SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
PIMARO 30 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance:
Cinacalcet ..... 30 mg (as hydrochloride)
Excipient(s):
Lactose monohydrate (from bovine milk) ... 0.3 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film coated tablets
Light green, oval, biconvex film coated tablets marked with "30" on one side.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of secondary hyperparathyroidism (HPT) in adult patients with end-stage renal disease (ESRD) on maintenance dialysis therapy.

PIMARO may be used as part of a therapeutic regimen including phosphate binders and/or vitamin D sterols, as appropriate (see section 5.1).

In the reduction of hypercalcaemia in the following patients:
- 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.

4.2 Posology and method of administration
Posology/frequency and duration of administration:
Secondary hyperparathyroidism
Adults and elderly (>65 years)
The recommended starting dose for adults is 30 mg once per day. PIMARO dosage 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 PIMARO. Reference should be made to current treatment guidelines.

PTH should be measured 1 to 4 weeks after initiation or dose adjustment of PIMARO. 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 PIMARO does not alter the relationship between iPTH and biPTH.

During dose titration, serum calcium levels should be monitored frequently, and within 1 week of initiation or dose adjustment of PIMARO. Once the maintenance dose has been established, serum calcium should be measured approximately monthly. In the event that corrected serum calcium levels fall below the normal range, appropriate steps should be taken to including adjustment of

concomitant therapy (see section 4.4).

Parathyroid carcinoma and primary hyperparathyroidism
Adults and elderly (>65 years)
The recommended starting dose of PIMARO for adults is 30 mg twice per day. The dose of PIMARO 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 PIMARO. Once maintenance dose levels have been established, serum calcium should be measured every 2 to 3 months. After titration to the maximum dose of PIMARO, serum calcium should be periodically monitored; if clinically relevant reductions in serum calcium are not maintained, discontinuation of PIMARO therapy should be considered (see section 5.1).

Method of administration:
For oral administration.

It is recommended that PIMARO 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 5.2). Tablets should be taken whole and should not be divided.

Additional information on special populations
Renal/Hepatic impairment:
No change in starting dose is necessary. PIMARO 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.

Pediatric population:
PIMARO is not indicated for use in children and adolescents less than 18 years of age due to a lack of data on safety and efficacy (see section 4.4).

Geriatric population:
No difference in the efficacy and safety of PIMARO was observed between patients older or younger than 65 years of age.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use
Serum calcium
PIMARO treatment should not be initiated in patients with a serum calcium (corrected for albumin) below the lower limit of the normal range.

Life threatening events and fatal outcomes associated with hypocalcaemia have been reported in adult and pediatric patients treated with PIMARO. 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 4.8). 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 4.2). Serum calcium should be measured within 1 week after initiation or dose adjustment of PIMARO. Once the maintenance dose has been established, serum calcium should be measured approximately monthly.

In the event that serum calcium levels fall below 8.4 mg/dl (2.1 mmol/L) and/or symptoms of hypocalcaemia occur the following management is recommended:

Serum calcium level or clinical symptoms of hypocalcemia	**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 hypocalcemia	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 hypocalcemia despite attempts to increase serum calcium	Reduce or withhold dose of PIMARO.
≤7.5 mg/dl (1.9 mmol/L) or persistent symptoms of hypocalcaemia and Vitamin D cannot be increased	Withhold administration of PIMARO until serum calcium levels reach 8 mg/dl (2 mmol/L) and/or symptoms of hypocalcaemia have resolved. Treatment should be reinitiated using the next lowest dose of PIMARO.

In chronic kidney disease patients receiving dialysis who were administered PIMARO, approximately 30% of patients had at least one serum calcium value less than 7.5 mg/dl (1.9 mmol/L).

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

Seizures
In clinical studies, seizures were observed in 1.4% of cinacalcet-treated patients and 0.7% of placebo-treated patients. While the basis for the reported difference in seizure rate is not clear, the threshold for seizures is lowered by significant reductions in serum calcium levels.

Hypotension and/or worsening heart failure
In post-marketing safety surveillance, isolated, idiosyncratic 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. Clinical trial data showed hypotension occurred in 7% of cinacalcet-treated patients, 12% of placebo-treated patients, and heart failure occurred in 2% of patients receiving cinacalcet or placebo.

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 PIMARO, the dose of PIMARO 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 end-stage renal disease 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), PIMARO should be used with caution in these patients and treatment should be closely monitored (see sections 4.2 and 5.2).

Lactose
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
Effects of other medicinal products on cinacalcet
Cinacalcet is metabolized 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 PIMARO may be required if a patient receiving PIMARO initiates or discontinues therapy with a strong inhibitor (e.g. ketoconazole, itraconazole, telithromycin, voriconazole, ritonavir) or inducer (e.g. rifampicin) of this enzyme (see section 4.4).

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 dose 1500 mg) did not alter the pharmacokinetics of cinacalcet.

Sevelamer:
Co-administration of sevelamer (2400 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 metabolized by the enzyme P450 2D6 (CYP2D6): Cinacalcet is a strong inhibitor of CYP2D6. Dose adjustments of concomitant medicinal products may be required when PIMARO is administered with individually titrated, narrow therapeutic index substances that are

predominantly metabolised by CYP2D6 (e.g. flecainide, propafenone, metoprolol, desipramine, nortriptyline, clomipramine) (see section 4.4).

Desipramine:
Concurrent administration of 90 mg cinacalcet once daily with 50 mg desipramine, a tricyclic antidepressant metabolized primarily by CYP2D6, significantly increased desipramine exposure 3.6-fold (90% confidence interval 3-4.4) in CYP2D6 normal metabolisers.

Warfarin:
Repeated 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.

Additional information on special populations
Pediatric population:
PIMARO is not indicated for use in children and adolescents due to a lack of data on safety and efficacy (see section 4.4).

4.6 Pregnancy and lactation
General recommendation
Pregnancy category: C

Women of child-bearing potential/Birth control (Contraception)
There is not enough data regarding the use of PIMARO in women of childbearing potential.

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, embryonal/fetal development, labour and postnatal development. No embryonal/fetal toxicities were seen in studies in rats and rabbits with the exception of decreased fetal body weights in rats at doses associated with maternal toxicities. Cinacalcet should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 PIMARO.

Reproductive ability/Fertility
In animal studies, no effect on male or female fertility was detected at exposure 4 times the human

dose of 180 mg/day.

4.7. Effects on ability to drive and use machinery

No studies have been conducted on the effects on the ability to drive and use machines. However, certain adverse reactions may affect the ability to drive and use machines (see section 4.8).

4.8. Undesirable effects

a) 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.

b) Tabulated list of adverse reactions

As a result of the best evaluation of the available data in terms of causality, adverse reactions identified in placebo-controlled studies and single-arm studies as at least possibly related to cinacalcet treatment are listed below using the following classification:

Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

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

MedDRA system organ class	**Patient incidence**	**Adverse reactions**
Immune system disorders	Common*	Hypersensitivity reactions
Metabolism and nutrition disorders	Common	Anorexia Decreased appetite
Nervous system disorders	Common	Seizures† Dizziness Paresthesia Headache
Cardiac disorders	Not known*	Worsening heart failure† QT prolongation and ventricular arrhythmia secondary to hypocalcemia†
Vascular disorders	Common	Hypotension
Respiratory, thoracic and mediastinal disorders	Common	Upper respiratory infection Dyspnea Cough
Gastrointestinal disorders	Very common	Nausea Vomiting
	Common	Dyspepsia Diarrhea Abdominal pain Abdominal pain – upper Constipation
Skin and subcutaneous tissue disorders	Common	Rash
Musculoskeletal, connective tissue and bone disorders	Common	Myalgia Muscle spasms Back pain
General disorders and diseases related to the	Common	Asthenia

application area		
Investigations	Common	Hypocalcaemia† Hyperkalemia Reduced testosterone levels†

† see section 4.4
*see section c

c) 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 hypocalcemia
QT prolongation and ventricular arrhythmia secondary to hypocalcaemia have been reported during post-marketing use of cinacalcet, the frequencies of which cannot be estimated from available data (see section 4.4).

d) Pediatric population
Cinacalcet is not indicated for use in pediatric patients. The safety and efficacy of cinacalcet in the pediatric population have not been established. A fatal outcome was reported in a pediatric clinical trial patient with severe hypocalcemia (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 the national reporting system.

4.9. Overdose and treatment
Doses titrated up to 300 mg once daily have been safely administered to patients receiving dialysis.

Overdosage of PIMARO may lead to hypocalcaemia. In the event of overdosage, patients should be monitored for signs and symptoms of hypocalcaemia and treatment should be symptomatic and supportive.
Since cinacalcet is highly protein bound, hemodialysis is not an effective treatment for overdosage of cinacalcet.

5. PHARMACOLOGICAL PROPERTIES
5.1. 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

Three, 6-month, double-blind, placebo-controlled clinical studies were conducted in 1136 end stage renal disease (ESRD) patients with uncontrolled secondary hyperparathyroidism receiving dialysis. Demographic and baseline characteristics were appropriate for the dialysis patient population with secondary hyperparathyroidism. 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×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 (HD or PD), 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 formation and destruction 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 chronic kidney disease and secondary hyperparathyroidism not undergoing dialysis indicated that cinacalcet reduced serum PTH levels to a similar extent as in patients with end-stage renal disease (ESRD) and secondary hyperparathyroidism 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 chronic kidney disease patients not undergoing dialysis treated with cinacalcet have an increased risk for hypocalcaemia compared with cinacalcet-treated end-stage renal disease patients receiving dialysis, which may be due to lower baseline calcium levels and/or the residual kidney function.

EVOLVE (Evaluation Of Cinacalcet HCl Therapy to Lower CardioVascular Events) was a randomized, 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 chronic kidney disease patients 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, hospitalization 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

In one study, 46 adult patients (29 with parathyroid carcinoma and 17 with primary HPT and severe hypercalcemia 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 ≥1 mg/dl (≥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). 18 of 29 patients (62%) with parathyroid carcinoma and 15 of 17 subjects (88%) with primary HPT achieved a reduction in serum calcium of ≥1 mg/dl (≥0.25 mmol/L).

In a 28 week placebo-controlled study, 67 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 ≤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 ≤10.3 mg/dl (2.57 mmol/L) and ≥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).

5.2. Pharmacokinetic properties

General properties

Absorption:

After oral administration of cinacalcet, maximum plasma concentration is achieved in approximately 2 to 6 hours.

Based on between-study comparisons, the absolute bioavailability of cinacalcet in fasted subjects has been estimated to be about 20-25%. Administration of cinacalcet with food results in an approximate 50–80% increase in cinacalcet bioavailability. Increases in plasma cinacalcet concentration are similar, regardless of the fat content of the meal.

At doses above 200 mg, the absorption was saturated probably due to poor solubility.

Distribution:

The volume of distribution is high (approximately 1000 liters), indicating extensive distribution. Cinacalcet is approximately 97% bound to plasma proteins and distributes minimally into red blood cells.

After absorption, cinacalcet concentrations decline in a biphasic fashion with an initial half-life of approximately 6 hours and a terminal half-life of 30 to 40 hours. Steady state levels of cinacalcet are achieved within 7 days with minimal accumulation. The pharmacokinetics of cinacalcet does not change over time.

Biotransformation:

Cinacalcet is metabolized by multiple enzymes, predominantly CYP3A4 and CYP1A2 (the contribution of CYP1A2 has not been characterized clinically). The major circulating metabolites are inactive.

Based on *in vitro* data, cinacalcet is a strong inhibitor of CYP2D6, but is neither an inhibitor of other CYP enzymes at concentrations achieved clinically, including CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 nor an inducer of CYP1A2, CYP2C19 and CYP3A4.

Elimination:
After administration of a 75 mg radiolabeled dose to healthy volunteers, cinacalcet was rapidly and extensively metabolized by oxidation followed by conjugation. Renal excretion of metabolites was the prevalent route of elimination of radioactivity. Approximately 80% of the dose was recovered in the urine and 15% in the feces.

Linearity/Non-linearity:
The AUC (Area Under the Curve) and C_{max} of cinacalcet increase approximately linearly over the dose range of 30 to 180 mg once daily.

Pharmacokinetic/pharmacodynamic relationship(s)
Soon after dose administration, PTH begins to decrease to reach a minimum point approximately 2 to 6 hours after the dose, corresponding to the C_{max} of cinacalcet. Thereafter, as cinacalcet levels begin to decline, PTH levels increase until 12 hours post-dose, and then PTH suppression remains approximately constant to the end of the once daily dosing interval. PTH levels in cinacalcet clinical trials were measured at the end of the dosing interval.

Characteristics in patients
Elderly:
There are no clinically relevant differences due to age in the pharmacokinetics of cinacalcet.

Renal insufficiency:
The pharmacokinetic profile of cinacalcet in patients with mild, moderate, and severe renal insufficiency, and those on hemodialysis or peritoneal dialysis is comparable to that in healthy volunteers.

Hepatic insufficiency:
Mild hepatic impairment did not notably affect the pharmacokinetics of cinacalcet. Compared to subjects with normal liver function, average AUC of cinacalcet was approximately 2-fold higher in subjects with moderate impairment and approximately 4-fold higher in subjects with severe impairment. The mean half-life of cinacalcet is prolonged by 33% and 70% in patients with moderate and severe hepatic impairment, respectively. Protein binding of cinacalcet is not affected by impaired hepatic function. Because doses are titrated for each subject based on safety and efficacy parameters, no additional dose adjustment is necessary for subjects with hepatic impairment (see sections 4.2 and 4.4).

Gender:
Clearance of cinacalcet may be lower in women than in men. Because doses are titrated for each subject, no additional dose adjustment is necessary based on gender.

Pediatric population:
The pharmacokinetics of cinacalcet have been studied in 12 pediatric patients (6-17 years) with

chronic kidney disease receiving dialysis following a single, oral, 15 mg dose. Mean AUC and C_{max} values (23.5 (range 7.22 to 77.2) ng*hr/ml and 7.26 (range 1.80 to 17.4) ng/ml, respectively) were within approximately 30% of the means for AUC and C_{max} values observed in a single study in healthy adults following a single 30 mg dose (33.6 (range 4.75 to 66.9) ng*hr/ml and 5.42 (range 1.41 to 12.7) ng/ml, respectively). Due to the limited data in pediatric subjects, the potential for higher exposures in the lighter/younger relative to heavier/older pediatric subjects for a given dose of cinacalcet cannot be excluded. The pharmacokinetics in pediatric subjects after multiple doses has not been studied.

Smoking:
Clearance of cinacalcet is higher in smokers than in non-smokers, likely due to induction of CYP1A2-mediated metabolism. If a patient stops or starts smoking, cinacalcet plasma levels may change and dose adjustment may be necessary.

5.3. Preclinical safety data
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 fetal 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.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Pregelatinised starch
Microcrystalline cellulose
Crospovidone
Colloidal anhydrous silica
Magnesium stearate
Sheffcoat Green L TN 1264G49 (Film coating agent)
- Hydroxypropylmethyl cellulose 6 cps
- Hydroxypropylmethyl cellulose 3 cps
- Titanium dioxide
- Lactose monohydrate (made from bovine milk)
- Triacetin (Glycerol triacetate)

Yellow iron oxide
FD&C Blue # 2 (Indigotine aluminum lake)
Opadry Transparent OY 29020 (Film coating material)
HPMC 2910 (Hypromellose 6 cp)
Macrogol (PEG 400)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store at room temperature below 30°C.

6.5 Nature and contents of container
Transparent PVC/Aclar - Aluminum foil
It is presented in blister packages containing 28 film coated tablets in a box, together with the package leaflet.

6.6. Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER
DEVA HOLDİNG A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad.
No: 1 34303 Küçükçekmece/İSTANBUL/TÜRKİYE
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8. MARKETING AUTHORIZATION NUMBER(S)
2017/275

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
Date of first authorization : 25.04.2017
Date of latest renewal :

10. DATE OF REVISION OF THE TEXT