Cilnidipine, and Chlorthalidone Tablets
Cilnikem CT 6.25/ Cilnikem CT 12.5

1. NAME OF THE MEDICINAL PRODUCT

Cilnikem CT6.25/ Cilnikem CT 12.5 (Cilnidipine, & Chlorthalidone Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Cilnikem CT 6.25

Each film coated tablet contains:

Cilnidipine .....10 mg
Chlorthalidone IP.....6.25 mg
Excipients.....q.s.

Cilnikem CT 12.5

Each film coated tablet contains:

Cilnidipine .....10 mg
Chlorthalidone IP.....12.5 mg
Excipients.....q.s.

3. PHARMACEUTICAL FORM

Film coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications:

Treatment of essential hypertension.

4.2 Posology and Method of Administration

General Considerations

Dose once daily.

The full blood pressure lowering effects are attained within 2 weeks after a change in dose. It may be taken with or without food.

Replacement Therapy

It may be substituted for its individually titrated components in patients controlled on stable doses of cilnidipine, and chlorthalidone taken at the same time.

Add-on/Switch Therapy

Fixed dose combination of cilnidipine, and chlorthalidone may be used to provide additional blood pressure lowering for patients not adequately controlled on maximally tolerated, labeled, or usual doses of any two of the following antihypertensive classes: calcium channel blockers (CCB), and diuretics.

Elderly (age 65 years or over)

Caution, including more frequent monitoring of blood pressure, is recommended in elderly patients. Very limited data are available on the use of this fixed dose combination in patients aged 75 years or older. Extreme caution, including more frequent monitoring of blood pressure, is recommended.

Renal impairment

The maximum dose of olmesartan medoxomil is 20 mg in patients with mild to moderate renal impairment (creatinine clearance of 30 - 60 mL/min), owing to limited experience of the 40 mg olmesartan medoxomil dosage in this patient group. Monitoring of serum concentrations of potassium and creatinine is advised in patients with moderate renal impairment. The use of fixed dose combination of cilnidipine, and chlorthalidone in patients with severe renal impairment (creatinine clearance < 30 mL/min) is contraindicated.

Hepatic impairment

Fixed dose combination of cilnidipine, and chlorthalidone should be used with caution in patients with mild hepatic impairment.

Fixed dose combination of cilnidipine, and chlorthalidone should not be used in patients with severe hepatic impairment, cholestasis or biliary obstruction.

Paediatric population

Fixed dose combination of cilnidipine, and chlorthalidone is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy.

4.3 Contraindications:

Contraindicated in patients with known hypersensitivity (e.g., anaphylaxis or angioedema) to cilinidipine or chlorthalidone any other component of this product.

Biliary obstruction.

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.

Known hypersensitivity to chlortalidone or any of the excipients.

Anuria, severe hepatic or renal failure (creatinine clearance <30ml/min), hypersensitivity to chlortalidone 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 and concomitant lithium therapy.

4.4 Special Warnings and Special Precautions for Use

Cilnidipine

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.

Administrations 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.

Chlorthalidone

Chlortalidone should be used with caution in patients with impaired hepatic function or progressive liver disease since minor changes in the fluid and electrolyte balance due to thiazide diuretics may precipitate hepatic coma, especially in patients with liver cirrhosis.

Chlortalidone should also be used with caution in patients with severe renal disease. Thiazides may precipitate azotaemia in such patients, and the effects of repeated administration may be cumulative.

Electrolytes:

Treatment with thiazide diuretics has been associated with electrolyte disturbances such as hypokalaemia, hypomagnesaemia, hyperglycaemia and hyponatraemia. Since the excretion of electrolytes is increased, a very strict low-salt diet should be avoided.

Hypokalaemia can sensitise the heart or exaggerate its response to the toxic effects of digitalis.

Like all thiazide diuretics, kaluresis induced by Chlortalidone is dose dependent and varies in extent from one subject to another. With 25 to 50mg/day, the decrease in serum potassium concentrations averages 0.5mmol/l. Periodic serum electrolyte determinations should be carried out, particularly in digitalised patients.

If necessary, Chlortalidone may be combined with oral potassium supplements or a potassium-sparing diuretic (eg triamterene).

If hypokalaemia is accompanied by clinical signs (eg muscular weakness, paresis and ECG alteration), Chlortalidone should be discontinued.

Combined treatment consisting of Chlortalidone and a potassium salt or a potassium-sparing diuretic should be avoided in patients also receiving ACE inhibitors.

Monitoring of serum electrolytes is particularly indicated in the elderly, in patients with ascites due to liver cirrhosis, and in patients with oedema due to nephrotic syndrome. There have been isolated reports of hyponatraemia with neurological symptoms (eg nausea, debility, progressive disorientation and apathy) following thiazide treatment.

For nephrotic syndrome, Chlortalidone should be used only under close control in normokalaemic patients with no signs of volume depletion.

Metabolic effects:

Chlortalidone may raise the serum uric acid level, but attacks of gout are uncommon during chronic treatment.

As with the use of other thiazide diuretics, glucose intolerance may occur; this is manifest as hyperglycaemia and glycosuria. Chlortalidone may very seldom aggravate or precipitate diabetes mellitus; this is usually reversible on stopping therapy.

Small and partly reversible increases in plasma concentrations of total cholesterol, triglycerides, or low-density lipoprotein cholesterol were reported in patients during long-term treatment with thiazides and thiazide-like diuretics. The clinical relevance of these findings is a matter for debate.

Chlortalidone should not be used as a first-line drug for long-term treatment in patients with overt diabetes mellitus or in subjects receiving therapy for hypercholesterolaemia (diet or combined).

As with all antihypertensive agents, a cautious dosage schedule is indicated in patients with severe coronary or cerebral arteriosclerosis.

Other effects:

The antihypertensive effect of ACE inhibitors is potentiated by agents that increase plasma renin activity (diuretics). It is recommended that the diuretic be reduced in dosage or withdrawn for 2 to 3 days and/or that the ACE inhibitor therapy be started with a low initial dose of the ACE inhibitor. Patients should be monitored for several hours after the first dose.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Cilnidipine

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.

Chlorthalidone

Diuretics potentiate the action of curare derivatives and antihypertensive drugs (e.g. guanethidine, methyldopa, β-blockers, vasodilators, calcium antagonists and ACE inhibitors).

The hypokalaemic effect of diuretics may be potentiated by corticosteroids, ACTH, ß2 – agonists, amphotericin and carbenoxolone.

It may prove necessary to adjust the dosage of insulin and oral anti-diabetic agents.

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

Concomitant administration of certain non-steroidal anti-inflammatory drugs (e.g. indometacin) may reduce the diuretic and antihypertensive activity of Chlortalidone; 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 (eg 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 colestyramine. A decrease in the pharmacological effect may be expected.

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 (eg cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

The pharmacological effects of both calcium salts and vitamin D may be increased to clinically significant levels if given with thiazide diuretics. The resultant hypercalcaemia is usually transient but may be persistent and symptomatic (weakness, fatigue, anorexia) in patients with hyperparathyroidism.

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

Thiazide and related diuretics can cause a rapid rise in serum lithium levels as the renal clearance of lithium is reduced by these compounds.

4.6 Fertility, Pregnancy and Lactation:

Cilnidipine

No data available with Cilnidipine in pregnancy and lactation. So this drug should be avoided in pregnancy and lactation.

Chloorthalidone

Diuretics are best avoided for the management of oedema or hypertension in pregnancy as their use may be associated with hypovolaemia, increased blood viscosity and reduced placental perfusion. There have been reports of foetal bone marrow depression, thrombocytopenia, and foetal and neonatal jaundice associated with the use of thiazide diuretics.

Chlortalidone passes into the breast milk; mothers taking Chlortalidone should refrain from breast-feeding their infants.

4.7 Effects on ability to drive and use machines

Patients should be warned of the potential hazards of driving or operating machinery if they experience side effects such as dizziness.

4.8 Undesirable Effects

Cilnidipine

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, Light headedness 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.

Chlorthalidone

Frequency estimate: very rare <0.01%, rare ≤0.01% to ≤0.1%;uncommon ≤0.1% to <1%; common ≤1% to <10%; very common ≥10%.

Electrolytes and metabolic disorders:

Very common: mainly at higher doses, hypokalaemia, hyperuricaemia, and rise in blood lipids.
Common: hyponatraemia, hypomagnesaemia and hyperglycaemia.
Uncommon: gout.
Rare: hypercalcaemia, glycosuria, worsening of diabetic metabolic state.
Very rare: hypochloraemic alkalosis.

Skin:

Common: urticaria and other forms of skin rash.
Rare: photosensitisation.

Liver:

Rare: intrahepatic cholestasis or jaundice.

Cardiovascular system:

Common: postural hypotension.
Rare: cardiac arrhythmias.

Central nervous system:

Common: Dizziness.
Rare: paraesthesia, headache.

Gastro-intestinal tract:

Common: loss of appetite and minor gastrointestinal distress.
Rare: mild nausea and vomiting, gastric pain, constipation and diarrhoea.
Very rare: pancreatitis.

Blood:

Rare: Thrombocytopenia, leucopenia, agranulocytosis and eosinophilia.

Other effects:

Common: impotence
Rare: Idiosyncratic pulmonary oedema (respiratory disorders), allergic interstitial nephritis

4.9 Overdose

Chlorthalidone

Signs and 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 to Chlortalidone. Gastric lavage, emesis or activated charcoal should be employed to reduce absorption. Blood pressure and fluid and electrolyte balance should be monitored and appropriate corrective measures taken. Intravenous fluid and electrolyte replacement may be indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties:

Cilnidipine

Unlike other calcium channel antagonists, cilnidipine blocks the influx of Ca2+ ions into both vascular smooth muscle at the level of L-type Ca2+ channels and neuronal cells at the level of Ntype Ca2+ channels. The L-type Ca2+ channel blockade by cilnidipine affects predominantly vascular smooth muscle, thereby producing vasodilation of peripheral resistance vessels and coronary arteries. The blockade of N-type Ca2+ channels affects 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

Chlorthalidone

Chlortalidone is a benzothiadiazine (thiazide)-related diuretic 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 collection 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 12.5mg Chlortalidone. 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 to 3 hours, reaches its maximum after 4 to 24 hours, and may persist for 2 to 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, chlortalidone gently reduces blood pressure. On continued administration, the hypotensive effect is maintained, probably due to the fall in peripheral resistance; cardiac output returns to pretreatment values, plasma volume remains somewhat reduced and plasma renin activity may be elevated.

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

As with other diuretics, when Chlortalidone 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 chlortalidone, reduces cerebrovascular (stroke), coronary heart and total cardiovascular morbidity and mortality.

Combined treatment with other antihypertensives potentiates the blood-pressure lowering effects. In the large proportion of patients failing to respond adequately to monotherapy, a further decrease in blood pressure can thus be achieved.
In renal diabetes insipidus, Chlortalidone paradoxically reduces polyuria. The mechanism of action has not been elucidated

5.2 Pharmacokinetic Properties

Cilnidipine
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.

Chlorthalidone
Absorption and plasma concentration
The bioavailability of an oral dose of 50mg Chlortalidone is approximately 64%, peak blood concentrations being attained after 8 to 12 hours. For doses of 25 and 50mg, Cmax values average 1.5µg/ml (4.4µmol/L) and 3.2µg/ml (9.4µmol/L) respectively. For doses up to 100mg there is a proportional increase in AUC. On repeated daily doses of 50mg, mean steady-state blood concentrations of 7.2µg/ml (21.2µmol/L), measured at the end of the 24 hour dosage interval, and are reached after 1 to 2 weeks.
Distribution
In blood, only a small fraction of chlortalidone is free, due to extensive accumulation in erythrocytes and binding to plasma proteins. Owing to the large degree of high affinity binding to the carbonic anhydrase of erythrocytes, only some 1.4% of the total amount of chlortalidone in whole blood was found in plasma at steady state during treatment with 50mg doses. In vitro, plasma protein binding of chlortalidone is about 76% and the major binding protein is albumin.
Chlortalidone crosses the placental barrier and passes into the breast milk. In mothers treated with 50mg chlortalidone daily before and after delivery, chlortalidone levels in fetal whole blood are about 15% of those found in maternal blood. Chlortalidone concentrations in amniotic fluid and in the maternal milk are approximately 4% of the corresponding maternal blood level.
Metabolism
Metabolism and hepatic excretion into bile constitute a minor pathway of elimination. Within 120 hours, about 70% of the dose is excreted in the urine and the faeces, mainly in unchanged form.
Elimination
Chlortalidone is eliminated from whole blood and plasma with an elimination half-life averaging 50 hours. The elimination half-life is unaltered after chronic administration. The major part of an absorbed dose of chlortalidone is excreted by the kidneys, with a mean renal clearance of 60ml/min.
Special patient groups
Renal dysfunction does not alter the pharmacokinetics of chlortalidone, the rate-limiting factor in the elimination of the drug from blood or plasma being most probably the affinity of the drug to the carbonic anhydrase of erythrocytes.

No dosage adjustment is needed in patients with impaired renal function.
In elderly patients, the elimination of chlortalidone is slower than in healthy young adults, although absorption is the same. Therefore, close medical observation is indicated when treating patients of advanced age with chlortalidone.

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf-life

24 months

6.2 Special Precautions for Storage

Store below 30^0C.
Protect from light.
Keep out of reach of children.

6.3 Nature and Contents of Container

10 X 10 tablets

7. MARKETED BY

Alkem Laboratories Ltd.
ALKEM HOUSE,
S. B. Road, Lower Parel (West),
Mumbai- 400 013.

8. DATE OF PREPARATION/REVISION OF THE TEXT

10/03/2017