New Zealand Data Sheet

CINACALCET TE ARAI

Cinacalcet hydrochloride

1. PRODUCT NAME

CINACALCET TE ARAI 30 mg, 60 mg, and 90 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CINACALCET TE ARAI 30 mg: Each tablet contains 30 mg cinacalcet (as hydrochloride).
CINACALCET TE ARAI 60 mg: Each tablet contains 60 mg cinacalcet (as hydrochloride).
CINACALCET TE ARAI 90 mg: Each tablet contains 90 mg cinacalcet (as hydrochloride).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

30mg: Light green, oval, biconvex film-coated tablet marked “C30” on one side, 6 x 11mm.
60mg: Light green, oval, biconvex film-coated tablet marked “C60” on one side, 7 x 15mm.
90mg: Light green, oval, biconvex film-coated tablet marked “C90” on one side, 8 x 16mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

CINACALCET TE ARAI is indicated for the treatment of hypercalcaemia in adult patients with parathyroid carcinoma.

CINACALCET TE ARAI 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

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

Patients with End Stage Renal Disease Receiving Dialysis

Cinacalcet Te Arai reduces 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.

Cinacalcet Te Arai 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 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 PRECAUTIONS).

Parathyroid Carcinoma and Primary HPT for Whom Parathyroidectomy is not a Treatment Option
The recommended starting dose of Cinacalcet Te Arai for adults is 30 mg twice daily.

The dosage of Cinacalcet Te Arai 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.

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

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

Patients with 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.

4.3 Contraindications
CINACALCET TE ARAI is contraindicated in patients with hypersensitivity to any component(s) of this product. (See 6.1 LIST OF EXCIPIENTS).

4.4 Special warnings and precautions for use
PRECAUTIONS
Seizures
In clinical studies, seizures (primarily generalized or tonic-clonic) were observed in 1.4% (43/3049) 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 paresthesias, 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 DOSAGE AND ADMINISTRATION).

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.

Cinacalet 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 PHARMACOKINETICS).

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.

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 DOSAGE AND ADMINISTRATION). 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 DOSAGE AND ADMINISTRATION).

Interference with Laboratory and Diagnostic Tests

None known.

Paediatric Use

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 PRECAUTIONS section: Serum Calcium).

Use in the Elderly

Of the 1136 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 DOSAGE AND ADMINISTRATION: Geriatric Patients).

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.

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

Sevelamer HCl
Co-administration of sevelamer HCl (2400 mg tid) did not alter the pharmacokinetics of cinacalcet.

Pantoprazole
Co-administration of pantoprazole (2400 mg) did not alter the pharmacokinetics of cinacalcet.

4.6 Fertility, pregnancy and lactation

Effects on 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.

Use in 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.

Use in Lactation

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.

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

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, 1126 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. The most frequently reported adverse events (incidence of at least 5% in the cinacalcet group) are provided in Table 3. The most frequently reported events 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.

Table 3. Adverse Event Reported (at least 5%) in Patients with Secondary Hyperparathyroidism (SHPT) Receiving Dialysis

	Percent of reports	
Body system and preferred terms	**Cinacalcet n = 656**	**Placebo n = 470**
Body as a whole		
Fever	7	10
Oedema peripheral	7	7
Fatigue	7	7
Asthenia	7	4
Pain chest (non-cardiac)	6	4
Access infection	5	4
Cardiovascular		
Hypotension	7	12
Hypertension	7	5
Thrombosis vascular access	6	7
CNS / PNS		
Headache	16	17
Dizziness	10	8
Gastrointestinal		
Nausea	31	19
Vomiting	27	15
Diarrhoea	21	20
Pain abdominal	12	14
Dyspepsia	8	8
Anorexia	6	4
Musculo-skeletal		
Myalgia	15	14

Pain limb	9	10
Arthralgia	7	9
Respiratory		
Infection upper respiratory	12	13
Dyspnoea	9	9
Cough	6	7
Skin and appendages		
Pruritus	6	7

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.

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, paresthesia, anxiety, asthenia, dizziness, and arthralgia. Most adverse events were mild to moderate in severity. The most common event considered related to cinacalcet was nausea, 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.

Post Marketing Data

Spontaneous post marketing reports have been received describing diarrhoea, myalgia, rash, seizures 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.

Very common: greater than 10%, common: between 1% and 10%; uncommon: between 0.1% and 1%; rare: between 0.01% and 0.1%; very rare: between 0.001% and 0.01%).

Immune system disorders

Common: hypersensitivity reactions

Metabolism and nutrition disorders

Common: decreased appetite

Nervous system disorders
Common: dizziness
Common: headache

Vascular disorders
Common: hypotension

Respiratory, thoracic and mediastinal disorders
Common: upper respiratory infection
Common: dyspnoea Common: cough

Skin and subcutaneous tissue disorders
Common: rash
Very rare: angioedema and urticaria

Gastrointestinal disorders
Very common: nausea
Very common: vomiting
Common: dyspepsia
Common: diarrhoea
Common: abdominal pain
Common: abdominal pain-upper
Common: constipation

Musculo-skeletal and connective tissue disorders
Common: muscle spasms
Common: myalgia
Common: back pain

General disorders and administration site conditions
Common: asthenia

Investigations
Common: hypocalcaemia
Common: hyperkalemia

Laboratory Values
Serum calcium levels should be monitored in patients receiving cinacalcet (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

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 PRECAUTIONS).

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

Contact the National Poisons Centre on 0800 764 766 for advice on the management of an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

5.2 Pharmacokinetic properties

Absorption and Distribution

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.

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 Cmax 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 1000 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.

Metabolism and Excretion

Cinacalcet is metabolised by multiple enzymes, primarily CYP3A4, CYP1A2 and CYP2D6. The major circulating metabolites are inactive. After administration of a 75 mg radiolabeled 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.

Special Populations

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 PRECAUTIONS). 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.

Paediatric Patients

The safety and efficacy of cinacalcet has not been studied in children and are not established.
(see PRECAUTIONS section: 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 summarized in Table 1:

Table 1. Paediatric Single Dose PK results

Parameter	15 mg in Paediatric Subjects				30 mg in Adult[a] N = 13
	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 PRECAUTIONS section: Serum Calcium and Paediatric Use).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Starch, pregelatinised (maize)
Cellulose, microcrystalline
Povidone K 25
Sodium Starch Glycolate (Type A)
Magnesium stearate
Silica, colloidal anhydrous

Tablet coat
Polyvinylalcohol
Titanium dioxide (E171)
Macrogol 3350
Talc
Indigo Carmine Aluminium Lake (E 132)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

PVC/PVdC-Aluminium-Blister containing 14 tablets.

Pack size of 2 blisters (28 tablets) per carton.

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Supplied in New Zealand by:

Te Arai BioFarma Ltd

91 Red Hill Rd, Te Arai

Wellsford, 0975

0800 TEARAI (832 724)

9. DATE OF FIRST APPROVAL

19/07/2018

10. DATE OF REVISION OF THE TEXT

19/07/2018