Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cinacalcet Rowex 30 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 30 mg cinacalcet (as hydrochloride).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Green oval biconvex film-coated tablets (dimension: 4.5 x 7 mm), debossed with 'C9CC' on one side and '30' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Secondary hyperparathyroidism

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

Paediatric population
Treatment of secondary hyperparathyroidism (HPT) in children aged 3 years and older with end-stage renal disease (ESRD) on maintenance dialysis therapy in whom secondary HPT is not adequately controlled with standard of care therapy (see section 4.4).

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

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.

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. Cinacalcet 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 cinacalcet. Reference should be made to current treatment guidelines.

PTH should be measured 1 to 4 weeks after initiation or dose adjustment of cinacalcet. 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 cinacalcet 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 Cinacalcet Rowex (see section 4.4). 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 cinacalcet. 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 Cinacalcet Rowex.

Corrected Serum calcium level or clinical symptoms of hypocalcaemia	**Recommendations**
≤ 7.5 mg/dL (1.9 mmol/L) or persistent symptoms of hypocalcaemia and Vitamin D cannot be increased	Withhold administration of Cinacalcet Rowex 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 Cinacalcet Rowex.

Paediatric population
Corrected serum calcium should be in the upper range of, or above, the age-specified reference interval prior to administration of first dose of Cinacalcet Rowex, and closely monitored (see section 4.4). The normal calcium range differs depending on the methods used by your local laboratory and the age of the child/patient.
The recommended starting dose for children aged ≥ 3 years to < 18 years is ≤ 0.20 mg/kg once daily based on the patient's dry weight (see table 1).

The dose can be increased to achieve a desired target iPTH range. The dose should be increased sequentially through available dose levels (see table 1) no more frequently than every 4 weeks. The dose can be increased up to a maximum dose of 2.5 mg/kg/day, not to exceed a total daily dose of 180 mg.

Table 1. Cinacalcet Rowex daily dose in paediatric patients

Patient dry weight (kg)	**Starting dose (mg)**	**Available sequential**

		dose levels (mg)
10 to < 12.5	1	1, 2.5, 5, 7.5, 10 and 15
≥ 12.5 to < 25	2.5	2.5, 5, 7.5, 10, 15, and 30
≥ 25 to < 36	5	5, 10, 15, 30, and 60
≥ 36 to < 50		5, 10, 15, 30, 60, and 90
≥ 50 to < 75	10	10, 15, 30, 60, 90, and 120
≥ 75	15	15, 30, 60, 90, 120, and 180

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

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 Cinacalcet Rowex to the next lower dose.
- If iPTH < 100 pg/mL (10.6 pmol/L), stop Cinacalcet Rowex treatment, restart Cinacalcet Rowex at the next lower dose once the iPTH is > 150 pg/mL (15.9 pmol/L). If Cinacalcet Rowex 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 Cinacalcet Rowex.

Once the maintenance dose has been established, weekly measurement of serum calcium is recommended. Serum calcium levels in paediatric patients should be maintained within the normal range. If serum calcium levels decrease below the normal range or symptoms of hypocalcaemia occur, appropriate dose adjustment steps should be taken as shown in table 2 below:

Table 2: Dose adjustment in paediatric patients ≥ 3 to < 18 years of age

Corrected Serum calcium value or clinical symptoms of hypocalcaemia	**Dosing recommendations**
Corrected serum calcium is at or below age-specified lower limit of normal or if symptoms of hypocalcaemia occur, regardless of calcium level.	Stop treatment with Cinacalcet Rowex.* Administer calcium supplements, calcium-containing phosphate binders and/or vitamin D sterols, as clinically indicated.
Corrected total serum calcium is above age-specified lower limit of normal, and Symptoms of hypocalcaemia have resolved.	Restart at the next lower dose. If Cinacalcet Rowex treatment has been stopped for more than 14 days, restart at the recommended starting dose. If patient was receiving the lowest dose (1 mg/day) prior to discontinuation, restart at the same dose (1 mg/day).

*If the dose has been stopped, corrected serum calcium should be measured within 5 to 7 days

The safety and efficacy of Cinacalcet Rowex in children aged less than 3 years for the treatment of secondary hyperparathyroidism have not been established. Insufficient data are available.

Parathyroid carcinoma and primary hyperparathyroidism
Adults and elderly (> 65 years)

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

Paediatric population
The safety and efficacy of Cinacalcet Rowex 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. Cinacalcet 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.
Tablets should be taken whole and should not be chewed, crushed or divided.

It is recommended that cinacalcet 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).

Cinacalcet is also available as granules for paediatric use. Children who require doses lower than 30 mg, or who are unable to swallow tablets should receive cinacalcet granules

4.3 Contraindications

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

Hypocalcaemia (see sections 4.2 and 4.4).

4.4 Special warnings and precautions for use

Serum calcium

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 cinacalcet.

Adults
Cinacalcet Rowex 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).

Paediatric population

Cinacalcet Rowex should only be initiated for the treatment of secondary HPT in children ≥ 3 years old with ESRD on maintenance dialysis therapy, in whom secondary HPT is not adequately controlled with standard of care therapy, where serum calcium is in the upper range of, or above, the age-specified reference interval.

Closely monitor serum calcium levels (see section 4.2) and patient compliance during treatment with cinacalcet. Do not initiate cinacalcet or increase the dose if non-compliance is suspected.

Prior to initiating cinacalcet and during treatment, consider the risks and benefits of treatment and the ability of the patient to comply with the recommendations to monitor and manage the risk of hypocalcaemia.

Inform paediatric patients and/or their caregivers about the symptoms of hypocalcaemia and about the importance of adherence to instructions about serum calcium monitoring, and posology and method of administration.

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 Rowex (see section 4.8). 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 Rowex, 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 4.8).

Co-administration with other medicinal products

Administer Cinacalcet Rowex with caution in patients receiving any other medicinal products known to lower serum calcium. Closely monitor serum calcium (see section 4.5).

Patients receiving Cinacalcet Rowex should not be given etelcalcetide. Concurrent administration may result in severe hypocalcaemia.

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 4.2 and 5.2).

4.5 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 Rowex may result in an increased risk of hypocalcaemia (see section 4.4). Patients receiving Cinacalcet Rowex should not be given etelcalcetide (see section 4.4).

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 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 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 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 (metabolized 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 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). 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.

4.7 Effects on ability to drive and use machines

Dizziness and seizures, which may have major influence on the ability to drive and use machines, have been reported by patients taking Cinacalcet Rowex (see section 4.4).

4.8 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), 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	**Subject incidence**	**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 4.4
*see section 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).

Paediatric population
The safety of Cinacalcet Rowex for the treatment of secondary HPT in paediatric patients with ESRD receiving dialysis was evaluated in two randomised controlled studies and one single-arm study (see section 5.1). Among all paediatric subjects exposed to cinacalcet in clinical studies a total of 19 subjects (24.1%; 64.5 per 100 subject years) had at least one adverse event of hypocalcaemia. A fatal outcome was reported in a paediatric clinical trial patient with severe hypocalcaemia (see section 4.4).

Cinacalcet Rowex should be used in paediatric patients only if the potential benefit justifies the potential risk.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Doses titrated up to 300 mg once daily have been administered to adult patients receiving dialysis without adverse outcome. A daily dose of 3.9 mg/kg was prescribed to a paediatric patient receiving dialysis in a clinical study with subsequent mild stomach ache, nausea and vomiting.

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.

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
Adults
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 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.

Paediatric population
The efficacy and safety of cinacalcet for the treatment of secondary HPT in paediatric patients with ESRD receiving dialysis was evaluated in two randomised controlled studies and one single-arm study.

Study 1 was a double-blind, placebo-controlled study in which 43 patients aged 6 to < 18 years were randomised to receive either cinacalcet (n = 22) or placebo (n = 21). The study consisted of a 24-week dose titration period followed by a 6-week efficacy assessment phase (EAP), and a 30-week open- label extension. The mean age at baseline was 13 (range 6 to 18) years. The majority of patients (91%) were using vitamin D sterols at baseline. The mean (SD) iPTH concentrations at baseline were 757.1 (440.1) pg/mL for the cinacalcet group and 795.8 (537.9) pg/mL for the placebo group. The mean (SD) corrected total serum calcium concentrations at baseline were 9.9 (0.5) mg/dL for the cinacalcet group and 9.9 (0.6) mg/dL for the placebo group. The mean maximum daily dose of cinacalcet was 1.0 mg/kg/day.

The percentage of patients who achieved the primary endpoint (≥ 30% reduction from baseline in mean plasma iPTH during the EAP; weeks 25 to 30) was 55% in the cinacalcet group and 19.0% in the placebo group (p = 0.02). The mean serum calcium levels during the EAP were within the normal range for the cinacalcet treatment group. This study was terminated early due to a fatality with severe hypocalcaemia in the cinacalcet group (see section 4.8).

Study 2 was an open-label study in which 55 patients aged 6 to < 18 years (mean 13 years) were randomised to receive either cinacalcet in addition to standard of care (SOC, n = 27) or SOC alone (n = 28). The majority of patients (75%) were using vitamin D sterols at baseline. The mean (SD) iPTH concentrations at baseline were 946 (635) pg/mL for the cinacalcet + SOC group and 1228 (732) pg/mL for the SOC group. The mean (SD) corrected total serum calcium concentrations at baseline were 9.8 (0.6) mg/dL for the cinacalcet + SOC group and 9.8 (0.6) mg/dL for the SOC group. 25 subjects received at least one dose of cinacalcet and the mean maximum daily dose of cinacalcet was 0.55 mg/kg/day. The study did not meet its primary endpoint (≥ 30% reduction from baseline in mean plasma iPTH during the EAP; weeks 17 to 20). Reduction of ≥ 30% from baseline in mean plasma iPTH during the EAP was achieved by 22% of patients in the cinacalcet + SOC group and 32% of patients in the SOC group.

Study 3 was a 26-week, open-label, single-arm safety study in patients aged 8 months to < 6 years (mean age 3 years). Patients receiving concomitant medications known to prolong the corrected QT interval were excluded from the study. The mean dry weight at baseline was 12 kg. The starting dose of cinacalcet was 0.20 mg/kg. The majority of patients (89%) were using vitamin D sterols at baseline.

Seventeen patients received at least one dose of cinacalcet and 11 completed at least 12 weeks of treatment. None had corrected serum calcium < 8.4 mg/dL (2.1 mmol/L) for ages 2-5 years. iPTH concentrations from baseline were reduced by ≥ 30% in 71% (12 out of 17) of patients in the study.

<u>Parathyroid carcinoma and Primary Hyperparathyroidism</u>
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 ≥ 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 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 ≤ 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 1,000 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 was studied in paediatric patients with ESRD receiving dialysis aged 3 to 17 years of age. After single and multiple once daily oral doses of cinacalcet, plasma cinacalcet concentrations (C_{max} and AUC values after normalization by dose and weight) were similar to those observed in adult patients. A population pharmacokinetic analysis was performed to evaluate the effects of demographic characteristics. This analysis showed no significant impact of age, sex, race, body surface area and body weight on cinacalcet pharmacokinetics.

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 KATP 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Maize starch, partially pregelatinized
Cellulose, microcrystalline
Povidone K29/32
Crospovidone type A
Crospovidone type B
Magnesium stearate
Silica, colloidal anhydrous

Tablet coating:
Polyvinyl alcohol-partially hydrolyzed

Titanium dioxide (E171)
Macrogol 4000
Talc Indigo carmine aluminum lake (E132)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PE/PVDC/Al blister

Pack sizes: 14, 28 and 84 film-coated tablets
Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/285/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th January 2018

10 DATE OF REVISION OF THE TEXT

July 2018