1. PRODUCT NAME

Sensipar® 30 mg film coated tablets

Sensipar® 60 mg film coated tablets

Sensipar® 90 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cinacalcet 30 mg (corresponding to 33 mg as the hydrochloride salt)

Cinacalcet 60 mg (corresponding to 66 mg as the hydrochloride salt)

Cinacalcet 90 mg (corresponding to 99 mg as the hydrochloride salt)

Excipient(s) with known effect

Each 30 mg tablet contains 2.74 mg of lactose

Each 60 mg tablet contains 5.47 mg of lactose

Each 90 mg tablet contains 8.21 mg of lactose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sensipar 30 mg tablets are formulated as light green, film-coated, oval-shaped tablets marked with “AMG” on one side and “30” on the opposite side.

Sensipar 60 mg tablets are formulated as light green, film-coated, oval-shaped tablets marked with “AMG” on one side and “60” on the opposite side.

Sensipar 90 mg tablets are formulated as light green, film-coated, oval-shaped tablets marked with “AMG” on one side and “90” on the opposite side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sensipar may be used to treat the biochemical manifestations of secondary hyperparathyroidism in adult patients with end stage renal disease, receiving dialysis. Sensipar should be used as adjunctive therapy.

Sensipar is indicated for the treatment of hypercalcaemia in adult patients with parathyroid carcinoma.

Sensipar may be used to treat the biochemical manifestations of primary hyperparathyroidism in adult patients for whom parathyroidectomy is not a treatment option.

4.2 Dose and method of administration

Dose

Patients with end stage renal disease receiving dialysis

Sensipar reduces parathyroid hormone (PTH) while simultaneously lowering Ca x P, calcium and phosphorus levels in patients receiving dialysis.

The recommended starting dose for adults is 30 mg once per day.

Sensipar should be titrated every 2 to 4 weeks to a maximum dose of 180 mg once daily to achieve a target PTH between 15.9 and 31.8 pmol/L (150-300 pg/mL).

In chronic kidney disease (CKD) patients, PTH levels should be assessed at least 12 hours after dosing with cinacalcet.

During dose titration, serum calcium levels should be monitored frequently and if serum calcium levels decrease below the normal range, appropriate steps should be taken to increase serum calcium levels (see section 4.4).

Parathyroid carcinoma and primary hyperparathyroidism (HPT) for whom parathyroidectomy is not a treatment option

The recommended starting dose of Sensipar for adults is 30 mg twice daily.

The dosage of Sensipar 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 normalise serum calcium.

Elderly

Age does not alter the pharmacokinetics of cinacalcet; no dosage adjustment is required for geriatric patients.

Renal impairment

Renal impairment does not alter the pharmacokinetics of cinacalcet; no dosage adjustment is necessary for renal impairment.

Hepatic impairment

Moderate to severe hepatic impairment (Child-Pugh classification) increases cinacalcet drug concentrations by approximately 2 to 4 fold. In patients with moderate-severe hepatic impairment, PTH and serum calcium concentrations should be closely monitored during dose titration of cinacalcet.

Paediatric population

The safety and efficacy of cinacalcet in paediatric patients have not been established (see section 4.4, Paediatric population).

Method of administration

Sensipar is administered orally. It is recommended that Sensipar be taken with food or shortly after a meal. Tablets should be taken whole and should not be divided.

4.3 Contraindications

Sensipar is contraindicated in patients with hypersensitivity to any component(s) of this product.

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

4.4 Special warnings and precautions for use

Seizures

In clinical studies, seizures (primarily generalized or tonic-clonic) were observed in 1.4% (43/3,049) of cinacalcet-treated patients and 0.7% (5/687) 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.

Adynamic bone

In CKD patients receiving dialysis adynamic bone may develop if PTH levels are suppressed below 100 pg/mL (10.6 pmol/L). If PTH levels decrease below the recommended target range in patients treated with cinacalcet, the dose of vitamin D sterols and/or cinacalcet should be reduced or therapy discontinued.

Serum calcium

Cinacalcet treatment should not be initiated in patients with CKD receiving dialysis if serum calcium is less than 8.4 mg/dL [2.1 mmol/L].

Life threatening events and fatal outcomes associated with hypocalcaemia have been reported in patients treated with cinacalcet including in paediatric patients. Decreases in serum calcium can prolong the QT interval, potentially resulting in ventricular arrhythmia. Cases of QT prolongation and ventricular arrhythmia secondary to hypocalcaemia have been reported in patients treated with cinacalcet. Manifestations of hypocalcaemia may also include paraesthesias, myalgias, cramping, tetany, and seizures.

Since cinacalcet lowers serum calcium, patients should be monitored for the occurrence of hypocalcaemia. Serum calcium should be measured within 1 week after initiation or dose adjustment of cinacalcet. Once the maintenance dose has been established, serum calcium should be measured approximately monthly. If serum calcium falls below 8.4 mg/dL but remains above 7.5 mg/dL, or if symptoms of hypocalcaemia occur, calcium-containing phosphate binders and/or vitamin D sterols can be used to raise serum calcium. If hypocalcaemia persists, reduce the dose or discontinue administration of cinacalcet. If serum calcium falls below 7.5 mg/dL, or if symptoms of hypocalcaemia persist and the dose of vitamin D cannot be increased, withhold administration of cinacalcet until serum calcium levels reach 8.0 mg/dL and/or symptoms of hypocalcaemia have resolved. Treatment should be reinitiated using the next lowest dose of cinacalcet (see section 4.2).

In CKD patients receiving dialysis who were administered cinacalcet, 29% of patients in the 6-month registrational trials and 21% and 33% of patients (within the first 6 months and overall, respectively) in the EVOLVE (Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events) clinical trial, had at least one serum calcium value less than 7.5 mg/dL (1.88 mmol/L). Less than 1% of patients receiving dialysis both in the group treated with cinacalcet and in the group treated with placebo permanently discontinued study drug due to hypocalcaemia in the registrational clinical trials. In the

EVOLVE clinical trial, 1.1% of patients in the cinacalcet group and 0.1% in the placebo group permanently discontinued study drug due to hypocalcaemia.

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

Hepatic insufficiency

Due to the potential for 2 to 4 times higher plasma levels of cinacalcet in patients with moderate to severe hepatic impairment, physicians should closely monitor these patients when initiating cinacalcet (see section 5.2).

Testosterone levels

Testosterone levels are often below the normal range in patients with end-stage renal disease. In a clinical study of CKD 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. The clinical significance of these reductions in serum testosterone is unknown. 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.

Neoplastic events

In a randomised, double-blind, placebo-controlled clinical study of 3,883 dialysis patients, neoplastic events were reported in 2.9 and 2.5 patients per 100 patient-years in cinacalcet and placebo-treatment groups, respectively. A causal relationship to cinacalcet has not been established.

Coadministration with other products

Administer cinacalcet with caution in patients receiving any other medications known to lower serum calcium. Closely monitor serum calcium levels in patients receiving other medications known to lower serum calcium.

Laboratory tests

Patients with CKD and secondary hyperparathyroidism

Serum calcium should be measured within 1 week and iPTH should be measured 1 to 4 weeks after initiation or dose adjustment of cinacalcet. Once the maintenance dose has been established, serum calcium should be measured approximately monthly, and PTH every 1 to 3 months (see section 4.2). 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.

Patients with parathyroid carcinoma and patients with primary hyperparathyroidism for whom parathyroidectomy is not a treatment option

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 (see section 4.2).

Interference with laboratory and diagnostic tests

None known.

Paediatric population

The safety and efficacy of cinacalcet in paediatric patients have not been established. Cinacalcet is not indicated for use in paediatric patients. A fatal outcome was reported in a paediatric clinical trial patient with severe hypocalcaemia. (see section 4.4, Serum Calcium).

Use in the elderly

Of the 1,136 patients enrolled in the cinacalcet phase 3 clinical programme, 26% were over 65 years old, and 9% were over 75 years old. No differences in the safety and efficacy of cinacalcet were observed in patients greater or less than 65 years of age (see section 4.2, Elderly).

4.5 Interaction with other medicines and other forms of interaction

Effect of cinacalcet on other drugs

Drugs metabolised by the enzyme cytochrome P450 2D6 (CYP2D6) – cinacalcet is an inhibitor of CYP2D6. Therefore, dose adjustments of concomitant medications may be required when cinacalcet is administered with medications that are predominantly metabolised by this enzyme (eg, metoprolol) and particularly those with a narrow

therapeutic index (eg, flecainide, vinblastine, thioridazine and most tricyclic antidepressants).

Desipramine: Concurrent administration of 90 mg cinacalcet with 50 mg desipramine, a tricyclic antidepressant metabolised primarily by CYP2D6, increased desipramine exposure approximately 3.6 times in CYP2D6 extensive metabolisers.

Amitriptyline: Co-administration of 25 mg or 100 mg cinacalcet with 50 mg amitriptyline, a tricyclic antidepressant metabolised in part by CYP2D6, increased exposure to amitriptyline and its active metabolite nortriptyline by approximately 20% in extensive metabolisers of CYP2D6 enzymes. Dose reductions of amitriptyline may be required in some subjects receiving cinacalcet concurrently.

Drugs metabolised by other cytochrome P450 (CYP) enzymes - based on in vitro data, cinacalcet is not an inhibitor of other CYP enzymes at concentrations achieved clinically, including CYP1A2, CYP2C9, CYP2C19, and CYP3A4.

Warfarin: Multiple oral doses of cinacalcet did not affect the pharmacokinetics or pharmacodynamics (as measured by prothrombin time and the 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 drugs that are metabolised by CYP3A4 and CYP3A5, such as certain immunosuppressants, including cyclosporin and tacrolimus.

Effect of other drugs on cinacalcet

Cinacalcet is metabolised by multiple cytochrome P450 enzymes, primarily CYP3A4, CYP1A2 and CYP2D6, which limit the potential for other drugs to increase cinacalcet concentrations.

Ketoconazole: Cinacalcet is metabolised in part by the enzyme CYP3A4. Co-administration of ketoconazole, a strong inhibitor of CYP3A4, caused an approximate 2-fold increase in cinacalcet exposure. Dose adjustment of cinacalcet may be required if a patient receiving cinacalcet initiates or discontinues therapy with a strong CYP3A4

inhibitor (eg, ketoconazole, erythromycin, itraconazole) or inducer (eg, rifampicin, phenytoin, St. John's Wort) of this enzyme.

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy Category: B3*

Cinacalcet crossed the placental barrier in rabbits; foetal plasma cinacalcet concentrations were about 10 –13 % of the maternal plasma concentrations. There was no evidence of teratogenicity in rats or rabbits. Foetal body weights were decreased in rats at 50 mg/kg/day PO (approximately 2 times the clinical exposure at the MRCD, based on AUC) and increased incidences of unossified sternebrae occurred in rats at exposures 0.1 – 2 times the clinical exposure, with maternal toxicity.

There are no adequate and well-controlled studies of cinacalcet in pregnant women. Because animal reproduction studies are not always predictive of human response, cinacalcet should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

*Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

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. Oral administration of cinacalcet to female rats during gestation and lactation at doses of 25 mg/kg/day and above (exposures at and above 1.5 times the clinical exposure at the MRCD, based on AUC)

was associated with increases in neonatal loss and reduced body weight gain of suckling rats.

Considering the rat study findings and because many drugs are excreted in breast milk, a decision should be made to discontinue nursing or discontinue cinacalcet, taking into account the importance of cinacalcet to the mother.

Fertility

Cinacalcet did not impair mating or fertility in rats at oral doses up to 75 mg/kg/day, with systemic exposures up to 2 times human exposure at the maximum recommended clinical dose (MRCD), based on AUC.

Studies in monkeys showed that cinacalcet depressed serum testosterone concentrations by 70-90% at oral doses 5-100 mg/kg/day, corresponding to systemic exposures 0.1-1 times the clinical exposure, on an AUC basis, at the MRCD of 360 mg/day. The highest dose also resulted in a 42% reduction in testicular weights.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive or operate machinery have been observed.

4.8 Undesirable effects

Summary of safety profile

Studies were conducted in patients with CKD receiving dialysis, and in patients with parathyroid carcinoma or primary HPT for whom parathyroidectomy is not a treatment option. Cinacalcet was safe and generally well tolerated. However, nausea and vomiting are very common adverse reactions.

Secondary hyperparathyroidism in patients with chronic kidney disease

In 3 double-blind placebo-controlled clinical trials, 1,126 CKD patients on dialysis received study drug (656 cinacalcet, 470 placebo) for up to 6 months. Adverse events reported during the studies were typical for the dialysis patient population. Adverse reactions are provided in Table 1. The most frequently reported reactions in the cinacalcet group were nausea and vomiting which were generally mild to moderate in severity, brief in duration, and infrequently led to discontinuation of study drug. Rash and hypocalcaemia have been observed.

Seizures were observed in 1.4% (13/910) of cinacalcet-treated patients and 0.7% (5/641) of placebo-treated patients across all completed placebo-controlled trials.

The incidence of serious adverse events (29 % vs 31%) and deaths (2% vs 3%) was similar in the cinacalcet and placebo groups, respectively.

12-Month experience with cinacalcet

Two hundred and sixty-six patients from the 2 pivotal phase 3 studies continued to receive cinacalcet or placebo treatment in a 6-month double-blind extension study (12-month total treatment duration). The incidence and nature of adverse events in this study were similar in the 2 treatment groups, and comparable to those observed in the pivotal phase 3 studies.

Parathyroid carcinoma and primary HPT for whom parathyroidectomy is not a treatment option

Overall, the safety profile in patients with parathyroid carcinoma or intractable (failed or contraindicated to surgery) primary HPT was similar to that seen in patients with CKD and secondary HPT; the most frequent adverse events in this patient group were nausea and vomiting (see Table 2).

Summary of the safety of cinacalcet in subjects with primary HPT

The safety profile of cinacalcet was similar across the 5 studies in primary HPT. Overall, common adverse events observed in these studies included gastrointestinal events (nausea, vomiting, abdominal pain), headache, paraesthesia, anxiety, asthenia, dizziness, and arthralgia. Most adverse events were mild to moderate in severity. The most common event considered related to cinacalcet was nausea (see Table 2), which was also the most common adverse event leading to withdrawal. The safety profile of cinacalcet in this subject population was generally consistent with that in subjects with CKD and no unique safety concern was identified for cinacalcet in the treatment of primary HPT.

Seizures were observed in 0.7% (1/140) of cinacalcet-treated patients and 0.0% (0/46) of placebo-treated patients in all clinical studies.

Tabulated summary of adverse reactions

Table 1 Adverse Reactions in Clinical Trials in Secondary Hyperparathyroidism in Patients with Chronic Kidney Disease Receiving Dialysis

System Organ Class	Very Common	Common
Gastrointestinal disorders	Nausea Vomiting Diarrhoea	
Musculoskeletal and connective tissue disorders	Myalgia	
Nervous system disorders		Dizziness Seizures
Vascular disorders		Hypertension
General disorders and administration site conditions		Asthenia Pain chest, non cardiac
Psychiatric disorders		Anorexia
Infections and infestations		Access infection
Skin and subcutaneous tissue disorders		Rash
Metabolism and nutrition disorders		Hypocalcaemia

Very common: greater than 10%, common: between 1% and 10%

Table 2 Adverse Reactions in Clinical Trials in Patients with Parathyroid Carcinoma/Intractable Primary HPT

System Organ Class	Very Common	Common
Gastrointestinal disorders	Nausea Vomiting Constipation	
Nervous system disorders	Paraesthesia Headache	
General disorders and administration site conditions	Fatigue Asthenia	
Injury, poisoning and procedural complications	Fracture	
Metabolism and nutrition disorders	Hypercalcaemia Dehydration	Hypocalcaemia
Psychiatric disorders	Anorexia Depression	

Blood and lymphatic system disorders	Anaemia	
Musculoskeletal and connective tissue disorders	Arthralgia Pain limb	
Infections and infestations	Infection upper respiratory	

Very common: greater than 10%, common: between 1% and 10%

Post-marketing data

Spontaneous post marketing reports have been received describing diarrhoea, myalgia, rash, seizures, chondrocalcinosis pyrophosphate and hypersensitivity reactions, including angioedema and urticaria, in association with cinacalcet HCl administration.

Isolated idiosyncratic cases of hypotension and/or worsening of heart failure have been reported in cinacalcet-treated patients with impaired cardiac function in post marketing safety surveillance.

Table 3 shows adverse events from subjects with primary HPT who were unable to undergo parathyroidectomy.

Table 3 Treatment of Hypercalcaemia in Adult Patients with Primary HPT for Whom Parathyroidectomy Would be Indicated on the Basis of Serum Calcium Levels, but who are Unable to Undergo Surgery

System Organ Class	Very Common	Common
Gastrointestinal disorders	Nausea Diarrhoea	
Musculoskeletal and connective tissue disorders	Muscle spasms Back pain	
Nervous system disorders	Headache	

Very common: greater than 10%, common: between 1% and 10%

Table 4 describes adverse reactions identified in the EVOLVE (EValuation Of Cinacalcet HCl Therapy to Lower CardioVascular Events) clinical trial.

Table 4 Adverse reactions in the EVOLVE (Evaluation Of Cinacalcet HCl Therapy to Lower CardioVascular Events) Clinical Trial

System Organ Class	Very Common	Common
Gastrointestinal disorders	Nausea Vomiting Diarrhoea Abdominal pain	Abdominal pain – upper Constipation Dyspepsia
Respiratory, thoracic and mediastinal disorders	Dyspnoea Cough	
Vascular disorders	Hypotension	
Musculoskeletal and connective tissue disorders	Muscle spasms	
Metabolism and nutrition disorders		Hyperkalaemia
Infections and infestations		Upper respiratory infection
Nervous system disorders	Headache	Convulsions
Skin and subcutaneous tissue disorders		Rash
Immune system disorders		Hypersensitivity

Very common: greater than 10%, common: between 1% and 10%

Description of selected adverse reactions

Laboratory values

Serum calcium levels should be monitored in patients receiving cinacalcet (see sections 4.4 and 4.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Doses titrated up to 300 mg once daily have been safely administered to patients receiving dialysis. Overdosage of cinacalcet may lead to hypocalcaemia. In the event of overdosage, patients should be monitored for signs and symptoms of hypocalcaemia and appropriate measures taken to correct serum calcium levels (see section 4.4).

Since cinacalcet is highly protein bound, haemodialysis is not an effective treatment for overdosage of cinacalcet.

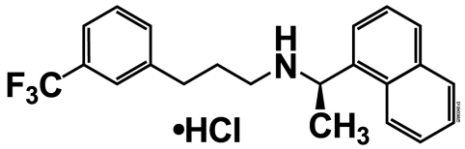
For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-Parathyroid Hormones, ATC code: H05BX01

Cinacalcet is presented in tablets as the hydrochloride salt. Cinacalcet hydrochloride is described chemically as N-[1-(R)-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]-1-aminopropane hydrochloride and has the following structural formula:



Cinacalcet is a calcimimetic agent that increases the sensitivity of the calcium sensing receptor to extracellular calcium. The empirical formula of cinacalcet hydrochloride is C22H22F3N·HCl and it has a molecular weight of 393.9 g/mol (hydrochloride salt) and 357.4 g/mol (free base). It has one chiral centre having an R-absolute configuration. The R-enantiomer is the more potent enantiomer and has been shown to be responsible for pharmacodynamic activity.

Cinacalcet hydrochloride is a white to off-white, crystalline solid that is soluble in methanol or 95% ethanol and poorly soluble in water.

Pharmacodynamic effects

Mechanism of action

Cinacalcet reduces PTH while simultaneously lowering Ca x P, calcium and phosphorus levels in chronic kidney disease in patients receiving dialysis.

Secondary hyperparathyroidism (HPT) is a progressive disease, which occurs in patients with chronic kidney disease (CKD) and manifests as increases in parathyroid hormone (PTH) levels and derangements in calcium and phosphorus metabolism. Increased PTH stimulates osteoclastic activity resulting in cortical bone resorption and marrow fibrosis. The calcium sensing receptor on the surface of the chief cell of the parathyroid gland is the principal regulator of PTH secretion. Cinacalcet 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.

In CKD patients with uncontrolled secondary HPT, reductions in PTH were associated with a favourable impact on bone specific alkaline phosphatase (BALP), N-telopeptide (N-Tx), bone turnover, bone fibrosis, and incidence of bone fracture.

Studies in a rat model of chronic renal insufficiency (CRI) (5/6 nephrectomy) assessed the effects of cinacalcet treatment on parathyroid gland hyperplasia. Cinacalcet treatment reduced PTH and parathyroid cell proliferation to levels comparable to vehicle-treated, non-nephrectomised animals, demonstrating that cinacalcet prevented the development of secondary HPT.

Pharmacodynamics

Reductions in PTH levels correlate with cinacalcet concentrations. Nadir PTH occurs approximately 2 to 6 hours post dose, corresponding with cinacalcet C_{max}. After steady state is reached, serum calcium concentrations remain constant over the dosing interval.

Clinical efficacy and safety

Secondary hyperparathyroidism in patients with chronic kidney disease

Three, 6-month, multicentre, randomised, double-blind, placebo-controlled clinical studies were conducted in CKD patients receiving dialysis with uncontrolled secondary HPT (n = 665 on cinacalcet, 471 on placebo). The patient population consisted of both recently established and long-standing dialysis patients, with a range of 1 to 359 months. Cinacalcet was administered either alone or in combination with vitamin D sterols; 34% of patients were not receiving vitamin D sterols at study entry. The majority (more than 90%) of patients were receiving phosphate binders. Dose adjustments in phosphate binder therapy were permitted throughout the study. Vitamin D doses remained constant unless the patient developed hypercalcaemia, hypocalcaemia, or hyperphosphataemia. Patients continued on their previously prescribed drugs including: calcium channel blockers, ACE inhibitors, beta-blockers, hypoglycaemics, and lipid lowering agents. Cinacalcet (or placebo) was initiated at a dose of 30 mg and titrated every 3 or 4 weeks to a maximum dose of 180 mg once daily to achieve an iPTH of 10.6 to 26.5 pmol/L (1.5 to 4 times the upper limit of normal). The severity of secondary HPT ranged from mild to severe (iPTH values of 28.8 to 969.5 pmol/L), with mean (SE) baseline iPTH concentrations across the 3 studies of 77.8 (2.2) and 72.5 (2.0) pmol/L for the cinacalcet and placebo groups, respectively. 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 (Table 5).

Table 5. Effects of Cinacalcet on iPTH, Ca x P, Serum Calcium, and Serum Phosphorus in 6-month Phase 3 Studies (Patients Receiving Dialysis)

	Study 1		Study 2		Study 3	
	Placebo (N = 205)	Cinacalcet (N = 205)	Placebo (N = 165)	Cinacalcet (N = 166)	Placebo (N = 101)	Cinacalcet (N = 294)
iPTH						
Baseline (pmol/L)	69.1 (2.9)	67.5 (2.5)	66.8 (2.6)	69.2 (3.1)	88.3 (5.1)	90.0 (4.3)
Evaluation Phase (pmol/L)	74.0 (3.5)	40.8 (2.6)	72.9 (3.4)	38.3 (3.1)	90.4 (5.8)	55.8 (3.2)
Percent Change	9.5 (2.8)	-38.4 (2.9)	8.7 (2.8)	-47.5 (2.8)	4.1 (3.4)	-40.3 (2.1)
Patients Achieving Primary Endpoint (iPTH ≤ 26.5 pmol/L) (%)	4%	41%**	7%	46%**	6%	35%**
Patients Achieving ≥ 30% Reduction in iPTH (%)	11%	61%**	12%	68%**	10%	59%**
Patients Achieving iPTH ≤ 31.8 pmol/L (%)	9%	55%**	11%	56%**	9%	45%**
Ca x P						
Baseline ($mmol^2/L^2$)	4.93 (0.09)	5.00 (0.09)	4.92 (0.09)	4.92 (0.10)	4.91 (0.11)	4.80 (0.08)
Evaluation Phase ($mmol^2/L^2$)	4.82 (0.08)	4.21 (0.08)	4.79 (0.09)	4.02 (0.10)	4.68 (0.11)	4.03 (0.07)
Percent Change	1.5 (1.8)	-13.0 (1.7)**	-0.7 (1.9)	-16.7 (2.1)**	-1.4 (2.4)	-12.8 (1.7)**
Calcium						
Baseline (mmol/L)	2.48 (0.01)	2.46 (0.01)	2.48 (0.01)	2.51 (0.01)	2.50 (0.02)	2.45 (0.01)
Evaluation Phase (mmol/L)	2.48 (0.01)	2.30 (0.02)	2.48 (0.01)	2.31 (0.02)	2.52 (0.02)	2.28 (0.01)
Percent Change	0.5 (0.4)	-6.3 (0.6)**	0.3 (0.4)	-7.5 (0.6)**	0.9 (0.5)	-6.5 (0.6)**
Phosphorus						
Baseline (mmol/L)	2.00 (0.04)	2.04 (0.04)	2.00 (0.04)	1.96 (0.04)	1.97 (0.05)	1.97 (0.03)
Evaluation Phase (mmol/L)	1.95 (0.03)	1.84 (0.04)	1.94 (0.04)	1.74 (0.04)	1.87 (0.04)	1.77 (0.03)
Percent Change	1.1 (1.8)	-7.1 (1.7)**	-0.9 (1.9)	-9.9 (2.0)**	-2.2 (2.5)	-7.2 (1.6)*

* P < 0.05; ** P < 0.001 compared to placebo

Data represent mean (standard error) or percent Mean iPTH and Ca x P by treatment group for the overall study population during the 6-month treatment period are presented in Figure 1 and Figure 2.

Figure 1. Mean (SE) Percent Change from Baseline in iPTH (Pooled Phase 3 Studies)

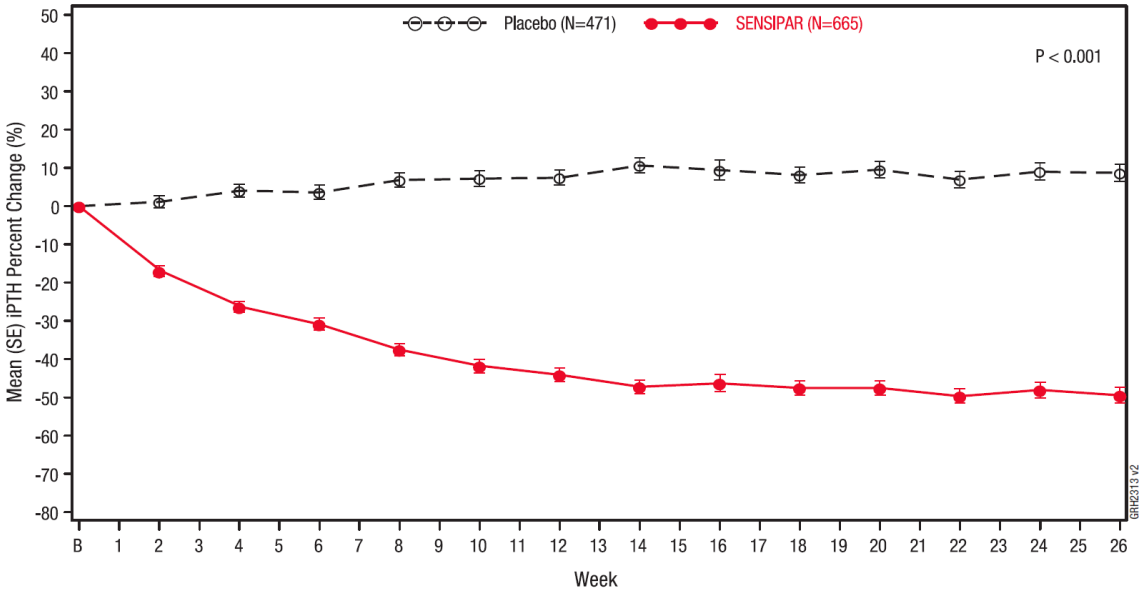
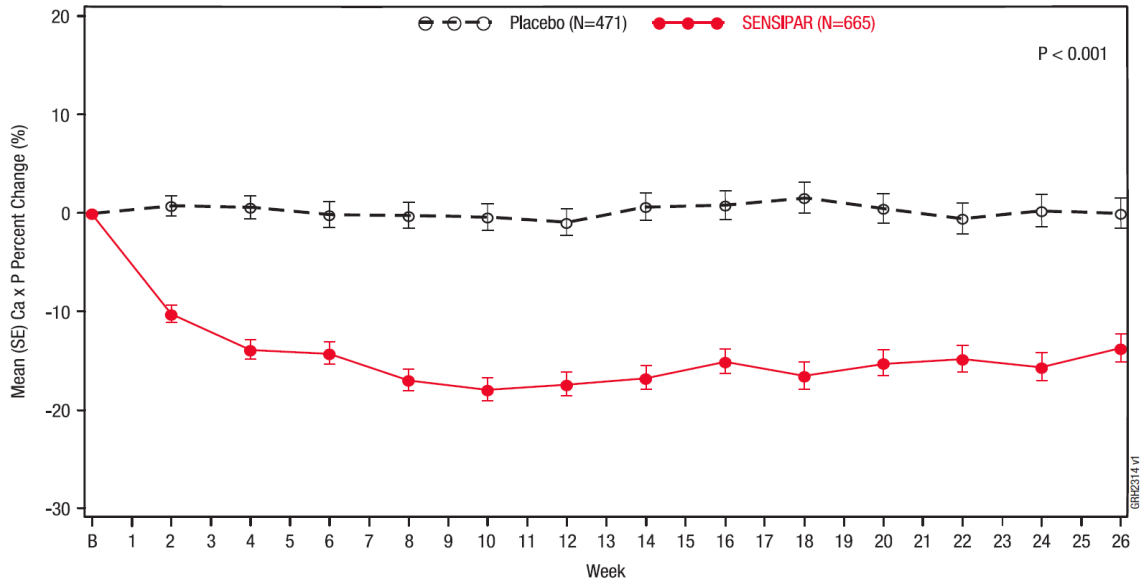


Figure 2. Mean (SE) Percent Change from Baseline in Ca x P (Pooled Phase 3 Studies)



In patients receiving cinacalcet, reductions in iPTH and Ca x P occurred within 2 weeks and were maintained for at least 12 months of treatment (n = 99 on cinacalcet, 111 on placebo).

Cinacalcet decreased iPTH and Ca x P levels regardless of disease severity (ie, baseline iPTH value), dialysis modality (PD vs HD), duration of dialysis, and whether or not vitamin D sterols were administered. Approximately 60% of patients with mild (iPTH from

31.8 to 53.0 pmol/L), moderate (iPTH between 53.0 and 84.8 pmol/L), or severe (iPTH above 84.8 pmol/L) secondary HPT achieved at least a 30% reduction in iPTH levels. Cinacalcet treatment also reduced iPTH and Ca x P in patients with elevated Ca x P levels.

The impact of cinacalcet on bone disease, including the risk of adynamic bone disease, has not been conclusively evaluated.

The pivotal clinical studies were designed to evaluate the effect of cinacalcet on biochemical parameters, including PTH, serum calcium and phosphorus. Clinical outcomes such as quality of life, rate of parathyroidectomy, symptomatic bone disease, hospitalisation, or mortality were not pre-specified endpoints and were not evaluated within individual studies. The pivotal efficacy and safety studies in patients with secondary hyperparathyroidism of chronic kidney disease, requiring dialysis, did not examine quality of life benefits. There were no differences between cinacalcet and placebo-treated patients in terms of statistically significant differences in self-reported cognitive functioning scale scores during the efficacy assessment phase.

Parathyroid carcinoma

Twenty-nine patients with parathyroid carcinoma were enrolled in an open-label study. Parathyroid carcinoma and severe hypercalcaemia in these patients was persistent despite previous parathyroidectomy and bisphosphonate therapy. The study consisted of two phases, a dose-titration phase and a maintenance phase. Cinacalcet was administered at doses ranging from 30 mg twice daily to 90 mg four times daily, and mean serum calcium declined from 3.53 to 3.10 mmol/L across the titration phase (up to 16 weeks). Sixty-two percent of patients (18 of 29) achieved a reduction in serum calcium of at least 0.25 mmol/L.

Primary HPT for whom parathyroidectomy is not a treatment option

Seventeen patients with primary HPT for whom parathyroidectomy was not a treatment option were enrolled in an open-label study. The study consisted of two phases, a dose-titration phase and a maintenance phase. Cinacalcet was administered at doses ranging from 30 mg twice daily to 90 mg four times daily, and mean serum calcium declined from 3.18 to 2.60 mmol/L across the titration phase (up to 16 weeks). Eighty-eight percent of patients (15 of 17) achieved a reduction in serum calcium of at least 0.25 mmol/L.

An additional 114 patients with primary HPT and hypercalcaemia, including 25 patients with recurrent primary HPT after parathyroidectomy, were enrolled in 3 controlled studies

and one open label study. In one study of 45 patients with primary HPT, including 12 patients with recurrent primary HPT after parathyroidectomy, cinacalcet normalised serum calcium in approximately 80% of patients, and this was sustained for up to 3 years.

5.2 Pharmacokinetic properties

Absorption

After oral administration of cinacalcet, maximum plasma concentration is achieved in approximately 2 to 6 hours. The absolute bioavailability of cinacalcet is approximately 25%. Administration of cinacalcet with food results in an approximate 50 to 80% increase in bioavailability. Increases in plasma concentrations are similar, regardless of the fat content of the meal.

Distribution

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 drug levels are achieved within 7 days with minimal accumulation. The AUC and C_{max} of cinacalcet increase linearly over the once daily dose range of 30 to 180 mg. The pharmacokinetics of cinacalcet do not change over time. The volume of distribution is high (approximately 1,000 L), indicating extensive distribution. Cinacalcet in plasma is approximately 97% bound to plasma proteins and in whole blood, cinacalcet distributes minimally into red blood cells.

Biotransformation

Cinacalcet is metabolised by multiple enzymes, primarily CYP3A4, CYP1A2 and CYP2D6. The major circulating metabolites are inactive. After administration of a 75 mg radiolabelled dose to healthy volunteers, cinacalcet was rapidly and extensively metabolised by oxidation followed by conjugation.

Elimination

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.

Paediatric population

The safety and efficacy of cinacalcet has not been studied in children and are not established (see section 4.4: Serum Calcium and Paediatric Use). A single dose pharmacokinetic study has been completed in paediatric patients 6-17 years of age

(N = 12). The pharmacokinetic parameters following a 15 mg dose are summarised in Table 6:

Table 6. Paediatric Single Dose PK results

	15 mg in Paediatric Subjects				30 mg in a Adults[a] N=13
Parameter	6-8 years N=3	9-11 years N=3	12-14 years N=3	15-17 years N=3	
AUC_{0-t} hr*ng/mL	29.5 (15.6)	35.9 (35.8)	11.3 (4.4)	17.5 (5.9)	40.4 (15.9)
C_{max} ng/mL	11.0 (3.22)	9.19 (7.28)	3.87 (1.82)	5.01 (2.15)	5.97 (3.06)

[a] Data are from a separate study in healthy adults
Data represent mean (standard deviation)

Whilst a 15 mg dose of cinacalcet was used in the paediatric PK study, this dose strength is not registered.

Six of the twelve subjects experienced decreases in serum calcium below the lower limit of normal (2.23 mmol/L). In these six subjects, baseline values were in the range of 2.20 to 2.52 mmol/L and the decreased values were in the range of 2.00 to 2.22 mmol/L. In the same study, QT interval prolongation, assessed as unrelated to cinacalcet, was reported in one of the twelve subjects.

The use of multiple doses in paediatric subjects has not been studied. On the basis of these limited data, there is a potential for higher exposures and greater pharmacodynamic effects in the lighter/younger relative to the heavier/old paediatric subjects when treated with identical doses of cinacalcet. (see section 4.4, Serum Calcium and Paediatric Use).

Hepatic insufficiency

Mild hepatic impairment did not alter the pharmacokinetics of cinacalcet. Compared to subjects with normal liver function, average AUC of cinacalcet was approximately 2 times higher in subjects with moderate impairment and approximately 4 times higher in subjects with severe impairment (see section 4.4). Because doses are titrated for each subject based on safety and efficacy parameters, no additional dose adjustment is necessary for subjects with hepatic impairment.

Renal insufficiency

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. No dosage adjustment based on the degree of renal function is necessary.

Geriatric patients

There are no clinically relevant differences due to age in the pharmacokinetics of cinacalcet. No dosage adjustment based on age is necessary.

5.3 Preclinical safety data

Carcinogenicity

Cinacalcet, administered orally at dietary doses up to 200 mg/kg to mice and 35 mg/kg/day to rats for 104 weeks, showed no evidence of carcinogenic potential. These doses resulted in total systemic exposure (AUCs) approximately equivalent to the exposures observed in humans given the maximum dose of 360 mg/day. A decreased incidence of thyroid C-cell adenomas was observed in rats treated with cinacalcet.

Genotoxicity

Cinacalcet was negative in the Ames assay, Chinese Hamster Ovary HGPT forward mutation assay, in vitro chromosome aberration assay and the mouse micronucleus assay. These tests indicate that cinacalcet is unlikely to pose a genotoxic risk to humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

pre-gelatinised starch

microcrystalline cellulose

povidone

crospovidone

colloidal silicon dioxide

magnesium stearate

water.

Tablets are coated with colour (Opadry® II green), a clear film-coat (Opadry® clear) and carnauba wax.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store below 30ºC.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Blister packs of 28 tablets.

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Amgen (New Zealand) Limited

Level 22, PwC Tower

15 Customs Street West

Auckland 1010 Telephone: 0800 443 885

Email: medinfo.JAPAC@amgen.com

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:

05 May 2005

10. DATE OF REVISION OF THE TEXT

05 November 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	Sponsor address revision