SCIENTIFIC DISCUSSION

1. Introduction

Amgen Europe B.V submitted a Marketing Authorisation Application through the Centralised Procedure, for the medicinal product Parareg, containing cinacalcet hydrochloride, intended for treatment of,

- Secondary hyperparathyroidism in patients with end-stage renal disease (ESRD) on maintenance dialysis therapy. Parareg may be used as part of a therapeutic regimen including phosphate binders and/or Vitamin D sterols, as appropriate.
- Reduction of hypercalcaemia in patients with parathyroid carcinoma.

This was a complete and independent marketing authorisation application, as stated in Art. 8 (3) of Directive 2001/83/EC, as amended. The provided data cover all aspects of the clinical characterization of safety and efficacy of cinacalcet. The applicant has submitted the results of non-clinical and clinical studies carried out for the application.

Secondary hyperparathyroidism in chronic kidney disease.
The prevalence of patients in the EU with chronic kidney disease (CKD) that are on dialysis ranges from approximately 500 per million population to over 1000 per million. Secondary hyperparathyroidism (HPT) is a common and serious disease that develops early in CKD (glomerular filtration rate [GFR] < 60 mL/min) before the initiation of dialysis and progresses as patients reach end-stage renal disease (ESRD). Multiple factors are involved in the pathogenesis of secondary HPT, including hypocalcaemia, phosphate retention, reduced synthesis of 1,25-dihydroxy vitamin D, and skeletal resistance to the calcaemic action of parathyroid hormone (PTH).

Approximately 40% of dialysis patients have elevated PTH levels (> 300 pg/mL), and approximately 10% of patients have PTH levels > 800 pg/mL (a level at which parathyroidectomy is frequently recommended). The primary clinical consequence of secondary HPT is the development of renal osteodystrophy. The increase in serum PTH stimulates osteoclastic activity resulting in bone resorption, primarily of the cortical bone. As the disease progresses, fibrosis of the marrow space may develop. Other symptoms include muscle weakness, fatigue, lethargy, pruritus, and gastrointestinal complaints. Secondary HPT may also be accompanied by bone and joint pain, vascular calcification, peri-articular calcium deposits, impaired cardiac function, proximal myopathy, spontaneous tendon rupture, pathological bone fracture, altered lipid metabolism, and in rare instances, skeletal deformities and calciphylaxis.

Secondary HPT is also complicated by an increase in calcium x phosphorus (Ca x P), which is elevated (> 55 [mg/dL]) in 50% of dialysis patients. The elevated levels have been associated with an increased risk of cardiac, visceral, and vascular calcification and cardiovascular mortality.

Current pharmacological therapy mainly consists of phosphate binders and vitamin D. Phosphate binders are used to reduce serum phosphorus levels while vitamin D is administered to control PTH. The most commonly prescribed binders are calcium-based (calcium carbonate and calcium acetate), which are limited by the development of hypercalcaemia in a considerable portion of the patients. Another type of phosphate binder is sevelamer, which is a non-calcium containing polymer. Compliance with phosphate binders is often poor because of the need to consume multiple tablets/capsules with each meal, and constipation, which is a chronic problem in this patient population.

The second class of drugs currently available for the treatment of secondary HPT includes vitamin D sterols. While these agents are effective in reducing PTH levels, they are limited by the development of hypercalcaemia and hyperphosphatemia due to enhanced gastrointestinal absorption. These agents are contraindicated in patients with hypercalcaemia.

Cinacalcet is a first-in-class calcimimetic that modulates the activity of the calcium-sensing receptor, the primary regulator of PTH secretion.

Parathyroid carcinoma
Parathyroid carcinoma is extremely rare and accounts for 0.5% of all primary HPT cases, with an estimated prevalence of 2 /1,000000. Most patients with parathyroid carcinoma have markedly elevated serum calcium concentrations (> 14 mg/dL) and complications of hypercalcaemia. Up to 80% of patients have renal involvement (nephrolithiasis, nephrocalcinosis and renal insufficiency); bone pain, fractures, and osteopenia occur in up to 70% of patients.

For these patients, complete surgical en bloc resection of the neoplasm is the preferred treatment. Local recurrence and/or metastases are common, and chemotherapy and radiotherapy show poor results. On average, hypercalcaemia recurs within 3 years after parathyroidectomy and approximately 50% of patients die within 10 years of the diagnosis.

The product and the development programme
Cinacalcet is proposed to exert calcimimetic action through allosteric modulation of the calcium-sensing receptor (CaR) on the parathyroid cell surface. The primary role of the CaR is control of parathyroid hormone (PTH) secretion in response to extracellular calcium concentration. Cinacalcet acts to reduce circulating PTH concentration through activation of the CaR by increasing its sensitivity to extracellular calcium.

The proposed dose range for the treatment of secondary HPT is 30 to 180 mg administered once daily. For hypercalcaemia in parathyroid carcinoma, the recommended starting dose is 30 mg twice daily. Some parathyroid carcinoma patients may require dosing more than twice daily; doses up to 90 mg 4 times daily have been administered. To make titration possible, cinacalcet is available in strengths of 30, 60 and 90 mg. Based on this posology, a combined package leaflet including all strengths has been adopted.

Much of the early preclinical pharmacology work on the use of calcimimetics in disease models was performed using the first generation calcimimetic R-568. Most of this work has been repeated with cinacalcet, a second generation calcimimetic with improved pharmacokinetic properties. Cinacalcet has undergone a full non-clinical development programme with studies addressing pharmacology, pharmacokinetics and metabolism, and toxicology.

The cinacalcet clinical programme consists of 47 studies in normal volunteers and patients with primary or secondary HPT performed from December 1997 to June 2003. Fifteen of these studies were conducted in subjects with secondary HPT, and 5 studies were performed in subjects with primary HPT. The remaining 27 studies provide biopharmaceutical and clinical pharmacology information as well as information on initial efficacy and tolerability of cinacalcet. Two thousand, five hundred twenty-three (2523) subjects have participated in the studies within the clinical program, including 1,677 subjects with secondary HPT and 151 subjects with primary HPT.

The clinical development programme performed for cinacalcet in the treatment of secondary HPT associated with CKD, includes subjects on dialysis (ESRD) and not receiving dialysis. The phase 3 program included 4 double-blind, placebo-controlled studies in subjects with secondary HPT receiving maintenance dialysis. Two randomised, placebo-controlled studies evaluated the effects of cinacalcet in CKD subjects not receiving dialysis. The 30 to 180 mg cinacalcet dose range and dose-titration study design were used, regardless of the stage of CKD.

The clinical development programme for cinacalcet was also considered for the treatment of primary HPT. It included subjects with parathyroid carcinoma and intractable primary HPT (subjects with unresolved primary HPT after unsuccessful parathyroidectomy or subjects contraindicated for parathyroidectomy). Five clinical studies were conducted in subjects with primary HPT (n = 151), and evaluated the efficacy and safety of cinacalcet in the treatment of primary HPT or intractable primary HPT/parathyroid carcinoma.

Non-clinical toxicology and safety pharmacology studies were conducted under GLP regulations where applicable.

The clinical studies were performed in accordance with current GCP guidelines.

2. Part II: Chemical, pharmaceutical and biological aspects

Introduction

Parareg contains cinacalcet hydrochloride as the active ingredient at strengths of 30, 60, and 90 mg, with the same proportional composition. It is presented as film coated tablets.

Other ingredients include pregelatinized starch, microcrystalline cellulose, povidone, crospovidone, colloidal silicon dioxide, magnesium stearate, Opadry®II green, Opadry® clear, carnauba wax and Opacode® black.

The medicinal product is packaged in Aclar blisters or in HDPE bottles with a child resistant polypropylene closure.

Drug Substance

The chemical name of cinacalcet hydrochloride is N-[1-(R)-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]-1-aminopropane hydrochloride. The molecule contains a chiral center and the active substance is the R-enantiomer. Cinacalcet hydrochloride is a white to off-white, non-hygroscopic crystalline powder with only one stable crystalline form at ambient temperature. It has a very low aqueous solubility, especially at basic pH (<0.001 mg/ml) and exhibits high permeability. These properties underline the effect of the particle size and physical form on the dissolution and hence the bioavailability of the active substance and therefore need to be tightly controlled to ensure the clinical safety and efficacy of the medicinal product.

- Manufacture

The manufacturing process has been adequately described, while the critical steps have been identified and are controlled by appropriate in process controls. The analytical methods used are sufficiently described and validated in accordance with the ICH guidelines.

The impurities, including the S-enantiomer of cinacalcet, are well characterised and controlled. All specified impurities have been qualified in pre-clinical studies. The other impurities are controlled at the < 0.1% level in the drug substance specification. The residual levels of solvents are adequately controlled according to the ICH guidelines.

- Specification

The active substance specification includes tests for the description, identification (IR, HPLC), assay (HPLC), optical rotation, impurities (HPLC), residual solvents, (GC) and particle size (Laser diffraction).

The absence of tests for the enantiomeric purity of the product has been appropriately justified and is supported by batch analysis data from seven batches produced using the commercial process. In all cases the results complied with the proposed specification.

- Stability

Three pilot scale and four commercial scale batches have been placed under stability studies according to the ICH guidelines. Samples were stored at long-term conditions (25°C/60%RH) for up to 30 months and accelerated (40°C/75%RH) conditions for 6 months. The product was tested for appearance, moisture content, chiral purity, assay and impurities using stability indicating analytical methods.

Forced degradation studies have also been conducted according to ICH Q1B requirements on one pilot scale batch. The results from all stability studies show that cinacalcet hydrochloride is a very stable compound that is not sensitive to light.

Drug Product

- Pharmaceutical Development

The three strengths of the final commercial film-coated tablets have a proportionally identical composition. During the development of the commercial formulation, critical parameters for the *in vivo* performance of the dosage form have been identified. Different formulations have been used in the various clinical phases. These formulations have been well described and bridged to each other by bioequivalence studies. The *in vivo* results have been used to develop a discriminating *in vitro* dissolution method. The excipients chosen are widely used in pharmaceutical preparations. Excipient compatibility studies were performed and demonstrated that there is no interaction with the active substance.

Other ingredients

Opadry® II Green and Opacode® Black are the only excipients that contain ingredients of animal origin. Opadry® II Green contains lactose monohydrate. However, the lactose has been certified as produced from milk obtained from healthy animals in the same condition as those used to collect milk for human consumption. Opacode Black contains shellac, which is derived from insects that are not implicated in TSE/BSE issues. All other ingredients are of non-animal origin and comply with Eur. Ph. requirements.

The tablets are packed in Al/Aclar/PVAc/PVC blisters or in high-density polyethylene (HDPE) bottles. The suitability and compatibility of the drug product with the primary packaging materials has been demonstrated in accelerated and long-term stability studies. The plastic materials used comply with Directive 2002/72/EC relating to plastic materials intended to come into contact with foodstuffs.

- Manufacture of the Product

The manufacturing method used is a standard wet granulation process. Further manufacturing steps are wet milling, fluid bed drying and dry milling. After blending with extra-granular excipients and lubrication the granules are compressed. Coating with aqueous film coatings, waxing and tablet printing are the final operations. The manufacturing process is satisfactorily described. The critical steps have been identified and are adequately controlled by appropriate in process controls. The analytical methods used have been validated in accordance with ICH guidelines. An acceptable process validation plan has been presented and the results from full-scale development batches indicate that a product of high quality can be consistently produced.

- Product Specification

The finished product specifications include tests for description, uniformity of content, assay (HPLC), identification (IR, HPLC), impurities, dissolution and water content.

Batch analysis data have been presented for six full-scale batches manufactured using the commercial process. All these batches comply with the release criteria that were in effect at the time of manufacture.

- Stability of the Product

The stability study design includes the bracketing of product strengths, container size/tablet counts (HDPE bottles) and container cavity sizes (blisters). This is justified by dose-proportional formulation, the use of equivalent materials of packing construction, proportional cavity size, and relationship of moisture vapour permeation to tablet weight. In addition, a photostability study according to ICH Q1B was performed

Product packaged in blisters and bottles have been stored at 25°C/60%RH for 18 months and 12 months, respectively, while accelerated storage (40°C/75%RH) of product in both package types has been conducted over 6 months.
All available results comply with the product specification. The results support the proposed shelf life of 30 months in HDPE bottles and 2 years for tablets in blisters. The 12-month extrapolation for both expiry periods is supported by the good stability of the drug product and the statistical analysis of critical stability parameters. No special storage precautions are warranted.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Parareg is adequately established. The active substance exhibits low solubility and high permeability making dissolution the rate-limiting step for its absorption. However *in vitro* control measures have been developed to provide a comfortable margin of confidence concerning the satisfactory and reproducible bioavailability of cinacalcet hydrochloride from this product.

The excipients used are typical for this type of formulation. The packaging materials are commonly used and adequately described. The manufacturing process is a standard wet granulation process followed by compression and film coating. In general, satisfactory chemical and pharmaceutical documentation has been submitted for the marketing authorisation. There are no major deviations from EU and ICH requirements.

3. Part III: Toxico-pharmacological aspects

Introduction

Cinacalcet acts on the parathyroid gland by increasing the CaR sensitivity to extracellular calcium. The primary role of the CaR is control of parathyroid hormone (PTH) secretion in response to extracellular calcium concentration. Cinacalcet acts to reduce circulating PTH concentration through activation of the CaR by increasing its sensitivity to extracellular calcium.

Several pharmacology models were investigated to assess the activity of cinacalcet in hyperparathyroidism. The core battery of safety pharmacology studies were conduced as well as additional studies looking at secondary organs. Pharmacokinetics and drug metabolism were evaluated in multiple species. Chronic toxicology studies were conducted in rats and monkeys. Full reproductive toxicology and genetic toxicology batteries were conducted. Two-year carcinogenicity studies were conducted in rats and mice. Toxicology studies were conducted to evaluate impurites, industrial toxicology, and other routes (i.v.) of administration. Juvenile toxicity studies were conducted in rats and dogs.

All pivotal toxicology studies were conducted in accordance with international GLP guidelines. Studies were designed based on ICH, FDA, CPMP, and OECD guidelines, applicable when the studies were conducted

Pharmacology

- Primary pharmacodynamics (*in vitro/in vivo*)

The distribution of CaR mRNA was studied with in situ hybridisation (ISH) and RT-PCR in postmortem tissues obtained from adult cynomolgus monkey and adult mouse and rat (Study R2002084). CaR is highly expressed on parathyroid cells and at lower levels in the kidney, gastrointestinal tract, pancreas, hypothalamus, thyroid gland and possibly in testes and bone (although

studies have failed to demonstrate the presence of functional CaR on osteoblasts or osteoclasts). The role of CaR in other tissues than the parathyroid and thyroid glands is not well understood.

- *In vitro* **studies**

In vitro studies showed that cinacalcet could activate the CaR in the presence of extracellular calcium Using different cell lines with CaR of human, bovine or rat origin, cinacalcet was shown to increase cytoplasmic calcium, inhibit PTH release in parathyroid cells, and increase calcitonin release from thyroid cells. A similar dose-response pattern was seen in all models showing limited species differences in activity. By titrating both calcium and cinacalcet it could be shown that cinacalcet shifted the calcium concentration response curves to the left, as expected for an allosteric enhancer. The S-enantiomer of cinacalcet was at least 75-fold less potent in these systems.

The major metabolites of cinacalcet showed no or minimal pharmacological activity *in vitro*.

- *In vivo* **studies**

Oral administration of cinacalcet (1, 3, 10 or 30 mg/kg) resulted in a decrease in serum PTH levels and blood calcium levels in normal rats (Study R2002063). The extent and duration of the suppression was dose-dependent.

. Secondary hyperparathyroidism (HPT) was induced by 5/6 nephrectomy (5/6 Nx). This model exhibits increased PTH levels, parathyroid gland hyperplasia and decreased blood calcium levels. Treatment with cinacalcet led to a dose-dependent decrease in PTH and blood calcium levels. Cinacalcet reduced parathyroid gland weight and the number of parathyroid PCNA positive cells, demonstrating its potential to prevent development of hyperparathyroidism

The effect of cinacalcet was evaluated in another rodent model of chronic renal failure, in which renal failure is induced in rats by administration of the antibiotic puromycin aminonucleoside (PAN). Oral administration of cinacalcet (10 mg/kg) caused a reduction in PTH levels and serum calcium levels in PAN-treated animals (Study R2002065).

In order to determine whether any tissues other than the parathyroid gland are targets for the *in vivo* pharmacologic action of cinacalcet, studies were performed in rats from which the thyroid and/or parathyroid glands had been surgically removed. Parathyroidectomy (PTX) caused a reduction in both serum PTH and calcium levels. Administration of PTH-Fc (a PTH analogue with extended half-life) produced a significant increase in blood calcium levels. Oral administration of cinacalcet (30 mg/kg) to PTX rats receiving PTH-Fc caused a significant reduction in blood calcium levels and an increase in serum calcitonin levels (Study R2002068). Cinacalcet had no effect on blood calcium levels in rats with both the thyroid and parathyroid glands removed (Study R2002070). These findings suggest that the parathyroid and thyroid glands are the only targets mediating the blood calcium lowering effect of cinacalcet in rats.

Secondary HPT has a negative impact on bone metabolism caused by high circulating levels of PTH, which results in the clinical condition of osteitis fibrosa cystica, characterised by high bone turnover rate and a subsequent increase in fracture rates. Studies were performed to address direct and indirect effects of cinacalcet on bone metabolism.

To evaluate potential effects of cinacalcet on bone formation, cinacalcet was administered daily by gastric lavage for 9 weeks at a dose of 20 mg/kg in sham and 5/6 Nx rats (Studies R2002125 and R2002067). Cinacalcet did not control bone loss during the 9 week study period when compared to vehicle treated 5/6 Nx animals. Cinacalcet treated animals had a less favourable mean change from baseline in bone mass measurements than vehicle treated animals**.**

In a recent preliminary study in 5/6 Nx rats using a lower dose of cinacalcet, amelioration of the osteitis fibrosa caused by elevated levels of PTH was demonstrated (Study 1493-09). This study demonstrated that 5/6 Nx rats treated with cinacalcet (15 mg/kg) had significantly decreased tibial

fibrosis volume and tibial cortical fibrosity, significantly increased femoral cortical bone mineral density and cortical bone strength when compared to 5/6 Nx animals treated with vehicle.

The different outcome in these studies is proposed to be due to a beneficial effect of oscillating rather than persistent PTH levels. By lowering the drug dose, the decrease in PTH levels is not sustained but intermittent. Previous studies with the first generation calcimimetic NPS R-568 showed beneficial effects with daily bolus dosing but detrimental effects with continuous infusion (Ishii et al. 2000, Bone 26:175). The maintenance of PTH dynamics may be of great clinical importance, and this is also addressed in the clinical assessment.

- Secondary pharmacodynamics

Secondary pharmacodynamic studies investigated the effects of cinacalcet in reducing blood calcium levels in models of hypercalcaemia of malignancy. Cinacalcet reduced hypercalcaemia caused by tumours (Rice H-500 Leydig Cell Tumor, CB17C26-DCT Tumor). This effect was dose-dependent and enantiomer specific. The mechanism for the reduction in hypercalcaemia is probably in part mediated through the CaR located on thyroid C-cells to stimulate the release of calcitonin.

Cinacalcet was shown to reduce hypercalcaemia resulting from administration of Vitamin D_3 in rats. In this study cinacalcet did not mediate or exacerbate Vitamin D_3 induced vascular mineralisation.

- Safety pharmacology and pharmacodynamic drug interactions

The safety pharmacology programme was comprehensive and covered CNS, cardiovascular, respiratory, renal, gastrointestinal, and glucose homeostatic systems. In most studies, cinacalcet was administered by oral dosing. Pharmacokinetic data were collected only in the cardiovascular study in dogs, where the C_{max} at the highest dose (50 mg/kg) was only 1.6-fold higher than the human C_{max} at the maximum human dose. For the other studies in rats and mice, based on pharmacokinetic studies showing substantially lower exposure in animals when compared to humans on a dose/bodyweight basis (both Cmax and AUC), it can be concluded that safety margins are in most cases relatively modest. Treatment-related effects were observed only in a few cases. Cinacalcet at 200 mg/kg produced decreased spontaneous motor activity in mice. This effect was attributed to hypocalcaemia resulting from the pharmacological effect of the drug. Increased gastric motility was observed in mice at a dose of 200 mg/kg. Cinacalcet administered intravenously at 20 mg/kg in guinea pigs produced a transient increase in airway resistance and one guinea pig died as the result of bronchoconstriction 6 minutes following dosing.

Safety pharmacology studies performed with cinacalcet are summarised in the following table.

Study Type and Study Number	GLP Status	Route of Administration and doses	Species	Findings
CNS Evaluation				
Neuropharmacological Profile	GLP	po 20, 60, 200	Mouse	No neuropharmacological signs or effect upon body

970091		mg/kg		temperature when observed through a 24 hour period.
Phenylquinone Writhing 970092	GLP	po 20, 60, 200 mg/kg	Mouse	No analgesic effects
Chemically-Induced Seizures 970095	GLP	po 200 mg/kg	Mouse	No anticonvulsant effect on pentylenetetrazol- or strychnine-induced seizures or death
Spontaneous Motor Activity 970100	GLP	po 20, 60, 200 mg/kg	Mouse	At 200 mg/kg, cinacalcet produced decreased spontaneous motor activity at the 10-15 and 15-20 minute intervals of 33 and 48%, respectively
Submaximal Electroshock 970096	GLP	po 200 mg/kg	Mouse	No inhibition of potentiation of the submaximal electroshock at 8 mA.
Barbiturate Sleep Time 970099	GLP	po20, 60, 200 mg/kg	Mouse	No increases in barbiturate-induced sleep time.
Antipyretic Evaluation 970097	GLP	po 20, 60, 200 mg/kg	Rat	No antipyretic effect.
Respiratory Evaluation				
Airway Resistance and Dynamic Lung Compliance 970090	GLP	iv 2, 6, 20 mg/kg	Guinea Pig	At 20 mg/kg a transient significant increase in airway resistance. One guinea pig died 6 minutes following cinacalcet administration, apparently due to bronchoconstriction. No toxicokinetic evaluations.
Gastrointestinal Evaluation				
Gastrointestinal Propulsion 970098	GLP	po 20, 60, 200 mg/kg	Mouse	At 200 mg/kg a statistically significant increase in gastric motility (34%).
Antagonism to Acetylcholine, Barium Chloride, and Histamine on Guinea Pig Ileum 970094	GLP	*in vitro* 0.1 µg/ml	Guinea Pig Ileum	No antagonism to acetylcholine, barium chloride or histamine on guinea pig ileum
Renal Evaluation				
Electrolyte Concentration and Volume Diuresis 970093	GLP	po 20, 60, 200 mg/kg	Rat	Statistically significant increases in Ca^{2+} at all doses. No changes in urine volume output, pH, Na^{+}, Ka^{+}, Cl^{-}
Hypoglycemic Potential				
Hypoglycemic Potential 970145	Non-GLP	po 10, 50 mg/kg once daily for five days	Rat	No hypoglycemic potential
Cardiovascular Evaluation				
Cardiovascular Profile in Dogs 970127	GLP	po 2, 10, 30 mg/kg	Dog	Emesis, reduction in ionised calcium. No effect on electrocardiographic or hemodynamic variables. The highest dose resulted in a C_{max} 1.6-fold higher than seen in humans at the maximum therapeutic dose.
Seven Cardiac Membrane Channel Assay 970035	Non-GLP	*in vitro* 500 ng/ml	---	95% block of K_{ATP} channel. Kv4.3, Kv1.5 and hcNA blocked between 20 and 50%. No effect on L-type Ca^{2+}, hKir2.2 and hERG.

The target selectivity of cinacalcet was addressed in a receptor screen and in a study that was part of the cardiovascular safety evaluation where seven cardiac membrane channels were studied. Cinacalcet at 10 µM showed activity at a number of receptors (8/63) in the receptor screen ($alpha_1$ adrenergic non-selective, the central muscarinic non-selective, the dopamine non-selective, the sigma non-selective, the sodium site 2, the NK_2 receptors and the dopamine and serotonin binding sites on each of the prospective transporter proteins). Cinacalcet at 500 ng/ml showed a 95% block of the K_{ATP} channel and a 20-50% block of the Kv4.3, Kv1.5 and hcNA channels. Further studies were performed to determine IC_{50} values for cinacalcet binding to the receptors/ion channels showing binding in the initial screens. The highest activities were observed with the serotonin transporter (IC_{50}=635 nM) and the K_{ATP} channel (IC_{50}=210 nM). Calculation of safety margins based on free fraction of drug would give margins >10. Although such calculations suggest a small risk for receptor interactions in the clinical situation, as a follow up measure, the applicant will perform additional non-clinical studies to confirm this. Considering the low safety margins in most safety pharmacology and toxicology studies, the presence of secondary pharmacological events cannot be excluded.

The possibility of an interaction with the K_{ATP} channel was addressed by studying the hypoglycaemic potential of cinacalcet, based on the fact that antidiabetic sulfonylurea compounds act through the K_{ATP} channel. The Applicant justified that the lack of effect in cardiac, blood pressure, and glucose parameters observed *in vivo* in rats, and the results of the Novascreen assay, are supportive that there

will be no effect of cinacalcet on K_{ATP} channels with clinical use. The Applicant commits to perform additional studies, to further address this issue.

- Summary of salient findings

Cinacalcet is an organic small molecule that acts as an allosteric modulator of the calcium-sensing receptor on the parathyroid cell surface. Cinacalcet will increase the sensitivity of the receptor to extracellular calcium. The result of this will be a reduction of circulating PTH concentrations.
Several *in vitro* and *in vivo* pharmacology models assessed the activity of cinacalcet in hyperparathyroidism. The parathyroid and thyroid glands appear to be the only targets mediating the blood calcium lowering effect of cinacalcet in rats.

Batteries of safety pharmacology studies were conduced as well as additional studies looking at secondary organs. This covered CNS, cardiovascular, respiratory, renal, gastrointestinal, and glucose homeostatic systems. The data from these studies do not raise major concerns. However, some studies performed to determine potential interaction with a selection of receptors, channels and enzymes, suggested a potential, small risk for receptor interactions in the clinical situation. Considering the low safety margins in most safety pharmacology and toxicology studies, the presence of secondary pharmacological events cannot be excluded and the applicant will perform further studies to address this.

Pharmacokinetics

Pharmacokinetic studies with cinacalcet have been performed in the mouse, rat, dog and monkey.
The studies were carried out primarily with oral administration, which is the clinical route of administration.

Analytical methods were developed and validated to quantitate unlabelled cinacalcet in mouse, rat, rabbit, dog, monkey and human plasma. These methods utilised heparinised plasma samples that were extracted using solid phase extraction. The samples were separated by liquid chromatography (LC) and cinacalcet was detected by tandem mass spectrometry (MS/MS). Validated analytical procedures were also developed for AMG102664 (M7), a dealkylated metabolite of cinacalcet in rat, mouse and cynomolgus plasma. These metabolite assays were used to verify that animals in the control groups in toxicology (carcinogenicity) studies were not exposed to parent drug. An analytical procedure was developed for the separation and quantitation of cinacalcet (the R enantiomer) and its S enantiomer.

- Absorption- Bioavailability

Cinacalcet was well absorbed upon oral administration. However, oral bioavailability was generally low, less than 10% (when calculated from data in the PK tabulated summary only 1.4%) in rats and approximately 20% in humans. This is likely due to extensive first-pass metabolism. No sex differences were seen in PK parameters in the nonclinical species. Nonlinear kinetics, due to saturable absorption, was observed at high doses in some toxicology studies. The difference in bioavailability between rats and humans needs to be considered when discussing safety margins, and safety margins should be based on exposure determinations whenever possible..

- Distribution

Cinacalcet is highly protein bound (93% to 99%) in all species. Studies with radiolabelled drug showed that cinacalcet is widely distributed in tissues without marked accumulation. The highest tissue levels were seen in the GI tract and the Harderian gland (a gland associated with the third eyelid, unique to rodents). The radioactivity in the CNS was relatively low. However, considering the high permeability of cinacalcet in Caco-2 cells, it is likely that the lower CNS radioactivity is mostly related to the lower penetration by polar metabolites and that the active compound will appear in CNS at levels not below those in plasma. Cinacalcet is not a substrate of P-glycoprotein. Cinacalcet was excreted into the milk of lactating rats and it crossed the placental barrier in rabbits.

- Metabolism

In vitro and *in vivo* studies were performed to elucidate the metabolic pathways for cinacalcet and to provide a comparison of the metabolism of cinacalcet in the toxicology species and in humans.

- *In vitro* studies

In vitro, cinacalcet undergoes NADPH-dependent oxidative metabolism in the presence of mouse, rat, dog, monkey and human liver microsomes, resulting in the formation of multiple metabolites. Similar metabolite patterns were seen across species when comparing chromatographic retention times. The major metabolites were dihydrodiols (4 regioisomeric forms) formed by oxidation of the naphtalene rings. Multiple CYP enzymes are capable of metabolising cinacalcet. Studies with specific CYP inhibitors suggested CYP3A4 and CYP1A2 as the major contributors of cinacalcet metabolism in humans.

- *In vivo* studies

In vivo, cinacalcet is metabolised extensively in mice, rats, monkeys and humans. The primary routes of metabolism are N-dealkylation leading to carboxylic acid derivatives and oxidation of the naphtalene ring system to form dihydrodiols. The oxidative metabolites are further conjugated before elimination. There do not appear to be human-specific routes of metabolism.

Several minor metabolites were observed in animal models but not in humans. In humans, there was no detectable stereoconversion of cinacalcet (the R-enantiomer) to form the S-enantiomer.
The circulating and excreted metabolite profile of cinacalcet in humans was similar to that observed in animal models, indicating that appropriate species were utilised in the toxicology studies.

- Excretion

After administration of radiolabelled drug to animals or humans, cinacalcet-derived radioactivity was rapidly eliminated. Both hepato-biliary and urinary elimination are major routes of elimination.
After administration of [^{14}C-CF_3] cinacalcet to lactating rats, radioactivity was excreted into milk to a moderate extent (milk to plasma AUC ratio of 0.46). However, the milk concentrations of parent cinacalcet were high, with a milk to plasma AUC ratio of 9.58.

- Summary of pharmacokinetic parameters

The Applicant has appropriately described the non-clinical pharmacokinetic properties for cinacalcet. A number of studies concerning the absorption, distribution, metabolism and excretion of cinacalcet in mice, rats, dogs and monkeys have been performed. Oral route of administration was used in the majority of the studies.

Cinacalcet showed good absorption, but low oral bioavailability, likely due to extensive first-pass metabolism. Cinacalcet presented high protein binding across all species; it is widely distributed in all tissues and is excreted into milk of lactating rats and it crossed the placental barrier in rabbits.
Multiple enzymes extensively metabolise cinacalcet. Studies with specific CYP inhibitors suggested CYP3A4 and CYP1A2 as the major contributors of cinacalcet metabolism in humans. The major circulating metabolites are inactive.

Cinacalcet is a potent inhibitor of CYP2D6 and this has been confirmed to be clinically relevant. A small increase (<2-fold) in CYP content was observed in the monkey toxicology at the highest dose (100mg/kg).
Similar metabolic pathways occur in humans and the non-clinical species. There was no evidence of human-specific metabolites. In humans, within 8 days after dosing, greater than 96% of a radioactive dose of cinacalcet is recovered, primarily as inactive urinary metabolites.

Toxicology

- Single dose toxicity

Single dose toxicity studies were performed in rats and mice via the oral and i.p. routes. I.v. dosing was not feasible due to the poor solubility of cinacalcet. They are summarised in the following table:

Study ID	Species/ Sex/Number/ Group	Dose/Route	Approx. lethal dose / observed max non-lethal dose	Major findings
970153	Mouse 5M/5F	0, 10, 100, 500 / oral	500 / 100	500 mg/kg: 1M died. Abnormal gait, decreased activity, quivering
970154	Mouse 5M/5F	0, 1, 5, 20 / i.p.	20 / 5	20 mg/kg: 1M/1F died. Abnormal gait, decreased activity, abnormal stance, prostration
970151	Rat 5M/5F	0, 10, 100, 500 / oral	500 / 100	500 mg/kg: 1F died.
100326	Rat 5M/5F	1000, 1500 / oral	1500/ 1000	1500 mg/kg: 2F died ≥1000 mg/kg: tremors, hypoactivity
970152	Rat 5M/5F	0, 1, 5, 20 / i.p.	- / 20	No clinical signs. ≥5 mg/kg: Adhesion of liver lobes; white discoloration, focal capsulitis and capsular fibrosis of liver and spleen

The toxicities seen in these studies were likely due to the hypocalcaemia resulting from the pharmacological effect of cinacalcet (tremors, hypoactivity). There were no toxicokinetic data from these studies.

- Repeat dose toxicity

Repeat dose toxicity studies were performed in rats, dogs and cynomolgus monkeys. Toxicokinetic data from the one-month dog study revealed low systemic exposure, possibly due to frequent emesis, and rats and monkeys were selected for the pivotal repeat dose toxicity studies. The hypocalcaemia resulting from the pharmacological effect of cinacalcet was the dose-limiting toxicity in most species.

Clinical signs in rats included laboured breathing, dehydration, salivation, skin pallor and thinness. Cataracts were seen in high-dose rats. Mild hyperplasia/inflammation was seen in the caecum. This inflammatory lesion was not seen in the rodent diet studies (carcinogenicity studies), indicating that it may be related to the method of administration; oral gavage dosing in a bolus of methylcellulose.
In the monkey studies, main clinical findings were poor appetite, sporadic emesis and soft to liquid faeces. QT-prolongation was seen in the 3-month study, and was proposed to be secondary to hypocalcaemia. There were dose-dependent declines in RBC and WBC. Testosterone levels were decreased at all dose levels without any histological correlates. There were increases in ALT and AST at the highest dose. Increased liver weights (absolute and relative) were observed without microscopic correlates. Total hepatic CYP450 increased at the high dose. Periportal vacuolation was observed in 3/3 females in the high dose group at the 6-month interim sacrifice. The toxicological importance of this finding is unknown.

Due to the dose-limiting toxicity associated with hypocalcaemia, safety margins achieved in the repeat-dose toxicity studies were small. In the clinical setting, calcium levels are carefully monitored and hypocalcaemia is not likely to be a clinical problem. The toxic findings are in most cases attributed to the hypocalcaemia, either directly or indirectly as a result of the decreased food intake and decreased body weight. The main toxicity findings, grouped according to target organs were:

- GI tract: Emesis, soft or liquid faeces, caecal hyperplasia/inflammation – Emesis could be due to hypocalcaemia or a direct CNS effect. Caecal hyperplasia/inflammation was considered to be dependent on the administration procedure, gavage using methylcellulose as vehicle, since

the corresponding finding did not occur in the carcinogenicity diet studies. A contribution of CaR in the GI tract is possible.

- Decreased testosterone levels were seen in monkeys . This was considered due to delayed maturation of animals secondary to decreased body weight gains. A direct effect on CaR in testes was considered unlikely since no other hormonal effects were seen and the testes were normal histologically.
- Liver effects – there was an increase in ALT, AST and triglyceride levels in monkeys and the levels were only partly normalised after 4 weeks recovery. Other liver-related findings were also observed.
- Cataracts were seen in rats only and proposed to be related to hypocalcaemia and/or accumulation in Harderian gland, which is found in rodents only. Cataract as a complication of hypocalcaemia has been described in the literature
- QT-findings – a direct correlation between QTc intervals and calcium levels could be observed. It should be pointed out that correlation does not necessarily imply a causative relation. A secondary pharmacological effect cannot be fully excluded. Risk assessment must be based on clinical data (see below).
- Lung – Abnormal breathing sounds and/or laboured breathing were reported as clinical signs in several of the toxicity studies. Increased airway resistance and bronchoconstriction was observed in guinea pigs in a safety pharmacology study. The laboured breathing observed in the repeat-dose toxicity studies is a known consequence of hypocalcemia. The rapid lung effects observed in the guinea pig study are not readily attributed to hypocalcemia. However, the exposure achieved after intravenous administration is likely to be several-fold higher than what is achieved in the clinical situation.

- Genotoxicity *in vitro* and *in vivo*

A conventional battery of genotoxicity studies was performed. The results from these studies are summarised in the following table:

Type of test/Study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
Gene mutations in bacteria	*Salmonella* TA98, TA100, TA1535, TA1537, *E Coli* WP2-uvrA	-S9: up to 250 µg/plate +S9: up to 750 µg/plate	Negative
Gene mutations in mammalian cells	CHO-cells, HGPRT-locus	- S9: 1.5 – 10 µg/ml +S9: 10 – 40 µg/ml	Negative (see discussion below)
Chromosomal aberrations *in vitro*	CHO-cells	-S9: 0.75 – 6 µg/ml +S9: 1.5 – 12 µg/ml	Negative
Chromosomal aberrations *in vivo*	Mouse, micronuclei in bone marrow	10, 100, 200 mg/kg single oral gavage	Negative

These studies gave no evidence for a genotoxic potential of cinacalcet. However, in particular in absence of metabolic activation, cinacalcet exhibited pronounced cytotoxicity, and that is why the studies with mammalian cells were performed at relatively low concentrations. Also, in the *in vitro* chromosomal aberration test, a significant increase in the number of chromosomal aberrations was seen with the highest dose (6 µg/ml) after 4 hours incubation but not after 20 hours incubation. The number of chromosomal aberrations was within the historical control range. The *in vivo* micronucleus assay was performed in mice. There were no positive findings; however exposure of the bone marrow to cinacalcet was not measured but only implied from a previous distribution study in rats.

- Carcinogenicity

Two-year carcinogenicity studies were performed in mice and rats. There were no tumour findings. In rats there was a decreased incidence in thyroid C-cell adenomas, likely to be related to the pharmacological activity of cinacalcet since C-cells express CaR. Plasma levels of cinacalcet were

observed in plasma samples taken from control animals in both the rat and mouse carcinogenicity studies. In contrast, very low or no metabolite was detected in the plasma of the control animals A full investigation was launched to determine the source of contamination, and it was considered that the AMG 099073-00 measured in control samples was possibly due to post-collection sample contamination. It could be concluded that the control animals were not exposed to the test article because the standard pharmacological effects (decreased PTH and Ca) were not seen and because virtually no metabolite (AMG 102664-00) was seen in the control samples. This metabolite was present at levels at least 20-fold higher than those of the parent in treated animals. The exposure to cinacalcet (AUC) in the high dose group was about 1.6-fold higher (mice), 2.5-fold higher (rat males) and 1.4-fold higher (rat females) than that observed for a human therapeutic dose.

- Reproductive and developmental studies

Reproduction and development studies were performed in rats and rabbits. There was no effect on fertility in rats. Embryotoxicity (lower foetal body weights) was observed in rats and rabbits at doses associated with maternal toxicity. There was no evidence for a teratogenic potential. It should be pointed out that maternal and foetal toxicity occurred at exposures close to or below the clinical exposure, and even at the highest dose evaluated in the main developmental toxicity studies the safety margins were small, in the rabbit study below one (0.4). This fact is clearly reflected in the SPC.

Juvenile toxicology studies were conducted in rats and dogs (28 days + 28 day recovery). In rats no important toxicological findings were observed at doses up to 5 mg/kg (representing an exposure 0.34-fold that of the adult human dose). In this study, there were a number of mortalities in the male high dose group, which were attributed to dosing accidents. In dogs, intramural left ventricular arterial hypertrophy was noted in a few animals at all dose groups, including the control, with increasing severity seen among animals administered 1.5 or 5.0 mg/kg at the end of the recovery period only. One male in the high dose group had multifocal left ventricular myocardial fibrosis. The relationship of these findings to the test article is unclear. The exposure to cinacalcet at the highest dose (5 mg/kg) was 0.1-fold that of the adult human dose.

- Local tolerance

Dermal exposure to cinacalcet (0.5 g/ml) produced slight skin irritation in one out of three rabbits. Cinacalcet was shown to be a mild dermal contact sensitiser in the guinea pig. Cinacalcet was a severe irritant to the conjunctiva of the rabbit eye. In addition, cinacalcet caused corneal opacity and iridial irritation.

- Other toxicity studies

Toxicity studies in rats and *in vitro* genotoxicity studies were performed on impurities to evaluate their toxic potential. Impurities were qualified according to ICH guidelines.

The potential synthetic and degradation impurities that are specified in the specification for control of the drug substance were qualified in pre-clinical studies. Any single unspecified impurity is controlled at a level of 0.10%. Additionally, the limit for total impurities is not greater than 0.70%.

Discussion on the non-clinical aspects

The extent and scope of the documentation provided in this application are appropriate to support the non-clinical-pharmacology profile of cinacalcet. A comprehensive non-clinical programme was performed to evaluate the pharmacology, pharmacokinetics (including drug metabolism) and the toxicology, based on the expected long-term dosing of the drug.

Cinacalcet is an organic small molecule that acts as an allosteric modulator of the calcium-sensing receptor on the parathyroid cell surface. Cinacalcet increases the sensitivity of the receptor to extracellular calcium. The result of this is a reduction of circulating PTH concentrations.

Various pharmacological studies demonstrate the activity of cinacalcet in hyperparathyroidism. The parathyroid and thyroid glands appear to be the only targets mediating the blood calcium lowering effect of cinacalcet in rodents.

Pharmacokinetic studies with cinacalcet have been performed in the mouse, rat, dog and monkey. Following oral administration, cinacalcet showed good absorption, but low bioavailability, likely due to extensive first-pass metabolism. It is also widely distributed in all tissues. Extensive metabolism suggests major involvement of CYP3A4 and CYP1A2 in humans.

A complete nonclinical toxicology programme was performed. It did not give rise to any serious safety concerns. However, the occurrence of non-tolerable hypocalcaemia already at exposure levels close to the clinical exposure severely limits the possibility to establish appropriate safety margins. The environmental risk assessment of cinacalcet is yet to be finalised.

4. Part IV: Clinical aspects

Introduction

A comprehensive clinical program was performed to evaluate the pharmacology, pharmacokinetics, efficacy and safety. The submission includes 47 clinical studies in normal volunteers and patients with primary or secondary HPT performed from December 1997 to June 2003. 15 of these studies were conducted in subjects with secondary HPT, and 5 studies were performed in subjects with primary HPT. The remaining 27 studies provide biopharmaceutic and clinical pharmacology information as well as information on initial efficacy and tolerability of cinacalcet. Two thousand, five hundred twenty-three (2523) subjects have participated in the studies within the clinical program, including 1677 subjects with secondary HPT and 151 subjects with primary HPT.

The clinical studies were conducted in accordance with the principles of Good Clinical Practice (GCP) regulations/guidelines available from regulatory authorities and the International Conference on Harmonisation (ICH).

Pharmacokinetics

The Applicant has performed a comprehensive clinical pharmacology programme (including in total 41 *in vivo* and *in vitro* studies). *In vitro* studies were performed using human biomaterials (including plasma, liver microsomes, expressed cytochrome P450 [CYP] enzymes, and CaCo-2 cells) to characterise the metabolism, permeability, and potential enzyme inhibition profile of cinacalcet.
12 clinical studies were conducted in healthy volunteers to characterise the pharmacokinetic profile of cinacalcet and to evaluate the potential for drug-drug interactions (amitriptyline, warfarin, calcium carbonate [$CaCO_3$], ketoconazole, sevelamer, and pantoprazole). Additional studies evaluated the effects on the pharmacokinetics of cinacalcet in patients with hepatic and renal dysfunction.
16 studies were performed in patients with primary HPT and patients with secondary HPT and chronic kidney disease (including both patients on dialysis and patients not yet requiring dialysis), which are pharmacological studies or studies primarily designed for efficacy and safety, but provided additional pharmacokinetic and pharmacodynamic data

The analytical methods have been sufficiently characterised. Samples were extracted using online or offline solid phase extraction. The extracted samples were separated by liquid chromatography (LC), and cinacalcet was detected by tandem mass spectrometry (MS/MS). Most analytical procedures have used electrospray LC/MS/MS in the positive ion mode. The LOQ was 1ng/ml in the majority of studies, but in a few studies 0.1ng/ml. Validation reports were provided.

Stability validation data demonstrated that cinacalcet was stable in human plasma (heparinised tubes) for up to 21h at ambient temperature storage. Stability in -20°C and -70°C was demonstrated for up to 5months and 99days, respectively.

- Absorption

Cinacalcet was rapidly absorbed with maximal concentrations in patients typically reached at 2 to 6h after oral administration. The *in vitro* results indicate that cinacalcet is permeable and is not a substrate for PgP *in vitro.* The extent of absorption was approximately 80%. However, the absorption is saturated at doses above 200mg, most likely due to poor solubility. The absolute bioavailability during fed conditions was approximately 30%. There is a substantial food-effect, with on average 70-80% higher AUC in the fed state, likely due to an increase in cinacalcet solubility from the tablet formulation at concomitant food intake. It is recommended that cinacalcet should be taken with food or shortly after a meal, as was done in the Phase III-programme. This recommendation is reasonable and reduces the possible intra individual variability due to food effect. But, even so, the compliance with the food recommendation will vary in the population and the food-effect will still contribute to the variability, especially in patients taking cinacalcet more than two times daily.

The Applicant has performed a comprehensive biopharmaceutical program showing bioequivalence between formulations used in the clinical trials..

- Distribution

The plasma protein binding was about 97% and distributes minimally into red blood cells. Steady-state volume of distribution was estimated to be 1,235L following 20mg IV, indicating extensive distribution outside the systemic circulation.

- Elimination

Cinacalcet is eliminated mainly through metabolism, the metabolites being excreted in urine.
In patients with primary and secondary HPT, CL/F was 222L/h and 234L/h, respectively. Cinacalcet levels declined in a biphasic fashion with an initial half-life of approximately 6h and a terminal half-life of 30-40h. At steady-state, the two-fold accumulation (once-daily dosing) is predictive from single-dose data. About 80% (66 out of 82%) of the radioactivity in urine was identified. The major metabolite, M5 accounted for overall 73% of radioactivity in plasma. Metabolites M6 and M2-Glu accounted for 9 and 11 %, respectively. Excretion in the faeces accounted for approximately 15% of the dosed radioactivity. Cinacalcet was a relatively minor component in plasma, being less than 0.3% of the plasma radioactivity at C_{max}. Cinacalcet appears to be metabolised by multiple CYP enzymes. The *in vitro* data indicate that CYP3A4, CYP1A2, CYP2D6 (at low concentrations) and perhaps CYP2C9 are responsible for cinacalcet metabolism but the study results are to some extent contradictory. Polymorphism in CYP2D6 is not considered to be clinically important.

- Dose proportionality and time dependencies

Approximate dose-proportionality has been shown between 30 and 180mg. Data indicate that there is non-linearity at low doses (5-25mg), possibly explained by saturation of CYP2D6-pathway.The steady-state pharmacokinetic profile of cinacalcet did not appear to change over time.

- Special populations

Studies 980126 and 980125 investigated the pharmacokinetics of cinacalcet after multiple doses in patients with secondary and primary hyperparathyroidism. After administration of 50 mg/day cinacalcet to patients with secondary HPT, C_{trough} and C_{max} were 3.53 and 20.2 ng/mL, respectively. After the same dose to patients with primary HPT, average C_{trough} and C_{max} were 3.44 and 18.6 ng/mL at steady-state, respectively. The maximal plasma cinacalcet concentrations achieved after administration of the highest dose studied for the treatment of primary HPT (90 mg 4 times daily) were approximately 2-fold greater than those typically obtained after once daily dosing of 180 mg. Steady-state is reached after approximately 4-5 days with a 2-fold accumulation compared with single-dose. No major difference in the pharmacokinetic behaviour was detected between subjects with primary and secondary HPT. There is large variability in pharmacokinetic parameters between patients (>50%). Given this large inter-patient variability in the pharmacokinetic parameters, dose titration appears to be justified. Inter occasion variability in CL/F was rather low (20%) further supporting the titration strategy.

Even though mean exposure is not changed with renal function, variability is increased, although the observed variability may be partially explained by the small sample size (6) in each group in the relevant study. There was, however, no clear relationship between AUC versus CL_{crea}. The metabolites of cinacalcet are eliminated through renal excretionand may accumulate during multiple dosing in the ESRD patient population compared with healthy volunteers. Mode of dialysis (haemodialysis or peritoneal dialysis) does not affect the pharmacokinetics of cinacalcet.

As predicted from the elimination mechanism, hepatic impairment had a significant effect on 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 adjustment is required for subjects with hepatic impairment in the SPC. However, cinacalcet should be used with caution in patients with moderate or severe hepatic impairments and treatment should be closely monitored during dose titration and continued treatment with cinacalcet.

There appears to be some gender difference in the pharmacokinetics, which at least to some extent may be explained, by the known gender difference in CYP1A2 expression. This gender difference does not warrant any labelling restrictions given the overall variability of the product, and because doses are titrated for each subject. The information is included in section in 5.2 of the SPC, and reflects the results from the population analysis.

The effect of body weight, age and race were limited and does not warrant any labelling restrictions.

- Pharmacokinetic interaction studies

The interaction potential for cinacalcet has only been investigated in part. The only *in vivo* study contributing to the assessment of interaction of cinacalcet is the ketoconazole study. A 2-fold increase in cinacalcet bioavailability, most likely through CYP3A4-inhibition, confirms the importance of CYP3A4 in cinacalcet metabolism. The effect of a potent CYP1A2 inhibitor (e.g. fluvoxamine, ciprofloxacin) has not been evaluated and it is not known, and a clinically relevant effect on cinacalcet clearance cannot be excluded. The following is included in the SPC: "caution should be exercised when cinacalcet is administered concomitantly with strong inhibitors or inducers of CYP3A4 and/or CYP1A2. Dose adjustment of cinacalcet may be necessary". Additionally, plasma levels of cinacalcet may be lower in smokers due to induction of CYP1A2-mediated metabolism. Dose adjustment may be necessary if a patient starts or stops smoking. The potential for cinacalcet to inhibit the major CYP enzymes was also evaluated *in vitro*. Cinacalcet does not potently inhibit CYP1A2, CYP2C9, CYP2C19 or CYP3A4. However, cinacalcet is a potent inhibitor of CYP2D6 and could therefore impair the elimination of drugs that are metabolised primarily by this enzyme. The *in vivo* inhibition potency, however, is not clear, since the substrate (amitriptyline) used in the interaction study is metabolised via also other enzymes. A cautionary statement is given in the SPC regarding CYP2D6-substrates with narrow therapeutic index (e.g., flecainide, propafenone, metoprolol given in heart failure, desimipramine, nortriptyline, clomipramine), indicating that dose adjustments may be required.

Pharmacodynamics

Cinacalcet is a second generation derivative of the parent calcimimetic compound R-568.
The clinical development program for cinacalcet investigated primary and secondary pharmacodynamic effects in volunteers, in patients with primary hyperparathyroidism and in patients with secondary hyperparathyroidism due to chronic renal failure or end-stage renal disease.

- Mechanism of action

Cinacalcet is a first-in-class calcimimetic that modulates the activity of the calcium-sensing receptor.

It is a small molecule that acts as an allosteric modulator of the calcium-sensing receptor (CaR) on the parathyroid cell surface.

The primary role of the CaR is control of parathyroid hormone (PTH) secretion in response to extracellular calcium concentration. Cinacalcet acts to reduce circulating PTH concentration through activation of the CaR by increasing its sensitivity to extracellular calcium.

- Primary and Secondary pharmacology

In the phase I studies cinacalcet given in single and multiple dose regimens (investigated in dose ranges between 1 and 100 mg) was demonstrated to reduce plasma iPTH and total calcium concentrations in a dose dependent manner in healthy volunteers (970241). After administration of cinacalcet, large intersubject variations in iPTH concentration were observed, though changes in each subject's plasma iPTH concentration appeared to inversely correlate with changes in cinacalcet concentration. Serum calcitonin concentrations remained essentially unaffected after cinacalcet administration.

In secondary HPT, escalating single doses of cinacalcet were associated with decreasing iPTH and serum calcium concentrations (980126). The iPTH nadir was 45%, 50%, 55%, and 70% below baseline values after doses of 25, 50, 75, and 100 mg, respectively, and iPTH concentrations remained below baseline for 24 hours after doses of 25, 50, and 100 mg. During the multiple-dose phase, iPTH was 21% and 39% below baseline concentrations 24 hours after the last 50/25- and 50-mg dose on day 8, respectively. Serum calcium was 6%, 4%, and 7% below baseline concentrations 24 hours after the last 25-, 50/25-, and 50-mg dose on day 8, respectively. In the titration study (20000187), a large decrease in PTH levels was evident up to the 75mg dose and a trend towards a moderate decrease was seen at higher doses and no additional effect was seen at doses over 200mg (as expected based on the limited absorption at higher doses). Large variability in pharmacokinetics was seen at higher doses. In primary HPT (980125), an inverse correlation was observed between mean iPTH and mean cinacalcet concentrations for both the QD (50-100mg) and BID (30-50mg) dose groups. Administration of multiple doses of cinacalcet at doses of 50, 75, and 100 mg QD or 30, 40, and 50 mg BID decreased elevated serum calcium to normal values that were sustained over the entire treatment period. iPTH decreased rapidly (approximately 50% 2- to 4-hours postdose) and returned to baseline concentrations approximately 12 hours after dosing in the QD and BID treatment groups.

In conclusion, the CHMP was of the opinion that the primary pharmacology programme sufficiently demonstrates the effects of cinacalcet on iPTH and calcium levels in healthy volunteers, in CKD with secondary HPT and in patients with primary HPT. The Applicant has provided sufficient arguments in support of the proposed dosing recommendations. The proposed posology is supported by the results of the pivotal clinical studies.

The clinical development program for cinacalcet included an evaluation of the effect of cinacalcet on ECG, in particular, the QT/QTc interval (studies 970241, 990751, and 20000187). ECG data collected in these studies were analysed to determine the QT interval; Bazett's and Fridericia's correction formulas were used for correction of the QT-interval data from Study 20000187. The proportion of subjects with an increase from baseline interval of < 30 msec, 30 to 60 msec, and > 60 msec and the interval mean, median, and range were calculated.

Subjects receiving cinacalcet and subjects receiving placebo had similar QTc intervals at any time point. Subjects participating in Study 20000187 received cinacalcet doses ranging from 25 to 300 mg once daily for 7 days. In this study, the results for QTc were similar among all dose groups and between cinacalcet and placebo groups regardless of the correction formulae. Likewise, the results of the categorical analyses did not reveal any differences or trends within or between treatment groups. The effects of cinacalcet on ECG were also examined rather extensively in the phase III programme.

Clinical efficacy

I. Treatment of secondary hyperparathyroidism in chronic kidney disease.

A total of 1597 CKD subjects with secondary HPT were enrolled in 15 clinical studies:

4 randomized, double blind, placebo-controlled Phase II dose-titration studies in ESRD patients on haemodialysis with secondary HPT (studies 20000237, 990740, 990101, 990102)

- 3 randomized, double blind, placebo-controlled main Phase III studies in hemodialysis or hemodialysis/ peritoneal dialysis patients with secondary HPT in ESRD (studies 20000172, 20000183, 20000188)
- 2 randomized, double blind, placebo-controlled phase II studies in patients with CKD and secondary HPT not receiving dialysis (studies 20000236, 20010239)
- 3 extension studies:
    - 1 double blind, placebo-controlled Phase III extension study (study 20010240; with patients, who completed studies 20000172 and 20000183)
    - 1 open label Phase II extension study (study 20000130; with patients who completed studies 990101, 990102, 990740, 20000237)
    - 1 open label extension study (20020158), which is still ongoing (including patients, who completed studies 20000172, 20000183, 20000188, 20010141, 20010240);
- A randomized, double-blind, placebo-controlled study (20010141) to examine the effects of cinacalcet on renal osteodystrophy in ESRD patients with secondary HPT on dialysis, and 1 ancillary placebo-controlled study in patients with osteitis fibrosa (990126)
- Study 20010142, an open-label extension study to assess the long-term safety and efficacy of cinacalcet in subjects with CKD not receiving dialysis and secondary HPT was discontinued.

- Dose response studies

In four randomised, double blind, placebo-controlled phase II studies (20000237, 990101, 990740, 990102) dose titration of cinacalcet was performed over 8-12 weeks in haemodialysis patients with secondary HPT (iPTH $\geq$ 300 pg/mL). The titration period was followed by a 6-week maintenance phase in 2 of the studies. The studies included altogether 147 cinacalcet treated patients compared with 146 placebo treated. The doses employed ranged from 20 mg to 180 mg/day with maximal doses varying between studies (50, 100 or 180 mg/day). Reductions in mean iPTH levels, as measured before cinacalcet administration, were observed in a dose dependent manner. After the titration the reductions varied between 26 and 47 % (in pre-dose samples), with more pronounced reductions obtained with the higher doses, and the reductions persisted during the maintenance phase. However, there were large interindividual variations. Calcium levels were modestly reduced (5-7%) as were the phosphorus levels (5-14%). In study 20000187 doses up to 300 mg were employed, but exposure did not appear to increase at doses greater than 200 mg. A starting dose of 30 mg was chosen because this dose was well tolerated and in general, lower doses did not appreciably lower PTH concentrations. A maximum once-daily dose of 180 mg was chosen because cinacalcet exposure increased proportionally with dose over the range of 30 to 180 and then plateaued at doses above approximately 180 mg (Study 20000187).

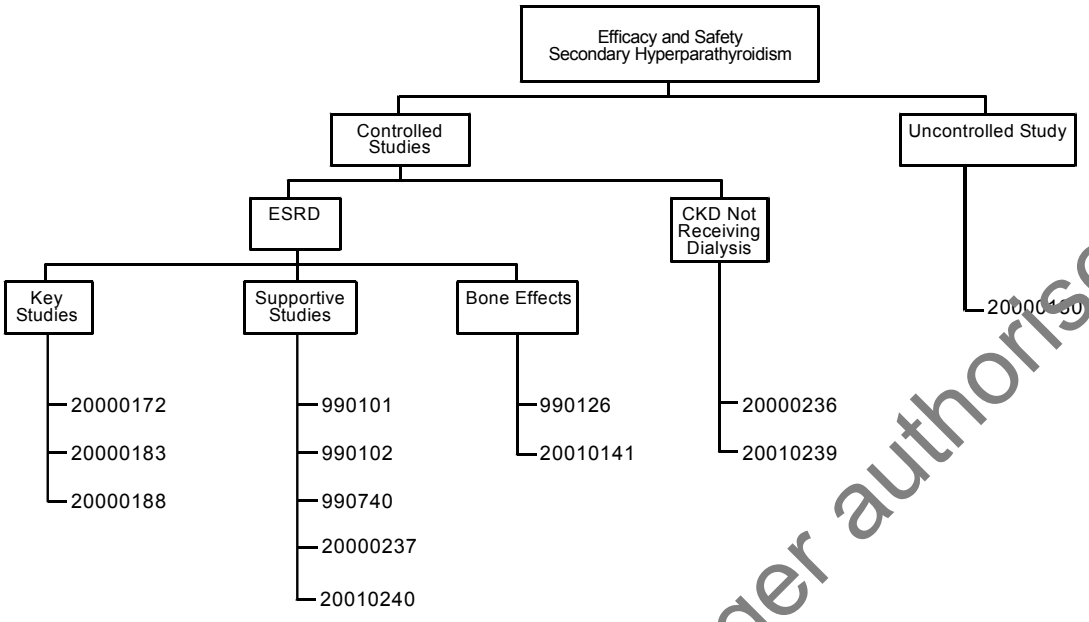
Across studies and individuals, no clear relationship was apparent between cinacalcet concentrations and the occurrence of adverse events.

The CHMP concluded that the primary pharmacological effects of different doses of cinacalcet were evaluated in a fairly large number of ESRD patients with secondary HPT and the dose titration regimen chosen for further evaluation in the phase III studies is judged to be well supported by the results.

- Main studies

The clinical development program performed for cinacalcet in the treatment of secondary HPT associated with CKD includes subjects on dialysis (ESRD) and patients not receiving dialysis. The phase 3 program included 4 double-blind, placebo-controlled studies in subjects with secondary HPT receiving maintenance dialysis. Two randomised placebo-controlled studies evaluated the effects of cinacalcet in CKD subjects not receiving dialysis. The 30 to 180 mg cinacalcet dose range and dose-titration study design were used, regardless of the stage of CKD.

In addition, seven supportive phase 2 studies in subjects with secondary HPT receiving maintenance haemodialysis (HD) were conducted, including 6 randomised, placebo-controlled trials.



I.A Secondary HPT in ESRD Subjects

METHODS

Study Participants

The efficacy of cinacalcet in the treatment of secondary HPT in ESRD subjects is mainly supported by three phase 3, 6-month, randomised, double-blind, placebo-controlled studies (20000172, 20000183, and 20000188) in patients on standard therapy (Vitamin D analogues and/or phosphate binders). In addition, a phase 3 extension study (20010240) provided 1-year, placebo-controlled safety and efficacy results in ESRD subjects with secondary HPT. Eligible subjects were adults with ESRD and iPTH > 300 pg/mL who were receiving HD. Study 20000188 also included subjects receiving peritoneal dialysis (PD). No eligibility restrictions were specified for Ca x P at baseline.

Treatments

Subjects were permitted to continue receiving standard of care (vitamin D and phosphate binders), if prescribed. During the 30-day period before day 1 (first dose of study drug in each study), the prescribed dose and brand of vitamin D sterols and phosphate binders were to remain constant. Once subjects were on study, investigators were at liberty to change phosphate binders at any time during the study. Vitamin D sterols could only be changed based upon the protocol-specified guidelines listed in the following table.

	30 Days Before Study	Day 1 to End of Study
Phosphate Binders	Fixed dose and brand	Complete flexibility of dose and brand

	30 Days Before Study	Day 1 to End of Study	
Vitamin D Sterols	Fixed dose, brand, and route of administration	Decrease permitted if: Serum calcium ≥ 11 mg/dL Serum phosphorus ≥ 6.5 mg/dL Ca x P ≥ 70 $(mg/dL)^2$ PTH <100 pg/mL on the lowest dose of study drug (30 mg cinacalcet/placebo)[a]	Increase permitted if: Serum calcium < 8.4 mg/dL Symptoms of hypocalcaemia PTH increases by ≥ 50% from baseline for 3 consecutive visits[a]

[a] Studies 20000172 and 20000183 only

Each study consisted of 2 phases: a 12-week (studies 20000172 and 20000183) or 16-week (study 20000188) dose-titration phase in which possible sequential daily doses of 30, 60, 90, 120, and 180 mg cinacalcet or placebo were evaluated, and a 14-week (or 10-week) efficacy-assessment phase (in which doses could also be titrated). Study 20000188 allowed dose titration every 4 weeks (instead of every 3 weeks) to gain experience with a different dose-titration frequency.

Key aspects of the design, entry criteria, and efficacy endpoints were consistent between studies

Study Number/ Type	Entry Criteria	No. of Patients Enrolled/Treatment	Geographic Region	Duration of Cinacalcet Exposure
20000172 Randomised, double blind, placebo control	ESRD and iPTH ≥ 300 pg/mL receiving haemodialysis for ≥ 3 months	410 enrolled: 205/cinacalcet (30 mg with dose titration to 60, 90, 120, and 180 mg) 205/placebo	US Canada	26 weeks (12-week dose titration and 14-week efficacy assessment)
20000183 Randomised, double blind, placebo control	ESRD and iPTH ≥ 300 pg/mL receiving haemodialysis for ≥ 3 months	331 enrolled: 166/cinacalcet (30 mg with dose titration to 60, 90, 120, and 180 mg) 165/placebo	EU Australia	26 weeks (12-week dose titration and 14-week efficacy assessment)
20000188 Randomised, double blind, placebo control	ESRD and iPTH ≥ 300 pg/mL receiving haemodialysis or peritoneal dialysis for ≥ 1 month	395 enrolled: 294/cinacalcet (30 mg with dose titration to 60, 90, 120, and 180 mg) 101/placebo	US Canada Australia	26 weeks (16-week dose titration and 10-week efficacy assessment)

Endpoints

Primary end-point in all studies was the proportion of subjects achieving a mean pre dose iPTH value ≤ 250 pg/mL.

Endpoint	Study 20000172	Study 20000183	Study 20000188

Proportion of subjects with a mean iPTH value ≤ 250 pg/mL	Primary	Primary	Primary
Proportion of subjects with a reduction from baseline in mean iPTH of ≥ 30%	Secondary	Secondary	Secondary
Percent change from baseline in mean Ca x P	Secondary	Secondary	--
Change from baseline in self-reported KDQOL cognitive functioning scale score	Secondary	Secondary	--
Percent change from baseline in mean iPTH	Tertiary	Tertiary	Secondary
Percent change from baseline in mean serum calcium	Tertiary	Tertiary	--
Percent change from baseline in mean serum phosphorus	Tertiary	Tertiary	--
Proportion of subjects with a mean iPTH ≤ 250 pg/mL and a reduction from baseline in Ca x P	Tertiary	Tertiary	--

Randomisation

The protocols for studies 20000172 and 20000183 were identical, with the studies being conducted in different geographic regions (North America and Europe/Australia, respectively). Both studies included a 1:1 randomisation to cinacalcet or placebo, whereas study 20000188 had a 3:1 randomisation. In all studies, randomisation was stratified by mean baseline iPTH level (> 300 and < 500, > 500 and < 800, > 800 pg/mL). In addition, studies 20000172 and 20000183 were stratified by baseline Ca x P (< 70, > 70 [mg/dL]), and study 20000188 was stratified by mode of dialysis (HD, PD). Enrolment of subjects with a baseline iPTH > 800 pg/mL was limited to 20% of subjects in studies 20000172 and 20000183, based upon the prevalence of severe secondary HPT in the dialysis population. In study 20000188, no limitations on enrolment were specified for this subgroup

Statistical methods

The primary analyses of the efficacy endpoints used the intention-to-treat (ITT) populations, which included all subjects who were randomised. The Cochran-Mantel-Haenszel (CMH) test was used for comparisons between treatment groups for the primary and secondary efficacy end-points. Since the populations and end-points were essentially similar in the three pivotal studies and since interaction tests for the primary end-point did not demonstrate any interaction between protocol and outcome or between treatment group and protocol, data were pooled for additional analyses. Subjects with no efficacy-assessment data were considered to be non-responders (PTH ≤ 250pmol/mL, PTH reduction ≥ 30%) or the LOCF method was used (change in mean CaxP, PTH, Ca, and P).

Study 20010240

A phase 3, placebo-controlled, double-blind extension study (study 20010240) was also conducted. In this study, subjects completing studies 20000172 and 20000183 could continue with their original treatment assignment for an additional 26 weeks, providing 12 months of overall exposure to cinacalcet or placebo. Although the primary objective of study 20010240 was to evaluate long-term safety, iPTH, Ca x P, serum calcium, and serum phosphorus data provide supportive information on the efficacy of cinacalcet over 1 year. Additional long-term efficacy data were also collected in study 20010141, a double-blind, placebo-controlled, 1-year study that evaluated the effects of cinacalcet on bone histomorphometry in ESRD subjects with secondary HPT, and study 20000130, an ongoing, open-label extension study in ESRD subjects with secondary HPT receiving HD.

RESULTS

The results were consistent in the three studies and mainly pooled data are presented below.

Subject disposition for the three phase 3 efficacy studies is shown in the following table. Across these studies, 71% of subjects randomised to cinacalcet and 78% of subjects randomised to placebo completed the study. In study 20000183, a higher withdrawal rate was observed for the cinacalcet group (36%) than for the placebo group (20%). Adverse events were the most common reason for

withdrawal in this study, leading to the discontinuation of 23% of the cinacalcet group and 5% of the placebo group (study 20000183). Since response rates were similar when using the ITT analysis set and the subset of subjects who had values during the efficacy-assessment phase, the difference in withdrawal rates between the cinacalcet and placebo groups in this study did not appear to impact the overall conclusions of the efficacy analysis. Otherwise, subject disposition and reasons for withdrawal were generally similar between treatment groups and across studies.

	Study 20000172		Study 20000183		Study 20000188		Total	
	Placebo n (%)	Cinacalcet n (%)	Placebo n (%)	Cinacalcet n (%)	Placebo n (%)	Cinacalcet n (%)	Placebo n (%)	Cinacalcet n (%)
Randomised	205 (100)	205 (100)	165 (100)	166 (100)	101 (100)	294 (100)	471 (100)	665 (100)
Received study drug	204 (100)	200 (98)	165 (100)	165 (99)	101 (100)	291 (99)	470 (100)	656 (99)
Completed	158 (77)	146 (71)	132 (80)	107 (64)	77 (76)	217 (74)	367 (78)	470 (71)
Discontinued	47 (23)	59 (29)	33 (20)	59 (36)	24 (24)	77 (26)	104 (22)	195 (29)
Ineligibility	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (0)
	Study 20000172		Study 20000183		Study 20000188		Total	
	Placebo n (%)	Cinacalcet n (%)	Placebo n (%)	Cinacalcet n (%)	Placebo n (%)	Cinacalcet n (%)	Placebo n (%)	Cinacalcet n (%)
Adverse event	19 (9)	19 (9)	9 (5)	38 (23)	8 (8)	39 (13)	36 (8)	96 (14)
Consent withdrawn	11 (5)	15 (7)	3 (2)	4 (2)	1 (1)	13 (4)	15 (3)	32 (5)
Administrative	3 (1)	7 (3)	2 (1)	0 (0)	3 (3)	6 (2)	8 (2)	13 (2)
Lost to follow-up	1 (0)	4 (2)	0 (0)	2 (1)	0 (0)	3 (1)	1 (0)	9 (1)
Death	5 (2)	6 (3)	5 (3)	3 (2)	2 (2)	3 (1)	12 (3)	12 (2)
Protocol-specified	7 (3)	8 (4)	12 (7)	8 (5)	8 (8)	10 (3)	27 (6)	26 (4)
Parathyroidectomy	2 (1)	0 (0)	3 (2)	0 (0)	2 (2)	0 (0)	7 (1)	0 (0)
Renal transplant	5 (2)	8 (4)	9 (5)	8 (5)	6 (6)	10 (3)	20 (4)	26 (4)
Other	0 (0)	0 (0)	2 (1)	4 (2)	2 (2)	2 (1)	4 (1)	6 (1)

Conduct of the study

The studies were well performed and were considered to be informative

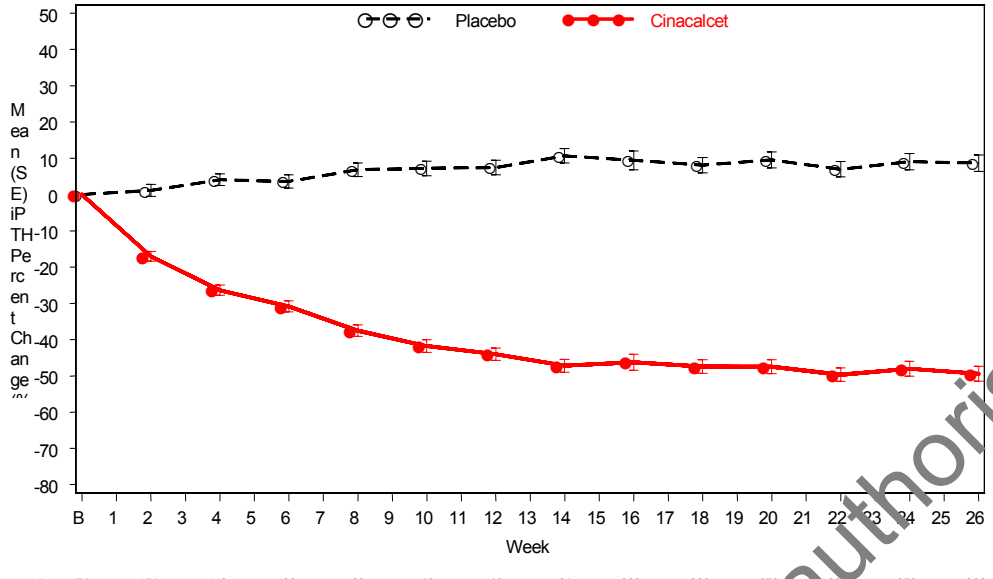
Baseline data

The study populations are judged to be essentially representative for the European ESRD target population with regard to demographic characteristics, baseline laboratory values, D-vitamin and phosphate binder use. Probably, the use of sevelamer has increased in Europe since the studies were performed.

Outcomes and estimation

For the primary endpoint in all three phase 3 studies, a significantly higher proportion of subjects ($p < .001$) in the cinacalcet group compared with the placebo group achieved the target iPTH level (iPTH < 250 pg/mL).

When the results of the three phase 3 studies were pooled, the iPTH concentration was reduced by 42% during the efficacy-assessment phase in the cinacalcet group (n=665) compared with an increase of 8% in the placebo group (n=471). The mean difference between treatment groups was –49.5 % (95% CI –54.1; –45.0 %). Mean iPTH concentrations at each measurement time point are provided in the following figure:



Placebo (N):	471	451	440	439	420	410	410	401	399	389	373	367	370	366
Cinacalcet(N):	664	640	610	600	581	559	547	536	535	514	504	492	473	473

B = Baseline
For total placebo and total cinacalcet, the least square means adjusted for the study are displayed.

Results were consistent within all strata defined by baseline iPTH and Ca x P, and in PD and HD populations. The efficacy of cinacalcet on iPTH and Ca x P was evaluated in subjects who had a decrease, no change, or an increase from baseline in vitamin D sterol dose during the study. Cinacalcet reduced iPTH and Ca x P levels regardless of vitamin D dose change group, and whether or not Vitamin D sterols were administered during the study.

In the pooled study population, Ca x P was reduced by 14% during the efficacy-assessment phase in the cinacalcet group, compared with an increase of 0.1% in the placebo group. The mean difference between treatment groups was 14.05 % (95% CI; -17.2, -10.9 %).

Serum calcium was reduced by 7% during the efficacy-assessment phase in the cinacalcet group compared with an increase of 0.6% in the placebo group (difference between treatment groups –7.3, 95% CI; –8.2%, -6.4%). When the results of the three phase 3 studies were pooled, serum phosphorus was reduced by 8% during the efficacy-assessment phase in the cinacalcet group compared with 0.4% in the placebo group (difference between treatment groups –7.5%, 95% CI; –10.6%, -4.4%).

Patient-reported outcomes were assessed in the controlled phase 3 studies using the KDQOL Cognitive Functioning scale and, as exploratory endpoints, scales in the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36). The change in mean KDQOL Cognitive Functioning scale score from baseline to the efficacy-assessment phase did not differ between the cinacalcet and placebo groups in any of the phase 3 studies. Similar results were observed for the SF-36 Physical Component Summary score.

In a pooled analysis of the controlled phase 3 studies, no notable differences were observed between subjects receiving cinacalcet and placebo for any Patient Reported Outcome (PRO) scale.

The lack of effects in the QoL measurements is not surprising in this severely affected population.

The proportion of subjects achieving the primary endpoint (iPTH ≤ 250 pg/mL) was analysed by age (< 65, ≥ 65 years), sex, race (black, white, other), and geographic region (US, European Union, Canada, Australia). For each of these subgroups, a greater proportion of subjects in the cinacalcet group compared with the placebo group achieved the primary endpoint (iPTH ≤ 250 pg/mL) as well as a ≤ 30% reduction in iPTH. Similarly, within each demographic subgroup, a greater percentage reduction in Ca x P, serum calcium, and serum phosphorus was observed in the cinacalcet group

compared with the placebo group. The magnitude of the treatment effect was similar across subgroups, indicating that the efficacy of cinacalcet was consistent regardless of baseline demographic characteristics

Ancillary analyses

The numbers of subjects at each dose level at end of studies are provided in the following table:

Dose	30 mg	60 mg	90 mg	120 mg	180 mg
N (%)	136 (21%)	109 (17%)	98 (15%)	89 (14%)	224 (34%)

Across the 4 Phase 3 ESRD studies, no subject in the cinacalcet group and 11 subjects in the placebo group withdrew from study due to parathyroidectomy.

Study 20010240 was a 6-month, double-blind, placebo-controlled extension study for subjects completing the 6-month phase 3 studies 20000172 or 20000183, providing an assessment of efficacy over 12 months.
Reductions in iPTH and CaxP were maintained over time.

Study 20000130 was an open-label, extension study providing an efficacy assessment for up to 3 years in total. After 100 weeks (n=60) on cinacalcet, the proportions of subjects with an iPTH ≤ 250 pg/mL or ≥ 30% reduction in iPTH from baseline were 52% and 65%, respectively (as compared with 44% and 56%, respectively, at week 52).

I.B Treatment of secondary HPT in CKD subjects not receiving dialysis

The efficacy of cinacalcet for the treatment of secondary HPT in CKD subjects not receiving dialysis is supported by the results of 2 individual studies (20000236 and 20010239). Data from these 2 studies were not pooled to evaluate efficacy since key eligibility criteria (ie, iPTH and serum calcium) and the primary endpoints differed in these studies.
Studies 20000236 and 20010239 were both randomised, double-blind, placebo-controlled, studies.

The mean magnitude of the reduction in iPTH in CKD subjects not receiving dialysis was comparable with that observed in ESRD subjects, as summarised in the following table:

	Study 20000236		Study 20010239	
	Placebo (N = 31)	Cinacalcet (N = 30)	Placebo (N = 27)	Cinacalcet (N = 27)
% Subjects with ≥ 30% reduction in iPTH	10%	90%	19%	56%
% Change in iPTH [a]	6%	-59%	6%	-32%

[a] During the efficacy-assessment phase (weeks 12 to 16 for study 20000236 and weeks 12 to 18 for study 20010239)

Subject disposition for studies 20000236 and 20010239 is provided in the following table. The numbers of subjects completing the titration and efficacy assessment phases were similar between treatment groups in each study.

	Study 20000236		Study 20010239	
	Placebo n (%)	Cinacalcet n (%)	Placebo n (%)	Cinacalcet n (%)
Randomised	31	30	27	27
Titration phase				
Started	31 (100)	30 (100)	27 (100)	27 (100)
Discontinued	2 (6)	3 (10)	6 (22)	7 (26)
Completed	29 (94)	27 (90)	21 (78)	20 (74)
Efficacy assessment phase				
Started	29 (94)	27 (90)	21 (19)	20 (18)
Discontinued	3 (10)	1 (3)	1 (4)	2 (7)
Completed	26 (84)	26 (87)	20 (74)	18 (67)
Total discontinued	5 (16)	4 (13)	7 (26)	9 (33)

I.C Bone Health in secondary HPT

Biochemical Markers of Bone Turnover

Bone specific alkaline phosphatase (BALP) was measured in the phase 3 ESRD studies and a reduction in median BALP levels was noted among the cinacalcet treated patients (from 23 to 16, n=656) as compared to the placebo treated (24 to 23, n=470). Serum NTx was measured in the phase II study 20010141, which included a small number of patients (12 cinacalcet treated, 16 placebo), and a reduction in median levels was noted among the cinacalcet treated patients after 52 weeks of treatment.

Bone Mineral Density

In the double-blind placebo-controlled phase 2 study 990740 in subjects with ESRD (Placebo n=35, Cinacalcet n=36), BMD was measured at various sites by dual X-ray absorptiometry scanning at baseline and after 54 weeks of treatment. For most sites, no significant differences were observed between treatment groups for percentage change from baseline in BMD. A statistically significant increase was observed at the end of the study for total body in the cinacalcet group, compared with placebo ($p = 0.031$).

Bone Histomorphometry

To investigate the effects of cinacalcet treatment on renal osteodystrophy, a 1-year, placebo-controlled, double-blind study (20010141) was conducted in ESRD subjects with secondary HPT (uncontrolled using current therapies) receiving dialysis. Nineteen cinacalcet subjects and 13 placebo subjects underwent paired bone biopsies at baseline and after 52 weeks of treatment.

There were trends to reductions in mean bone turnover parameters (activation frequency, BFR, fibrosis surface, and the number of osteoblasts and osteoclasts) among the cinacalcet treated patients that did not, however, differ significantly from placebo.

At baseline, 16 of 19 subjects in the cinacalcet group and 11 of 13 subjects in the placebo group were classified as having mild hyperparathyroid bone disease. Three subjects in the cinacalcet group developed adynamic bone disease during the study, which appeared to result from sustained over-suppression of iPTH (< 100 pg/mL) in 2 subjects (1 of which was diabetic) and immobilisation and hypercalcaemia in 1 subject. Two subjects in the cinacalcet group and 4 subjects in the placebo group developed mixed uraemic osteodystrophy (defined as a normal or elevated activation frequency/BFR in the presence of an elevated MLT).

Fractures

To evaluate the incidence of fractures in the phase 3 ESRD population, the database was screened and a total of 18 (4%) placebo subjects and 10 (2%) cinacalcet subjects experienced one of these events

while on study. Kaplan-Meier estimates of the cumulative probability of fractures were lower for the cinacalcet group, as compared with placebo.

II. Treatment in intractable primary HPT and parathyroid cancer

The clinical program evaluating the efficacy of cinacalcet in the treatment of primary HPT included 3 completed, double-blind, placebo-controlled studies (980125, 990120, and 990160) and 2 ongoing, open-label studies (20000159 and 20000204). Study 20000159 is an ongoing open-label extension study for subjects completing study 990120. Study 20000204 was designed as an open-label, single-arm study, and is the pivotal study for this indication, recruiting patients with intractable primary HPT or parathyroid cancer. Studies 980125, 990120, and 990160 included altogether 136 patients with primary HPT and iPTH levels ≥ 45 pg/mL and serum calcium above 10.3 mg/dl. Cinacalcet reduced Calcium levels by approximately 10-15% and this effect was essentially maintained over 1-2 years (study 20000159).

The primary objective for efficacy in all 5 studies was to evaluate the ability of cinacalcet to reduce serum calcium concentrations in subjects with primary HPT.

Overview of Cinacalcet Studies for the Treatment of Primary HPT

Study Number/ Type	Entry Criteria	No. of Subjects Enrolled/Treatment	Geographic Region	Duration of Cinacalcet Exposure
980125 Randomised, double-blind, placebo-controlled, dose-ranging	Primary HPT iPTH ≥ 45 pg/mL Serum calcium > 10.3 mg/dL and ≤ 12.5 mg/dL	48 total[a] 39/cinacalcet 50, 75, 100 mg QD 30, 40, 50 mg BID 9/placebo	US	QD phase, 6 weeks BID phase, 15 days
990120 Randomised, double-blind, placebo-controlled, dose titration	Primary HPT iPTH ≥ 45 pg/mL Serum calcium > 10.3 mg/dL and ≤ 12.5 mg/dL	78 total 40/cinacalcet (30 mg BID with dose titration to 40 and 50 mg BID) 38/placebo	US	12 weeks (titration) 12 weeks (maintenance) 28 weeks (follow up)
990160 Randomised, double-blind, placebo-controlled fixed-dose	Primary HPT iPTH ≥ 45 pg/mL Serum calcium ≥ 11.0 mg/dL	10 total 6/cinacalcet (65 mg BID) 4/Placebo	US	4 weeks (treatment) 1 week (follow up)
20000159 Open-label, single-arm, dose-titration extension	Patients with primary HPT who completed protocol-specified treatment and end-of-study assessments from study 990120	45/cinacalcet (30 mg BID with dose titration to 50 mg BID)	US	12 weeks (titration) 3 years planned (maintenance)
20000204 Open-label, single-arm, dose titration	Parathyroid carcinoma or intractable primary HPT with a serum calcium > 12.5 mg/dL	29/cinacalcet (30 mg BID to 90 mg QID)	US/Canada	16 weeks (titration) 3 years planned (maintenance)

QD: once daily

BID: twice daily

iPTH: intact parathyroid hormone

[a] Forty subjects (32 cinacalcet, 8 placebo) were originally enrolled in this study. Eight additional subjects (7 cinacalcet, 1 placebo) were enrolled as replacements for the BID phase of the study.

Study 20000204

The pivotal study 20000204 is a multicentre, open label, single arm, dose titration study evaluating the efficacy, safety, and pharmacokinetics of cinacalcet in subjects with parathyroid carcinoma or intractable primary HPT (failed or contraindicated for parathyroidectomy) with a serum calcium > 12.5 mg/dL at screening. The primary endpoint is the proportion of subjects with ≥ 1 mg/dL reduction in serum calcium at the end of the titration phase. The variable-length titration phase (2 to 16 weeks) continued until the serum calcium concentration was ≤ 10 mg/dL, the subject had reached the highest dose (90 mg QID), or adverse events precluded further dose increases.

Treatment with cinacalcet produced a reduction in serum calcium by ≥1mg/dl for 15/21 patients with parathyroid carcinoma and for 6/8 with intractable primary HPT. Mean reductions were 14% and 12% in the parathyroid carcinoma and intractable primary HPT groups, respectively.

Individual fluctuations of the serum calcium levels were noted during treatment in the parathyroid carcinoma patients. Upon CHMP request, the Applicant has clarified that the calcium levels in 9 out of 10 patients with parathyroid cancer remained below the baseline values during the cinacalcet titration and maintenance phases. The increase in the mean serum calcium concentration in 3/10 patients of ≥ 1 mg/dL during the maintenance phase as compared to the end of the titration phase remains unexplained. As a consequence of this discussion, a recommendation in the SPC has been included, informing that if clinically relevant reductions in serum calcium are not maintained during treatment in parathyroid cancer, discontinuation of therapy should be considered.

As discussed by the CHMP, no consistent trend in the PTH levels could be seen during treatment in the few patients included in the study with intractable primary HPT and in some of the patients an increase was noted. Overall, the information regarding use of cinacalcet in intractable primary hyperparathyroidism remains extremely limited and the data on the few patients available is somewhat patchy and not fully consistent.

- Discussion on clinical efficacy

The Applicant has convincingly demonstrated the capacity of cinacalcet to reduce iPTH levels in patients with secondary HPT in CKD with ESRD. The effect is sustained over time and is consistent in different subgroups and in different degrees of disease severity. Importantly, the reduction of iPTH is accompanied by moderate but significant and consistent reductions in calcium, phosphate and CaxP product levels. The size and general design of the studies on the efficacy of cinacalcet in the treatment of secondary HPT in patients with CKD being on dialysis is judged to be adequate. The primary biochemical end-point focused at is considered to be a relevant surrogate marker, which is used in clinical routine today to balance currently available therapy for secondary HPT in CKD

Considering that cinacalcet represents a new treatment principle, further clinical trials should be conducted to more fully understand the effects of improved control of laboratory markers of secondary HPT on more obviously important endpoints (bone morphology, fracture incidences, extraskeletal calcium deposits, need for parathyroidectomy, other symptoms and signs associated with secondary HPT). Support for efficacy in these respects is also important in consideration of the suspected increase in the incidence of "adynamic bone disease" in ESRD patients within the western society, the clinical consequences of which are largely unknown, but which has been suggested to be associated with increased extraskeletal calcification. It has been suggested that the treatment possibilities for secondary HPT in CKD (more effective phosphate binders, active vitamin D) that have become available during recent years have contributed to a shift from the classical high turnover bone pathology (osteitis fibrosa) towards a low turn-over bone pathology ("adynamic bone disease"). Thus, there is today some concern for the possible risks associated with "over-treatment" of secondary HPT in CKD.

The data on bone health related parameters during cinacalcet treatment is limited in this application excluding conclusions that can be regarded as well supported. However, the sparse data available provide some limited support for the assumption that cinacalcet treatment may improve bone health in

secondary HPT in ESRD patients. This should be confirmed in further long-term studies, which should also focus on effects on vascular and cardiac calcifications

It seems plausible that cinacalcet is able to reduce elevated iPTH levels also in predialytic CKD patients. However, the small number of patients, the relatively short observation times, and the apparent lack of adequate background treatment hamper the interpretation of these findings. Clinically relevant effects of cinacalcet treatment initiated in predialytic CKD patients have not been acceptably demonstrated, especially since PTH targets in these patients are even less well validated than in the ESRD population, and as safety aspects (including bone safety) associated with long-term treatment in this patient group are insufficiently elucidated.

Therefore it is concluded that in CKD patients with secondary HPT not undergoing dialysis, there is limited data from short-term studies indicating that cinacalcet reduces PTH levels to a similar extent as in patients with secondary HPT receiving dialysis. Additionally, the existing limited experience suggests that CKD patients not undergoing dialysis have an increased risk for hypocalcaemia compared with CKD patients receiving dialysis, which may be due to lower baseline calcium levels. There are no clinical data to support an indication in prevention of secondary HPT.

The submitted studies are deemed to provide sufficient evidence for a modest capacity of cinacalcet to reduce serum calcium levels in patients with parathyroid carcinoma. In individual patients rather impressive reductions seem to be achievable. In light of the lack of pharmacological therapeutic alternatives for the long-term management of hypercalcaemia in this small group of often severely ill patients, cinacalcet is recommended for approval provided that the Applicant commits to regularly report the results of the ongoing study 20000204 and if a continuous close surveillance of treatment results in these patients can be accomplished.

The results in treatment of intractable primary HPT are difficult to interpret due to the few included patients (n=8). Overall, the information regarding use of cinacalcet in intractable primary hyperparathyroidism remains extremely limited and the data on the few patients available are somewhat patchy and not fully consistent. The target population remains incompletely defined and would, in clinical practice, be influenced by variations in surgical practice and experience, attitudes as regards operability etc. Some wording in section 5.1 regarding the limited experience gained has been included.

Clinical safety

The cinacalcet clinical program consists of 47 studies in healthy volunteers and subjects with primary and secondary HPT conducted between December 1997 and June 2003. The clinical trials supporting this submission were conducted in the US, Europe, Canada, and Australia. The primary focus of the clinical programme was on the development of cinacalcet for the treatment of secondary HPT in patients with CKD.

- Patient exposure

Overall total cincalcet exposure is summarised in the following table

	At least one dose	At least 26 weeks	At least 52 weeks
Cinacalcet	1,749	732	325
Placebo	774	493	196

Exposure to cinacalcet was in accordance with guidance from Health Authorities and International Conference on Harmonisation (ICH) guidelines, which recommend that exposure to study drug be at least 1500 subjects for ≥ 1 dose, at least 600 subjects for ≥ 6 months, and at least 100 subjects for ≥ 12 months. The number of subjects within each of these exposure categories for cinacalcet was 1749, 732, and 325, respectively.

A total of 1136 subjects with secondary HPT and ESRD were enrolled in the 3 key phase 3 studies (471 placebo, 665 cinacalcet). These studies included a titration phase followed by an efficacy-assessment phase and were 26 weeks in duration.

Overall exposure to cinacalcet in the phase 3 ESRD clinical program ranged from < 1 to 58 (mean 25.1) weeks. Subject exposure was greatest at the starting dose of ≥ 30 to < 60 mg, with 713 subjects exposed to this dose at least once and 218 subjects receiving this dose range as their most frequent daily dose. The highest dose, 180 mg, was received at least once by 277 subjects and was the most frequent daily dose in 176 subjects.

The duration of the studies in subjects with CKD not receiving dialysis was shorter than in the ESRD studies, with exposure ranging from 1 to 19 (mean 15) weeks in study 20010239 and from 3 to 17 (mean 16) weeks in study 20000236. Consistent with milder secondary HPT in CRI, the most frequent dosing in subjects with CKD not receiving dialysis was lower than that in subjects with ESRD. Subjects with CKD not receiving dialysis were exposed to each cinacalcet dose level and 9% of subjects titrated to the highest daily dose (180 mg)

- Adverse events

During the pooled 6-month phase 3 studies in ESRD patients, 1,126 subjects (470 placebo, 656 cinacalcet) received study drug and were evaluable for safety. Treatment related (as assigned by the investigator) adverse events were more common among the cinacalcet treated patients. However, the incidences of all adverse events, serious adverse events, and deaths were similar between the cinacalcet and placebo groups, see table below:

	Placebo (N = 470) n (%)	Cinacalcet (N = 656) n (%)
Subjects evaluable for safety	470	656
All adverse events	440 (94)	599 (91)
Serious adverse events	148 (31)	187 (29)
All treatment-related adverse events	116 (25)	283 (43)
Related serious adverse events	5 (1)	20 (3)
Discontinuation due to adverse events	37 (8)	96 (15)
Deaths on study	15 (3)	14 (2)

In the pooled phase 3 studies, the subject incidence of adverse events considered by the investigator to be related to treatment was 25% in the placebo group and 43% in the cinacalcet group. Adverse events occurring more frequently in the cinacalcet group compared to placebo, and included on the SPC as at least possibly attributable to cinacalcet are included in the table below. As discussed in relation to the CHMP questions the mechanisms behind the GI associated adverse events are unknown. However, these reactions are often transient and commonly of mild or moderate severity.

Subject incidence of adverse events Preferred Term	Placebo (N = 470) n (%)	Cinacalcet (N = 656) n (%)
Nausea	91 (19)	204 (31)
Vomiting	69 (15)	178 (27)
Myalgia	64 (14)	98 (15)
Dizziness	36 (8)	64 (10)
Dyspepsia	36 (8)	50 (8)
Asthenia	17 (4)	44 (7)
Anorexia	19 (4)	40 (6)
Paraesthesia	5 (1)	25 (4)
Hypocalcaemia	6 (1)	27 (4)
Rash	4 (<1)	19 (3)
Convulsions	2 (<1)	8 (1)

Hypocalcaemia

To evaluate whether episodes of low serum calcium levels were associated with clinical symptoms, a list of adverse events potentially associated with hypocalcaemia was defined. These include paresthesias, myalgias, cramping, tetany and convulsions. The subject incidence of these events was similar between treatment groups in the ESRD studies with only paresthesia (1% placebo, 4% cinacalcet), asthenia (4% placebo, 7% cinacalcet) occurring with a >1% greater frequency in the cinacalcet group. Overall, adverse events potentially associated with hypocalcaemia did not differ between treatment groups and were generally mild to moderate in severity, transient, and rarely led to study withdrawal.

In the pooled phase 3 studies, < 1% of calcium measurements in the placebo group and 4% of calcium measurements in the cinacalcet group were < 7.5 mg/dL. The cumulative subject incidence of 2 consecutive serum calcium measurements < 7.5 mg/dL was < 1% in the placebo group and 5% in the cinacalcet group. Including data from the long-term extension study, the weekly subject incidence of serum calcium levels < 7.5 mg/dL was relatively constant over 52 weeks. Confirmed low serum calcium concentrations were generally managed by adjustments in the dose of cinacalcet, vitamin D sterols or calcium-containing phosphate binders. The results from the studies in subjects with CKD not receiving dialysis suggested that treatment-related hypocalcaemia was more common as compared with the ESRD population.

The SPC states that serum calcium levels are to be monitored frequently, within 1 week of initiation or dose adjustment of cinacalcet. Once the maintenance dose has been established, serum calcium should be measured approximately monthly. If serum calcium levels decrease below the normal range, appropriate steps should be taken. These steps are well described in the SPC.

Convulsions

In the phase 3 ESRD studies, adverse events of convulsions (including convulsions, convulsions local and status epilepticus) were reported in 11 cinacalcet treated patients, as compared with 2 on placebo. Five of the 11 on cinacalcet and one of the two on placebo had low calcium levels near the time of the event. It cannot be excluded that the few observed reactions of convulsions are partly due to other mechanisms than hypocalcemia,. The Applicant has committed to carefully follow the incidence of convulsions in ongoing and planned clinical studies and in spontaneous reporting as a part of regular post-marketing surveillance.

Cataracts

The pre-clinical program showed an increased incidence of cataracts in rodents. Specific ophthalmological examinations were included in study 990120, a phase 2 study of 1-year duration. No increase in incidence of either hypocalcaemic cataracts or senile cataracts was observed for patients treated with cinacalcet. In addition, results from the pooled 6-month phase 3 studies showed an incidence of cataracts of < 1% (1 subject) in the placebo group and < 1% (1 subject) in the cinacalcet group, suggesting no relationship between cinacalcet treatment and cataract formation.

- Serious adverse event/deaths/other significant events

The overall incidence of serious adverse events in the three Phase 3 ESRD studies was similar between treatment groups (31% placebo, 29% cinacalcet). The most common serious adverse events included (placebo, cinacalcet) vascular access thrombosis (2%, 2%), pneumonia (2%, 2%), sepsis (2%, 2%), and non-cardiac chest pain (<1%, 2%). These events occurred at similar incidences in the placebo and cinacalcet groups. The same pattern of severe adverse events were recorded in the 6 month placebo-controlled extension study (20010240).

In the 6-month ESRD phase 3 studies, 15 (3%) subjects receiving placebo and 14 (2%) subjects receiving cinacalcet died; none of these deaths was considered by the investigator to be related to study drug. The causes of death were similar between the cinacalcet and placebo groups. Ten and 9 subjects (placebo, cinacalcet) in each treatment group (2%, 1%) died from cardiovascular causes.
In the 6-month extension study 20010240, 7 (5%) deaths occurred in the placebo group and 4 (3%) deaths occurred in the cinacalcet group. Six deaths in the placebo group were cardiovascular in nature compared with 3 in the cinacalcet group. In the studies in subjects with CKD not receiving dialysis (20000236 and 20010239) two subjects (7%) who received placebo died and none of the patients on cinacalcet.

- Laboratory findings

Clinical laboratory values in the phase 3 studies were typical for the ESRD population. Other than the effects on PTH, serum calcium and phosphorus levels in the cinacalcet group, no notable differences between treatment groups were seen for measures of liver and kidney function, haematology, or electrolytes. No significant changes were noted during the study in either group, for glucose, hemoglobin A1c, total protein, uric acid, total cholesterol, lactate dehydrogenase, and triglycerides.
Systolic and diastolic blood pressures were measured at baseline, week 16, week 26, and at the end of study in the principal CKD studies. No clinically important differences in either systolic pressure or diastolic pressure were apparent during this interval.

The possible effects of cinacalcet on ECG were extensively and sufficiently evaluated in the clinical study programme, and it can be concluded that cinacalcet appears to have no direct effect on the QTc interval.

<u>Testosterone Levels</u>
A more pronounced reduction of median testosterone levels was noted among the cinacalcet treated patients (median reductions 31% and 16% in the cinacalcet and placebo groups after 26 weeks, respectively). A description of this side effect, for which the mechanism and clinical significance are unknown, has been included in section 4.4 of the SPC. The Applicant has committed to a long-term follow up of the testosterone levels in cinacalcet treated ESRD patients.

- Safety in primary hyperparathyroidism and parathyroid cancer subjects.

The safety profile of cinacalcet was similar across the 5 studies in primary HPT (n = 151). 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.

However, the limited safety data for the target population must be taken into account, althoughthe rarity of parathyroid cancer is acknowledged..

- Discontinuation due to adverse events

Withdrawals due to adverse events in the ESRD studies occurred in 8% of subjects receiving placebo compared with 15% of subjects receiving cinacalcet. The difference in withdrawal rates between treatment groups was mainly due to different rates of gastrointestinal symptoms; nausea (1% and 5% in the placebo and cinacalcet treatment groups, respectively), vomiting (< 1%, 4%, placebo, cinacalcet), diarrhoea (< 1%, 2%), and abdominal pain (< 1%, 2%). Similar differences were seen in the 6-month extension study 20010240 and in the studies in subjects with CKD not receiving dialysis. In the pooled phase 3 ESRD dataset, 53% of placebo and 64% of cinacalcet subjects experienced at least one gastrointestinal adverse event

- Discussion on clinical safety

From a clinical point of view the safety of cinacalcet treatment in secondary HPT in ESRD patients has essentially been sufficiently documented in a fairly large number of patients. Exposure to cinacalcet in the key CKD studies (3 phase III ESRD studies and 2 Phase II studies in subjects with CKD not receiving dialysis) was adequate to evaluate safety in subjects across all dose levels.
A higher incidence of nausea and vomiting among the cinacalcet treated patients was analysed. This was considered of some clinical relevance in this population, which often suffers from an impaired quality of life and where nausea and gastrointestinal symptoms are common.
Additionally, the changes in body weight over time in the two treatment groups in the pivotal phase III studies in secondary HPT in ESRD were compared. Reassuring data have been provided that seem to demonstrate that treatment with cinacalcet was not associated with a loss of weight.

The more pronounced reduction of median testosterone levels noted among the cinacalcet treated patients has been analysed, and a long-term follow up of the testosterone levels in cinacalcet treated ESRD patients has been proposed by the Applicant.

An increased incidence of convulsions during cinacalcet treatment was reported. The conclusion that hypocalcemia is associated with an increased risk for convulsions seems uncontroversial. Although preclinical and clinical safety data seem to indicate that there may be a decreased threshold for seizures that may be independent of the calcium levels, if such a risk exists, it does not seem to be great and it is adequately addressed in the SPC. Collection of further data from the on-going and planned clinical studies will be carried out.

The SPC states that serum calcium levels are to be monitored frequently, within 1 week of initiation or dose adjustment of cinacalcet. Once the maintenance dose has been established, serum calcium should be measured approximately monthly. If serum calcium levels decrease below the normal range, appropriate steps should be taken. These steps are well described in the SPC.

The safety data obtained from the studies in parathyroid cancer and primary hyperparathyroidism were consistent with the data obtained in ESRD patients with the most common adverse events being nausea, vomiting, anorexia and asthenia. The low number of patients included in the on-going study 20000204, which is designed to reflect the target population, is a matter of concern, although the rarity of parathyroid cancer is acknowledged.The Applicant commits to provide the CHMP with future results from study 20000204.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

Overall the pharmacodynamic studies showed that cinacalcet acts as an allosteric modulator of the calcium-sensing receptor on the parathyroid cell surface. This modulation leads to increase sensitivity of the receptor to extracellular calcium, which results in a reduction of circulating iPTH concentrations.Several in *vitro* and *in vivo* pharmacology models assessed the activity of cinacalcet in hyperparathyroidism.

The general pharmacology studies are appropriate to support the non-clinical pharmacology profile of cinacalcet. Safety pharmacology studies have not given rise to any serious safety concerns. However, the occurrence of non-tolerable hypocalcaemia at exposure levels close to the clinical exposure limits the possibility to establish appropriate safety margins. In particular, the possibility of adverse effects due to secondary pharmacology cannot be entirely excluded and the applicant has been requested to perform further non-clinical studies to address this.

From the pharmacokinetic point of view, mice, rats, dogs and monkeys were the most relevant species for non-clinical efficacy and safety studies. The non-clinical pharmacokinetics properties for cinacalcet have been appropriately described. A number of studies concerning the absorption, distribution, metabolism, and excretion of cinacalcet have been performed. The studies were carried out with the oral formulation, which is the proposed clinical route of administration. Cinacalcet is well absorbed in all studied species, but showed low oral bioavailability. It is widely distributed in all tissues, and excreted into milk of lactating rats. It also crossed the placental barrier in rabbits. Cinacalcet is extensively metabolised, appearing CYP3A4 and CYP1A2 as the major contributors involved.

Overall, the toxicology programme did not raise any serious safety concerns. Dogs and monkeys were chosen as non-rodent species for use in toxicology programme.
Adequate genotoxicity and carcinogenicity studies were performed, and did not reveal special concerns.

Efficacy

The efficacy of cinacalcet to reduce iPTH levels in patients with secondary hyperparathyroidism in patients with end-stage renal disease (ESRD) on maintenance dialysis therapy has been established. The effect is sustained over time and is consistent in different subgroups and in different degrees of disease severity. Importantly, the reduction of iPTH was accompanied by moderate but significant and consistency reductions in calcium, phosphate and CaxP product levels.

Three phase 3 studies, and one additional phase 3 extension study provided placebo-controlled safety and efficacy evidence in patients with CKD being on dialysis and with secondary HPT. Eligible subjects were adults with ESRD and iPTH > 300 pg/mL who were receiving HD. The primary biochemical end-point (proportion of subjects achieving a mean pre dose iPTH value ≤ 250 pg/mL) is considered to be a relevant surrogate marker, which is used in clinical routine today to balance currently available therapy for secondary HPT in CKD.

Considering that cinacalcet represents a new treatment principle, further clinical trials should be conducted in the future to more fully understand the effects of improved control of laboratory markers of secondary HPT on more obviously important endpoints such as bone morphology, fracture

incidences, extraskeletal calcium deposits, need for parathyroidectomy, and other symptoms and signs associated with secondary HPT.

The submitted studies are deemed to provide sufficient evidence for a modest capacity of cinacalcet to reduce serum calcium levels in patients with parathyroid carcinoma. In individual patients rather impressive reductions seem to be achievable. In light of the lack of pharmacological therapeutic alternatives for the long-term management of hypercalcaemia in this small group of often severely ill patients, cinacalcet is recommended for approval provided that the Applicant commits to regularly report the results of the ongoing study 20000204 and if a continuous close surveillance of treatment results in these patients can be accomplished.

Safety

From a clinical point of view the safety of cinacalcet treatment in secondary HPT in ESRD patients has essentially been sufficiently documented in a fairly large number of patients. Exposure to cinacalcet in the key CKD studies was adequate to evaluate safety in subjects across all dose levels.
A total of 1136 subjects with secondary HPT and ESRD were enrolled in the 3 key phase 3 studies (471 placebo, 665 cinacalcet). These studies included a titration phase followed by an efficacy-assessment phase and were 26 weeks in duration.

The most commonly reported undesirable effects were nausea and vomiting, occurring in 31% cinacalcet and 19% placebo treated patients and 27% cinacalcet and 15% placebo treated patients, respectively. 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 (1% placebo; 5% cinacalcet) and vomiting (<1% placebo; 4% cinacalcet).

The fact that cinacalcet lowers serum calcium has been adequately analysed and reflected in the SPC. Patients are to be monitored carefully for the occurrence of hypocalcemia, and if serum calcium levels decrease below the normal range, appropriate steps should be taken.

The safety profile of cinacalcet in patients with parathyroid carcinoma is generally consistent with that seen in patients with chronic kidney disease. The most frequent adverse reactions were nausea and vomiting

Benefit/risk assessment

Following evaluation of the documentation submitted it is concluded that data on pharmaceutical quality of the medicinal product is considered acceptable.

The nonclinical toxicology and safety pharmacology studies have not given rise to any serious safety concerns, although appropriate safety margins were not established due to the occurrence of hypocalcaemia at exposure levels close to the clinical exposure.

The pharmacokinetics of cinacalcet was rather extensively studied and is judged to be sufficiently characterised.

Overall, the clinical programme for cinacalcet in treatment of secondary HPT in ESRD patients is to be regarded as rather extensive and sufficient for an approval. The Applicant has convincingly demonstrated the capacity of cinacalcet to reduce iPTH levels in patients with secondary HPT in CKD with ESRD treated with maintenance dialysis. The effect is sustained over time and is consistent in different subgroups and in different disease severity categories. Nevertheless, more data from bone health related parameters during cinacalcet treatment will need to be provided through post-marketing studies.

With regard to the use of cinacalcet in patients with parathyroid carcinoma, and considering the lack of therapeutic alternatives for the long-term management of hypercalcaemia in this small group, the CHMP concluded that there is sufficient evidence for a modest capacity of cinacalcet to reduce serum

calcium levels in these patients, while close surveillance of treatment results in these patients will be accomplished. Additionally individual impressive reductions on serum calcium levels were reported.
The safety of cinacalcet treatment in the intended population has essentially been sufficiently documented in a fairly large number of patients, and the tolerability profile of cinacalcet seems acceptable. Therefore, taking all these considerations into account the CHMP was of the opinion that a positive benefit/risk can be concluded.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk ratio of cinacalcet in the treatment of "secondary hyperparathyroidism in patients with end-stage renal disease (ESRD) on maintenance dialysis therapy. Cinacalcet may be used as part of a therapeutic regimen including phosphate binders and/or Vitamin D sterols as appropriate. Reduction of hypercalcaemia in patients with parathyroid carcinoma" was favourable and therefore recommended the granting of the marketing authorisation.