SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<PRODUCT NAME> 30 mg film-coated tablets
<PRODUCT NAME> 60 mg film-coated tablets
<PRODUCT NAME> 90 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30 mg cinacalcet (as hydrochloride).
Each tablet contains 60 mg cinacalcet (as hydrochloride).
Each tablet contains 90 mg cinacalcet (as hydrochloride).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

30 mg tablets: Light green to green, film-coated, oval shaped tablet (10 mm X 6 mm), debossed with "C30" on one side of the tablet and plain on the other side.

60 mg tablets: Light green to green, film-coated, oval shaped tablet (13 mm X 8 mm), debossed with "C60" on one side of the tablet and plain on the other side.

90 mg tablets: Light green to green, film-coated, oval shaped tablet (15 mm X 9mm), debossed with "C90" on one side of the tablet and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

<PRODUCT NAME> may be used as part of a therapeutic regimen including phosphate binders and/or Vitamin D sterols, as appropriate (see section 5.1).

Reduction of hypercalcaemia in 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.

4.2 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. <PRODUCT NAME> 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 <PRODUCT NAME>. Reference should be made to current treatment guidelines.

PTH should be measured 1 to 4 weeks after initiation or dose adjustment of <PRODUCT NAME>. 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 <PRODUCT NAME> 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 <PRODUCT NAME>. Once the maintenance dose has been established, serum calcium should be measured approximately monthly. If serum calcium levels decrease below the normal range, appropriate steps should be taken, including adjustment of concomitant therapy (see section 4.4).

Paediatric population

<PRODUCT NAME> is not indicated for use in children and adolescents due to a lack of data on safety and efficacy (see section 4.4).

Parathyroid carcinoma and primary hyperparathyroidism

Adults and elderly (> 65 years)

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

Paediatric population

<PRODUCT NAME> is not indicated for use in children and adolescents due to a lack of data on safety and efficacy (see section 4.4).

Hepatic impairment

No change in starting dose is necessary. <PRODUCT NAME> 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 4.4 and 5.2).

Method of administration

For oral use. It is recommended that <PRODUCT NAME> 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 not divided.

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

<PRODUCT NAME> 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 paediatric 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 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 <PRODUCT NAME>. 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 value 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 <PRODUCT NAME>.
≤ 7.5 mg/dl (1.9 mmol/l) or persistent symptoms of hypocalcemia and Vitamin D cannot be increased	Withhold administration of <PRODUCT NAME> 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 <PRODUCT NAME>.

In CKD patients receiving dialysis who were administered with cinacalcet, 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 CKD patients not on dialysis. Investigational studies have shown that 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

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 <PRODUCT NAME>, the dose of <PRODUCT NAME> 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 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), <PRODUCT NAME>should be used with caution in these patients and treatment should be closely monitored (see sections 4.2 and 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medications 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 <PRODUCT NAME> may be required if a patient receiving <PRODUCT NAME> initiates or discontinues therapy with a strong inhibitor (e.g. ketoconazole, itraconazole, telithromycin, voriconazole, ritonavir) or inducer (eg 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 1,500 mg dose) 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 medications

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 <PRODUCT NAME> 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 metabolised primarily by CYP2D6, significantly increased desipramine exposure 3.6-fold (90 % CI 3.0, 4.4) 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 metabolized by CYP3A4 and CYP3A5, such as certain immunosuppressants, including cyclosporine and tacrolimus.

4.6 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 5.3). <PRODUCT NAME> 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 <PRODUCT NAME>.

Fertility

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. 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

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	**Subject incidence**	**Adverse reaction**
Immune system disorders	Common*	Hypersensitivity reactions
Metabolism and nutrition disorders	Common	Anorexia
	Common	Decreased appetite
Nervous system disorders	Common	Seizures†
	Common	Dizziness
	Common	Paraesthesia
	Common	Headache
Cardiac disorders	Not known*	Worsening heart failure†
	Not known*	QT prolongation and ventricular arrhythmia secondary to hypocalcaemia†
Vascular disorders	Common	Hypotension
Respiratory, thoracic and mediastinal disorders	Common	Upper respiratory infection
	Common	Dyspnoea
	Common	Cough
Gastrointestinal disorders	Very common	Nausea
	Very common	Vomiting
	Common	Dyspepsia
	Common	Diarrhoea
	Common	Abdominal pain
	Common	Abdominal pain – upper
	Common	Constipation
Skin and subcutaneous tissue disorders	Common	Rash
Musculoskeletal and connective	Common	Myalgia

tissue disorders	Common	Muscle spasms
	Common	Back pain
General disorders and administration site conditions	Common	Asthenia
Investigations	Common	Hypocalcaemia†
	Common	Hyperkalaemia
	Common	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 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 4.4).

d) Paediatric population

<PRODUCT NAME> is not indicated for use in paediatric patients. The safety and efficacy of cinacalcet in the paediatric population have not been established. A fatal outcome was reported in a paediatric clinical trial patient with severe hypocalcaemia (see section 4.4).

Reporting of suspected adverse reactions
Reporting of 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 the national reporting system listed in Appendix V.

4.9 Overdose

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

Overdose of <PRODUCT NAME> 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.

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 ESRD patients with uncontrolled secondary HPT receiving dialysis (n=1136). 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 HCl Therapy to Lower CardioVascular Events) was a randomized, double-blind clinical study evaluating cinacalcet HCl vs. 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, 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 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 ≥ 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). Eighteen 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

Absorption

After oral administration of cinacalcet, maximum plasma cinacalcet 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 litres), 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 metabolised by multiple enzymes, predominantly CYP3A4 and CYP1A2 (the contribution of CYP1A2 has not been characterised 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 radiolabelled dose to healthy volunteers, cinacalcet was rapidly and extensively metabolised 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 faeces.

Linearity/non-linearity

The AUC 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 dosing, PTH begins to decrease until a nadir at approximately 2 to 6 hours post-dose, corresponding with cinacalcet C_{max}. 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.

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

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

Hepatic impairment: 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.

Paediatric Population: The pharmacokinetics of cinacalcet have been studied in 12 paediatric patients (6-17 years) with CKD 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 paediatric subjects, the potential for higher exposures in the lighter/younger relative to heavier/older paediatric subjects for a given dose of cinacalcet cannot be excluded. The pharmacokinetics in paediatric 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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Starch, pre-gelatinised (maize)
Cellulose, microcrystalline
Crospovidone (type B)
Magnesium stearate
Silica, colloidal anhydrous

Tablet coat

Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc
Yellow iron oxide (E172)
Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blisters:
PVC/ACLAR/PVC - aluminum blister packs containing 14, 14x1, 28, 28x1, 30, 30x1, 84, 84x1 tablets per carton.
PVC/ACLAR/PVdC/PVC - aluminum blister packs containing 14, 14x1, 28, 28x1, 30, 30x1, 84, 84x1 tablets per carton.

Bottles
White High Density Polyethylene (HDPE) bottle with child resistant, polypropylene screw cap with heat induction sealing.
White High Density Polyethylene (HDPE) bottle containing a white HDPE silica gel desiccant canister with child resistant, polypropylene screw cap with heat induction sealing.
Each bottle contains 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>
<Date of latest renewal: {DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>

<[To be completed nationally]>