# Mimcipar Tablets

## Cinacalcet HCl

# ممسی پار گولیاں

سینا کیلسٹ ایچ سی ایل

**Composition:**
**Mimcipar-30mg:**
Each film coated tablet contains:
Cinacalcet (as HCl) .....30mg.
**Mimcipar-60mg:**
Each film coated tablet contains:
Cinacalcet (as HCl) .....60mg.
(Innovator's Specs.)

**INDICATIONS AND USAGE:**

***Secondary Hyperparathyroidism:***
Mimcipar is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on dialysis.

***Parathyroid Carcinoma***
Mimcipar is indicated for the treatment of hypercalcemia in adult patients with Parathyroid Carcinoma.

***Primary Hyperparathyroidism***
Mimcipar is indicated for the treatment of hypercalcemia in adult patients with primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels, but who are unable to undergo parathyroidectomy.

**DOSAGE AND ADMINISTRATION:**
Mimcipar tablets should be taken whole and should not be divided. Mimcipar should be taken with food or shortly after a meal.
Dosage must be individualized.

***Secondary Hyperparathyroidism***
in Adult Patients with Chronic Kidney Disease on Dialysis
The recommended starting oral dose of Mimcipar is 30 mg once daily. Serum calcium and serum phosphorus should be measured within 1 week and intact parathyroid hormone (iPTH) should be measured 1 to 4 weeks after initiation or dose adjustment of Mimcipar. Mimcipar should be titrated no more frequently than every 2 to 4 weeks through sequential doses of 30, 60, 90, 120, and 180 mg once daily to target iPTH levels of 150 to 300 pg/mL. Serum iPTH levels should be assessed no earlier than 12 hours after dosing with Mimcipar.
Mimcipar can be used alone or in combination with vitamin D sterols and/or phosphate binders.
During dose titration, serum calcium levels should be monitored frequently and if levels decrease below the normal range, appropriate steps should be taken to increase serum calcium levels, such as by providing supplemental calcium, initiating or increasing the dose of vitamin D sterols, or temporarily withholding treatment with Mimcipar

***Parathyroid Carcinoma and Primary Hyperparathyroidism***
The recommended starting oral dose of Mimcipar is 30 mg twice daily.
The dose of Mimcipar should be titrated every 2 to 4 weeks through sequential doses of 30 mg twice daily,60 mg twice daily, 3 or 4 times daily as necessary to normalize serum calcium levels. Serum calcium should be measured within 1 week after initiation or dose adjustment of Mimcipar.

***Monitoring for Hypocalcemia***
Once the maintenance dose has been established, serum calcium should be measured approximately monthly for patients with secondary hyperparathyroidism with CKD on dialysis, and every 2 months for patients with parathyroid carcinoma or primary hyperparathyroidism.
For secondary hyperparathyroidism patients with CKD on dialysis, if serum calcium falls below 8.4 mg/dL but remains above 7.5 mg/dL, or if symptoms of hypocalcemia occur, supplemental calcium and/or vitamin D sterols can be used to raise serum calcium. If serum calcium falls below 7.5 mg/dL, or if symptoms of hypocalcemia persist and the dose of vitamin D cannot be increased, withhold administration of Mimcipar until serum calcium levels reach 8.0 mg/dL and/or symptoms of hypocalcemia have resolved. Treatment should be reinitiated using the next lowest dose of Mimcipar.

**CONTRAINDICATIONS:**
Mimcipar treatment initiation is contraindicated if serum calcium is less than the lower limit of the normal range.

**WARNINGS AND PRECAUTIONS:**

***Hypocalcemia:***
Mimcipar lowers serum calcium and, therefore, patients should be carefully monitored for the occurrence of hypocalcemia during treatment and Adverse Reactions Life threatening events and fatal outcomes associated with hypocalcemia have been reported in patients treated with Mimcipar, including pediatric patients. Potential manifestations of hypocalcemia include paresthesias, myalgias, muscle cramping, tetany, and convulsions.
Clinical studies indicate that Mimcipar-treated patients with CKD not on dialysis have an increased risk for hypocalcemia compared with Mimcipar-treated patients with CKD on dialysis, which may be due to lower baseline calcium levels. In study of 32 weeks duration and including 404 patients with CKD not on dialysis (302 cinacalcet, 102 placebo), in which the median dose for cinacalcet was 60

mg per day at the completion of the study, 80% of cinacalcet treated patients experienced at least one serum calcium value < 8.4 mg/dL compared with 5% of patients receiving placebo.

***QT Prolongation***

Decreases in serum calcium can also prolong the QT interval, potentially resulting in ventricular arrhythmia. Cases of QT prolongation and ventricular arrhythmia secondary to hypocalcemia have been reported in patients treated with cinacalcet.

**Seizures**

serum calcium levels should be closely monitored in patients receiving cinacalcet , particularly in patients with a history of a seizure disorder.

***Hypotension and/or Worsening Heart Failure***

In safety surveillance, isolated, idiosyncratic cases of hypotension, worsening heart failure, and/or arrhythmia have been reported in patients with impaired cardiac function, in which a causal relationship to cinacalcet could not be completely excluded and which may be mediated by reductions in serum calcium levels.

***Upper Gastrointestinal Bleeding***

Cases of gastrointestinal bleeding, mostly upper gastrointestinal bleeding, have occurred in patients using calcimimetics, including cinacalcet, from clinical trial sources. The exact cause of GI bleeding in these patients is unknown.

Patients with risk factors for upper GI bleeding (such as known gastritis, esophagitis, ulcers or severe vomiting) may be at increased risk for GI bleeding when receiving cinacalcet treatment. Monitor patients for worsening of common GI adverse reactions of nausea and vomiting associated with cinacalcet and for signs and symptoms of GI bleeding and ulcerations during cinacalcet therapy. Promptly evaluate and treat any suspected GI bleeding.

***Adynamic Bone Disease***

Adynamic bone disease may develop if iPTH levels are suppressed below 100 pg/mL. One clinical study evaluated bone histomorphometry in patients treated with cinacalcet for 1 year. Three patients with mild hyperparathyroid bone disease at the beginning of the study developed adynamic bone disease during treatment with cinacalcet. Two of these patients had iPTH levels below 100 pg/mL at multiple time points during the study. In three 6-month, phase 3 studies conducted in patients with CKD on dialysis, 11% of patients treated with cinacalcet had mean iPTH values below 100 pg/mL during the efficacy-assessment phase. If iPTH levels decrease below 150 pg/mL in patients treated with cinacalcet, the dose of cinacalcet and/or vitamin D sterols should be reduced or therapy discontinued.

***Hepatic Impairment***

Cinacalcet exposure, as defined by the Area under the Plasma Drug Concentration Time Curve (AUC0-infinite), is increased by 2.4 and 4.2 fold in patients with moderate and severe hepatic impairment, respectively. These patients should be monitored throughout treatment with Mimcipar.

**ADVERSE REACTIONS**

The following adverse reactions are discussed in greater detail in other sections of labeling:

- Hypocalcemia
- Upper Gastrointestinal Bleeding
- Adynamic Bone Disease
- Hepatic Impairment

***Clinical Trials Experience***

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

**Secondary Hyperparathyroidism** in Patients with Chronic Kidney Disease on Dialysis

In a randomized, double-blind placebo-controlled study of 3883 patients with secondary HPT and CKD receiving dialysis in which patients were treated for up to 64 months (mean duration of treatment was 21 months in the cinacalcet group), the most frequently reported adverse reactions (incidence of ≥ 5% in the cinacalcet group and a difference ≥ 1% compared to placebo) .

**Parathyroid Carcinoma and Primary Hyperparathyroidism**

The safety profile of cinacalcet in these patient populations is generally consistent with that seen in patients with CKD on dialysis. Forty-six patients were treated with cinacalcet in a single-arm study, 29 with Parathyroid Carcinoma and 17 with intractable pHPT. Nine (20%) of the patients withdrew from the study due to adverse events. The most frequent adverse reactions and the most frequent cause of withdrawal in these patient populations were nausea and vomiting. Severe or prolonged cases of nausea and vomiting can lead to dehydration and worsening hypercalcemia so careful monitoring of electrolytes is recommended in patients with these symptoms.

In a randomized double-blind, placebo-controlled study of 67 patients with primary hyperparathyroidism for whom parathyroidectomy would be indicated on the basis of serum calcium levels, but who are unable to undergo surgery, the most common adverse reactions

Hypocalcemia

In 26-week studies of patients with secondary HPT and CKD on dialysis 66% of patients receiving cinacalcet compared with 25% of patients receiving placebo developed at least one serum calcium value less than 8.4 mg/dL, whereas, 29% of patients receiving cinacalcet compared with 11% of patients receiving placebo developed at least one serum calcium value less than 7.5 mg/dL. Less than 1% of patients in each group permanently discontinued study drug due to

hypocalcemia.

**DRUG INTERACTIONS**

***Strong CYP3A4 Inhibitors***

Cinacalcet is partially metabolized by CYP3A4. Dose adjustment of cinacalcet may be required if a patient initiates or discontinues therapy with a strong CYP3A4 inhibitor (e.g., ketoconazole, itraconazole). The iPTH and serum calcium concentrations should be closely monitored in these patients .

***CYP2D6 Substrates***

Cinacalcet is a strong inhibitor of CYP2D6. Dose adjustments may be required for concomitant medications that are predominantly metabolized by CYP2D6 (e.g., desipramine, metoprolol, and carvedilol) and particularly those with a narrow therapeutic index (e.g., flecainide and most tricyclic antidepressants).

**USE IN SPECIFIC POPULATIONS**

***Pregnancy: Category C***

There are no adequate and well-controlled studies of cinacalcet in pregnant women. Mimcipar should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

***Nursing Mothers***

Because many drugs are excreted in human milk and there is a potential for clinically significant adverse reactions in infants who ingest cinacalcet, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the lactating woman.

***Pediatric Use***

The safety and efficacy of cinacalcet in pediatric patients have not been established. Mimcipar is not indicated for use in pediatric patients. A fatal outcome was reported in a pediatric clinical trial patient with severe hypocalcemia.

***Geriatric Use***

Reported clinical experience has not identified differences in responses between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

***Renal Impairment***

No dosage adjustment is necessary for renal impairment.

***Hepatic Impairment***

Patients with moderate and severe hepatic impairment should have serum calcium, serum phosphorus, and iPTH levels monitored closely throughout treatment with Mimcipar because cinacalcet exposure (AUC0-infinite) is increased by 2.4 and 4.2 fold, respectively, in these patients.

**OVERDOSAGE**

Doses titrated up to 300 mg once daily have been safely administered to patients on dialysis. Overdosage of Mimcipar may lead to hypocalcemia. In the event of overdosage, patients should be monitored for signs and symptoms of hypocalcemia and appropriate measures taken to correct serum calcium levels.

Since Mimcipar is highly protein bound, hemodialysis is not an effective treatment for overdosage of Mimcipar.

**DESCRIPTIONS**

Mimcipar (cinacalcet) is a calcimimetic agent that increases the sensitivity of the calcium-sensing receptor to activation by extracellular calcium. Mimcipar tablets contain the hydrochloride salt of cinacalcet. Its empirical formula is C22H22F3N

HCl with a molecular weight of 393.9 g/mol (hydrochloride salt) and 357.4 g/mol (free base). It has one chiral center having an R-absolute configuration. The R-enantiomer is the more potent enantiomer and has been shown to be responsible for pharmacodynamic activity.

The hydrochloride salt of cinacalcet is a white to off-white, crystalline solid that is soluble in methanol or 95% ethanol and slightly soluble in water.

The hydrochloride salt of cinacalcet is described chemically as N-[1-(R)-(-)-(1-naphthyl) ethyl]-3-[3-(trifluoromethyl)phenyl]-1-aminopropane hydrochloride

**CLINICAL PHARMACOLOGY**

***Mechanism of Action***

The calcium-sensing receptor on the surface of the chief cell of the parathyroid gland is the principal regulatorof PTH synthesis and secretion. Cinacalcet, the active ingredient in Mimcipar, directly lowers PTH levels byincreasing the sensitivity of the calcium-sensing receptor to extracellular calcium. The reduction in PTH isassociated with a concomitant decrease in serum calcium levels.

***Pharmacodynamics***

Reduction in iPTH levels correlated with the plasma cinacalcet concentrations in patients with CKD.

The nadir (low point) in iPTH level occurs approximately 2 to 6 hours post dose, corresponding with the maximum plasmaconcentration (Cmax) of cinacalcet. After steady-state cinacalcet concentrations are reached (which occurswithin 7 days of dose change), serum calcium concentrations remain constant over the dosing interval inpatients with CKD.

Reductions in PTH are associated with a decrease in bone turnover and bone fibrosis in patients with CKD ondialysis and uncontrolled secondary HPT.

***Pharmacokinetics***

Absorption and Distribution

After oral administration of cinacalcet, Cmax is achieved in approximately 2 to 6 hours. CinacalcetCmax andAUC(0-infinite) were increased by 82% and 68%, respectively, following administration with a high-fat mealcompared with fasting in healthy volunteers.

The Cmax and AUC(0-infinite) of cinacalcet were increased by 65%and 50%, respectively, when cinacalcet was administered with a low-fat meal compared with fasting.After absorption, cinacalcet concentrations decline in a biphasic fashion with a terminal half-life of 30 to 40hours.

Steady-state drug levels are achieved within 7 days, and the mean accumulation ratio is approximately 2with once daily oral administration. The median accumulation ratio is approximately 2 to 5 with twice dailyoral administration. The AUC and Cmax of cinacalcet increase proportionally over the dose range of 30 to180 mg once daily. The pharmacokinetic profile of cinacalcet does not change over time with once daily dosingof 30 to 180 mg. The volume of distribution is approximately 1000 L, indicating extensive distribution.

Cinacalcet is approximately 93% to 97% bound to plasma protein(s). The ratio of blood cinacalcet

Concentration to plasma cinacalcet concentration is 0.80 at a blood cinacalcet concentration of 10 ng/mL.

Metabolism and Excretion

Cinacalcet is metabolized by multiple enzymes, primarily CYP3A4, CYP2D6, and CYP1A2.

Renal excretion of metabolites was the primary route of elimination of radioactivity. Approximately 80% of the dose was recovered in the urine and 15% in the feces.

Specific Populations

Age: Geriatric Population

The pharmacokinetic profile of cinacalcet in geriatric patients (age ≥ 65 years, n = 12) is similar to that for patients who are < 65 years of age (n = 268).

Age: Pediatric Population

The pharmacokinetics of cinacalcet has not been studied in patients < 18 years of age.

**Hepatic Impairment:**

Protein binding of cinacalcet is not affected by impaired hepatic function.

**Renal Impairment:**

The pharmacokinetic profile of a 60 mg Mimcipar single dose in patients with mild, moderate, and severe renal impairment, and those on hemodialysis or peritoneal dialysis is comparable with that in healthy volunteers.

**Drug Interactions:**

In vitro studies indicate that cinacalcet is a strong inhibitor of CYP2D6, but not an inhibitor of CYP1A2, CYP2C9, CYP2C19, and CYP3A4. In vitro induction studies indicate that cinacalcet is not an inducer of CYP450 enzymes.

**NONCLINICAL TOXICOLOGY:**

Carcinogenesis, Mutagenesis, and Impairment of Fertility

***Carcinogenicity***

No increased incidence of tumors was observed following treatment with cinacalcet.

***Mutagenicity***

Cinacalcet was not genotoxic in the Ames bacterial mutagenicity assay, nor in the Chinese Hamster Ovary (CHO) cell HGPRT forward mutation assay and CHO cell chromosomal aberration assay, with and without metabolic activation

***Impairment of Fertility***

No effects were observed in male or female fertility at 5 and 25 mg/kg/day

(Exposures up to 3 times those resulting with a human oral dose of 180 mg/day based on AUC comparison).

**Presentation:**

Mimcipar 30mg Tablet is available in 10's pack.

Mimcipar 60mg Tablet is available in 10's pack.

**Storage:**

Protect from sunlight and moisture.

Keep out of the reach of children.

Store below 30°C.

خوراک:

دواڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

احتیاط:

روشنی، نمی اور گرمی سے بچائیں۔

دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

***Manufactured by:***

GENOME PHARMACEUTICALS (PVT.) LTD.

Plot # 16/1, Phase IV, Industrial Estate Hattar-Pakistan.

***Marketed by:***

ALLIANZE MED PHARMA