adjusted or discontinued.	Although the mechanism has not been fully elucidated, it is believed that extrarenal clearance of digoxin is reduced.
Cimetidine	May enhance the antihypertensive effect of Cilnidipine.	Cimetidine reduces hepatic blood flow and inhibits CYP3A4 enzymes which metabolize Cilnidipine while decreasing gastric acid and increasing absorption of calcium antagonists.
Rifampicin	The antihypertensive of may be attenuated.	Rifampicin induces CYP3A4 and may promote metabolism and clearance of Cilnidipine.
Azole antifungal agents i.e., itraconazole, miconazole, etc.	May enhance the antihypertensive effect of Cilnidipine.	Azole antifungal agent inhibits CYP3A4, a drug metabolizing enzyme of Cilnidipine.
Grapefruit juice	May enhance the antihypertensive effect of Cilnidipine.	Mechanism of action is unknown but components contained in grapefruit juice likely suppress CYP3A4 activity which metabolizes Cilnidipine.

ADVERSE EFFECTS
Adverse reactions including abnormal variations in clinical laboratory values were observed in 414 of 5,958 patients (6.95%) in clinical and post marketing surveillance studies. Adverse effects associated with Cilnidipine included dizziness, flushing, headache, hypotension, peripheral edema,

tachycardia, palpitations, gastrointestinal disturbances. Increased frequency of micturition, lethargy, eye pain, depression, ischemic chest pain, cerebral or myocardial ischemia, transient blindness. Rashes, fever, abnormal liver function, gingival hyperplasia, myalgia, tremor, impotence may be seen. Serious adverse effects included liver dysfunction and jaundice with unknown frequency. Liver dysfunction accompanied by elevated AST (GOT), ALT (GPT), γ-GTP etc., jaundice may appear which should be observed thoroughly. If abnormality is found, discontinue administration and appropriate measures should be taken. Thrombocytopenia (<0.1%) may occur, administration should be discontinued and appropriate measures should be taken immediately if abnormalities are observed.

	Less than 0.1 to 5%	Less than 0.1%	Frequency unknown
Liver [1]	Elevated AST (GOT), ALT (GPT), LDH etc.	Increased Al – P	
Kidney	Creatinine, elevation of urea nitrogen, urine protein positive	Urine sediment positive	
Psychoneurotic	Headache, dizziness, shoulder stiffness	Drowsiness, insomnia, tremor, memory loss	Numbness
Circulatory organ	Facial flushing, palpitation, heat sensation, electrocardiogram abnormality (ST decline, T wave reversal), decrease blood pressure	Chest pain, increase in heart thoracic ratio, tachycardia, atrioventricular block, cold feeling	Extra systole, bradycardia
Digestive organ	Nausea, vomiting, abdominal pain	Constipation, abdominal bloating feeling, dry mouth, gingival hypertrophy, heartburn, diarrhea	
Hypersensitivity [2]	Rash	Redness, itching sensation	Light hypersensitivity
Blood	Variation of white blood cell count, neutrophils, hemoglobin	Variation of red blood cell count, hematocrit, eosinophil, lymphocyte	
Others	Edema (face, lower limb etc.), general malaise, frequent urination, elevation of serum cholesterol, changes in CK (CPK), uric acid, serum K, serum P	Weakness sensation, gall bladder spasm, dryness around the eyes, sense of hyperemia of eyes, dysgeusia, urine sugar positive, fasting blood glucose, total protein, serum Ca, CRP fluctuation, cough	Tinnitus

Liver[1]: Observe for such symptom and stop administration if abnormalities are observed. Hypersensitivity[2]: If such symptom develops, administration should be discontinued.

OVERDOSE AND TREATMENT
Overdosage with calcium channel blockers can cause confusion, dizziness, irregular heartbeat, nausea, slurred speech, or difficulty in breathing. Treatment must be instituted based on symptoms. Blood levels can be used to confirm elevated levels if the diagnosis is in doubt.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

STORE AT TEMPERATURES NOT EXCEEDING 30°C.

AVAILABILITY
Cilnidipine (Cildine®) 10mg Film-Coated Tablet in Alu-alu blister pack, box of 30's
Cilnidipine (Cildine®) 20mg Film-Coated Tablet in Alu-alu blister pack, box of 30's

CILDINE® is a registered trademark of Ajanta Pharma Philippines, Inc.

FOR SUSPECTED ADVERSE DRUG REACTION, REPORT TO THE FDA: www.fda.gov.ph
Seek medical attention immediately at the first sign of any adverse drug reaction.

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