

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cinacalcet Mylan 30 mg film-coated tablets.
Cinacalcet Mylan 60 mg film-coated tablets.
Cinacalcet Mylan 90 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cinacalcet Mylan 30 mg film-coated tablets

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

Cinacalcet Mylan 60 mg film-coated tablets

Each film-coated tablet contains 60 mg of cinacalcet (as hydrochloride).

Cinacalcet Mylan 90 mg film-coated tablets

Each film-coated tablet contains 90 mg of cinacalcet (as hydrochloride).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Cinacalcet Mylan 30 mg film-coated tablets

10.0 mm x 6.4 mm, green, film-coated, oval, biconvex, bevelled edge tablet debossed with M on one side of the tablet and CI30 on the other side.

Cinacalcet Mylan 60 mg film-coated tablets

12.5 mm x 8.0 mm, green, film-coated, oval, biconvex, bevelled edge tablet debossed with M on one side of the tablet and CI60 on the other side.

Cinacalcet Mylan 90 mg film-coated tablets

14.3 mm x 9.0 mm, green, film-coated, oval, biconvex, bevelled edge tablet debossed with M on one side of the tablet and CI90 on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Secondary hyperparathyroidism

Adults

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

Paediatric population

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

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

Parathyroid carcinoma and primary hyperparathyroidism in adults

Reduction of hypercalcaemia in adult patients with:

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

4.2 Posology and method of administration

Posology

Secondary hyperparathyroidism:

Adults and elderly (> 65 years)

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

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

Dose adjustment based on serum calcium levels

Corrected serum calcium should be measured and monitored and should be at or above the lower limit of the normal range prior to administration of first dose of cinacalcet (see section 4.4). The normal calcium range may differ depending on the methods used by your local laboratory.

During dose titration, serum calcium levels should be monitored frequently, and within 1 week of initiation or dose adjustment of cinacalcet. Once the maintenance dose has been established, serum calcium should be measured approximately monthly. In the event that corrected serum calcium levels fall below 8.4 mg/dl (2.1 mmol/l) and/or symptoms of hypocalcaemia occur the following management is recommended:

Corrected Serum calcium level or clinical symptoms of hypocalcaemia	Recommendations
< 8.4 mg/dL (2.1 mmol/L) and > 7.5 mg/dL (1.9 mmol/L), or in the presence of clinical symptoms of hypocalcaemia	Calcium-containing phosphate binders, vitamin D sterols and/or adjustment of dialysis fluid calcium concentrations can be used to raise serum calcium according to clinical judgment.
< 8.4 mg/dL (2.1 mmol/L) and > 7.5 mg/dL (1.9 mmol/L) or persistent symptoms of	Reduce or withhold dose of cinacalcet.

hypocalcaemia despite attempts to increase serum calcium	
≤ 7.5 mg/dL (1.9 mmol/L) or persistent symptoms of hypocalcaemia and vitamin D cannot be increased	Withhold administration of cinacalcet until serum calcium levels reach 8.0 mg/dL (2.0 mmol/L) and/or symptoms of hypocalcaemia have resolved. Treatment should be reinitiated using the next lowest dose of cinacalcet.

Paediatric population

Corrected serum calcium should be in the upper range of, or above, the age-specified reference interval prior to administration of first dose of cinacalcet, and closely monitored (see section 4.4). The normal calcium range differs depending on the methods used by your local laboratory and the age of the child/patient.

The recommended starting dose for children aged ≥ 3 years to < 18 years is ≤ 0.20 mg/kg once daily based on the patient's dry weight (see table 1).

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

Table 1. Cinacalcet Mylan daily dose in paediatric patients

Patient dry weight (kg)	Starting dose (mg)	Available sequential dose levels (mg)
10 to < 12.5	1	1, 2.5, 5, 7.5, 10 and 15
≥ 12.5 to < 25	2.5	2.5, 5, 7.5, 10, 15, and 30
≥ 25 to < 36	5	5, 10, 15, 30, and 60
≥ 36 to < 50		5, 10, 15, 30, 60, and 90
≥ 50 to < 75	10	10, 15, 30, 60, 90, and 120
≥ 75	15	15, 30, 60, 90, 120, and 180

Children who require doses lower than 30 mg or who are unable to swallow tablets, should use other more suitable pharmaceutical forms of cinacalcet products.

Dose adjustment based on PTH levels

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

The dose should be adjusted based on iPTH as shown below:

- If iPTH is < 150 pg/mL (15.9 pmol/L) and ≥ 100 pg/mL (10.6 pmol/L), decrease the dose of cinacalcet to the next lower dose.
- If iPTH < 100 pg/mL (10.6 pmol/L), stop cinacalcet treatment, restart cinacalcet at the next lower dose once the iPTH is > 150 pg/mL (15.9 pmol/L). If cinacalcet treatment has been stopped for more than 14 days, restart at the recommended starting dose.

Dose adjustment based on serum calcium levels

Serum calcium should be measured within 1 week after initiation or dose adjustment of cinacalcet.

Once the maintenance dose has been established, weekly measurement of serum calcium is recommended. Serum calcium levels in paediatric patients should be maintained within the normal

range. If serum calcium levels decrease below the normal range or symptoms of hypocalcaemia occur, appropriate dose adjustment steps should be taken as shown in table 2 below:

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

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

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

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

Switch from etelcalcetide to Cinacalcet Mylan

The switch from etelcalcetide to Cinacalcet Mylan and the appropriate wash out period has not been studied in patients. In patients who have discontinued etelcalcetide, Cinacalcet Mylan should not be initiated until at least three subsequent haemodialysis sessions have been completed, at which time serum calcium should be measured. Ensure serum calcium levels are within the normal range before Cinacalcet Mylan is initiated (see sections 4.4 and 4.8).

Parathyroid carcinoma and primary hyperparathyroidism:

Adults and elderly (> 65 years)

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

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

Paediatric population

The safety and efficacy of cinacalcet in children for the treatment of parathyroid carcinoma and primary hyperparathyroidism have not been established. No data are available.

Hepatic impairment

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

Method of administration

For oral use.

Tablets should be taken whole and should not be chewed, crushed or divided.

It is recommended that Cinacalcet Mylan 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).

4.3 Contraindications

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

Hypocalcaemia (see sections 4.2 and 4.4).

4.4 Special warnings and precautions for use

Serum calcium

Life threatening events and fatal outcomes associated with hypocalcaemia have been reported in adult and paediatric patients treated with cinacalcet. Manifestations of hypocalcaemia may include paraesthesias, myalgias, cramping, tetany and convulsions. Decreases in serum calcium can also prolong the QT interval, potentially resulting in ventricular arrhythmia secondary to hypocalcaemia. Cases of QT prolongation and ventricular arrhythmia have been reported in patients treated with cinacalcet (see section 4.8). Caution is advised in patients with other risk factors for QT prolongation such as patients with known congenital long QT syndrome or patients receiving medicinal products known to cause QT prolongation.

Since cinacalcet lowers serum calcium, patients should be monitored carefully for the occurrence of hypocalcaemia (see section 4.2). Serum calcium should be measured within 1 week after initiation or dose adjustment of cinacalcet.

Adults

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

In Chronic Kidney Disease (CKD) patients receiving dialysis who were administered cinacalcet, approximately 30% of patients had at least one serum calcium value less than 7.5 mg/dl (1.9 mmol/l).

Paediatric population

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

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

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

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

CKD patients not on dialysis

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

Seizures

Cases of seizures have been reported in patients treated with cinacalcet (see section 4.8). The threshold for seizures is lowered by significant reductions in serum calcium levels. Therefore, serum calcium levels should be closely monitored in patients receiving cinacalcet, particularly in patients with a history of a seizure disorder.

Hypotension and/or worsening heart failure

Cases of hypotension and/or worsening heart failure have been reported in patients with impaired cardiac function, in which a causal relationship to cinacalcet could not be completely excluded and may be mediated by reductions in serum calcium levels (see section 4.8).

Co-administration with other medicinal products

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

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

General

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

Testosterone levels

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

Hepatic impairment

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

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products known to reduce serum calcium

Concurrent administration of other medicinal products known to reduce serum calcium and cinacalcet may result in an increased risk of hypocalcaemia (see section 4.4). Patients receiving cinacalcet should not be given etelcalcetide (see section 4.4).

Effect of other medicinal products on cinacalcet

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

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

Calcium carbonate

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

Sevelamer

Co-administration of sevelamer (2,400 mg, three times a day) did not affect the pharmacokinetics of cinacalcet.

Pantoprazole

Co-administration of pantoprazole (80 mg, once daily) did not alter the pharmacokinetics of cinacalcet.

Effect of cinacalcet on other medicinal products

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

Desipramine

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

Dextromethorphan

Multiple doses of 50 mg cinacalcet increased the AUC of 30 mg dextromethorphan (metabolised primarily by CYP2D6) by 11-fold in CYP2D6 extensive metabolisers.

Warfarin

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

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

Midazolam

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

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

Fertility

There are no clinical data relating to the effect of cinacalcet on fertility. There were no effects on fertility in animal studies.

4.7 Effects on ability to drive and use machines

Cinacalcet may have major influence on the ability to drive and use machines, since dizziness and seizures have been reported by patients taking this medicinal product (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile

Secondary hyperparathyroidism, parathyroid carcinoma and primary hyperparathyroidism

Based on available data from patients receiving cinacalcet in placebo controlled studies and single-arm studies the most commonly reported adverse reactions were nausea and vomiting. Nausea and vomiting were mild to moderate in severity and transient in nature in the majority of patients. Discontinuation of therapy as a result of undesirable effects was mainly due to nausea and vomiting.

Tabulated list of adverse reactions

Adverse reactions, considered at least possibly attributable to cinacalcet treatment in the placebo controlled studies and single-arm studies based on best-evidence assessment of causality are listed below using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data).

Incidence of adverse reactions from controlled clinical studies and post-marketing experience

System organ class	Very Common	Common	Not known
Immune system disorders		Hypersensitivity reactions*	
Metabolism and nutrition disorders		Anorexia Decreased appetite	
Nervous system disorders		Seizures† Dizziness Paraesthesia Headache	
Cardiac disorders			Worsening heart failure* † QT prolongation and ventricular arrhythmia secondary to hypocalcaemia* †
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders		Upper respiratory infection Dyspnoea Cough	
Gastrointestinal disorders	Nausea Vomiting	Dyspepsia Diarrhoea Abdominal pain Abdominal pain - upper Constipation	
Skin and subcutaneous tissue disorders		Rash	
Musculoskeletal and connective tissue disorders		Myalgia Muscle spasms Back pain	
General disorders and administration site conditions		Asthenia	
Investigations		Hypocalcaemia† Hyperkalaemia Reduced testosterone levels†	

* see section description of selected adverse reactions

† see section 4.4

Description of selected adverse reactions

Hypersensitivity reactions

Hypersensitivity reactions including angioedema and urticaria have been identified during post-marketing use of cinacalcet. The frequencies of the individual preferred terms including angioedema and urticaria cannot be estimated from available data.

Hypotension and/or worsening heart failure

There have been reports of idiosyncratic cases of hypotension and/or worsening heart failure in cinacalcet-treated patients with impaired cardiac function in post-marketing safety surveillance, the frequencies of which cannot be estimated from available data.

QT prolongation and ventricular arrhythmia secondary to hypocalcaemia

QT prolongation and ventricular arrhythmia secondary to hypocalcaemia have been identified during post-marketing use of cinacalcet, the frequencies of which cannot be estimated from available data (see section 4.4).

Paediatric population

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium homeostasis, anti-parathyroid agents, ATC code: H05BX01

Mechanism of action

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

Reductions in PTH levels correlate with cinacalcet concentration.

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

Secondary hyperparathyroidism

Adults

Three, 6 month, double-blind, placebo-controlled clinical studies were conducted in ESRD patients with uncontrolled secondary HPT receiving dialysis (n=1,136). 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 care, and the results were consistent across the 3 studies. In each of the studies, the primary endpoint (proportion of patients with an iPTH \leq 250 pg/ml (\leq 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 \geq 30% reduction in iPTH levels, and this effect was consistent across the spectrum of baseline iPTH levels. The mean reductions in serum Ca x P, calcium, and phosphorus were 14%, 7% and 8%, respectively.

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

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

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

EVOLVE (EValuation Of Cinacalcet Therapy to Lower CardioVascular Events) was a randomised, double-blind clinical study evaluating cinacalcet versus placebo for the reduction of the risk of all-cause mortality and cardiovascular events in 3,883 patients with secondary HPT and CKD receiving dialysis. The study did not meet its primary objective of demonstrating a reduction in risk of all-cause mortality or cardiovascular events including myocardial infarction, hospitalisation for unstable angina, heart failure or peripheral vascular event (HR 0.93; 95% CI: 0.85, 1.02; p = 0.112). After adjusting for baseline characteristics in a secondary analysis, the HR for the primary composite endpoint was 0.88; 95% CI: 0.79, 0.97.

Paediatric population

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

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

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

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

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

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

Parathyroid carcinoma and primary hyperparathyroidism

In one study, 46 adult patients (29 with parathyroid carcinoma and 17 with primary HPT and severe hypercalcaemia (who had failed or had contraindications to parathyroidectomy) received cinacalcet for up to 3 years (mean of 328 days for patients with parathyroid carcinoma and mean of 347 days for patients with primary HPT). Cinacalcet was administered at doses ranging from 30 mg twice daily to 90 mg four times daily. The primary endpoint of the study was a reduction of serum calcium of ≥ 1 mg/dl (≥ 0.25 mmol/l). In patients with parathyroid carcinoma, mean serum calcium declined from 14.1 mg/dl to 12.4 mg/dl (3.5 mmol/l to 3.1 mmol/l), while in patients with primary HPT, serum calcium levels declined from 12.7 mg/dl to 10.4 mg/dl (3.2 mmol/l to 2.6 mmol/l). Eighteen (18) of 29 patients (62%) with parathyroid carcinoma and 15 of 17 subjects (88%) with primary HPT achieved a reduction in serum calcium of ≥ 1 mg/dl (≥ 0.25 mmol/l).

In a 28 week placebo-controlled study, 67 adult patients with primary HPT who met criteria for parathyroidectomy on the basis of corrected total serum calcium (> 11.3 mg/dl (2.82 mmol/l) but ≤ 12.5 mg/dl (3.12 mmol/l)), but who were unable to undergo parathyroidectomy were included. Cinacalcet was initiated at a dose of 30 mg twice daily and titrated to maintain a corrected total serum

calcium concentration within the normal range. A significantly higher percentage of cinacalcet treated patients achieved mean corrected total serum calcium concentration ≤ 10.3 mg/dl (2.57 mmol/l) and ≥ 1 mg/dl (0.25 mmol/l) decrease from baseline in mean corrected total serum calcium concentration, when compared with the placebo treated patients (75.8% versus 0% and 84.8% versus 5.9% respectively).

5.2 Pharmacokinetic properties

Absorption

After oral administration of cinacalcet, maximum plasma cinacalcet concentration is achieved in approximately 2 to 6 hours. Based on between-study comparisons, the absolute bioavailability of cinacalcet in fasted subjects has been estimated to be about 20-25%. Administration of cinacalcet with food results in an approximate 50-80% increase in cinacalcet bioavailability. Increases in plasma cinacalcet concentration are similar, regardless of the fat content of the meal.

At doses above 200 mg, the absorption was saturated probably due to poor solubility.

Distribution

The volume of distribution is high (approximately 1,000 litres), indicating extensive distribution. Cinacalcet is approximately 97% bound to plasma proteins and distributes minimally into red blood cells.

After absorption, cinacalcet concentrations decline in a biphasic fashion with an initial half-life of approximately 6 hours and a terminal half-life of 30 to 40 hours. Steady state levels of cinacalcet are achieved within 7 days with minimal accumulation. The pharmacokinetics of cinacalcet does not change over time.

Biotransformation

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

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

Elimination

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

Linearity/non-linearity

The AUC and C_{\max} of cinacalcet increase approximately linearly over the dose range of 30 to 180 mg once daily.

Pharmacokinetic/pharmacodynamic relationships

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

Special populations

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.

Paediatric population

The pharmacokinetics of cinacalcet was studied in paediatric patients with ESRD receiving dialysis aged 3 to 17 years of age. After single and multiple once daily oral doses of cinacalcet, plasma cinacalcet concentrations (C_{max} and AUC values after normalisation by dose and weight) were similar to those observed in adult patients.

A population pharmacokinetic analysis was performed to evaluate the effects of demographic characteristics. This analysis showed no significant impact of age, sex, race, body surface area, and body weight on cinacalcet pharmacokinetics.

Smoking

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

5.3 Preclinical safety data

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

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

Cinacalcet did not show any genotoxic or carcinogenic potential. Safety margins from the toxicology studies are small due to the dose-limiting hypocalcaemia observed in the animal models. Cataracts and lens opacities were observed in the repeat dose rodent toxicology and carcinogenicity studies, but were not observed in dogs or monkeys or in clinical studies where cataract formation was monitored. Cataracts are known to occur in rodents as a result of hypocalcaemia.

In *in vitro* studies, IC₅₀ values for the serotonin transporter and K_{ATP} channels were found to be 7 and 12 fold greater, respectively, than the EC₅₀ for the calcium-sensing receptor obtained under the same experimental conditions. The clinical relevance is unknown, however, the potential for cinacalcet to act on these secondary targets cannot be fully excluded.

In toxicity studies in juvenile dogs, tremors secondary to decreased serum calcium, emesis, decreased body weight and body weight gain, decreased red cell mass, slight decreases in bone densitometry parameters, reversible widening of the growth plates of long bones, and histological lymphoid changes (restricted to the thoracic cavity and attributed to chronic emesis) were observed. All of these effects were seen at a systemic exposure, on an AUC basis, approximately equivalent to the exposure in patients at the maximum dose for secondary HPT.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Cellulose, microcrystalline
Silica, colloidal anhydrous
Povidone
Crospovidone (type A)
Magnesium stearate

Film-coat

Hypromellose
Titanium dioxide (E171)
Triacetin
Indigo carmine aluminium lake (E132)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Cinacalcet Mylan 30 mg, 60 mg and 90 mg film-coated tablets

PVC/PVdC/Alu blisters of 28 film-coated tablets and perforated unit dose blisters of 28 x 1, 30 x 1 and 84 x 1 tablets.

Cinacalcet Mylan 30 mg film-coated tablets

HDPE bottle with polypropylene (PP) screw cap closure with induction sealing liner containing 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Mylan Pharmaceuticals Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

8. MARKETING AUTHORISATION NUMBERS

EU/1/15/1054/001
EU/1/15/1054/002
EU/1/15/1054/003
EU/1/15/1054/004
EU/1/15/1054/005
EU/1/15/1054/006
EU/1/15/1054/007
EU/1/15/1054/008
EU/1/15/1054/009
EU/1/15/1054/010
EU/1/15/1054/011
EU/1/15/1054/012
EU/1/15/1054/013
EU/1/15/1054/014

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 November 2015

Date of latest renewal: 24 September 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Mylan Hungary Kft
H-2900 Komárom, Mylan utca 1
Hungary

McDermott Laboratories Limited trading as Gerard Laboratories
35/36 Baldoyle Industrial Estate, Grange Road, Dublin 13
Ireland

Mylan Germany GmbH
Zweigniederlassung Bad Homburg v. d. Hoehe, Benzstrasse 1
Bad Homburg v. d. Hoehe
Hessen, 61352,
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Cinacalcet Mylan 30 mg film-coated tablets
cinacalcet

2. STATEMENT OF ACTIVE SUBSTANCE

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

28 film-coated tablets
28 x 1 film-coated tablets
30 x 1 film-coated tablets
84 x 1 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

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

Keep out of the sight and reach 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

Mylan Pharmaceuticals Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBERS

EU/1/15/1054/001 (28 tablets)
EU/1/15/1054/003 (28 x 1 tablets)
EU/1/15/1054/004(30 x 1 tablets)
EU/1/15/1054/011(84 x 1 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cinacalcet Mylan 30 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Cinacalcet Mylan 30 mg film-coated tablets
cinacalcet

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Mylan Pharmaceuticals Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Cinacalcet Mylan 30 mg film-coated tablets
cinacalcet

2. STATEMENT OF ACTIVE SUBSTANCE

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

100 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

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

Keep out of the sight and reach 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

Mylan Pharmaceuticals Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBERS

EU/1/15/1054/014

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cinacalcet Mylan 30 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL - BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Cinacalcet Mylan 30 mg film-coated tablets
cinacalcet

2. STATEMENT OF ACTIVE SUBSTANCE

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

100 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

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

Keep out of the sight and reach 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

Mylan Pharmaceuticals Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBERS

EU/1/15/1054/014

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL bottle with Blue Box -WITHOUT OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Cinacalcet Mylan 30 mg film-coated tablets
cinacalcet

2. STATEMENT OF ACTIVE SUBSTANCE

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

100 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

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

Keep out of the sight and reach 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

Mylan Pharmaceuticals Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBERS

EU/1/15/1054/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cinacalcet Mylan 30 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Cinacalcet Mylan 60 mg film-coated tablets
cinacalcet

2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 60 mg of cinacalcet (as hydrochloride).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

28 film-coated tablets
28 x 1 film-coated tablets
30 x 1 film-coated tablets
84 x 1 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

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

Keep out of the sight and reach 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

Mylan Pharmaceuticals Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBERS

EU/1/15/1054/005 (28 tablets)
EU/1/15/1054/006 (28 x 1 tablets)
EU/1/15/1054/007 (30 x 1 tablets)
EU/1/15/1054/012 (84 x 1 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cinacalcet Mylan 60 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Cinacalcet Mylan 60 mg film-coated tablets
cinacalcet

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Mylan Pharmaceuticals Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Cinacalcet Mylan 90 mg film-coated tablets
cinacalcet

2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 90 mg of cinacalcet (as hydrochloride).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

28 film-coated tablets
28 x 1 film-coated tablets
30 x 1 film-coated tablets
84 x 1 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

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

Keep out of the sight and reach 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

Mylan Pharmaceuticals Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBERS

EU/1/15/1054/008 (28 tablets)
EU/1/15/1054/009 (28 x 1 tablets)
EU/1/15/1054/010(30 x 1 tablets)
EU/1/15/1054/013(84 x 1 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cinacalcet Mylan 90 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Cinacalcet Mylan 90 mg film-coated tablets
cinacalcet

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Mylan Pharmaceuticals Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Cinacalcet Mylan 30 mg film-coated tablets
Cinacalcet Mylan 60 mg film-coated tablets
Cinacalcet Mylan 90 mg film-coated tablets
cinacalcet

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Cinacalcet Mylan is and what it is used for
2. What you need to know before you take Cinacalcet Mylan
3. How to take Cinacalcet Mylan
4. Possible side effects
5. How to store Cinacalcet Mylan
6. Contents of the pack and other information

1. What Cinacalcet Mylan is and what it is used for

Cinacalcet Mylan contains the active ingredient cinacalcet, which 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).

Cinacalcet Mylan is used in adults:

- to treat secondary hyperparathyroidism in adults with serious kidney disease who need dialysis to clear their blood of waste products
- to reduce high levels of calcium in the blood (hypercalcaemia) in adult patients with parathyroid cancer
- to reduce high levels of calcium in the blood (hypercalcaemia) in adult patients with primary hyperparathyroidism when removal of the parathyroid gland is not possible.

Cinacalcet Mylan is used in children aged 3 years to less than 18 years of age:

- to treat secondary hyperparathyroidism in patients with serious kidney disease who need dialysis to clear their blood of waste products, whose condition is not controlled with other treatments.

In primary and secondary hyperparathyroidism too much PTH is produced by the parathyroid glands. “Primary” means that the hyperparathyroidism is not caused by any other condition and “secondary” means that the hyperparathyroidism is caused by another condition, e.g. kidney disease. Both primary and secondary hyperparathyroidism 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. What you need to know before you take Cinacalcet Mylan

Do not take Cinacalcet Mylan

- if you are allergic to cinacalcet or any of the other ingredients of this medicine (listed in section 6).
- if you have low levels of calcium in your blood. Your doctor will monitor your blood calcium levels.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Cinacalcet Mylan.

Before you start taking Cinacalcet Mylan, 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;
- heart failure.

Cinacalcet Mylan reduces calcium levels. Life threatening events and fatal outcomes associated with low calcium levels (hypocalcaemia) have been reported in adults and children treated with cinacalcet.

Please tell your doctor if you experience any of the following which may be signs of low calcium levels: spasms, twitches, or cramps in your muscles, or numbness or tingling in your fingers, toes or around your mouth or seizures, confusion or loss of consciousness while being treated with Cinacalcet Mylan.

Low calcium levels can have an effect on your heart rhythm. Tell your doctor if you experience an unusually fast or pounding heartbeat, if you have heart rhythm problems, or if you take medicines known to cause heart rhythm problems, while taking Cinacalcet Mylan.

For additional information see section 4.

During treatment with Cinacalcet Mylan, tell your doctor:

- if you start or stop smoking, as this may affect the way Cinacalcet Mylan works.

Children and adolescents

Children under the age of 18 with parathyroid cancer or primary hyperparathyroidism must not take Cinacalcet Mylan.

If you are being treated for secondary hyperparathyroidism, your doctor should monitor your calcium levels before starting treatment with Cinacalcet Mylan and during treatment with Cinacalcet Mylan. You should inform your doctor if you experience any of the signs of low calcium levels as described above.

It is important that you take your dose of Cinacalcet Mylan as advised by your doctor.

Note:

For children who require doses lower than 30 mg, or who are unable to swallow tablets, other strengths/pharmaceutical forms of cinacalcet may be available.

Other medicines and Cinacalcet Mylan

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines particularly etelcalcetide or any other medicines that lower the level of calcium in your blood.

You should not take Cinacalcet Mylan together with etelcalcetide.

Tell your doctor if you are taking the following medicines.

Medicines such as these can affect how Cinacalcet Mylan works:

- medicines used to treat skin and fungal infections (ketoconazole, itraconazole and voriconazole)

- medicines used to treat bacterial infections (telithromycin, rifampicin and ciprofloxacin)
- a medicine used to treat HIV infection and AIDS (ritonavir)
- a medicine used to treat depression (fluvoxamine).

Cinacalcet Mylan may affect how medicines such as the following work:

- medicines used to treat depression (amitriptyline, desipramine, nortriptyline and clomipramine)
- a medicine used to relieve cough (dextromethorphan)
- medicines used to treat changes in heart rate (flecainide and propafenone)
- a medicine used to treat high blood pressure (metoprolol).

Cinacalcet Mylan with food and drink

Cinacalcet Mylan should be taken with or shortly after food.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Cinacalcet has not been tested in pregnant women. In case of pregnancy, your doctor may decide to modify your treatment, as cinacalcet might harm the unborn baby.

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

Driving and using machines

Dizziness and seizures have been reported by patients taking cinacalcet. If you experience these side effects do not drive or operate machines.

3. How to take Cinacalcet Mylan

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are unsure. Your doctor will tell you how much Cinacalcet Mylan you must take.

Cinacalcet Mylan must be taken orally, with or shortly after food. The tablets must be taken whole and are not to be chewed, crushed or 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 recommended starting dose for Cinacalcet Mylan in adults is 30 mg (one tablet) once per day.

The recommended starting dose of Cinacalcet Mylan for children aged 3 years to less than 18 years of age is no more than 0.20 mg/kg of body weight daily.

If you are being treated for parathyroid cancer or primary hyperparathyroidism

The recommended starting dose for Cinacalcet Mylan in adults is 30 mg (one tablet) twice per day.

If you take more Cinacalcet Mylan than you should

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

Possible signs of overdose include numbness or tingling around the mouth, muscle aches or cramps and seizures.

If you forget to take Cinacalcet Mylan

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

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

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Please tell your doctor immediately:

- If you start to get numbness or tingling around the mouth, muscle aches or cramps and seizures. These may be signs that your calcium levels are too low (hypocalcaemia).
- If you experience swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing (angioedema).

Other possible side effects:

Very common: may affect more than 1 in 10 people

- nausea and vomiting, these side effects are normally quite mild and do not last for long.

Common: may affect up to 1 in 10 people

- dizziness
- numbness or tingling sensation (paraesthesia)
- loss (anorexia) or decrease of appetite
- muscle pain (myalgia)
- weakness (asthenia)
- rash
- reduced testosterone levels
- high potassium levels in the blood (hyperkalaemia)
- allergic reactions (hypersensitivity)
- headache
- seizures (convulsions or fits)
- low blood pressure (hypotension)
- upper respiratory infection
- breathing difficulties (dyspnoea)
- cough
- indigestion (dyspepsia)
- diarrhoea
- abdominal pain, abdominal pain - upper
- constipation
- muscle spasms
- back pain
- low calcium levels in the blood (hypocalcaemia).

Not known: frequency cannot be estimated from the available data

- Hives (urticaria).
- Swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing (angioedema).
- Unusually fast or pounding heart beat which may be associated with low levels of calcium in your blood (QT prolongation and ventricular arrhythmia secondary to hypocalcaemia).

After taking cinacalcet a very small number of patients with heart failure had worsening of their condition and/or low blood pressure (hypotension).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cinacalcet Mylan

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister, carton or bottle after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Cinacalcet Mylan 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 cellulose, microcrystalline; silica, colloidal anhydrous; povidone; crospovidone; magnesium stearate.

The tablet coating contains hypromellose, titanium dioxide (E171), triacetin, indigo carmine (E132), iron oxide yellow (E172).

What Cinacalcet Mylan looks like and contents of the pack

Cinacalcet Mylan 30 mg film-coated tablets are 10.0 mm x 6.4 mm, green, oval, biconvex, bevelled edge tablets marked with M on one side of the tablet and CI30 on the other side.

Cinacalcet Mylan 60 mg film-coated tablets are 12.5 mm x 8.0 mm, green, oval, biconvex, bevelled edge tablets marked with M on one side of the tablet and CI60 on the other side.

Cinacalcet Mylan 90 mg film-coated tablets are 14.3 mm x 9.0 mm, green, oval, biconvex, bevelled edge tablets marked with M on one side of the tablet CI90 on the other side.

Cinacalcet Mylan 30 mg, 60 mg, 90 mg film-coated tablets are available in blister packs of 28 tablets and perforated unit dose blister packs of 28 x 1, 30 x 1 and 84 x 1 tablets.

Cinacalcet Mylan 30 mg film-coated tablets are available in plastic bottles of 100 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Mylan Pharmaceuticals Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

Manufacturers

Mylan Hungary Kft
H-2900 Komárom, Mylan utca 1
Hungary

McDermott Laboratories Limited trading as Gerard Laboratories
35/36 Baldoyle Industrial Estate, Grange Road, Dublin 13
Ireland

Mylan Germany GmbH
Zweigniederlassung Bad Homburg v. d. Hoehe, Benzstrasse 1
Bad Homburg v. d. Hoehe
Hessen, 61352,
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien

Mylan bvba/sprl
Tél/Tel: + 32 (0)2 658 61 00

Lietuva

Mylan Healthcare UAB
Tel: + 370 5 205 1288

България

Майлан ЕООД
Тел: +359 2 44 55 400

Luxembourg/Luxemburg

Mylan bvba/sprl
Tél/Tel: + 32 (0)2 658 61 00
(Belgique/Belgien)

Česká republika

Viatris CZ s.r.o.
Tel: + 420 222 004 400

Magyarország

Mylan EPD Kft.
Tel.: + 36 1 465 2100

Danmark

Viatris ApS
Tlf: +45 28 11 69 32

Malta

V.J. Salomone Pharma Ltd
Tel: + 356 21 22 01 74

Deutschland

Viatris Healthcare GmbH
Tel: +49 800 0700 800

Nederland

Mylan BV
Tel: +31 (0)20 426 3300

Eesti

BGP Products Switzerland GmbH Eesti filiaal
Tel: + 372 6363 052

Norge

Viatris AS
Tlf: + 47 66 75 33 00

Ελλάδα

Generics Pharma Hellas ΕΠΕ
Τηλ: +30 210 993 6410

Österreich

Arcana Arzneimittel GmbH
Tel: +43 1 416 2418

España

Viatriis Pharmaceuticals, S.L.U.
Tel: + 34 900 102 712

France

Viatriis Santé
Tél: + 33 4 37 25 75 00

Hrvatska

Viatriis Hrvatska d.o.o.
Tel: +385 1 23 50 599

Ireland

Mylan Ireland Limited
Tel: +353 1 8711600

Ísland

Icepharma hf.
Sími: +354 540 8000

Italia

Mylan Italia S.r.l.
Tel: + 39 02 612 46921

Κύπρος

Varnavas Hadjipanayis Ltd
Τηλ: +357 2220 7700

Latvija

Mylan Healthcare SIA
Tel: +371 676 055 80

Polska

Mylan Healthcare Sp. z.o.o.
Tel.: + 48 22 546 64 00

Portugal

Mylan, Lda.
Tel: + 351 214 127 200

România

BGP Products SRL
Tel: +40 372 579 000

Slovenija

Viatriis d.o.o.
Tel: + 386 1 23 63 180

Slovenská republika

Viatriis Slovakia s.r.o.
Tel: +421 2 32 199 100

Suomi/Finland

Viatriis Oy
Puh/Tel: +358 20 720 9555

Sverige

Viatriis AB
Tel: + 46 (0)8 630 19 00

United Kingdom (Northern Ireland)

Mylan IRE Healthcare Limited
Tel: +353 18711600

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.