ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Parareg 30 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30 mg cinacalcet (as hydrochloride).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

30 mg: Light green, oval, film-coated tablets marked "AMGEN" on one side and "30" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of secondary hyperparathyroidism (HPT) 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 (see section 5.1).

Reduction of hypercalcaemia in patients with:
- parathyroid carcinoma.
- primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom parathyroidectomy is not clinically appropriate or is contraindicated.

4.2 Posology and method of administration

For oral use. It is recommended that Parareg be taken with food or shortly after a meal, as studies have shown that bioavailability of cinacalcet is increased when taken with food (see section 5.2). Tablets should be taken whole and not divided.

Hepatic impairment

No change in starting dose is necessary. Parareg should be used with caution in patients with moderate to severe hepatic impairment and treatment should be closely monitored during dose titration and continued treatment (see sections 4.4 and 5.2).

Secondary Hyperparathyroidism

Adults and elderly (> 65 years)

The recommended starting dose for adults is 30 mg once per day. Parareg should be titrated every 2 to 4 weeks to a maximum dose of 180 mg once daily to achieve a target parathyroid hormone (PTH) in dialysis patients of between 150-300 pg/ml (15.9-31.8 pmol/l) in the intact PTH (iPTH) assay. PTH levels should be assessed at least 12 hours after dosing with Parareg. Reference should be made to current treatment guidelines.

PTH should be measured 1 to 4 weeks after initiation or dose adjustment of Parareg. PTH should be monitored approximately every 1-3 months during maintenance. Either the intact PTH (iPTH) or bio-intact PTH (biPTH) may be used to measure PTH levels; treatment with Parareg does not alter the relationship between iPTH and biPTH.

Information regarding the pharmacokinetic/pharmacodynamic (PK/PD) profile of cinacalcet is given in section 5.1

During dose titration, serum calcium levels should be monitored frequently, and within 1 week of initiation or dose adjustment of Parareg. 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 (see section 4.4). Concomitant therapy with phosphate binders and/or vitamin D sterols should be adjusted as appropriate.

Children and adolescents

Safety and efficacy have not been established in patients below the age of 18 years.

Parathyroid Carcinoma and Primary Hyperparathyroidism

Adults and elderly (> 65 years)

The recommended starting dose of Parareg for adults is 30 mg twice per day. The dosage of Parareg should be titrated every 2 to 4 weeks through sequential doses of 30 mg twice daily, 60 mg twice daily, 90 mg twice daily, and 90 mg three or four times daily as necessary to reduce serum calcium concentration to or below the upper limit of normal. The maximum dose used in clinical trials was 90 mg four times daily.

Serum calcium should be measured within 1 week after initiation or dose adjustment of Parareg. Once maintenance dose levels have been established, serum calcium should be measured every 2 to 3 months. After titration to the maximum dose of Parareg, serum calcium should be periodically monitored; if clinically relevant reductions in serum calcium are not maintained, discontinuation of Parareg therapy should be considered (see section 5.1).

Children and adolescents

Safety and efficacy have not been established in patients below the age of 18 years.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Seizures

In three clinical studies of Chronic Kidney Disease (CKD) patients on dialysis, five percent of the patients in both the Parareg and placebo groups reported a history of seizure disorder at baseline. In these studies, seizures were observed in 1.4% of Parareg treated patients and 0.4% of placebo-treated patients. While the basis for the reported difference in seizure rate is not clear, the threshold for seizures is lowered by significant reductions in serum calcium levels.

Hypotension and/or worsening heart failure

In post-marketing safety surveillance, isolated, idiosyncratic cases of hypotension and/or worsening heart failure have been reported in patients with impaired cardiac function, in which a causal relationship to cinacalcet could not be completely excluded and may be mediated by reductions in serum calcium levels. Clinical trial data showed hypotension occurred in 7% of cinacalcet-treated patients, 12% of placebo-treated patients, and heart failure occurred in 2% of patients receiving cinacalcet or placebo.

Serum Calcium

Parareg treatment should not be initiated in patients with a serum calcium (corrected for albumin) below the lower limit of the normal range. Since cinacalcet lowers serum calcium, patients should be monitored carefully for the occurrence of hypocalcaemia (see section 4.2). In CKD patients receiving dialysis who were administered Parareg, 4% of serum calcium values were less than 7.5 mg/dl (1.875 mmol/l). In the event of hypocalcaemia, calcium-containing phosphate binders, vitamin D sterols and/or adjustment of dialysis fluid calcium concentrations can be used to raise serum calcium. If hypocalcaemia persists, reduce the dose or discontinue administration of Parareg. Potential manifestations of hypocalcaemia may include paraesthesias, myalgias, cramping, tetany and convulsions.

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

General

Adynamic bone disease may develop if PTH levels are chronically suppressed below approximately 1.5 times the upper limit of normal with the iPTH assay. If PTH levels decrease below the recommended target range in patients treated with Parareg, the dose of Parareg and/or vitamin D sterols should be reduced or therapy discontinued.

Testosterone Levels

Testosterone levels are often below the normal range in patients with end-stage renal disease. In a clinical study of ESRD patients on dialysis, free testosterone levels decreased by a median of 31.3% in the Mimpara-treated patients and by 16.3% in the placebo-treated patients after 6 months of treatment. An open-label extension of this study showed no further reductions in free and total testosterone concentrations over a period of 3 years in Mimpara-treated patients. The clinical significance of these reductions in serum testosterone is unknown.

Hepatic Insufficiency

Due to the potential for 2 to 4 fold higher plasma levels of cinacalcet in patients with moderate to severe hepatic impairment (Child-Pugh classification), Parareg should be used with caution in these patients and treatment should be closely monitored (see sections 4.2 and 5.2).

Interactions

Caution should be exercised when administering Parareg concomitantly with strong inhibitors or inducers of CYP3A4 and/or CYP1A2. Dose adjustment of Parareg may be necessary (see section 4.5).

Caution should be exercised when Parareg is administered with individually titrated, narrow therapeutic index medications that are predominantly metabolised by CYP2D6. Dose adjustments of concomitant medications may be necessary (see section 4.5).

Plasma levels of cinacalcet may be lower in smokers due to induction of CYP1A2-mediated metabolism. Dose adjustments may be necessary if a patient starts or stops smoking during cinacalcet treatment (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medications on cinacalcet

Cinacalcet is metabolised in part by the enzyme CYP3A4. Co-administration of 200 mg bid ketoconazole, a strong inhibitor of CYP3A4, caused an approximate 2-fold increase in cinacalcet levels. Dose adjustment of Parareg may be required if a patient receiving Parareg initiates or discontinues therapy with a strong inhibitor (e.g. ketoconazole, itraconazole, telithromycin, voriconazole, ritonavir) or inducer (eg rifampicin) of this enzyme (see Section 4.4).

In vitro data indicate that cinacalcet is in part metabolised by CYP1A2. Smoking induces CYP1A2; the clearance of cinacalcet was observed to be 36-38% higher in smokers than non-smokers. The effect of CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) on cinacalcet plasma levels has not been studied. Dose adjustment may be necessary if a patient starts or stops smoking or when concomitant treatment with strong CYP1A2 inhibitors is initiated or discontinued.

Calcium carbonate: Co-administration of calcium carbonate (single 1500 mg dose) did not alter the pharmacokinetics of cinacalcet.

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

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

Effect of cinacalcet on other medications

Medicinal products metabolised by the enzyme P450 2D6 (CYP2D6): Cinacalcet is a strong inhibitor of CYP2D6. Dose adjustments of concomitant medicinal products may be required when Parareg is administered with individually titrated, narrow therapeutic index substances that are predominantly metabolised by CYP2D6 (e.g. flecainide, propafenone, metoprolol given in heart failure, desipramine, nortriptyline, clomipramine) (see section 4.4).

Desipramine: Concurrent administration of 90 mg cinacalcet once daily with 50 mg desipramine, a tricyclic antidepressant metabolised primarily by CYP2D6, significantly increased desipramine exposure 3.6-fold (90 % CI 3.0, 4.4) in CYP2D6 extensive metabolisers.

Warfarin: Multiple oral doses of cinacalcet did not affect the pharmacokinetics or pharmacodynamics (as measured by prothrombin time and clotting factor VII) of warfarin.

The lack of effect of cinacalcet on the pharmacokinetics of R- and S-warfarin and the absence of auto-induction upon multiple dosing in patients indicates that cinacalcet is not an inducer of CYP3A4, CYP1A2 or CYP2C9 in humans.

Midazolam: Co-administration of cinacalcet (90 mg) with orally administered midazolam (2 mg), a CYP3A4 and CYP3A5 substrate, did not alter the pharmacokinetics of midazolam. These data suggest that cinacalcet would not affect the pharmacokinetics of those classes of drugs that are metabolized by CYP3A4 and CYP3A5, such as certain immunosuppressants, including cyclosporine and tacrolimus.

4.6 Pregnancy and lactation

There are no clinical data from the use of cinacalcet in pregnant women. Animal studies do not indicate direct harmful effects with respect to pregnancy, parturition or postnatal development. No embryonal/foetal toxicities were seen in studies in pregnant rats and rabbits with the exception of decreased foetal body weights in rats at doses associated with maternal toxicities (see section 5.3). Parareg should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

It is not known whether cinacalcet is excreted in human milk. Cinacalcet is excreted in the milk of lactating rats with a high milk to plasma ratio. Following careful benefit/risk assessment, a decision should be made to discontinue either breast-feeding or treatment with Parareg.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Secondary Hyperparathyroidism

Data presented from controlled studies include 656 patients who received Parareg and 470 patients who received placebo for up to 6 months. The most commonly reported undesirable effects were nausea and vomiting, occurring in 31% Parareg and 19% placebo treated patients, and 27% Parareg 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).

Adverse reactions, defined as adverse events considered at least possibly attributable to cinacalcet treatment based on best-evidence assessment of causality and reported in excess of placebo in double-blind clinical studies are listed below using the following convention: very common (> 1/10); common (> 1/100, < 1/10); uncommon (> 1/1,000, < 1/100); rare (> 1/10,000, < 1/1,000); very rare (< 1/10,000).

Immune system disorders
Uncommon: hypersensitivity reactions

Metabolism and nutrition disorders
Common: anorexia

Nervous system disorders
Common: dizziness, paraesthesia
Uncommon: seizures

Gastrointestinal disorders
Very common: nausea, vomiting
Uncommon: dyspepsia, diarrhoea

Skin and subcutaneous tissue disorders
Common: rash

Musculoskeletal, connective tissue and bone disorders
Common: myalgia

General disorders and administration site conditions
Common: asthenia

Investigations
Common: hypocalcaemia (see section 4.4), reduced testosterone levels (see section 4.4)

Parathyroid Carcinoma and Primary Hyperparathyroidism

The safety profile of Parareg in these patient populations is generally consistent with that seen in patients with Chronic Kidney Disease. The most frequent ADRs in these patient populations were nausea and vomiting.

Post-marketing Experience

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

4.9 Overdose

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

Overdosage of Parareg may lead to hypocalcaemia. In the event of overdosage, patients should be monitored for signs and symptoms of hypocalcaemia, and treatment should be symptomatic and supportive. Since cinacalcet is highly protein-bound, haemodialysis is not an effective treatment for overdosage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-parathyroid agents. ATC code: H05BX01.

Mechanism of action

The calcium sensing receptor on the surface of the chief cell of the parathyroid gland is the principal regulator of PTH secretion. Cinacalcet is a calcimimetic agent which directly lowers PTH levels by increasing the sensitivity of the calcium sensing receptor to extracellular calcium. The reduction in PTH is associated with a concomitant decrease in serum calcium levels.

Reductions in PTH levels correlate with cinacalcet concentration. Soon after dosing, PTH begins to decrease until a nadir at approximately 2 to 6 hours postdose, corresponding with cinacalcet C_{max}. Thereafter, as cinacalcet levels begin to decline, PTH levels increase until 12 hours post-dose, and then PTH suppression remains approximately constant to the end of the once-daily dosing interval. PTH levels in Parareg clinical trials were measured at the end of the dosing interval.

After steady state is reached, serum calcium concentrations remain constant over the dosing interval.

Secondary Hyperparathyroidism

Three, 6-month, double-blind, placebo-controlled clinical studies were conducted in ESRD patients with uncontrolled secondary HPT receiving dialysis (n=1136). Demographic and baseline characteristics were representative of the dialysis patient population with secondary HPT. Mean baseline iPTH concentrations across the 3 studies were 733 and 683 pg/ml (77.8 and 72.4 pmol/l) for the cinacalcet and placebo groups, respectively. 66% of patients were receiving vitamin D sterols at study entry, and > 90% were receiving phosphate binders. Significant reductions in iPTH, serum calcium-phosphorus product (Ca x P), calcium, and phosphorus were observed in the cinacalcet treated patients compared with placebo-treated patients receiving standard of care, and the results were

consistent across the 3 studies. In each of the studies, the primary endpoint (proportion of patients with an iPTH ≤ 250 pg/ml (≤ 26.5 pmol/l)) was achieved by 41%, 46%, and 35% of patients receiving cinacalcet, compared with 4%, 7%, and 6% of patients receiving placebo. Approximately 60% of cinacalcet-treated patients achieved a ≥ 30% reduction in iPTH levels, and this effect was consistent across the spectrum of baseline iPTH levels. The mean reductions in serum Ca x P, calcium, and phosphorus were 14%, 7% and 8%, respectively.

Reductions in iPTH and Ca x P were maintained for up to 12 months of treatment. Cinacalcet decreased iPTH and Ca x P, calcium and phosphorus levels regardless of baseline iPTH or Ca x P level, dialysis modality (PD versus HD), duration of dialysis, and whether or not vitamin D sterols were administered.

Reductions in PTH were associated with non-significant reductions of bone metabolism markers (bone specific alkaline phosphatase, N-telopeptide, bone turnover and bone fibrosis). In post-hoc analyses of pooled data from 6 and 12 months clinical studies, Kaplan-Meier estimates of bone fracture and parathyroidectomy were lower in the cinacalcet group compared with the control group.

Investigational studies in patients with CKD and secondary HPT not undergoing dialysis indicated that cinacalcet reduced PTH levels to a similar extent as in patients with ESRD and secondary HPT receiving dialysis. However, efficacy, safety, optimal doses and treatment targets have not been established in treatment of predialytic renal failure patients. These studies show that CKD patients not undergoing dialysis treated with cinacalcet have an increased risk for hypocalcaemia compared with cinacalcet-treated ESRD patients receiving dialysis, which may be due to lower baseline calcium levels.

Parathyroid carcinoma and Primary Hyperparathyroidism

In a key study,46 patients (29 with parathyroid carcinoma and 17 with primary HPT (who had failed or had contraindications to parathyroidectomy) received cinacalcet for up to 3 years (mean of 328 days for patients with parathyroid carcinoma and mean of 347 days for patients with primary HPT). . Cinacalcet was administered at doses ranging from 30 mg twice daily to 90 mg four times daily. The primary endpoint of the study was a reduction of serum calcium of ≥ 1 mg/dl (≥ 0.25 mmol/l). In patients with parathyroid carcinoma, mean serum calcium declined from 14.1 mg/dl to 12.4 mg/dl (3.5 mmol/l to 3.1 mmol/l), while in patients with primary HPT, serum calcium levels declined from 12.7 mg/dl to 10.4 mg/dl (3.2 mmol/l to 2.6 mmol/l). Eighteen of 29 patients (62 %) with parathyroid carcinoma and 15 of 17 subjects (88 %) with primary HPT achieved a reduction in serum calcium of ≥ 1 mg/dl (≥ 0.25 mmol/l).

5.2 Pharmacokinetic properties

After oral administration of Parareg, maximum plasma cinacalcet concentration is achieved in approximately 2 to 6 hours.

Based on between-study comparisons, the absolute bioavailability of cinacalcet in fasted subjects has been estimated to be about 20-25%. Administration of Parareg with food results in an approximate 50 – 80% increase in cinacalcet bioavailability. Increases in plasma cinacalcet concentration are similar, regardless of the fat content of the meal.

After absorption, cinacalcet concentrations decline in a biphasic fashion with an initial half-life of approximately 6 hours and a terminal half-life of 30 to 40 hours. Steady state drug levels are achieved within 7 days with minimal accumulation. The AUC and C_{max} of cinacalcet increase approximately linearly over the dose range of 30 to 180 mg once daily. At doses above 200 mg, the absorption was saturated probably due to poor solubility. The pharmacokinetics of cinacalcet does not change over time. The volume of distribution is high (approximately 1000 litres), indicating extensive distribution. Cinacalcet is approximately 97% bound to plasma proteins and distributes minimally into red blood cells.

Cinacalcet is metabolised by multiple enzymes, predominantly CYP3A4 and CYP1A2 (the contribution of CYP1A2 has not been characterised clinically). The major circulating metabolites are inactive.

Based on *in vitro* data, cinacalcet is a strong inhibitor of CYP2D6, but is neither an inhibitor of other CYP enzymes at concentrations achieved clinically, including CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 nor an inducer of CYP1A2, CYP2C19 and CYP3A4.

After administration of a 75 mg radiolabelled dose to healthy volunteers, cinacalcet was rapidly and extensively metabolised by oxidation followed by conjugation. Renal excretion of metabolites was the prevalent route of elimination of radioactivity. Approximately 80% of the dose was recovered in the urine and 15% in the faeces.

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

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

Hepatic Insufficiency: Mild hepatic impairment did not notably affect the pharmacokinetics of cinacalcet. Compared to subjects with normal liver function, average AUC of cinacalcet was approximately 2-fold higher in subjects with moderate impairment and approximately 4-fold higher in subjects with severe impairment. The mean half-life of cinacalcet is prolonged by 33% and 70% in patients with moderate and severe hepatic impairment, respectively. Protein binding of cinacalcet is not affected by impaired hepatic function. Because doses are titrated for each subject based on safety and efficacy parameters, no additional dose adjustment is necessary for subjects with hepatic impairment. (see sections 4.2 and 4.4).

Gender: Clearance of cinacalcet may be lower in women than in men. Because doses are titrated for each subject, no additional dose adjustment is necessary based on gender.

Children and adolescents: The pharmacokinetics of cinacalcet have not been studied in patients < 18 years of age.

Smoking: Clearance of cinacalcet is higher in smokers than in non-smokers, likely due to induction of CYP1A2- mediated metabolism. If a patient stops or starts smoking, cinacalcet plasma levels may change and dose adjustment may be necessary.

5.3 Preclinical safety data

Cinacalcet was not teratogenic in rabbits when given at a dose of 0.4 times, on an AUC basis, the maximum human dose for secondary HPT (180 mg daily). The non-teratogenic dose in rats was 4.4 times, on an AUC basis, the maximum dose for secondary HPT. There were no effects on fertility in males or females at exposures up to 4 times a human dose of 180 mg/day (safety margins in the small population of patients administered a maximum clinical dose of 360 mg daily would be approximately half those given above).

In pregnant rats, there were slight decreases in body weight and food consumption at the highest dose. Decreased foetal weights were seen in rats at doses where dams had severe hypocalcaemia. Cinacalcet has been shown to cross the placental barrier in rabbits.

Cinacalcet did not show any genotoxic or carcinogenic potential. Safety margins from the toxicology studies are small due to the dose-limiting hypocalcaemia observed in the animal models. Cataracts and lens opacities were observed in the repeat dose rodent toxicology and carcinogenicity studies, but were

not observed in dogs or monkeys or in clinical studies where cataract formation was monitored. Cataracts are known to occur in rodents as a result of hypocalcaemia.

In *in vitro* studies, IC_{50} values for the serotonin transporter and K_{ATP} channels were found to be 7 and 12 fold greater, respectively, than the EC_{50} for the calcium-sensing receptor obtained under the same experimental conditions. The clinical relevance is unknown, however, the potential for cinacalcet to act on these secondary targets cannot be fully excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core

Pre-gelatinised starch (maize)
Microcrystalline cellulose
Povidone
Crospovidone
Magnesium stearate
Colloidal anhydrous silica

Tablet Coat

Carnauba Wax
Opadry II green: (Lactose monohydrate, hypromellose, titanium dioxide (E171), glycerol triacetate, FD&C Blue (E132), iron oxide yellow (E172)
Opadry clear: (Hypromellose, macrogol)
Opacode Black, printing ink: (Shellac glaze (shellac), iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister: 4 years.
Bottle: 4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aclar/PVC/PVAc/Aluminium blister containing 14 tablets. Pack sizes of 1 blister (14 tablets), 2 blisters (28 tablets), 6 blisters (84 tablets) per carton.

High Density Polyethylene (HDPE) bottle with a desiccant canister and polyester coil, and a child-resistant polypropylene cap with an induction seal, packed into a carton. Each bottle contains 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/293/001-003
EU/1/04/293/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 October 2004

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Parareg 60 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 60 mg cinacalcet (as hydrochloride).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

60 mg: Light green, oval, film-coated tablets marked "AMGEN" on one side and "60" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of secondary hyperparathyroidism (HPT) 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 (see section 5.1).

Reduction of hypercalcaemia in patients with:

- parathyroid carcinoma.
- primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom parathyroidectomy is not clinically appropriate or is contraindicated.

4.2 Posology and method of administration

For oral use. It is recommended that Parareg be taken with food or shortly after a meal, as studies have shown that bioavailability of cinacalcet is increased when taken with food (see section 5.2). Tablets should be taken whole and not divided.

Hepatic impairment

No change in starting dose is necessary. Parareg should be used with caution in patients with moderate to severe hepatic impairment and treatment should be closely monitored during dose titration and continued treatment (see sections 4.4 and 5.2).

Secondary Hyperparathyroidism

Adults and elderly (> 65 years)

The recommended starting dose for adults is 30 mg once per day. Parareg should be titrated every 2 to 4 weeks to a maximum dose of 180 mg once daily to achieve a target parathyroid hormone (PTH) in dialysis patients of between 150-300 pg/ml (15.9-31.8 pmol/l) in the intact PTH (iPTH) assay. PTH levels should be assessed at least 12 hours after dosing with Parareg. Reference should be made to current treatment guidelines.

PTH should be measured 1 to 4 weeks after initiation or dose adjustment of Parareg. PTH should be monitored approximately every 1-3 months during maintenance. Either the intact PTH (iPTH) or bio-intact PTH (biPTH) may be used to measure PTH levels; treatment with Parareg does not alter the relationship between iPTH and biPTH.

Information regarding the pharmacokinetic/pharmacodynamic (PK/PD) profile of cinacalcet is given in section 5.1

During dose titration, serum calcium levels should be monitored frequently, and within 1 week of initiation or dose adjustment of Parareg. 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 (see section 4.4). Concomitant therapy with phosphate binders and/or vitamin D sterols should be adjusted as appropriate.

Children and adolescents

Safety and efficacy have not been established in patients below the age of 18 years.

Parathyroid Carcinoma and Primary Hyperparathyroidism

Adults and elderly (>65 years)

The recommended starting dose of Parareg for adults is 30 mg twice per day. The dosage of Parareg should be titrated every 2 to 4 weeks through sequential doses of 30 mg twice daily, 60 mg twice daily, 90 mg twice daily, and 90 mg three or four times daily as necessary to reduce serum calcium concentration to or below the upper limit of normal. The maximum dose used in clinical trials was 90 mg four times daily.

Serum calcium should be measured within 1 week after initiation or dose adjustment of Parareg. Once maintenance dose levels have been established, serum calcium should be measured every 2 to 3 months. After titration to the maximum dose of Parareg, serum calcium should be periodically monitored; if clinically relevant reductions in serum calcium are not maintained, discontinuation of Parareg therapy should be considered (see section 5.1).

Children and adolescents

Safety and efficacy have not been established in patients below the age of 18 years.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Seizures

In three clinical studies of Chronic Kidney Disease (CKD) patients on dialysis, five percent of the patients in both the Parareg and placebo groups reported a history of seizure disorder at baseline. In these studies, seizures were observed in 1.4% of Parareg treated patients and 0.4% of placebo-treated patients. While the basis for the reported difference in seizure rate is not clear, the threshold for seizures is lowered by significant reductions in serum calcium levels.

Hypotension and/or worsening heart failure

In post-marketing safety surveillance, isolated, idiosyncratic cases of hypotension and/or worsening heart failure have been reported in patients with impaired cardiac function, in which a causal relationship to cinacalcet could not be completely excluded and may be mediated by reductions in serum calcium levels. Clinical trial data showed hypotension occurred in 7% of cinacalcet-treated patients, 12% of placebo-treated patients, and heart failure occurred in 2% of patients receiving cinacalcet or placebo.

Serum Calcium

Parareg treatment should not be initiated in patients with a serum calcium (corrected for albumin) below the lower limit of the normal range. Since cinacalcet lowers serum calcium, patients should be monitored carefully for the occurrence of hypocalcaemia (see section 4.2). In CKD patients receiving dialysis who were administered Parareg, 4% of serum calcium values were less than 7.5 mg/dl (1.875 mmol/l). In the event of hypocalcaemia, calcium-containing phosphate binders, vitamin D sterols and/or adjustment of dialysis fluid calcium concentrations can be used to raise serum calcium. If hypocalcaemia persists, reduce the dose or discontinue administration of Parareg. Potential manifestations of hypocalcaemia may include paraesthesias, myalgias, cramping, tetany and convulsions.

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

General

Adynamic bone disease may develop if PTH levels are chronically suppressed below approximately 1.5 times the upper limit of normal with the iPTH assay. If PTH levels decrease below the recommended target range in patients treated with Parareg, the dose of Parareg and/or vitamin D sterols should be reduced or therapy discontinued.

Testosterone Levels

Testosterone levels are often below the normal range in patients with end-stage renal disease. In a clinical study of ESRD patients on dialysis, free testosterone levels decreased by a median of 31.3% in the Mimpara-treated patients and by 16.3% in the placebo-treated patients after 6 months of treatment. An open-label extension of this study showed no further reductions in free and total testosterone concentrations over a period of 3 years in Mimpara-treated patients. The clinical significance of these reductions in serum testosterone is unknown.

Hepatic Insufficiency

Due to the potential for 2 to 4 fold higher plasma levels of cinacalcet in patients with moderate to severe hepatic impairment (Child-Pugh classification), Parareg should be used with caution in these patients and treatment should be closely monitored (see sections 4.2 and 5.2).

Interactions

Caution should be exercised when administering Parareg concomitantly with strong inhibitors or inducers of CYP3A4 and/or CYP1A2. Dose adjustment of Parareg may be necessary (see section 4.5).

Caution should be exercised when Parareg is administered with individually titrated, narrow therapeutic index medications that are predominantly metabolised by CYP2D6. Dose adjustments of concomitant medications may be necessary (see section 4.5).

Plasma levels of cinacalcet may be lower in smokers due to induction of CYP1A2-mediated metabolism. Dose adjustments may be necessary if a patient starts or stops smoking during cinacalcet treatment (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medications on cinacalcet

Cinacalcet is metabolised in part by the enzyme CYP3A4. Co-administration of 200 mg bid ketoconazole, a strong inhibitor of CYP3A4, caused an approximate 2-fold increase in cinacalcet levels. Dose adjustment of Parareg may be required if a patient receiving Parareg initiates or discontinues therapy with a strong inhibitor (e.g. ketoconazole, itraconazole, telithromycin, voriconazole, ritonavir) or inducer (eg rifampicin) of this enzyme (see Section 4.4).

In vitro data indicate that cinacalcet is in part metabolised by CYP1A2. Smoking induces CYP1A2; the clearance of cinacalcet was observed to be 36-38% higher in smokers than non-smokers. The effect of CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) on cinacalcet plasma levels has not been studied. Dose adjustment may be necessary if a patient starts or stops smoking or when concomitant treatment with strong CYP1A2 inhibitors is initiated or discontinued.

Calcium carbonate: Co-administration of calcium carbonate (single 1500 mg dose) did not alter the pharmacokinetics of cinacalcet.

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

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

Effect of cinacalcet on other medications

Medicinal products metabolised by the enzyme P450 2D6 (CYP2D6): Cinacalcet is a strong inhibitor of CYP2D6. Dose adjustments of concomitant medicinal products may be required when Parareg is administered with individually titrated, narrow therapeutic index substances that are predominantly metabolised by CYP2D6 (e.g. flecainide, propafenone, metoprolol given in heart failure, desimipramine, nortriptyline, clomipramine) (see section 4.4).

Desipramine: Concurrent administration of 90 mg cinacalcet once daily with 50 mg desipramine, a tricyclic antidepressant metabolised primarily by CYP2D6, significantly increased desipramine exposure 3.6-fold (90 % CI 3.0, 4.4) in CYP2D6 extensive metabolisers.

Warfarin: Multiple oral doses of cinacalcet did not affect the pharmacokinetics or pharmacodynamics (as measured by prothrombin time and clotting factor VII) of warfarin.

The lack of effect of cinacalcet on the pharmacokinetics of R- and S-warfarin and the absence of auto-induction upon multiple dosing in patients indicates that cinacalcet is not an inducer of CYP3A4, CYP1A2 or CYP2C9 in humans.

Midazolam: Co-administration of cinacalcet (90 mg) with orally administered midazolam (2 mg), a CYP3A4 and CYP3A5 substrate, did not alter the pharmacokinetics of midazolam. These data suggest that cinacalcet would not affect the pharmacokinetics of those classes of drugs that are metabolized by CYP3A4 and CYP3A5, such as certain immunosuppressants, including cyclosporine and tacrolimus.

4.6 Pregnancy and lactation

There are no clinical data from the use of cinacalcet in pregnant women. Animal studies do not indicate direct harmful effects with respect to pregnancy, parturition or postnatal development. No embryonal/foetal toxicities were seen in studies in pregnant rats and rabbits with the exception of decreased foetal body weights in rats at doses associated with maternal toxicities (see section 5.3). Parareg should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

It is not known whether cinacalcet is excreted in human milk. Cinacalcet is excreted in the milk of lactating rats with a high milk to plasma ratio. Following careful benefit/risk assessment, a decision should be made to discontinue either breast-feeding or treatment with Parareg.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Secondary Hyperparathyroidism

Data presented from controlled studies include 656 patients who received Parareg and 470 patients who received placebo for up to 6 months. The most commonly reported undesirable effects were nausea and vomiting, occurring in 31% Parareg and 19% placebo treated patients, and 27% Parareg 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).

Adverse reactions, defined as adverse events considered at least possibly attributable to cinacalcet treatment based on best-evidence assessment of causality and reported in excess of placebo in double-blind clinical studies are listed below using the following convention: very common (> 1/10); common (> 1/100, < 1/10); uncommon (> 1/1,000, < 1/100); rare (> 1/10,000, < 1/1,000); very rare (< 1/10,000).

Immune system disorders
Uncommon: hypersensitivity reactions

Metabolism and nutrition disorders
Common: anorexia

Nervous system disorders
Common: dizziness, paraesthesia
Uncommon: seizures

Gastrointestinal disorders
Very common: nausea, vomiting
Uncommon: dyspepsia, diarrhoea

Skin and subcutaneous tissue disorders
Common: rash

Musculoskeletal, connective tissue and bone disorders
Common: myalgia

General disorders and administration site conditions
Common: asthenia

Investigations
Common: hypocalcaemia (see section 4.4), reduced testosterone levels (see section 4.4)

Parathyroid Carcinoma and Primary Hyperparathyroidism

The safety profile of Parareg in these patient populations is generally consistent with that seen in patients with Chronic Kidney Disease. The most frequent ADRs in these patient populations were nausea and vomiting.

Post-marketing Experience

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

4.9 Overdose

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

Overdosage of Parareg may lead to hypocalcaemia. In the event of overdosage, patients should be monitored for signs and symptoms of hypocalcaemia, and treatment should be symptomatic and supportive. Since cinacalcet is highly protein-bound, haemodialysis is not an effective treatment for overdosage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-parathyroid agents. ATC code: H05BX01.

Mechanism of action

The calcium sensing receptor on the surface of the chief cell of the parathyroid gland is the principal regulator of PTH secretion. Cinacalcet is a calcimimetic agent which directly lowers PTH levels by increasing the sensitivity of the calcium sensing receptor to extracellular calcium. The reduction in PTH is associated with a concomitant decrease in serum calcium levels.

Reductions in PTH levels correlate with cinacalcet concentration. Soon after dosing, PTH begins to decrease until a nadir at approximately 2 to 6 hours postdose, corresponding with cinacalcet C_{max}. Thereafter, as cinacalcet levels begin to decline, PTH levels increase until 12 hours post-dose, and then PTH suppression remains approximately constant to the end of the once-daily dosing interval. PTH levels in Parareg clinical trials were measured at the end of the dosing interval.

After steady state is reached, serum calcium concentrations remain constant over the dosing interval.

Secondary Hyperparathyroidism

Three, 6-month, double-blind, placebo-controlled clinical studies were conducted in ESRD patients with uncontrolled secondary HPT receiving dialysis (n=1136). Demographic and baseline characteristics were representative of the dialysis patient population with secondary HPT. Mean baseline iPTH concentrations across the 3 studies were 733 and 683 pg/ml (77.8 and 72.4 pmol/l) for the cinacalcet and placebo groups, respectively. 66% of patients were receiving vitamin D sterols at study entry, and > 90% were receiving phosphate binders. Significant reductions in iPTH, serum calcium-phosphorus product (Ca x P), calcium, and phosphorus were observed in the cinacalcet treated patients compared with placebo-treated patients receiving standard of care, and the results were

consistent across the 3 studies. In each of the studies, the primary endpoint (proportion of patients with an iPTH ≤ 250 pg/ml (≤ 26.5 pmol/l)) was achieved by 41%, 46%, and 35% of patients receiving cinacalcet, compared with 4%, 7%, and 6% of patients receiving placebo. Approximately 60% of cinacalcet-treated patients achieved a ≥ 30% reduction in iPTH levels, and this effect was consistent across the spectrum of baseline iPTH levels. The mean reductions in serum Ca x P, calcium, and phosphorus were 14%, 7% and 8%, respectively.

Reductions in iPTH and Ca x P were maintained for up to 12 months of treatment. Cinacalcet decreased iPTH and Ca x P, calcium and phosphorus levels regardless of baseline iPTH or Ca x P level, dialysis modality (PD versus HD), duration of dialysis, and whether or not vitamin D sterols were administered.

Reductions in PTH were associated with non-significant reductions of bone metabolism markers (bone specific alkaline phosphatase, N-telopeptide, bone turnover and bone fibrosis). In post-hoc analyses of pooled data from 6 and 12 months clinical studies, Kaplan-Meier estimates of bone fracture and parathyroidectomy were lower in the cinacalcet group compared with the control group.

Investigational studies in patients with CKD and secondary HPT not undergoing dialysis indicated that cinacalcet reduced PTH levels to a similar extent as in patients with ESRD and secondary HPT receiving dialysis. However, efficacy, safety, optimal doses and treatment targets have not been established in treatment of predialytic renal failure patients. These studies show that CKD patients not undergoing dialysis treated with cinacalcet have an increased risk for hypocalcaemia compared with cinacalcet-treated ESRD patients receiving dialysis, which may be due to lower baseline calcium levels and/or the presence of residual kidney function.

Parathyroid carcinoma and Primary Hyperparathyroidism

In a key study,46 patients (29 with parathyroid carcinoma and 17 with primary HPT (who had failed or had contraindications to parathyroidectomy) received cinacalcet for up to 3 years (mean of 328 days for patients with parathyroid carcinoma and mean of 347 days for patients with primary HPT). . Cinacalcet was administered at doses ranging from 30 mg twice daily to 90 mg four times daily. The primary endpoint of the study was a reduction of serum calcium of ≥ 1 mg/dl (≥ 0.25 mmol/l). In patients with parathyroid carcinoma, mean serum calcium declined from 14.1 mg/dl to 12.4 mg/dl (3.5 mmol/l to 3.1 mmol/l), while in patients with primary HPT, serum calcium levels declined from 12.7 mg/dl to 10.4 mg/dl (3.2 mmol/l to 2.6 mmol/l). Eighteen of 29 patients (62 %) with parathyroid carcinoma and 15 of 17 subjects (88 %) with primary HPT achieved a reduction in serum calcium of ≥ 1 mg/dl (≥ 0.25 mmol/l).

5.2 Pharmacokinetic properties

After oral administration of Parareg, maximum plasma cinacalcet concentration is achieved in approximately 2 to 6 hours.

Based on between-study comparisons, the absolute bioavailability of cinacalcet in fasted subjects has been estimated to be about 20-25%. Administration of Parareg with food results in an approximate 50 – 80% increase in cinacalcet bioavailability. Increases in plasma cinacalcet concentration are similar, regardless of the fat content of the meal.

After absorption, cinacalcet concentrations decline in a biphasic fashion with an initial half-life of approximately 6 hours and a terminal half-life of 30 to 40 hours. Steady state drug levels are achieved within 7 days with minimal accumulation. The AUC and C_{max} of cinacalcet increase approximately linearly over the dose range of 30 to 180 mg once daily. At doses above 200 mg, the absorption was saturated probably due to poor solubility. The pharmacokinetics of cinacalcet does not change over time. The volume of distribution is high (approximately 1000 litres), indicating extensive distribution. Cinacalcet is approximately 97% bound to plasma proteins and distributes minimally into red blood cells.

Cinacalcet is metabolised by multiple enzymes, predominantly CYP3A4 and CYP1A2 (the contribution of CYP1A2 has not been characterised clinically). The major circulating metabolites are inactive.

Based on *in vitro* data, cinacalcet is a strong inhibitor of CYP2D6, but is neither an inhibitor of other CYP enzymes at concentrations achieved clinically, including CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 nor an inducer of CYP1A2, CYP2C19 and CYP3A4.

After administration of a 75 mg radiolabelled dose to healthy volunteers, cinacalcet was rapidly and extensively metabolised by oxidation followed by conjugation. Renal excretion of metabolites was the prevalent route of elimination of radioactivity. Approximately 80% of the dose was recovered in the urine and 15% in the faeces.

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

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

Hepatic Insufficiency: Mild hepatic impairment did not notably affect the pharmacokinetics of cinacalcet. Compared to subjects with normal liver function, average AUC of cinacalcet was approximately 2-fold higher in subjects with moderate impairment and approximately 4-fold higher in subjects with severe impairment. The mean half-life of cinacalcet is prolonged by 33% and 70% in patients with moderate and severe hepatic impairment, respectively. Protein binding of cinacalcet is not affected by impaired hepatic function. Because doses are titrated for each subject based on safety and efficacy parameters, no additional dose adjustment is necessary for subjects with hepatic impairment. (see sections 4.2 and 4.4).

Gender: Clearance of cinacalcet may be lower in women than in men. Because doses are titrated for each subject, no additional dose adjustment is necessary based on gender.

Children and adolescents: The pharmacokinetics of cinacalcet have not been studied in patients < 18 years of age.

Smoking: Clearance of cinacalcet is higher in smokers than in non-smokers, likely due to induction of CYP1A2- mediated metabolism. If a patient stops or starts smoking, cinacalcet plasma levels may change and dose adjustment may be necessary.

5.3 Preclinical safety data

Cinacalcet was not teratogenic in rabbits when given at a dose of 0.4 times, on an AUC basis, the maximum human dose for secondary HPT (180 mg daily). The non-teratogenic dose in rats was 4.4 times, on an AUC basis, the maximum dose for secondary HPT. There were no effects on fertility in males or females at exposures up to 4 times a human dose of 180 mg/day (safety margins in the small population of patients administered a maximum clinical dose of 360 mg daily would be approximately half those given above).

In pregnant rats, there were slight decreases in body weight and food consumption at the highest dose. Decreased foetal weights were seen in rats at doses where dams had severe hypocalcaemia. Cinacalcet has been shown to cross the placental barrier in rabbits.

Cinacalcet did not show any genotoxic or carcinogenic potential. Safety margins from the toxicology studies are small due to the dose-limiting hypocalcaemia observed in the animal models. Cataracts and lens opacities were observed in the repeat dose rodent toxicology and carcinogenicity studies, but were

not observed in dogs or monkeys or in clinical studies where cataract formation was monitored. Cataracts are known to occur in rodents as a result of hypocalcaemia.

In *in vitro* studies, IC_{50} values for the serotonin transporter and K_{ATP} channels were found to be 7 and 12 fold greater, respectively, than the EC_{50} for the calcium-sensing receptor obtained under the same experimental conditions. The clinical relevance is unknown, however, the potential for cinacalcet to act on these secondary targets cannot be fully excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core

Pre-gelatinised starch (maize)
Microcrystalline cellulose
Povidone
Crospovidone
Magnesium stearate
Colloidal anhydrous silica

Tablet Coat

Carnauba Wax
Opadry II green: (Lactose monohydrate, hypromellose, titanium dioxide (E171), glycerol triacetate, FD&C Blue (E132), iron oxide yellow (E172)
Opadry clear: (Hypromellose, macrogol)
Opacode Black, printing ink: (Shellac glaze (shellac), iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister: 4 years.
Bottle: 4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aclar/PVC/PVAc/Aluminium blister containing 14 tablets. Pack sizes of 1 blister (14 tablets), 2 blisters (28 tablets), 6 blisters (84 tablets) per carton.

High Density Polyethylene (HDPE) bottle with a desiccant canister and polyester coil, and a child-resistant polypropylene cap with an induction seal, packed into a carton. Each bottle contains 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/293/005-007
EU/1/04/293/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 October 2004

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Parareg 90 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 90 mg cinacalcet (as hydrochloride).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

90 mg: Light green, oval, film-coated tablets marked "AMGEN" on one side and "90" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of secondary hyperparathyroidism (HPT) 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 (see section 5.1).

Reduction of hypercalcaemia in patients with:
- parathyroid carcinoma.
- primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom parathyroidectomy is not clinically appropriate or is contraindicated.

4.2 Posology and method of administration

For oral use. It is recommended that Parareg be taken with food or shortly after a meal, as studies have shown that bioavailability of cinacalcet is increased when taken with food (see section 5.2). Tablets should be taken whole and not divided.

Hepatic impairment

No change in starting dose is necessary. Parareg should be used with caution in patients with moderate to severe hepatic impairment and treatment should be closely monitored during dose titration and continued treatment (see sections 4.4 and 5.2).

Secondary Hyperparathyroidism

Adults and elderly (> 65 years)

The recommended starting dose for adults is 30 mg once per day. Parareg should be titrated every 2 to 4 weeks to a maximum dose of 180 mg once daily to achieve a target parathyroid hormone (PTH) in dialysis patients of between 150-300 pg/ml (15.9-31.8 pmol/l) in the intact PTH (iPTH) assay. PTH levels should be assessed at least 12 hours after dosing with Parareg. Reference should be made to current treatment guidelines.

PTH should be measured 1 to 4 weeks after initiation or dose adjustment of Parareg. PTH should be monitored approximately every 1-3 months during maintenance. Either the intact PTH (iPTH) or bio-intact PTH (biPTH) may be used to measure PTH levels; treatment with Parareg does not alter the relationship between iPTH and biPTH.

Information regarding the pharmacokinetic/pharmacodynamic (PK/PD) profile of cinacalcet is given in section 5.1

During dose titration, serum calcium levels should be monitored frequently, and within 1 week of initiation or dose adjustment of Parareg. 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 (see section 4.4). Concomitant therapy with phosphate binders and/or vitamin D sterols should be adjusted as appropriate.

Children and adolescents

Safety and efficacy have not been established in patients below the age of 18 years.

Parathyroid Carcinoma and Primary Hyperparathyroidism

Adults and elderly (>65 years)

The recommended starting dose of Parareg for adults is 30 mg twice per day. The dosage of Parareg should be titrated every 2 to 4 weeks through sequential doses of 30 mg twice daily, 60 mg twice daily, 90 mg twice daily, and 90 mg three or four times daily as necessary to reduce serum calcium concentration to or below the upper limit of normal. The maximum dose used in clinical trials was 90 mg four times daily.

Serum calcium should be measured within 1 week after initiation or dose adjustment of Parareg. Once maintenance dose levels have been established, serum calcium should be measured every 2 to 3 months. After titration to the maximum dose of Parareg, serum calcium should be periodically monitored; if clinically relevant reductions in serum calcium are not maintained, discontinuation of Parareg therapy should be considered (see section 5.1).

Children and adolescents

Safety and efficacy have not been established in patients below the age of 18 years.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Seizures

In three clinical studies of Chronic Kidney Disease (CKD) patients on dialysis, five percent of the patients in both the Parareg and placebo groups reported a history of seizure disorder at baseline. In these studies, seizures were observed in 1.4% of Parareg treated patients and 0.4% of placebo-treated patients. While the basis for the reported difference in seizure rate is not clear, the threshold for seizures is lowered by significant reductions in serum calcium levels.

Hypotension and/or worsening heart failure

In post-marketing safety surveillance, isolated, idiosyncratic cases of hypotension and/or worsening heart failure have been reported in patients with impaired cardiac function, in which a causal relationship to cinacalcet could not be completely excluded and may be mediated by reductions in serum calcium levels. Clinical trial data showed hypotension occurred in 7% of cinacalcet-treated patients, 12% of placebo-treated patients, and heart failure occurred in 2% of patients receiving cinacalcet or placebo.

Serum Calcium

Parareg treatment should not be initiated in patients with a serum calcium (corrected for albumin) below the lower limit of the normal range. Since cinacalcet lowers serum calcium, patients should be monitored carefully for the occurrence of hypocalcaemia (see section 4.2). In CKD patients receiving dialysis who were administered Parareg, 4% of serum calcium values were less than 7.5 mg/dl (1.875 mmol/l). In the event of hypocalcaemia, calcium-containing phosphate binders, vitamin D sterols and/or adjustment of dialysis fluid calcium concentrations can be used to raise serum calcium. If hypocalcaemia persists, reduce the dose or discontinue administration of Parareg. Potential manifestations of hypocalcaemia may include paraesthesias, myalgias, cramping, tetany and convulsions.

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

General

Adynamic bone disease may develop if PTH levels are chronically suppressed below approximately 1.5 times the upper limit of normal with the iPTH assay. If PTH levels decrease below the recommended target range in patients treated with Parareg, the dose of Parareg and/or vitamin D sterols should be reduced or therapy discontinued.

Testosterone Levels

Testosterone levels are often below the normal range in patients with end-stage renal disease. In a clinical study of ESRD patients on dialysis, free testosterone levels decreased by a median of 31.3% in the Mimpara-treated patients and by 16.3% in the placebo-treated patients after 6 months of treatment. An open-label extension of this study showed no further reductions in free and total testosterone concentrations over a period of 3 years in Mimpara-treated patients. The clinical significance of these reductions in serum testosterone is unknown.

Hepatic Insufficiency

Due to the potential for 2 to 4 fold higher plasma levels of cinacalcet in patients with moderate to severe hepatic impairment (Child-Pugh classification), Parareg should be used with caution in these patients and treatment should be closely monitored (see sections 4.2 and 5.2).

Interactions

Caution should be exercised when administering Parareg concomitantly with strong inhibitors or inducers of CYP3A4 and/or CYP1A2. Dose adjustment of Parareg may be necessary (see section 4.5).

Caution should be exercised when Parareg is administered with individually titrated, narrow therapeutic index medications that are predominantly metabolised by CYP2D6. Dose adjustments of concomitant medications may be necessary (see section 4.5).

Plasma levels of cinacalcet may be lower in smokers due to induction of CYP1A2-mediated metabolism. Dose adjustments may be necessary if a patient starts or stops smoking during cinacalcet treatment (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

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Cinacalcet is metabolised in part by the enzyme CYP3A4. Co-administration of 200 mg bid ketoconazole, a strong inhibitor of CYP3A4, caused an approximate 2-fold increase in cinacalcet levels. Dose adjustment of Parareg may be required if a patient receiving Parareg initiates or discontinues therapy with a strong inhibitor (e.g. ketoconazole, itraconazole, telithromycin, voriconazole, ritonavir) or inducer (eg rifampicin) of this enzyme (see Section 4.4).

In vitro data indicate that cinacalcet is in part metabolised by CYP1A2. Smoking induces CYP1A2; the clearance of cinacalcet was observed to be 36-38% higher in smokers than non-smokers. The effect of CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) on cinacalcet plasma levels has not been studied. Dose adjustment may be necessary if a patient starts or stops smoking or when concomitant treatment with strong CYP1A2 inhibitors is initiated or discontinued.

Calcium carbonate: Co-administration of calcium carbonate (single 1500 mg dose) did not alter the pharmacokinetics of cinacalcet.

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

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

Effect of cinacalcet on other medications

Medicinal products metabolised by the enzyme P450 2D6 (CYP2D6): Cinacalcet is a strong inhibitor of CYP2D6. Dose adjustments of concomitant medicinal products may be required when Parareg is administered with individually titrated, narrow therapeutic index substances that are predominantly metabolised by CYP2D6 (e.g. flecainide, propafenone, metoprolol given in heart failure, desimipramine, nortriptyline, clomipramine) (see section 4.4).

Desipramine: Concurrent administration of 90 mg cinacalcet once daily with 50 mg desipramine, a tricyclic antidepressant metabolised primarily by CYP2D6, significantly increased desipramine exposure 3.6-fold (90 % CI 3.0, 4.4) in CYP2D6 extensive metabolizers.

Warfarin: Multiple oral doses of cinacalcet did not affect the pharmacokinetics or pharmacodynamics (as measured by prothrombin time and clotting factor VII) of warfarin.

The lack of effect of cinacalcet on the pharmacokinetics of R- and S-warfarin and the absence of auto-induction upon multiple dosing in patients indicates that cinacalcet is not an inducer of CYP3A4, CYP1A2 or CYP2C9 in humans.

Midazolam: Co-administration of cinacalcet (90 mg) with orally administered midazolam (2 mg), a CYP3A4 and CYP3A5 substrate, did not alter the pharmacokinetics of midazolam. These data suggest that cinacalcet would not affect the pharmacokinetics of those classes of drugs that are metabolized by CYP3A4 and CYP3A5, such as certain immunosuppressants, including cyclosporine and tacrolimus.

4.6 Pregnancy and lactation

There are no clinical data from the use of cinacalcet in pregnant women. Animal studies do not indicate direct harmful effects with respect to pregnancy, parturition or postnatal development. No embryonal/foetal toxicities were seen in studies in pregnant rats and rabbits with the exception of decreased foetal body weights in rats at doses associated with maternal toxicities (see section 5.3). Parareg should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

It is not known whether cinacalcet is excreted in human milk. Cinacalcet is excreted in the milk of lactating rats with a high milk to plasma ratio. Following careful benefit/risk assessment, a decision should be made to discontinue either breast-feeding or treatment with Parareg.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Secondary Hyperparathyroidism

Data presented from controlled studies include 656 patients who received Parareg and 470 patients who received placebo for up to 6 months. The most commonly reported undesirable effects were nausea and vomiting, occurring in 31% Parareg and 19% placebo treated patients, and 27% Parareg 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).

Adverse reactions, defined as adverse events considered at least possibly attributable to cinacalcet treatment based on best-evidence assessment of causality and reported in excess of placebo in double-blind clinical studies are listed below using the following convention: very common (> 1/10); common (> 1/100, < 1/10); uncommon (> 1/1,000, < 1/100); rare (> 1/10,000, < 1/1,000); very rare (< 1/10,000).

Immune system disorders
Uncommon: hypersensitivity reactions

Metabolism and nutrition disorders
Common: anorexia

Nervous system disorders
Common: dizziness, paraesthesia
Uncommon: seizures

Gastrointestinal disorders
Very common: nausea, vomiting
Uncommon: dyspepsia, diarrhoea

Skin and subcutaneous tissue disorders
Common: rash

Musculoskeletal, connective tissue and bone disorders
Common: myalgia

General disorders and administration site conditions
Common: asthenia

Investigations
Common: hypocalcaemia (see section 4.4), reduced testosterone levels (see section 4.4)

Parathyroid Carcinoma and Primary Hyperparathyroidism

The safety profile of Parareg in these patient populations is generally consistent with that seen in patients with Chronic Kidney Disease. The most frequent ADRs in these patient populations were nausea and vomiting.

Post-marketing Experience

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

4.9 Overdose

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

Overdosage of Parareg may lead to hypocalcaemia. In the event of overdosage, patients should be monitored for signs and symptoms of hypocalcaemia, and treatment should be symptomatic and supportive. Since cinacalcet is highly protein-bound, haemodialysis is not an effective treatment for overdosage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-parathyroid agents. ATC code: H05BX01.

Mechanism of action

The calcium sensing receptor on the surface of the chief cell of the parathyroid gland is the principal regulator of PTH secretion. Cinacalcet is a calcimimetic agent which directly lowers PTH levels by increasing the sensitivity of the calcium sensing receptor to extracellular calcium. The reduction in PTH is associated with a concomitant decrease in serum calcium levels.

Reductions in PTH levels correlate with cinacalcet concentration. Soon after dosing, PTH begins to decrease until a nadir at approximately 2 to 6 hours postdose, corresponding with cinacalcet C_{max}. Thereafter, as cinacalcet levels begin to decline, PTH levels increase until 12 hours post-dose, and then PTH suppression remains approximately constant to the end of the once-daily dosing interval. PTH levels in Parareg clinical trials were measured at the end of the dosing interval.

After steady state is reached, serum calcium concentrations remain constant over the dosing interval.

Secondary Hyperparathyroidism

Three, 6-month, double-blind, placebo-controlled clinical studies were conducted in ESRD patients with uncontrolled secondary HPT receiving dialysis (n=1136). Demographic and baseline characteristics were representative of the dialysis patient population with secondary HPT. Mean baseline iPTH concentrations across the 3 studies were 733 and 683 pg/ml (77.8 and 72.4 pmol/l) for the cinacalcet and placebo groups, respectively. 66% of patients were receiving vitamin D sterols at study entry, and > 90% were receiving phosphate binders. Significant reductions in iPTH, serum calcium-phosphorus product (Ca x P), calcium, and phosphorus were observed in the cinacalcet treated patients compared with placebo-treated patients receiving standard of care, and the results were

consistent across the 3 studies. In each of the studies, the primary endpoint (proportion of patients with an iPTH ≤ 250 pg/ml (≤ 26.5 pmol/l)) was achieved by 41%, 46%, and 35% of patients receiving cinacalcet, compared with 4%, 7%, and 6% of patients receiving placebo. Approximately 60% of cinacalcet-treated patients achieved a ≥ 30% reduction in iPTH levels, and this effect was consistent across the spectrum of baseline iPTH levels. The mean reductions in serum Ca x P, calcium, and phosphorus were 14%, 7% and 8%, respectively.

Reductions in iPTH and Ca x P were maintained for up to 12 months of treatment. Cinacalcet decreased iPTH and Ca x P, calcium and phosphorus levels regardless of baseline iPTH or Ca x P level, dialysis modality (PD versus HD), duration of dialysis, and whether or not vitamin D sterols were administered.

Reductions in PTH were associated with non-significant reductions of bone metabolism markers (bone specific alkaline phosphatase, N-telopeptide, bone turnover and bone fibrosis). In post-hoc analyses of pooled data from 6 and 12 months clinical studies, Kaplan-Meier estimates of bone fracture and parathyroidectomy were lower in the cinacalcet group compared with the control group.

Investigational studies in patients with CKD and secondary HPT not undergoing dialysis indicated that cinacalcet reduced PTH levels to a similar extent as in patients with ESRD and secondary HPT receiving dialysis. However, efficacy, safety, optimal doses and treatment targets have not been established in treatment of predialytic renal failure patients. These studies show that CKD patients not undergoing dialysis treated with cinacalcet have an increased risk for hypocalcaemia compared with cinacalcet-treated ESRD patients receiving dialysis, which may be due to lower baseline calcium levels and/or the presence of residual kidney function.

Parathyroid carcinoma and Primary Hyperparathyroidism

In a key study,46 patients (29 with parathyroid carcinoma and 17 with primary HPT (who had failed or had contraindications to parathyroidectomy) received cinacalcet for up to 3 years (mean of 328 days for patients with parathyroid carcinoma and mean of 347 days for patients with primary HPT). . Cinacalcet was administered at doses ranging from 30 mg twice daily to 90 mg four times daily. The primary endpoint of the study was a reduction of serum calcium of ≥ 1 mg/dl (≥ 0.25 mmol/l). In patients with parathyroid carcinoma, mean serum calcium declined from 14.1 mg/dl to 12.4 mg/dl (3.5 mmol/l to 3.1 mmol/l), while in patients with primary HPT, serum calcium levels declined from 12.7 mg/dl to 10.4 mg/dl (3.2 mmol/l to 2.6 mmol/l). Eighteen of 29 patients (62 %) with parathyroid carcinoma and 15 of 17 subjects (88 %) with primary HPT achieved a reduction in serum calcium of ≥ 1 mg/dl (≥ 0.25 mmol/l).

5.2 Pharmacokinetic properties

After oral administration of Parareg, maximum plasma cinacalcet concentration is achieved in approximately 2 to 6 hours.

Based on between-study comparisons, the absolute bioavailability of cinacalcet in fasted subjects has been estimated to be about 20-25%. Administration of Parareg with food results in an approximate 50 – 80% increase in cinacalcet bioavailability. Increases in plasma cinacalcet concentration are similar, regardless of the fat content of the meal.

After absorption, cinacalcet concentrations decline in a biphasic fashion with an initial half-life of approximately 6 hours and a terminal half-life of 30 to 40 hours. Steady state drug levels are achieved within 7 days with minimal accumulation. The AUC and C_{max} of cinacalcet increase approximately linearly over the dose range of 30 to 180 mg once daily. At doses above 200 mg, the absorption was saturated probably due to poor solubility. The pharmacokinetics of cinacalcet does not change over time. The volume of distribution is high (approximately 1000 litres), indicating extensive distribution. Cinacalcet is approximately 97% bound to plasma proteins and distributes minimally into red blood cells.

Cinacalcet is metabolised by multiple enzymes, predominantly CYP3A4 and CYP1A2 (the contribution of CYP1A2 has not been characterised clinically). The major circulating metabolites are inactive.

Based on *in vitro* data, cinacalcet is a strong inhibitor of CYP2D6, but is neither an inhibitor of other CYP enzymes at concentrations achieved clinically, including CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 nor an inducer of CYP1A2, CYP2C19 and CYP3A4.

After administration of a 75 mg radiolabelled dose to healthy volunteers, cinacalcet was rapidly and extensively metabolised by oxidation followed by conjugation. Renal excretion of metabolites was the prevalent route of elimination of radioactivity. Approximately 80% of the dose was recovered in the urine and 15% in the faeces.

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

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

Hepatic Insufficiency: Mild hepatic impairment did not notably affect the pharmacokinetics of cinacalcet. Compared to subjects with normal liver function, average AUC of cinacalcet was approximately 2-fold higher in subjects with moderate impairment and approximately 4-fold higher in subjects with severe impairment. The mean half-life of cinacalcet is prolonged by 33% and 70% in patients with moderate and severe hepatic impairment, respectively. Protein binding of cinacalcet is not affected by impaired hepatic function. Because doses are titrated for each subject based on safety and efficacy parameters, no additional dose adjustment is necessary for subjects with hepatic impairment. (see sections 4.2 and 4.4).

Gender: Clearance of cinacalcet may be lower in women than in men. Because doses are titrated for each subject, no additional dose adjustment is necessary based on gender.

Children and adolescents: The pharmacokinetics of cinacalcet have not been studied in patients < 18 years of age.

Smoking: Clearance of cinacalcet is higher in smokers than in non-smokers, likely due to induction of CYP1A2- mediated metabolism. If a patient stops or starts smoking, cinacalcet plasma levels may change and dose adjustment may be necessary.

5.3 Preclinical safety data

Cinacalcet was not teratogenic in rabbits when given at a dose of 0.4 times, on an AUC basis, the maximum human dose for secondary HPT (180 mg daily). The non-teratogenic dose in rats was 4.4 times, on an AUC basis, the maximum dose for secondary HPT. There were no effects on fertility in males or females at exposures up to 4 times a human dose of 180 mg/day (safety margins in the small population of patients administered a maximum clinical dose of 360 mg daily would be approximately half those given above).

In pregnant rats, there were slight decreases in body weight and food consumption at the highest dose. Decreased foetal weights were seen in rats at doses where dams had severe hypocalcaemia. Cinacalcet has been shown to cross the placental barrier in rabbits.

Cinacalcet did not show any genotoxic or carcinogenic potential. Safety margins from the toxicology studies are small due to the dose-limiting hypocalcaemia observed in the animal models. Cataracts and lens opacities were observed in the repeat dose rodent toxicology and carcinogenicity studies, but were

not observed in dogs or monkeys or in clinical studies where cataract formation was monitored. Cataracts are known to occur in rodents as a result of hypocalcaemia.

In *in vitro* studies, IC_{50} values for the serotonin transporter and K_{ATP} channels were found to be 7 and 12 fold greater, respectively, than the EC_{50} for the calcium-sensing receptor obtained under the same experimental conditions. The clinical relevance is unknown, however, the potential for cinacalcet to act on these secondary targets cannot be fully excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core

Pre-gelatinised starch (maize)
Microcrystalline cellulose
Povidone
Crospovidone
Magnesium stearate
Colloidal anhydrous silica

Tablet Coat

Carnauba Wax
Opadry II green: (Lactose monohydrate, hypromellose, titanium dioxide (E171), glycerol triacetate, FD&C Blue (E132), iron oxide yellow (E172)
Opadry clear: (Hypromellose, macrogol)
Opacode Black, printing ink: (Shellac glaze (shellac), iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister: 4 years.
Bottle: 4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aclar/PVC/PVAc/Aluminium blister containing 14 tablets. Pack sizes of 1 blister (14 tablets), 2 blisters (28 tablets), 6 blisters (84 tablets) per carton.

High Density Polyethylene (HDPE) bottle with a desiccant canister and polyester coil, and a child-resistant polypropylene cap with an induction seal, packed into a carton. Each bottle contains 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/293/009-011
EU/1/04/293/012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 October 2004

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version 3 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version of 9 November 2007 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

ANNEX III

LABELLING AND PACKAGING LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Parareg 30 mg film-coated tablets
Cinacalcet

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 30 mg of cinacalcet (as hydrochloride)

3. LIST OF EXCIPIENTS

Lactose monohydrate

4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets
28 tablets
84 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP..

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/293/001 – carton of 14 tablets
EU/1/04/293/002 – carton of 28 tablets
EU/1/04/293/003 – carton of 84 tablets

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Parareg 30 mg tablet
Cinacalcet

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Parareg 30 mg film-coated tablets
Cinacalcet

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 30 mg of cinacalcet (as hydrochloride)

3. LIST OF EXCIPIENTS

Lactose monohydrate

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/293/004

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON FOR BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Parareg 30 mg film-coated tablets
Cinacalcet

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 30 mg of cinacalcet (as hydrochloride)

3. LIST OF EXCIPIENTS

Lactose monohydrate

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/293/004

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Parareg 60 mg film-coated tablets
Cinacalcet

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 60 mg of cinacalcet (as hydrochloride)

3. LIST OF EXCIPIENTS

Lactose monohydrate

4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets
28 tablets
84 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP..

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/293/005 – carton of 14 tablets
EU/1/04/293/006 – carton of 28 tablets
EU/1/04/293/007 – carton of 84 tablets

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Parareg 60 mg tablet
Cinacalcet

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Parareg 60 mg film-coated tablets
Cinacalcet

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 60 mg of cinacalcet (as hydrochloride)

3. LIST OF EXCIPIENTS

Lactose monohydrate

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP..

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/293/008

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON FOR BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Parareg 60 mg film-coated tablets
Cinacalcet

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 60 mg of cinacalcet (as hydrochloride)

3. LIST OF EXCIPIENTS

Lactose monohydrate

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/293/008

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Parareg 90 mg film-coated tablets
Cinacalcet

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 90 mg of cinacalcet (as hydrochloride)

3. LIST OF EXCIPIENTS

Lactose monohydrate

4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets
28 tablets
84 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP..

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/293/009 – carton of 14 tablets
EU/1/04/293/010 – carton of 28 tablets
EU/1/04/293/011 – carton of 84 tablets

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Parareg 90 mg tablet
Cinacalcet

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Parareg 90 mg film-coated tablets
Cinacalcet

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 90 mg of cinacalcet (as hydrochloride)

3. LIST OF EXCIPIENTS

Lactose monohydrate

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/293/012

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON FOR BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Parareg 90 mg film-coated tablets
Cinacalcet

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 90 mg of cinacalcet (as hydrochloride)

3. LIST OF EXCIPIENTS

Lactose monohydrate

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/293/012

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

PACKAGE LEAFLET : INFORMATION FOR THE USER

Parareg 30 mg film-coated tablets
Parareg 60 mg film-coated tablets
Parareg 90 mg film-coated tablets
Cinacalcet

Read all of this leaflet carefully before you start taking this medicine.

Keep this leaflet. You may need to read it again.

If you have further questions, please ask your doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet

1. WHAT PARAREG IS AND WHAT IT IS USED FOR

Parareg works by controlling the levels of parathyroid hormone (PTH), calcium and phosphorous in your body. It is used to treat problems with organs called parathyroid glands. The parathyroids are four small glands in the neck, near the thyroid gland, that produce parathyroid hormone (PTH).

Parareg is used:
- to treat secondary hyperparathyroidism in patients with kidney disease on dialysis.
- to reduce high levels of calcium in the blood (hypercalcaemia) in patients with parathyroid cancer
- to reduce high levels of calcium in the blood (hypercalcaemia) in patients with primary hyperparathyroidism who still have high calcium levels after removal of the parathyroid gland or when removal of the gland is not possible.

In primary and secondary hyperparathyroidism too much PTH is produced by the parathyroids. This can cause the loss of calcium in the bones, which can lead to bone pain and fractures, problems with blood and heart vessels, kidney stones, mental illness and coma.

2. BEFORE YOU TAKE PARAREG

Do not take Parareg:

- **DO NOT** take Parareg if you are **allergic** (hypersensitive) to cinacalcet or any of the other ingredients of Parareg.

Take special care with Parareg:

Before you start taking Parareg, tell your doctor if you have or have ever had

- **seizures** (fits or convulsions). The risk of having seizures is higher if you have had them before;
- **liver problems**

During treatment with Parareg, tell your doctor:
- if you start or stop smoking, as this may affect the way Parareg works.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Please tell your doctor if you are taking the following medicines.

These can affect how Parareg works:
- medicines used to treat **skin** and **fungal infections** (ketoconazole, itraconazole, voriconazole);
- antibiotics used to treat **bacterial infections** (telithromycin, rifampicin);
- medicine used to treat **HIV** infection and AIDS (ritonavir).

Parareg may affect how the following work:
- medicines used to treat **depression** (amitriptyline, desipramine, nortriptyline, clomipramine and fluvoxamine);
- medicines used to treat **changes in heart rate** (flecainide and propafenone);
- medicine used to treat **high blood pressure** (metoprolol when given in heart failure) ,
- antibiotic used to treat **bacterial infections** (ciprofloxacin).

Taking Parareg with food and drink

Parareg should be taken with or shortly after food.

Pregnancy and breast-feeding

Always tell your doctor if you are pregnant or planning to become pregnant. Parareg has not been tested in pregnant women. In case of pregnancy, your doctor may decide to modify your treatment, as Parareg might harm the foetus. .

It is not known whether Parareg is excreted in human milk. Your doctor will discuss with if you should discontinue either breast-feeding or treatment with Parareg.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Parareg should not affect your ability to drive and use machines. However, it is advisable to wait and see how you feel after taking Parareg and before driving or operating machinery.

If you have an intolerance to some sugars

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE PARAREG

Children under the age of 18 must not take Parareg.

Always take Parareg exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure. Your doctor will tell you how much Parareg you must take.

Parareg must be taken orally, with or shortly after food. The tablets must be taken whole and are not to be divided.

Your doctor will take regular blood samples during treatment to monitor your progress and will adjust your dose if necessary.

If you are being treated for secondary hyperparathyroidism

The usual starting dose for Parareg is 30 mg (one tablet) once per day.

If you are being treated for parathyroid cancer or primary hyperparathyroidism

The usual starting dose for Parareg is 30 mg (one tablet) twice per day.

If you take more Parareg than you should

If you take more Parareg than you should you must contact your doctor immediately.

If you forget to take Parareg

Do not take a double dose to make up for forgotten doses.

If you have forgotten a dose of Parareg, you should take your next dose as normal.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Parareg can have side effects, although not everybody gets them.

Very common side effects (seen in more than 1 in 10 people taking Parareg):
- nausea and vomiting, these side effects are normally quite mild and do not last for long.

Common side effects (seen in more than 1 in 100 people taking Parareg):
- dizziness
- numbness or tingling sensation (paraesthesia)
- loss of appetite (anorexia)
- muscle pain (myalgia)
- weakness (asthenia)
- rash
- reduced testosterone levels

Uncommon side effects (seen in more than 1 in 1000 people taking Parareg):
- seizures
- indigestion (dyspepsia)
- diarrhoea
- allergic reaction (hypersensitivity)

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

If you start to get numbness or tingling around the mouth, muscle aches or cramps and seizures **you should tell you doctor immediately.** These may be signs that your calcium levels are too low (hypocalcaemia).

After taking Parareg a very small number of patients with heart failure had worsening of their condition. Low blood pressure (hypotension) has also been seen in a very small number of these patients. As so few cases have been seen it is not known whether they are due to Parareg, or not.

5. HOW TO STORE PARAREG

Keep out of the reach and sight of children.

This medicinal product does not require any special storage conditions

Do not use Parareg after the expiry date which is stated on the outer carton and on the blister. The expiry date refers to the last day of that month.
(or) Do not use Parareg after the expiry date which is stated on the outer carton and on the bottle.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Parareg contains

The active substance is cinacalcet. Each film-coated tablet contains 30 mg, 60 mg or 90 mg of cinacalcet (as hydrochloride).

The other ingredients are:
- Pre-gelatinised maize starch
- Microcrystalline cellulose
- Povidone
- Crospovidone
- Magnesium stearate
- Colloidal anhydrous silica.

The tablets are coated with:
- Carnauba wax
- Opadry green (containing lactose monohydrate, hypromellose, titanium dioxide (E171), glycerol triacetate, FD&C Blue (E132), iron oxide yellow (E172))
- Opadry clear (containing hypromellose, macrogol)

The printing ink contains: shellac glaze, iron oxide black (E172).

What Parareg looks like and contents of the pack

Parareg is a light green film-coated tablet. They are oval-shaped and have “30”, “60” or “90” printed on one side and “Amgen” on the other side.

Parareg is available in blisters of 30 mg, 60 mg or 90 mg film-coated tablets. Each blister pack contains either 14, 28 or 84 tablets in a carton.

Parareg is available in bottles of 30 mg, 60 mg or 90 mg film-coated tablets, inside a carton. Each bottle holds 30 tablets.

Not all pack sizes may be marketed.

Manufacturer:
Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

Marketing Authorisation Holder:
Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/