CALCET
Cinacalcet
Film coated tablets 30 mg
Film coated tablets 60 mg
Film coated tablets 90 mg

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

Calcet 30 mg film-coated tablets
Each tablet contains 33,06 mg cinacalcet hydrochloride equivalent to 30 mg cinacalcet.

Calcet 60 mg film-coated tablets
Each tablet contains 66,12 mg cinacalcet hydrochloride equivalent to 60 mg cinacalcet.

Calcet 90 mg film-coated tablets
Each tablet contains 99,18 mg cinacalcet hydrochloride equivalent to 90 mg cinacalcet.

2. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Calcet 30 mg film-coated tablets

Green oval biconvex coated tablets, debossed with C9CC on one side and 30 on the other side.

Calcet 60 mg film-coated tablets

Green oval biconvex coated tablets, debossed with C9CC on one side and 60 on the other side.

Calcet 90 mg film-coated tablets

Green oval biconvex coated tablets, debossed with C9CC on one side and 90 on the other side.

3. CLINICAL PARTICULARS

Therapeutic indications

Secondary hyperparathyroidism

Adults
Treatment of secondary hyperparathyroidism (HPT) in adult patients with end-stage renal disease (ESRD) on maintenance dialysis therapy.

Calcet may be used as part of a therapeutic regimen including phosphate binders and/or Vitamin D sterols, as appropriate (see section Pharmacodynamic properties).

Parathyroid carcinoma and primary hyperparathyroidism in adults

Reduction of hypercalcaemia in adult patients with:
- parathyroid carcinoma.
- primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom parathyroidectomy is not clinically appropriate or is contraindicated.

Posology and method of administration

Posology

Secondary hyperparathyroidism

Adults and elderly (> 65 years)
The recommended starting dose for adults is 30 mg once per day. Calcet should be titrated every 2 to 4 weeks to a maximum dose of 180 mg once daily to achieve a target parathyroid hormone (PTH) in dialysis patients of between 150-300 pg/mL (15.9-31.8 pmol/L) in the intact PTH (iPTH) assay.
PTH levels should be assessed at least 12 hours after dosing with Calcet. Reference should be made to current treatment guidelines.

PTH should be measured 1 to 4 weeks after initiation or dose adjustment of Calcet. PTH should be monitored approximately every 1-3 months during maintenance. Either the intact PTH (iPTH) or bio-intact PTH (biPTH) may be used to measure PTH levels; treatment with Calcet does not alter the relationship between iPTH and biPTH.

Dose adjustment based on serum calcium levels
Corrected serum calcium should be measured and monitored and should be at or above the lower limit of the normal range prior to administration of first dose of Calcet (see section Therapeutic indications). The normal calcium range may differ depending on the methods used by your local laboratory.

During dose titration, serum calcium levels should be monitored frequently, and within 1 week of initiation or dose adjustment of Calcet. Once the maintenance dose has been established, serum calcium should be measured approximately monthly. In the event that corrected serum calcium levels fall below 8.4 mg/dL (2.1 mmol/L) and/or symptoms of hypocalcaemia occur the following management is recommended:

Corrected Serum calcium level or clinical symptoms of hypocalcaemia	**Recommendations**
< 8.4 mg/dL (2.1 mmol/L) and > 7.5 mg/dL (1.9 mmol/L), or in the presence of clinical symptoms of hypocalcaemia	Calcium-containing phosphate binders, vitamin D sterols and/or adjustment of dialysis fluid calcium concentrations can be used to raise serum calcium according to clinical judgment.
< 8.4 mg/dL (2.1 mmol/L) and > 7.5 mg/dL (1.9 mmol/L) or persistent symptoms of hypocalcaemia despite attempts to increase serum calcium	Reduce or withhold dose of Calcet.
≤ 7.5 mg/dL (1.9 mmol/L) or persistent symptoms of hypocalcaemia and Vitamin D cannot be increased	Withhold administration of Calcet until serum calcium levels reach 8.0 mg/dL (2.0 mmol/L) and/or symptoms of hypocalcaemia have resolved. Treatment should be reinitiated using the next lowest dose of Calcet.

Dose adjustment based on PTH levels
PTH levels should be assessed at least 12 hours after dosing with Calcet and iPTH should be measured 1 to 4 weeks after initiation or dose adjustment of Calcet.

The dose should be adjusted based on iPTH as shown below:

- If iPTH is < 150 pg/mL (15.9 pmol/L) and ≥ 100 pg/mL (10.6 pmol/L), decrease the dose of Calcet to the next lower dose.
- If iPTH < 100 pg/mL (10.6 pmol/L), stop Calcet treatment, restart Calcet at the next lower dose once the iPTH is > 150 pg/mL (15.9 pmol/L). If Calcet treatment has been stopped for more than 14 days, restart at the recommended starting dose.

Dose adjustment based on serum calcium levels
Serum calcium should be measured within 1 week after initiation or dose adjustment of Calcet.

Once the maintenance dose has been established, weekly measurement of serum calcium is recommended.

Parathyroid carcinoma and primary hyperparathyroidism

Adults and elderly (> 65 years)
The recommended starting dose of Calcet for adults is 30 mg twice per day. The dose of Calcet should be titrated every 2 to 4 weeks through sequential doses of 30 mg twice daily, 60 mg twice daily, 90 mg twice daily, and 90 mg three or four times daily as necessary to reduce serum calcium concentration to or below the upper limit of normal. The maximum dose used in clinical trials was 90 mg four times daily.

Serum calcium should be measured within 1 week after initiation or dose adjustment of Calcet. Once maintenance dose levels have been established, serum calcium should be measured every 2 to 3 months. After titration to the maximum dose of Calcet, serum calcium should be periodically monitored; if clinically relevant reductions in serum calcium are not maintained, discontinuation of Calcet therapy should be considered (see section Pharmacodynamic properties).

Paediatric population
The safety and efficacy of Cinacalcet in children for the treatment of parathyroid carcinoma and primary hyperparathyroidism have not been established. No data are available.

Hepatic impairment

No change in starting dose is necessary. Calcet should be used with caution in patients with moderate to severe hepatic impairment and treatment should be closely monitored during dose titration and continued treatment (see sections Therapeutic indications and Pharmacokinetic properties).

Method of administration

For oral use.
Tablets should be taken whole and should not be chewed, crushed or divided.

It is recommended that Calcet be taken with food or shortly after a meal, as studies have shown that bioavailability of cinacalcet is increased when taken with food (see section Pharmacokinetic properties).

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section List of excipients.
Hypocalcaemia (see sections Posology and method of administration and Therapeutic indications).

Special warnings and precautions for use

Serum calcium

Life threatening events and fatal outcomes associated with hypocalcaemia have been reported in adult patients treated with Cinacalcet. Manifestations of hypocalcaemia may include paraesthesias, myalgias, cramping, tetany and convulsions. Decreases in serum calcium can also prolong the QT interval, potentially resulting in ventricular arrhythmia secondary to hypocalcaemia. Cases of QT prolongation and ventricular arrhythmia have been reported in patients treated with cinacalcet (see section Undesirable effects). Caution is advised in patients with other risk factors for QT prolongation such as patients with known congenital long QT syndrome or patients receiving medicinal products known to cause QT prolongation.

Since cinacalcet lowers serum calcium, patients should be monitored carefully for the occurrence of hypocalcaemia (see section Posology and method of administration). Serum calcium should be measured within 1 week after initiation or dose adjustment of Cinacalcet.

Adults
Cinacalcet treatment should not be initiated in patients with a serum calcium (corrected for albumin) below the lower limit of the normal range.

In CKD patients receiving dialysis who were administered Cinacalcet, approximately 30% of patients had at least one serum calcium value less than 7.5 mg/dL (1.9 mmol/L).

CKD patients not on dialysis
Cinacalcet is not indicated for CKD patients not on dialysis. Investigational studies have shown that adult CKD patients not on dialysis treated with cinacalcet have an increased risk for hypocalcaemia (serum calcium levels < 8.4 mg/dL [2.1 mmol/L]) compared with cinacalcet-treated CKD patients on dialysis, which may be due to lower baseline calcium levels and/or the presence of residual kidney function.

Seizures

Cases of seizures have been reported in patients treated with Cinacalcet (see section Undesirable effects). The threshold for seizures is lowered by significant reductions in serum calcium levels. Therefore, 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

Cases of hypotension and/or worsening heart failure have been reported in patients with impaired cardiac function, in which a causal relationship to cinacalcet could not be completely excluded and may be mediated by reductions in serum calcium levels (see section Undesirable effects).

Co-administration with other medicinal products

Administer Cinacalcet with caution in patients receiving any other medicinal products known to lower serum calcium. Closely monitor serum calcium (see section Interaction with other medicinal products and other forms of interaction).

General

Adynamic bone disease may develop if PTH levels are chronically suppressed below approximately 1.5 times the upper limit of normal with the iPTH assay. If PTH levels decrease below the recommended target range in patients treated with Cinacalcet, the dose of Cinacalcet and/or vitamin D sterols should be reduced or therapy discontinued.

Testosterone levels

Testosterone levels are often below the normal range in patients with end-stage renal disease. In a clinical study of adult ESRD patients on dialysis, free testosterone levels decreased by a median of 31.3% in the Cinacalcet-treated patients and by 16.3% in the placebo-treated patients after 6 months of treatment. An open-label extension of this study showed no further reductions in free and total testosterone concentrations over a period of 3 years in Cinacalcet-treated patients. The clinical significance of these reductions in serum testosterone is unknown.

Hepatic impairment

Due to the potential for 2 to 4 fold higher plasma levels of cinacalcet in patients with moderate to severe hepatic impairment (Child-Pugh classification), Cinacalcet should be used with caution in these patients and treatment should be closely monitored (see sections Posology and method of administration and Pharmacokinetic properties).

Interaction with other medicinal products and other forms of interaction

Medicinal products known to reduce serum calcium

Concurrent administration of other medicinal products known to reduce serum calcium and Cinacalcet may result in an increased risk of hypocalcaemia (see section Therapeutic indications).

Effect of other medicinal products on cinacalcet

Cinacalcet is metabolised in part by the enzyme CYP3A4. Co-administration of 200 mg bid ketoconazole, a strong inhibitor of CYP3A4, caused an approximate 2-fold increase in cinacalcet levels. Dose adjustment of Cinacalcet may be required if a patient receiving Cinacalcet initiates or discontinues therapy with a strong inhibitor (e.g. ketoconazole, itraconazole, telithromycin, voriconazole, ritonavir) or inducer (e.g. rifampicin) of this enzyme.

In vitro data indicate that cinacalcet is in part metabolised by CYP1A2. Smoking induces CYP1A2; the clearance of cinacalcet was observed to be 36-38% higher in smokers than non-smokers. The effect of CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) on cinacalcet plasma levels has not been studied. Dose adjustment may be necessary if a patient starts or stops smoking or when concomitant treatment with strong CYP1A2 inhibitors is initiated or discontinued.

Calcium carbonate
Co-administration of calcium carbonate (single 1,500 mg dose) did not alter the pharmacokinetics of cinacalcet.

Sevelamer
Co-administration of sevelamer (2,400 mg tid) did not affect the pharmacokinetics of cinacalcet.

Pantoprazole
Co-administration of pantoprazole (80 mg od) did not alter the pharmacokinetics of cinacalcet.

Effect of cinacalcet on other medicinal products

Medicinal products metabolised by the enzyme P450 2D6 (CYP2D6): Cinacalcet is a strong inhibitor of CYP2D6. Dose adjustments of concomitant medicinal products may be required when Cinacalcet is administered with individually titrated, narrow therapeutic index substances that are predominantly metabolised by CYP2D6 (e.g. flecainide, propafenone, metoprolol, desipramine, nortriptyline, clomipramine).

Desipramine: Concurrent administration of 90 mg cinacalcet once daily with 50 mg desipramine, a tricyclic antidepressant metabolised primarily by CYP2D6, significantly increased desipramine exposure 3.6-fold (90% CI 3.0, 4.4) in CYP2D6 extensive metabolisers.

Dextromethorphan: Multiple doses of 50 mg cinacalcet increased the AUC of 30 mg dextromethorphan (metabolised primarily by CYP2D6) by 11-fold in CYP2D6 extensive metabolisers.

Warfarin: Multiple oral doses of cinacalcet did not affect the pharmacokinetics or pharmacodynamics (as measured by prothrombin time and clotting factor VII) of warfarin.

The lack of effect of cinacalcet on the pharmacokinetics of R- and S-warfarin and the absence of auto-induction upon multiple dosing in patients indicates that cinacalcet is not an inducer of CYP3A4, CYP1A2 or CYP2C9 in humans.

Midazolam: Co-administration of cinacalcet (90 mg) with orally administered midazolam (2 mg), a CYP3A4 and CYP3A5 substrate, did not alter the pharmacokinetics of midazolam. These data suggest that cinacalcet would not affect the pharmacokinetics of those classes of medicines that are metabolised by CYP3A4 and CYP3A5, such as certain immunosuppressants, including cyclosporine and tacrolimus.

Fertility, pregnancy and lactation

Pregnancy

There are no clinical data from the use of cinacalcet in pregnant women. Animal studies do not indicate direct harmful effects with respect to pregnancy, parturition or postnatal development. No embryonal/foetal toxicities were seen in studies in pregnant rats and rabbits with the exception of decreased foetal body weights in rats at doses associated with maternal toxicities (see section Preclinical safety data). Cinacalcet should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

It is not known whether cinacalcet is excreted in human milk. Cinacalcet is excreted in the milk of lactating rats with a high milk to plasma ratio. Following careful benefit/risk assessment, a decision should be made to discontinue either breast-feeding or treatment with Cinacalcet.

Fertility

There are no clinical data relating to the effect of cinacalcet on fertility. There were no effects on fertility in animal studies.

Effects on ability to drive and use machines

Cinacalcet may have major influence on the ability to drive and use machines, since dizziness and seizures have been reported by patients taking this medicinal product (see section Therapeutic indications).

Undesirable effects

Summary of the safety profile

Secondary hyperparathyroidism, parathyroid carcinoma and primary hyperparathyroidism

Based on available data from patients receiving cinacalcet in placebo-controlled studies and single-arm studies the most commonly reported adverse reactions were nausea and vomiting. Nausea and vomiting were mild to moderate in severity and transient in nature in the majority of patients.
Discontinuation of therapy as a result of undesirable effects was mainly due to nausea and vomiting.

Tabulated list of adverse reactions

Adverse reactions, considered at least possibly attributable to cinacalcet treatment in the placebo-controlled studies and single-arm studies based on best-evidence assessment of causality are listed below using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Incidence of adverse reactions from controlled clinical studies and post-marketing experience are:

MedDRA system organ class	**Frequency**	**Adverse reaction**
Immune system disorders	Common*	Hypersensitivity reactions
Metabolism and nutrition disorders	Common	Anorexia Decreased appetite
Nervous system disorders	Common	Seizures† Dizziness Paraesthesia Headache
Cardiac disorders	Not known*	Worsening heart failure† QT prolongation and ventricular arrhythmia secondary to hypocalcaemia†
Vascular disorders	Common	Hypotension

Respiratory, thoracic and mediastinal disorders	Common	Upper respiratory infection Dyspnoea Cough
Gastrointestinal disorders	Very common	Nausea Vomiting
	Common	Dyspepsia Diarrhoea Abdominal pain Abdominal pain – upper Constipation
Skin and subcutaneous tissue disorders	Common	Rash
Musculoskeletal and connective tissue disorders	Common	Myalgia Muscle spasms Back pain
General disorders and administration site conditions	Common	Asthenia
Investigations	Common	Hypocalcaemia† Hyperkalaemia Reduced testosterone levels†

†see section "Therapeutic indications"
*see section "Description of selected adverse reactions"

Description of selected adverse reactions

Hypersensitivity reactions
Hypersensitivity reactions including angioedema and urticaria have been identified during post-marketing use of Cinacalcet. The frequencies of the individual preferred terms including angioedema and urticaria cannot be estimated from available data.

Hypotension and/or worsening heart failure
There have been reports of idiosyncratic cases of hypotension and/or worsening heart failure in cinacalcet-treated patients with impaired cardiac function in post-marketing safety surveillance, the frequencies of which cannot be estimated from available data.

QT prolongation and ventricular arrhythmia secondary to hypocalcaemia
QT prolongation and ventricular arrhythmia secondary to hypocalcaemia have been identified during post-marketing use of Cinacalcet, the frequencies of which cannot be estimated from available data (see section Therapeutic indications).

Reporting

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Pusat Farmakovigilans/ MESO Nasional Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif Badan Pengawas Obat dan Makanan
https://e-meso.pom.go.id/ADR

Overdose

Doses titrated up to 300 mg once daily have been administered to adult patients receiving dialysis without adverse outcome.

Overdose of Cinacalcet may lead to hypocalcaemia. In the event of overdose, patients should be monitored for signs and symptoms of hypocalcaemia, and treatment should be symptomatic and supportive. Since cinacalcet is highly protein-bound, haemodialysis is not an effective treatment for overdose.

4. PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Calcium homeostasis, anti-parathyroid agents. ATC code: H05BX01.

Mechanism of action

The calcium sensing receptor on the surface of the chief cell of the parathyroid gland is the principal regulator of PTH secretion. Cinacalcet is a calcimimetic agent which directly lowers PTH levels by increasing the sensitivity of the calcium sensing receptor to extracellular calcium. The reduction in PTH is associated with a concomitant decrease in serum calcium levels.

Reductions in PTH levels correlate with cinacalcet concentration.

After steady state is reached, serum calcium concentrations remain constant over the dosing interval.

Secondary hyperparathyroidism

Adults
Based on clinical study conducted by the innovator as follows:
Three, 6-month, double-blind, placebo-controlled clinical studies were conducted in ESRD patients with uncontrolled secondary HPT receiving dialysis (n = 1,136). Demographic and baseline characteristics were representative of the dialysis patient population with secondary HPT. Mean baseline iPTH concentrations across the 3 studies were 733 and 683 pg/mL (77.8 and 72.4 pmol/L) for the cinacalcet and placebo groups, respectively. 66% of patients were receiving vitamin D sterols at study entry, and > 90% were receiving phosphate binders. Significant reductions in iPTH, serum calcium-phosphorus product (Ca x P), calcium, and phosphorus were observed in the cinacalcet-treated patients compared with placebo-treated patients receiving standard of care, and the results were consistent across the 3 studies. In each of the studies, the primary endpoint (proportion of patients with an iPTH ≤ 250 pg/mL (≤ 26.5 pmol/L)) was achieved by 41%, 46%, and 35% of patients receiving cinacalcet, compared with 4%, 7%, and 6% of patients receiving placebo. Approximately 60% of cinacalcet-treated patients achieved a ≥ 30% reduction in iPTH levels, and this effect was consistent across the spectrum of baseline iPTH levels. The mean reductions in serum Ca x P, calcium, and phosphorus were 14%, 7% and 8%, respectively.

Reductions in iPTH and Ca x P were maintained for up to 12 months of treatment. Cinacalcet decreased iPTH and Ca x P, calcium and phosphorus levels regardless of baseline iPTH or Ca x P level, dialysis modality (PD versus HD), duration of dialysis, and whether or not vitamin D sterols were administered.

Reductions in PTH were associated with non-significant reductions of bone metabolism markers (bone specific alkaline phosphatase, N-telopeptide, bone turnover and bone fibrosis). In post-hoc analyses of pooled data from 6 and 12 months clinical studies, Kaplan-Meier estimates of bone fracture and parathyroidectomy were lower in the cinacalcet group compared with the control group.

Investigational studies in patients with CKD and secondary HPT not undergoing dialysis indicated that cinacalcet reduced PTH levels to a similar extent as in patients with ESRD and secondary HPT receiving dialysis. However, efficacy, safety, optimal doses and treatment targets have not been established in treatment of predialytic renal failure patients. These studies show that CKD patients not undergoing dialysis treated with cinacalcet have an increased risk for hypocalcaemia compared with cinacalcet-treated ESRD patients receiving dialysis, which may be due to lower baseline calcium levels and/or the presence of residual kidney function.

EVOLVE (EValuation Of Cinacalcet Therapy to Lower CardioVascular Events) was a randomised, double-blind clinical study evaluating cinacalcet versus placebo for the reduction of the risk of all-cause mortality and cardiovascular events in 3,883 patients with secondary HPT and CKD receiving dialysis. The study did not meet its primary objective of demonstrating a reduction in risk of all-cause mortality or cardiovascular events including myocardial infarction, hospitalisation for unstable angina, heart failure or peripheral vascular event (HR 0.93; 95% CI: 0.85, 1.02; p = 0.112). After adjusting for baseline characteristics in a secondary analysis, the HR for the primary composite endpoint was 0.88; 95% CI: 0.79, 0.97.

Parathyroid carcinoma and primary hyperparathyroidism

Based on clinical study conducted by the innovator as follows:

In one study, 46 adult patients (29 with parathyroid carcinoma and 17 with primary HPT and severe hypercalcaemia who had failed or had contraindications to parathyroidectomy) received cinacalcet for up to 3 years (mean of 328 days for patients with parathyroid carcinoma and mean of 347 days for patients with primary HPT). Cinacalcet was administered at doses ranging from 30 mg twice daily to 90 mg four times daily. The primary endpoint of the study was a reduction of serum calcium of $\geq$ 1 mg/dL ($\geq$ 0.25 mmol/L). In patients with parathyroid carcinoma, mean serum calcium declined from 14.1 mg/dL to 12.4 mg/dL (3.5 mmol/L to 3.1 mmol/L), while in patients with primary HPT, serum calcium levels declined from 12.7 mg/dL to 10.4 mg/dL (3.2 mmol/L to 2.6 mmol/L). Eighteen (18) of 29 patients (62%) with parathyroid carcinoma and 15 of 17 subjects (88%) with primary HPT achieved a reduction in serum calcium of $\geq$ 1 mg/dL ($\geq$ 0.25 mmol/L).

In a 28 week placebo-controlled study, 67 adult patients with primary HPT who met criteria for parathyroidectomy on the basis of corrected total serum calcium (> 11.3 mg/dL (2.82 mmol/L) but $\leq$ 12.5 mg/dL (3.12 mmol/L), but who were unable to undergo parathyroidectomy were included. Cinacalcet was initiated at a dose of 30 mg twice daily and titrated to maintain a corrected total serum calcium concentration within the normal range. A significantly higher percentage of cinacalcet-treated patients achieved mean corrected total serum calcium concentration $\leq$ 10.3 mg/dL (2.57 mmol/L) and $\geq$ 1 mg/dL (0.25 mmol/L) decrease from baseline in mean corrected total serum calcium concentration, when compared with the placebo-treated patients (75.8% versus 0% and 84.8% versus 5.9% respectively).

Pharmacokinetic properties

The bioequivalence of a single dose of the Test Product (Cinacalcet Synthon 90 mg film-

coated tablets) and the Reference Product (Mimpara 90 mg film-coated tablets, containing 90 mg cinacalcet per film-coated tablet) was assessed under fed conditions in healthy male and female subjects.

Total 60 subjects were enrolled for the study and 38 subjects were completed the study. The pharmacokinetics parameters of 38 subjects were calculated and results were statistically analyzed to demonstrate bioequivalence in a randomized, single dose, laboratory-blinded, two-way, crossover design study. After oral administration of single dose of test product in the fed state, the mean of the maximum plasma concentration (C_{max}) (Rate of absorption) was 30.021 ng/ml, the median T_{max} was 5.25 h. The extent of absorption is expressed in Area Under Curve AUC_{0-72} , the mean values were 342.581 ng.h/ml. The mean elimination half life ($T_{1/2}$) of Cinacalcet 90 mg film coated tablets was 15.82 h.
The ratios and confidence intervals between test and reference product were as following : for C_{max} the ratio was 95.45% (88.09% – 103.42%), for AUC_{0-72} the ratio was 99.86% (96.17% – 103.70%). The result of the study showed that the ratios and confidence intervals are within the acceptance range for bioequivalence (80.00 – 125.00%), therefore it can be conluded that the test product, Cinacalcet 90 mg film-coated tablets, is bioequivalence with the reference product.

Preclinical safety data

Based on data from the innovator, Cinacalcet was not teratogenic in rabbits when given at a dose of 0.4 times, on an AUC basis, the maximum human dose for secondary HPT (180 mg daily). The non-teratogenic dose in rats was
4.4 times, on an AUC basis, the maximum dose for secondary HPT. There were no effects on fertility in males or females at exposures up to 4 times a human dose of 180 mg/day (safety margins in the small population of patients administered a maximum clinical dose of 360 mg daily would be approximately half those given above).

In pregnant rats, there were slight decreases in body weight and food consumption at the highest dose. Decreased foetal weights were seen in rats at doses where dams had severe hypocalcaemia. Cinacalcet has been shown to cross the placental barrier in rabbits.

Cinacalcet did not show any genotoxic or carcinogenic potential. Safety margins from the toxicology studies are small due to the dose-limiting hypocalcaemia observed in the animal models. Cataracts and lens opacities were observed in the repeat dose rodent toxicology and carcinogenicity studies, but were not observed in dogs or monkeys or in clinical studies where cataract formation was monitored.
Cataracts are known to occur in rodents as a result of hypocalcaemia.

In *in vitro* studies, IC_{50} values for the serotonin transporter and K_{ATP} channels were found to be 7 and 12-fold greater, respectively, than the EC_{50} for the calcium-sensing receptor obtained under the same experimental conditions. The clinical relevance is unknown, however, the potential for cinacalcet to act on these secondary targets cannot be fully excluded.

In toxicity studies in juvenile dogs, tremors secondary to decreased serum calcium, emesis, decreased body weight and body weight gain, decreased red cell mass, slight decreases in bone densitometry parameters, reversible widening of the growth plates of long bones, and histological lymphoid changes (restricted to the thoracic cavity and attributed to chronic emesis) were observed. All of these effects were seen at a systemic exposure, on an AUC basis, approximately

equivalent to the exposure in patients at the maximum dose for secondary HPT.

5. PHARMACEUTICAL PARTICULARS

List of excipients

Tablet core

Starch, pregelatinised (maize)
Cellulose, microcrystalline (E460)
Povidone (K-29/32)
Crospovidone (Type A and B)
Magnesium stearate (E572)
Silica, colloidal anhydrous

Tablet coating

Polyvinyl alcohol-partially hydrolyzed (E1203)
Titanium dioxide (E171)
Macrogol (L 4000)
Talc (E553b)
FD&C Blue #2/Indigo carmine aluminum lake (E132)
Iron oxide yellow (E172)

Incompatibilities

Not applicable

Shelf life

3 years.

Storage

Store below 30^0C

Special precautions for disposal

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6. PRESENTATION

Calcet 30 mg	: Dus, 2 blisters @ 15 film coated tablets	Reg. No. :
Calcet 60 mg	: Dus, 2 blisters @ 15 film coated tablets	Reg. No. :
Calcet 90 mg	: Dus, 3 blisters @ 10 film coated tablets	Reg. No. :

HARUS DENGAN RESEP DOKTER

Manufactured by:
Synthon Chile Ltda, Santiago – Chile

Released by:
Synthon Hispania S.L., Sant Boi de Llobregat – Spain

Imported by:
PT. Pratapa Nirmala, Tangerang - Indonesia

Informasi Produk Untuk Pasien

Calcet 30 mg tablet salut selaput
Calcet 60 mg tablet salut selaput
Calcet 90 mg tablet salut selaput
Cinacalcet

Baca seluruh leaflet ini dengan seksama sebelum mulai penggunaan obat ini.

- Simpanlah leaflet ini, agar dapat dibaca kembali jika diperlukan.
- Jika ada pertanyaan lebih lanjut, hubungi dokter atau apoteker.
- Obat ini diresepkan untuk Anda. Jangan diberikan kepada orang lain. Hal tersebut dikarenakan obat ini dapat saja membahayakan orang lain, walaupun gejala yang dialami sama dengan Anda.
- Jika salah satu efek samping dirasakan menjadi serius atau jika terjadi efek samping apapun yang tidak tercantum di leaflet ini, mohon sampaikan kepada dokter atau apoteker.

Pada leaflet ini terdapat informasi berikut:

1. Apakah CALCET dan kegunaannya

Cinacalcet bekerja dengan mengontrol kadar hormon paratiroid (PTH), kalsium dan fosfor dalam tubuh Anda. Ini digunakan untuk mengobati masalah dengan organ yang disebut kelenjar paratiroid. Paratiroid adalah empat kelenjar kecil di leher, dekat kelenjar tiroid, yang menghasilkan hormon paratiroid (PTH).

Cinacalcet digunakan pada orang dewasa:

- untuk mengobati hiperparatiroidisme sekunder pada orang dewasa dengan penyakit ginjal serius yang memerlukan dialisis untuk membersihkan darah dari zat-zat sisa metabolisme tubuh.
- untuk menurunkan kadar kalsium yang tinggi dalam darah (hiperkalsemia) pada pasien dewasa dengan kanker paratiroid.
- untuk mengurangi kadar kalsium yang tinggi dalam darah (hiperkalsemia) pada pasien dewasa dengan hiperparatiroidisme primer saat pengangkatan kelenjar tidak memungkinkan.

Pada hiperparatiroidisme primer dan sekunder, terlalu banyak PTH diproduksi oleh kelenjar paratiroid. “Primer” berarti hiperparatiroidisme tidak disebabkan oleh kondisi lain dan “sekunder” berarti hiperparatiroidisme disebabkan oleh kondisi lain, misal penyakit ginjal. Hiperparatiroidisme primer dan sekunder dapat menyebabkan hilangnya kalsium pada tulang, yang dapat menyebabkan nyeri tulang dan patah tulang, masalah dengan darah dan pembuluh jantung, batu ginjal, penyakit mental, dan koma.

2. Hal yang harus diperhatikan sebelum pemberian CALCET

Jangan minum Cinacalcet jika pasien alergi terhadap cinacalcet atau bahan lain dari obat ini (tercantum di bagian 6).
Jangan minum Cinacalcet jika pasien memiliki kadar kalsium dalam darah yang rendah. Dokter akan memantau kadar kalsium darah pasien.

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Peringatan dan perhatian
Bicaralah dengan dokter, apoteker atau perawat sebelum meminum Cinacalcet.

Sebelum pasien mulai meminum Cinacalcet, beri tahu dokter jika pasien mengalami atau pernah mengalami:
- kejang. Risiko kejang lebih tinggi jika pasien pernah mengalaminya sebelumnya;
- gangguan hati;
- gagal jantung.

Cinacalcet mengurangi kadar kalsium. Efek samping yang terjadi yang terkait dengan kadar kalsium rendah (hipokalsemia) telah dilaporkan pada orang dewasa yang diobati dengan Cinacalcet.

Tolong beritahu dokter jika pasien mengalami salah satu dari yang berikut yang mungkin merupakan tanda-tanda kadar kalsium rendah: kejang, kedutan, atau kram pada otot, atau mati rasa atau kesemutan di jari tangan, jari kaki atau di sekitar mulut atau kejang, kebingungan atau kehilangan kesadaran saat dirawat dengan Cinacalcet.

Kadar kalsium yang rendah dapat mempengaruhi ritme jantung pasien. Beri tahu dokter jika pasien mengalami detak jantung yang sangat cepat atau berdebar kencang, jika pasien memiliki masalah irama jantung, atau jika pasien mengonsumsi obat yang diketahui menyebabkan masalah irama jantung, saat mengonsumsi Cinacalcet.

Untuk informasi tambahan, lihat bagian 4.

Selama perawatan dengan Cinacalcet, beri tahu dokter:
- jika pasien mulai atau berhenti merokok, karena ini dapat memengaruhi mekanisme kerja Cinacalcet.

Anak-anak dan remaja
Anak-anak di bawah usia 18 tahun tidak boleh menggunakan Cinacalcet.

Obat-obatan lain dan Cinacalcet
Beri tahu dokter atau apoteker jika pasien sedang meminum, baru saja meminum atau mungkin meminum obat lain yang menurunkan kadar kalsium dalam darah.

Beritahu dokter jika pasien menggunakan obat-obatan berikut:

Obat-obatan seperti ini dapat memengaruhi mekanisme kerja Cinacalcet:
- obat-obatan yang digunakan untuk mengobati infeksi kulit dan jamur (ketokonazol, itrakonazol, dan vorikonazol);
- obat-obatan yang digunakan untuk mengobati infeksi bakteri (telitromisin, rifampisin, dan ciprofloxacin);
- obat yang digunakan untuk mengobati infeksi HIV dan AIDS (ritonavir);
- obat yang digunakan untuk mengobati depresi (fluvoxamine).

Cinacalcet dapat mempengaruhi bagaimana obat-obatan seperti berikut ini bekerja:
- obat-obatan yang digunakan untuk mengobati depresi (amitriptyline, desipramine, nortriptyline dan clomipramine);
- obat yang digunakan untuk meredakan batuk (dekstrometorfan);
- obat-obatan yang digunakan untuk mengobati perubahan detak jantung (flecainide dan propafenone);
- obat yang digunakan untuk mengobati tekanan darah tinggi (metoprolol).

Cinacalcet dengan makanan dan minuman
Cinacalcet harus diminum dengan atau segera setelah makan.

Kehamilan, menyusui dan kesuburan
Jika pasien sedang hamil atau menyusui, atau kemungkinan pasien hamil atau berencana untuk memiliki

bayi, tanyakan kepada dokter atau apoteker sebelum meminum obat ini.

Cinacalcet belum diuji pada wanita hamil. Dalam kasus kehamilan, dokter mungkin memutuskan untuk mengubah pengobatan pasien, karena Cinacalcet dapat membahayakan bayi yang belum lahir.

Tidak diketahui apakah Cinacalcet diekskresikan dalam ASI. Dokter akan berdiskusi dengan pasien jika pasien harus menghentikan menyusui atau pengobatan dengan Cinacalcet.

Mengemudi dan menggunakan mesin
Pusing dan kejang telah dilaporkan oleh pasien yang memakai Cinacalcet. Jika pasien mengalami efek samping ini, jangan mengemudi atau mengoperasikan mesin.

3. Bagaimana cara CALCET diberikan

Selalu minum obat ini persis seperti yang dikatakan dokter atau apoteker. Tanyakan kepada dokter atau apoteker jika pasien tidak yakin. Dokter akan memberi tahu pasien berapa banyak Cinacalcet yang harus diminum.

Cinacalcet harus diminum secara oral, dengan atau segera setelah makan. Tablet harus diminum utuh dan tidak untuk dikunyah, dihancurkan atau dibagi.

Dokter akan mengambil sampel darah secara teratur selama pengobatan untuk memantau kemajuan pasien dan akan menyesuaikan dosis jika perlu.

Jika pasien sedang dirawat karena hiperparatiroidisme sekunder
Dosis awal yang biasa untuk Cinacalcet pada orang dewasa adalah 30 mg (satu tablet) sekali sehari.

Jika pasien sedang dirawat karena kanker paratiroid atau hiperparatiroidisme primer
Dosis awal yang biasa untuk Cinacalcet pada orang dewasa adalah 30 mg (satu tablet) dua kali sehari.

Jika pasien meminum lebih banyak Cinacalcet dari yang seharusnya
Jika pasien mengonsumsi lebih banyak Cinacalcet dari yang seharusnya, pasien harus segera menghubungi dokter. Tanda-tanda overdosis yang mungkin termasuk mati rasa atau kesemutan di sekitar mulut, nyeri otot atau kram dan kejang.

Jika Anda lupa mengonsumsi Cinacalcet
Jangan mengambil dosis ganda untuk mengganti dosis yang terlupakan.

Jika pasien lupa dosis Cinacalcet, pasien harus mengambil dosis berikutnya seperti biasa.
Jika pasien memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter, apoteker atau perawat.

4. Kemungkinan efek samping yang terjadi

Seperti semua obat, obat ini bisa menimbulkan efek samping, meski tidak semua orang mengalaminya.

Tolong beritahu dokter segera:
- Jika pasien mulai mati rasa atau kesemutan di sekitar mulut, nyeri otot atau kram dan kejang. Ini mungkin tanda bahwa kadar kalsium pasien terlalu rendah (hipokalsemia).
- Jika pasien mengalami pembengkakan pada wajah, bibir, mulut, lidah atau tenggorokan yang dapat menyebabkan kesulitan menelan atau bernapas (angioedema).

Sangat umum: dapat mempengaruhi lebih dari 1 dari 10 orang
- mual dan muntah, efek samping ini biasanya cukup ringan dan tidak berlangsung lama.

Umum: dapat mempengaruhi hingga 1 dari 10 orang
- pusing

- mati rasa atau kesemutan (paresthesia)
- kehilangan (anoreksia) atau penurunan nafsu makan
- nyeri otot (mialgia)
- kelemahan (astenia)
- ruam
- penurunan kadar testosteron
- kadar kalium tinggi dalam darah (hiperkalemia)
- reaksi alergi (hipersensitivitas)
- sakit kepala
- kejang (kejang atau kejang)
- tekanan darah rendah (hipotensi)
- infeksi saluran pernapasan atas
- kesulitan bernapas (dispnea)
- batuk
- gangguan pencernaan (dispepsia)
- diare
- sakit perut, sakit perut - bagian atas
- sembelit
- kejang otot
- sakit punggung
- rendahnya kadar kalsium dalam darah (hipokalsemia).

Tidak diketahui: frekuensi tidak dapat diperkirakan dari data yang tersedia
- Biduran (urtikaria)
- Pembengkakan pada wajah, bibir, mulut, lidah atau tenggorokan yang dapat menyebabkan kesulitan menelan atau bernapas (angioedema)
- Denyut jantung yang sangat cepat atau berdebar kencang yang mungkin terkait dengan rendahnya kadar kalsium dalam darah Anda (perpanjangan interval QT dan aritmia ventrikel akibat hipokalsemia).

Setelah mengonsumsi Cinacalcet, sejumlah kecil pasien gagal jantung mengalami perburukan kondisinya dan / atau tekanan darah rendah (hipotensi).

Pelaporan efek samping
Jika Anda mengalami efek samping, bicarakan dengan dokter, apoteker atau perawat. Ini termasuk kemungkinan efek samping yang tidak tercantum dalam brosur ini.

5. Bagaimana menyimpan CALCET

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah tanggal kadaluwarsa yang tertera di karton dan blister.
Tanggal kedaluwarsa mengacu pada hari terakhir bulan itu.

6. Isi kemasan dan informasi lainnya

Tampilan Obat
Calcet 30 mg tablet salut selaput
Tablet salut bikonveks oval berwarna hijau, memiliki tanda C9CC di satu sisi dan 30 di sisi lainnya

Calcet 60 mg tablet salut selaput
Tablet salut bikonveks oval berwarna hijau, memiliki tanda C9CC di satu sisi dan 60 di sisi lainnya

Calcet 90 mg tablet salut selaput
Tablet salut bikonveks oval berwarna hijau, memiliki tanda C9CC di satu sisi dan 90 di sisi lainnya

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Kandungan Calcet

- Zat aktif Calcet adalah cinacalcet. Tiap tablet salut selaput mengandung cinacalcet hydrochloride setara dengan cinacalcet 30 mg, 60 mg atau 90 mg.

- Zat tambahan lainnya sebagai berikut :

  Tablet inti:
  Starch, pregelatinised (maize)
  Cellulose, microcrystalline (E460)
  Povidone (K-29/32)
  Crospovidone (Type A and B)
  Magnesium stearate (E572)
  Silica, colloidal anhydrous

  Tablet salut:
  Polyvinyl alcohol-partially hydrolyzed (E1203)
  Titanium dioxide (E171)
  Macrogol (L 4000)
  Talc (E553b)
  FD&C Blue #2/Indigo carmine aluminum lake (E132)
  Iron oxide yellow (E172)

Isi Kemasan Calcet

- Calcet 30 mg : Dus, 2 blister @ 15 tablet salut selaput Reg. No. :
- Calcet 60 mg : Dus, 2 blister @ 15 tablet salut selaput Reg. No. :
- Calcet 90 mg : Dus, 3 blister @ 10 tablet salut selaput Reg. No. :

HARUS DENGAN RESEP DOKTER

Diproduksi oleh:
Synthon Chile Ltda, Santiago – Chili

Di-*released* oleh:
Synthon Hispania S.L., Sant Boi de Llobregat – Spanyol

Di impor oleh:
PT. Pratapa Nirmala, Tangerang - Indonesia