PRODUCT MONOGRAPH

PrM-CINACALCET

Cinacalcet Tablets

30 mg, 60 mg, 90 mg Cinacalcet (as Cinacalcet Hydrochloride)

Calcimimetic agent

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PRM-CINACALCET

Cinacalcet Tablets
30 mg, 60 mg and 90 mg Cincalcet (as Cinacalcet Hydrochloride)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet/30 mg, 60 mg, 90 mg	*For a complete listing of the nonmedicinal ingredients see Dosage Forms, Composition and Packaging section*

INDICATIONS AND CLINICAL USE

M-CINACALCET (cinacalcet hydrochloride) is indicated for the treatment of secondary hyperparathyroidism (HPT) in patients with Chronic Kidney Disease (CKD) receiving dialysis.

M-CINACALCET controls parathyroid hormone levels, calcium and phosphorous levels, and the serum calcium-phosphorous product (Ca x P), in patients with CKD receiving dialysis.

M-CINACALCET is indicated for the reduction of hypercalcemia in patients with parathyroid carcinoma.

M-CINACALCET is indicated for the reduction of clinically significant hypercalcemia, as defined by relevant treatment guidelines, in patients with primary HPT for whom parathyroidectomy is not clinically appropriate or is contraindicated.

Geriatrics (>65 years of age)

No overall differences in safety and efficacy of M-CINACALCET were observed in patients greater or less than 65 years of age (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics** and **DOSAGE AND ADMINISTRATION**).

Pediatrics (<18 years of age)

The safety and efficacy of M-CINACALCET in pediatric patients have not been established. M-CINACALCET is not indicated for use in pediatric patients (see **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypocalcemia** and **Special Populations, Pediatrics**).

CONTRAINDICATIONS

M-CINACALCET (cinacalcet hydrochloride) is contraindicated in patients with hypersensitivity to any of the components of this product.

M-CINACALCET (cinacalcet hydrochloride) should not be initiated in patients with a serum calcium (corrected for albumin) below the lower limit of the normal range.

For a complete listing of the nonmedicinal ingredients see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

WARNINGS AND PRECAUTIONS

General

Adynamic bone disease may develop if intact parathyroid hormone (iPTH) levels are suppressed below 11.0 pmol/L. If iPTH levels decrease below 11.0 pmol/L in patients receiving dialysis treated with M-CINACALCET, the dose of M-CINACALCET and/or vitamin D sterols should be reduced or therapy discontinued.

Carcinogenesis and Mutagenesis

Cinacalcet Hydrochloride, administered orally for 104 weeks, showed no evidence of carcinogenic potential in mice and rats. Doses administered to mice and rats resulted in total systemic exposure (AUCs) 2 times the exposures observed in humans. The nature, incidence, and distribution of tumours in rats and mice of both sexes did not indicate any Cinacalcet Hydrochloride-induced carcinogenesis. A decreased incidence of thyroid C-cell adenomas was observed in rats treated with Cinacalcet Hydrochloride.

Cinacalcet Hydrochloride was negative in the Ames assay, chromosomal aberration assay, Chinese Hamster Ovary HGPRT forward mutation assay, and in the mouse micronucleus assay. These tests indicate Cinacalcet Hydrochloride has no genetic toxicity either with respect to DNA damage, including gene mutations, large scale chromosomal damage, recombination's or numerical changes.

Cardiovascular

Hypotension and/or Worsening Heart Failure

In post-marketing safety surveillance, 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 Hydrochloride 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 Hydrochloride - treated patients, 12% of placebo-treated patients, and heart failure occurred in 2% of patients receiving Cinacalcet Hydrochloride or placebo.

QT Prolongation and Ventricular Arrhythmias

Cases of QT prolongation and ventricular arrhythmia secondary to hypocalcemia have been reported in patients treated with Cinacalcet Hydrochloride. (see **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypocalcemia**).

Endocrine and Metabolism

Hypocalcemia

Life-threatening events and fatal outcomes associated with hypocalcemia have been reported in patients treated with Cinacalcet Hydrochloride including pediatric patients. M-CINACALCET is not indicated for use in pediatric patients (see **WARNINGS and PRECAUTIONS, Special Populations, Pediatrics**).

M-CINACALCET lowers serum calcium, and therefore patients should be carefully monitored for the occurrence of hypocalcemia (see Monitoring and Laboratory Tests). Potential manifestations of hypocalcemia include paresthesias, myalgias, cramping, tetany, and convulsions. Decreases in serum calcium can also prolong the QT interval, potentially resulting in ventricular arrhythmia. Cases of QT prolongation and ventricular arrhythmia secondary to hypocalcemia have been reported in patients treated with Cinacalcet Hydrochloride. Caution is advised in patients with other risk factors for QT prolongation such as patients with known congenital long QT syndrome or patients receiving drugs known to cause QT prolongation or lower serum calcium.

M-CINACALCET treatment should not be initiated in patients with CKD receiving dialysis if serum calcium is <2.1 mmol/L. If serum calcium falls below 2.1 mmol/L but remains above 1.88 mmol/L or if symptoms of hypocalcemia occur, calcium-containing phosphate binders and/or vitamin D sterols can be used to raise serum calcium. If hypocalcemia or symptoms of QT prolongation/ventricular arrhythmia persist, reduce the dose or discontinue administration of M-CINACALCET (see **DOSAGE AND ADMINISTRATION**).

In CKD patients receiving dialysis who were administered Cinacalcet Hydrochloride, 29% of patients had at least one serum calcium value less than 1.88 mmol/L. In a randomized, double-blind, placebo-controlled study in patients with secondary HPT and CKD receiving dialysis, in which patients were treated for up to 64 months (median duration of treatment was 21 months in the Cinacalcet Hydrochloride group and 17 months in the placebo group), 21% and 33% of Cinacalcet Hydrochloride patients had at least one serum calcium less than 1.88 mmol/L within the first 6 months and overall, respectively (see ADVERSE REACTIONS). In this trial, 1.1% of patients in the Cinacalcet Hydrochloride group and 0.1% in the placebo group permanently discontinued study drug due to hypocalcemia.

M-CINACALCET is not indicated for CKD patients not receiving dialysis. Investigational studies have shown that Cinacalcet Hydrochloride -treated CKD patients not receiving dialysis have an increased risk for hypocalcemia (serum calcium levels < 2.1 mmol/L) compared with Cinacalcet Hydrochloride -treated CKD patients receiving dialysis, which may be due to lower baseline calcium levels and/or the presence of residual kidney function.

Testosterone Levels

Testosterone levels are often below the normal range in patients with end stage renal disease. In a

clinical study of CKD patients receiving dialysis, free testosterone levels decreased by a median of 31.3% in the Cinacalcet Hydrochloride -treated patients and by 16.3% in the placebo-treated patients after 6 months of treatment. The clinical significance of these reductions in serum testosterone is unknown. An open label extension of this study showed no further reductions in free and total testosterone concentrations over a period of 3 years in Cinacalcet Hydrochloride -treated patients.

Hepatic

Due to the potential for 2- to 4-fold higher plasma levels of M-CINACALCET, patients with moderate to severe hepatic impairment should be closely monitored when initiating treatment (see **ACTION AND CLINICAL PHARMACOLOGY**).

Malignancies

In a randomized, double-blind, placebo-controlled clinical study of 3,883 CKD patients receiving dialysis, neoplastic events were reported in 2.9 and 2.5 patients per 100 patient-years in the Cinacalcet Hydrochloride and placebo-treatment groups, respectively. Serious neoplastic events were reported in 2.0 and 1.8 patients per 100 patient-years, in the Cinacalcet Hydrochloride and placebo-treatment groups, respectively. Fatal neoplastic events were reported in 0.6 patients per 100 patient-years for both groups. A causal relationship to Cinacalcet Hydrochloride has not been established.

Neurologic

Seizures

In clinical studies, seizures (primarily generalized or tonic-clonic) were observed in 1.4% (43/3049) of Cinacalcet Hydrochloride -treated patients and 0.7% (5/687) of placebo-treated patients. While the basis for the reported difference in seizure rate is not clear, the threshold for seizures is lowered by significant reductions in serum calcium levels. Therefore, serum calcium levels should be closely monitored in patients receiving M-CINACALCET, particularly in patients with a history of a seizure disorder.

Effect on the Ability to Drive and Use Machines

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

Sexual Function / Reproduction

Impairment of Fertility

M-CINACALCET had no effect on fertility in animal studies.

Special Populations

Pregnant Women

There are no studies on the use of M-CINACALCET in pregnant women. Cinacalcet Hydrochloride was not teratogenic in rabbits when given a dose of 0.4 times, on an area under the curve (AUC) basis, the maximum human dose for secondary HPT (180 mg once daily). There were no effects on fertility in males or females at exposures up to 4 times a human dose of 180 mg/day. In pregnant rats, there were slight decreases in body weight and food consumption at the highest dose. The non-teratogenic dose in rats was 4.4 times, on an AUC basis, the maximum dose for patients with secondary HPT (180 mg once daily). Decreased fetal weights were seen in rats at doses where dams had severe

hypocalcemia. M-CINACALCET has been shown to cross the placental barrier in rabbits. Although animal studies have shown no evidence of teratogenicity, M-CINACALCET should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women

It is not known whether M-CINACALCET is excreted in human milk. Studies in rats have shown that Cinacalcet Hydrochloride is excreted in the milk with a high milk to plasma ratio. A decision should be made whether to discontinue nursing or discontinue M-CINACALCET, taking into account the importance of M-CINACALCET to the mother.

Pediatrics (<18 years of age)

The safety and efficacy of M-CINACALCET in pediatric patients have not been established. M-CINACALCET is not indicated for use in pediatric patients.
A fatal outcome was reported in a pediatric clinical trial patient with severe hypocalcemia (see **WARNINGS and PRECAUTIONS, Endocrine and Metabolism, Hypocalcemia**).

Geriatrics (>65 years of age)

Of the 1136 patients enrolled in the Cinacalcet Hydrochloride phase 3 clinical program, 26% were > 65 years old, while 9% were > 75 years old. No overall differences in safety and efficacy of Cinacalcet Hydrochloride were observed in patients greater or less than 65 years of age (see **DOSAGE AND ADMINISTRATION**).

Monitoring and Laboratory Tests

Patients with CKD and Secondary Hyperparathyroidism
Serum calcium should be measured within 1 week and iPTH should be measured 1 to 4 weeks after initiation or dose adjustment of M-CINACALCET. Once the maintenance dose levels have been established, serum calcium and serum phosphorus should be measured approximately monthly,and PTH (iPTH) every 1 to 3 months (see DOSAGE AND ADMINISTRATION). Either the intact PTH (iPTH) or bio-active PTH (biPTH) may be used to measure plasma PTH levels. Treatment with M-CINACALCET does not alter the relationship between iPTH and biPTH.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Studies were conducted in patients with secondary hyperparathyroidism (HPT) and Chronic Kidney Disease (CKD) receiving dialysis, parathyroid carcinoma or primary HPT. M-CINACALCET (cinacalcet hydrochloride) was safe and generally well tolerated.

Hypocalcemia

M-CINACALCET lowers serum calcium, and therefore patients should be carefully monitored for the

occurrence of hypocalcemia (see Monitoring and Laboratory Tests). Potential manifestations of hypocalcemia include paresthesias, myalgias, cramping, tetany, and convulsions. Decreases in serum calcium can also prolong the QT interval, potentially resulting in ventricular arrhythmia. Cases of QT prolongation and ventricular arrhythmia secondary to hypocalcemia have been reported in patients treated with M-CINACALCET. Caution is advised in patients with other risk factors for QT prolongation such as patients with known congenital long QT syndrome or patients receiving drugs known to cause QT prolongation or lower serum calcium (see **WARNINGS AND PRECAUTIONS**).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Secondary Hyperparathyroidism in Patients with CKD Receiving Dialysis

In three double-blind placebo-controlled clinical trials, 1126 CKD patients receiving dialysis received study drug (656 Cinacalcet Hydrochloride, 470 placebo) for up to six months. Adverse events reported during the studies were typical for the dialysis patient population. The most frequently reported adverse events (incidence of at least 5% in the Cinacalcet Hydrochloride -treated group) are provided in Table 1. The most frequently reported events in the Cinacalcet Hydrochloride group were nausea and vomiting which were generally mild to moderate in severity, brief in duration, and infrequently led to discontinuation of study drug.

Table 1. Adverse Event Incidence (≥ 5%) in Patients Receiving Dialysis

Preferred Term	Placebo (n = 470) %	Cinacalcet Hydrochloride (n = 656) %
Nausea	19	31
Vomiting	15	27
Diarrhea	20	21
Headache	17	16
Myalgia	14	15
Pain Abdominal	14	12
Infection Upper Respiratory	13	12
Dizziness	8	10
Dyspnea	9	9
Pain Limb	10	9
Dyspepsia	8	8
Arthralgia	9	7
Fever	10	7
Fatigue	7	7
Hypertension	5	7
Hypotension	12	7
Edema Peripheral	7	7

Preferred Term	Placebo (n = 470) %	Cinacalcet Hydrochloride (n = 656) %
Asthenia	4	7
Cough	7	6
Pruritus	7	6
Anorexia	4	6
Thrombosis Vascular Access	7	6
Pain Chest, Non-Cardiac	4	6
Access Infection	4	5

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

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

Seizures were observed in 1.2% (8/656) of Cinacalcet Hydrochloride -treated patients and 0.4% (2/470) of placebo-treated patients in the three double-blind placebo-controlled clinical trials in CKD patients receiving dialysis (see **WARNINGS AND PRECAUTIONS**).

12-Month Experience with Cinacalcet Hydrochloride in Secondary Hyperparathyroidism

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

Parathyroid Carcinoma and Primary Hyperparathyroidism (HPT)

One hundred sixty patients with primary HPT or parathyroid carcinoma participated in Cinacalcet Hydrochloride clinical trials with exposure for up to 5.5 years.

The safety profile of Cinacalcet Hydrochloride in these patient populations is generally consistent with that seen in patients with CKD receiving dialysis. The most frequent adverse drug reactions in these patient populations were nausea and vomiting.

Seizures were observed in 0.7% (1/140) of Cinacalcet Hydrochloride -treated patients and 0% (0/46) of placebo-treated patients in the clinical trials in patients with primary HPT or parathyroid carcinoma (see **WARNINGS AND PRECAUTIONS**).

Laboratory Values

Serum calcium levels should be monitored in patients receiving M-CINACALCET (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). In the three phase 3 studies in patients with CKD receiving dialysis, 29% of patients receiving Cinacalcet

Hydrochloride had at least one serum calcium value < 1.88 mmol/L. In a randomized, double-blind, placebo- controlled study in patients with secondary HPT and CKD receiving dialysis, in which patients were treated for up to 64 months (median duration of treatment was 21 months in the Cinacalcet Hydrochloride group and 17 months in the placebo group), 21% and 33% of Cinacalcet Hydrochloride patients had at least one serum calcium less than 1.88 mmol/L within the first 6 months and overall, respectively.

Post-Market Adverse Drug Reactions

Additional adverse events have been identified during post-marketing use of M-CINACALCET. These adverse events include, but are not limited to, the following (listed by body system):

Cardiac disorders:	hypotension, worsening heart failure, QT prolongation and ventricular arrhythmia secondary to hypocalcemia
Gastrointestinal disorders:	abdominal pain upper, constipation
Immune system disorders:	hypersensitivity reactions (including angioedema and urticaria), severe hypersensitivity reaction
Metabolism and nutrition disorders:	hypocalcemia (some cases with fatal outcomes), hyperkalemia
Musculoskeletal and connective tissue disorders:	back pain, muscle spasms, calcium pyrophosphate deposition (CPPD; pseudogout)
Skin and subcutaneous tissue disorders:	rash

DRUG INTERACTIONS

Drug-Drug Interactions

Effect of M-CINACALCET on other drugs

Drugs metabolized by CYP450 2D6: M-CINACALCET (cinacalcet hydrochloride) is an inhibitor of CYP2D6. Therefore, dose adjustments of concomitant medications that are predominantly metabolized by CYP2D6 (eg, metoprolol) and particularly those with a narrow therapeutic index (eg, flecainide, vinblastine, thioridazine and most tricyclic antidepressants) may be required.

Desipramine: Concurrent administration of 90 mg M-CINACALCET with 50 mg desipramine, a tricyclic antidepressant metabolized primarily by CYP2D6, increased desipramine exposure by approximately 3.6-fold in CYP2D6 extensive metabolizers.

Amitriptyline: Concurrent administration of 25 mg or 100 mg M-CINACALCET with 50 mg amitriptyline, a tricyclic antidepressant metabolized in part by CYP2D6, increased exposure to

amitriptyline and its active metabolite nortriptyline by approximately 20% in extensive metabolizers of CYP2D6 enzymes. Dose reductions of amitriptyline may be required in some subjects receiving M-CINACALCET concurrently.

Drugs metabolized by other CYP enzymes

Based on *in vitro* data, M-CINACALCET is not an inhibitor of other CYP enzymes at concentrations achieved clinically, including CYP1A2, CYP2C9, CYP2C19, and CYP3A4. *In vitro* studies indicate that M-CINACALCET is not an inducer of CYP1A2, CYP2C19 and CYP3A4.

Midazolam: Co-administration of M-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 M-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.

Warfarin: M-CINACALCET does not affect the pharmacokinetics or pharmacodynamics (as measured by prothrombin time and clotting factor VII) of warfarin.

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

Effect of other drugs on M-CINACALCET

M-CINACALCET is metabolized by multiple cytochrome P450 enzymes, primarily CYP3A4 and CYP1A2, which limits the potential for other drugs to increase cinacalcet concentrations.

Ketoconazole: M-CINACALCET is metabolized in part by the enzyme CYP3A4. Co-administration of 200 mg bid of ketoconazole, a strong inhibitor of CYP3A4, caused an approximate 2-fold increase in cinacalcet exposure. Dose adjustment of M-CINACALCET may be required if a patient initiates or discontinues therapy with a strong CYP3A4 inhibitor (eg, ketoconazole, erythromycin, itraconazole) or inducer (eg, rifampin, phenytoin) of this enzyme.

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

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

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

Drug-Food Interactions

After oral administration of M-CINACALCET (cinacalcet hydrochloride), maximum plasma

concentration is achieved in approximately 2 to 6 hours. Administration of M-CINACALCET with food results in an approximate 50 to 80% increase in bioavailability. Increases in plasma concentration are similar, regardless of the fat content of the meal.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

M-CINACALCET (cinacalcet hydrochloride) can be used alone or in combination with vitamin D sterols and/or phosphate binders.

M-CINACALCET (cinacalcet hydrochloride) is administered orally. Tablets should be taken whole and should not be chewed, crushed, or divided. Take M-CINACALCET with food or shortly after a meal (see **DRUG INTERACTIONS**).

Secondary Hyperparathyroidism in Patients with Chronic Kidney Disease (CKD) Receiving Dialysis

The recommended starting oral dose of M-CINACALCET is 30 mg once daily. M-CINACALCET should be titrated every 2 to 4 weeks to a maximum dose of 180 mg once daily to achieve a target PTH between 1.5 to 5 times the upper limit of normal.

In CKD patients, PTH levels should be assessed at least 12 hours after dosing with M-CINACALCET.

Low serum calcium levels should be corrected before initiating therapy (see **WARNINGS and PRECAUTIONS, Endocrine and Metabolism, Hypocalcemia).**

During dose titration, serum calcium levels should be monitored frequently and if serum calcium levels decrease below the normal range, appropriate steps should be taken to increase serum calcium levels (see **WARNINGS AND PRECAUTIONS**). Calcium levels should be corrected for albumin or ionized calcium levels should be measured.

Parathyroid Carcinoma and Primary Hyperparathyroidism (HPT)

The recommended starting dose of M-CINACALCET for adults is 30 mg twice per day.

The dosage of M-CINACALCET should be titrated sequentially every 2 to 4 weeks through dosages of 30 mg twice daily, 60 mg twice daily, and 90 mg twice daily to reduce serum calcium levels. For further information on higher dosages (90 mg 3 or 4 times daily) see **CLINICAL TRIALS: Parathyroid Carcinoma and Primary HPT for Whom Parathyroidectomy is not a Treatment**

Option.

Special Populations

Geriatric patients

Age does not alter the pharmacokinetics of M-CINACALCET; no dose adjustment is required for geriatric patients.

Patients with renal impairment

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

Patients with hepatic impairment

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

OVERDOSAGE

Doses titrated up to 300 mg once daily have been safely administered to patients receiving dialysis. Overdosage of M-CINACALCET (cinacalcet hydrochloride) may lead to hypocalcemia. In the event of overdosage, patients should be monitored for signs and symptoms of hypocalcemia and appropriate measures taken to correct serum calcium levels (see **WARNINGS AND PRECAUTIONS**).

Since M-CINACALCET is highly protein bound, hemodialysis is not an effective treatment for overdosage of M-CINACALCET.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

Pharmacodynamics

Reduction in iPTH levels is correlated with cinacalcet concentration. The nadir in iPTH level occurs approximately 2 to 6 hours post dose, corresponding with the C_{max} of cinacalcet. After steady state is reached, serum calcium concentrations remain constant over the dosing interval.

Pharmacokinetics

Absorption and Distribution

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

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

Metabolism and Excretion

Cinacalcet is metabolized by multiple enzymes, primarily CYP3A4 and CYP1A2. The major circulating metabolites are inactive. After administration of a 75 mg radio-labeled dose to healthy volunteers, cinacalcet was rapidly and extensively metabolized 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 feces.

Special Populations and Conditions

Geriatric Patients

The pharmacokinetics of M-CINACALCET are similar in patients greater than, or less than, 65 years of age. No dosage adjustment based on age is necessary.

Pediatric Patients

The pharmacokinetics of M-CINACALCET have not been studied in patients < 18 years of age (see WARNINGS AND PRECAUTIONS**).**

Hepatic Insufficiency

Mild hepatic impairment did not notably affect the pharmacokinetics of M-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 (see **WARNINGS AND PRECAUTIONS**). Because doses are titrated for each subject based on safety and efficacy parameters, no additional dose adjustment is necessary for subjects with hepatic impairment.

Renal Insufficiency

The pharmacokinetic profile of M-CINACALCET in patients with mild, moderate, and severe renal insufficiency, and those on hemodialysis or peritoneal dialysis is comparable to that in healthy volunteers. No dosage adjustment based on renal function is necessary.

STORAGE AND STABILITY

Store at 15ºC to 30ºC. Keep in a safe place out of the reach and sight of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

M-CINACALCET (cinacalcet hydrochloride) tablets are composed of cinacalcet hydrochloride, Microcrystalline Cellulose, Low Substituted Hydroxy Propyl Cellulose, Lactose Monohyrate , Colloidal Silicon Dioxide, Magnesium Stearate and Purified water.
Tablets are coated with colour (Opadry® II green).

M-CINACALCET 30 mg tablets are formulated as light green, film-coated, oval-shaped tablets debossed with “HP” on one side and “363” on the other side, packaged in bottles of 30’s, 100’s and 500’s tablets.

M-CINACALCET 60 mg tablets are formulated as light green, film-coated, oval-shaped tablets debossed with “HP” on one side and “364” on the other side, packaged in bottles of 30’s, 100’s and 500’s tablets.

M-CINACALCET 90 mg tablets are formulated as light green, film-coated, oval-shaped tablets debossed with “HP” on one side and “365” on the other side, packaged in bottles of 30’s, 100’s and 500’s tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

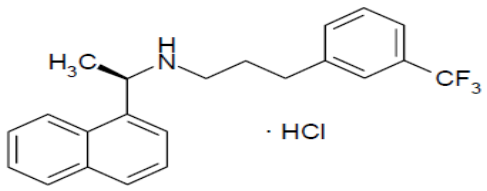
Drug Substance

Proper name: Cinacalcet Hydrochloride

Chemical name: *N*-[1-(R)-(-)-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]-1-aminopropane hydrochloride

Molecular weight: 393.87 g/mol

Structural formula:



Physicochemical properties:

Appearance: White to off-white powder.

Solubility: Solubility profile of Cinacalcet Hydrochloride in different solvents is tabulated below:

Solvent	**Observation**
Methanol	Freely soluble
DMF (Dimethylformamide)	Freely soluble
Dimethylsulphoxide	Freely soluble
Dichloromethane	Freely soluble
Ethanol	Freely soluble
THF (Tetrahydrofuran)	Freely soluble
Chloroform	Soluble
Acetone	Soluble
Isopropyl Alcohol	Sparingly soluble
Toluene	Sparingly soluble
Ethyl acetate	Sparingly soluble
Water	Insoluble

pH: The approximate aqueous solubility of Cinacalcet Hydrochloride at different pH conditions is summarized below:

Buffer pH	Solubility (mg/mL)
1.18	878.10^{-2}
4.11	153.10^{-1}
6.77	358.10^{-2}
7.51	906.10^{-3}
9.61	139.10^{-4}
10.86	259.10^{-5}

pKa: The theoretical pKa value is between 8.90 and 9.48

Melting point range: 177°C - 183°C

Hygroscopicity: Cinacalcet Hydrochloride is non-hygroscopic product.

Partition coefficient : The theoretical partition coefficient for Cinacalcet Hydrochloride is logP = 5.735 ± 0.331

CLINICAL TRIALS

Comparative Bioavailability

Fasting Conditions

A randomized, double blind, balanced, two treatment, two period, two sequence, single dose, two way crossover, truncated, bioequivalence study of M-Cinacalcet tablets 90 mg (cinacalcet hydrochloride; Mantra Pharma Inc., Canada) with [Pr]Sensipar® (cinacalcet hydrochloride) tablets 90 mg (Amgen Canada Inc., Mississauga, Ontario L5N 0A4) was conducted in 26 healthy human adult subjects, under fasting conditions. The results are summarized in the table below:

Cinacalcet (1 x 90 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-72} (ng.h/mL)	459.84 501.06 (46.81)	418.85 443.44 (35.97)	109.79	(98.14,122.81)
C_{max} (ng/mL)	52.66 56.10 (39.44)	46.94 50.27 (39.23)	112.19	(99.90,126.00)
T_{max}§ (h)	4.500 (1.50-5.50)	5.000 (2.00-6.52)		

*M-Cinacalcet (cinacalcet hydrochloride) 90 mg tablets (Mantra Pharma Inc., Canada)
† Sensipar® (cinacalcet hydrochloride) tablets 90 mg (Amgen Canada Inc.)
§ Expressed as the median (range) only

Secondary Hyperparathyroidism in Patients with Chronic Kidney Disease Receiving Dialysis

Three, 6-month, multicenter, randomized, double-blind, placebo-controlled clinical studies were conducted in CKD patients receiving dialysis with uncontrolled secondary HPT (n = 1136). The patient population consisted of both recently established and long-standing dialysis patients, with a duration of dialysis treatment that ranged from 1 to 359 months. Cinacalcet hydrochloride was administered either alone or in combination with vitamin D sterols; 34% of patients were not receiving vitamin D sterols at study entry. The majority (> 90%) of patients were receiving phosphate binders. Dose adjustments in phosphate binder therapy were permitted throughout the study. Vitamin D doses remained constant unless the patient developed hypercalcemia, hypocalcemia, or hyperphosphatemia. Patients continued on their previously prescribed drugs including: calcium channel blockers, ACE inhibitors, beta-blockers, hypoglycemics, and lipid lowering agents. Cinacalcet hydrochloride (or placebo) was initiated at a dose of 30 mg and titrated every 3 or 4 weeks to a maximum dose of 180 mg once daily to achieve an iPTH of 11 to 27.5 pmol/L (1.5 to 4 times the upper limit of normal). The severity of secondary HPT ranged from mild to severe (iPTH values of 29.8 to 1005.2 pmol/L), with mean (SE) baseline iPTH concentrations across the three studies of 78 (2.2) and 72 (2.0) pmol/L for the Cinacalcet hydrochloride and placebo groups, respectively. Significant reductions in iPTH, serum calcium- phosphorus product (Ca x P), calcium, and phosphorus were observed in the Cinacalcet hydrochloride treated patients compared with placebo-treated patients receiving standard of care, and the results were consistent across the three studies (Table 2). Mean iPTH and Ca x P by treatment group for the overall study population during the 6-month treatment period are presented in Figures 1 and 2.

Table 2. Effects of Cinacalcet hydrochloride on iPTH, Ca x P, Serum Calcium, and Serum Phosphorus in 6-month Phase 3 Studies (Patients Receiving Dialysis)

		Placebo (n = 205)	Study 1 Cinacalcet hydrochloride (n = 205)	Placebo (n = 165)	Study 2 Cinacalcet hydrochloride (n = 166)	Placebo (n = 101)	Study 3 Cinacalcet hydrochloride (n = 294)
iPTH	Baseline (pmol/L)	69 (2.9)	67 (2.5)	67 (2.5)	69 (3.1)	88 (5.1)	90 (4.3)
	Evaluation Phase (pmol/L)	74 (3.5)	41 (2.6)	73 (3.4)	38 (3.1)	90 (5.8)	56 (3.2)
	Percent Change	9.5 (2.8)	-38.4 (2.9)	8.7 (2.8)	-47.5 (2.8)	4.1 (3.4)	-40.3 (2.1)
	Patients Achieving Primary	4%	41%**	7%	46%**	6%	35%**
	Endpoint (iPTH ≤ 250 pg/mL; 27.5 pmol/L) (%) Patients Achieving ≥ 30%	11%	61%**	12%	68%**	10%	59%**
	Reduction in iPTH (%) Patients Achieving iPTH	9%	55%**	11%	56%**	9%	45%**
	≤ 300 pg/mL; (33 pmol/L) (%)						
Ca x P	Baseline ($mmol^2/L^2$)	4.9 (0.09)	5 (0.09)	4.9 (0.01)	4.9 (0.01)	4.9 (0.11)	4.8 (0.08)
	Evaluation Phase ($mmol^2/L^2$)	4.8 (0.08)	4.2 (1.0)	4.8 (0.01)	4.0 (0.10)	4.7 (0.10)	4.0 (0.07)
	Percent Change	1.5 (1.8)	-13.0 (1.7)**	-0.7 (1.9)	-16.7 (2.1)**	-1.4 (2.4)	-12.8 (1.7)**
Calcium	Baseline (mmol/L)	2.48 (0.025)	2.45 (0.025)	2.48 (0.025)	2.5 (0.025)	2.5 (0.025)	2.45 (0.0125)
	Evaluation Phase (mmol/L)	2.48 (0.025)	2.3 (0.025)	2.48 (0.025)	2.3 (0.025)	2.5 (0.025)	2.28 (0.025)
	Percent Change	0.5 (0.3)	-6.3 (0.6)**	0.3 (0.4)	-7.5 (0.6)**	0.9 (0.5)	-6.5 (0.6)**
Phosphorus	Baseline (mmol/L)	2 (0.032)	2.03 (0.032)	2 (0.032)	1.97 (0.1)	1.97 (0.032)	1.97 (0.032)
	Evaluation Phase (mmol/L)	1.94 (0.032)	1.84 (0.032)	1.94 (0.1)	1.74 (0.032)	1.87 (0.032)	1.78 (0.032)
	Percent Change	1.1 (1.8)	-7.1 (1.7)**	-0.9 (1.9)	-9.9 (2.0)**	-2.2 (2.5)	-7.2 (1.6)*

* $p < 0.05$; ** $p < 0.001$ compared to placebo

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

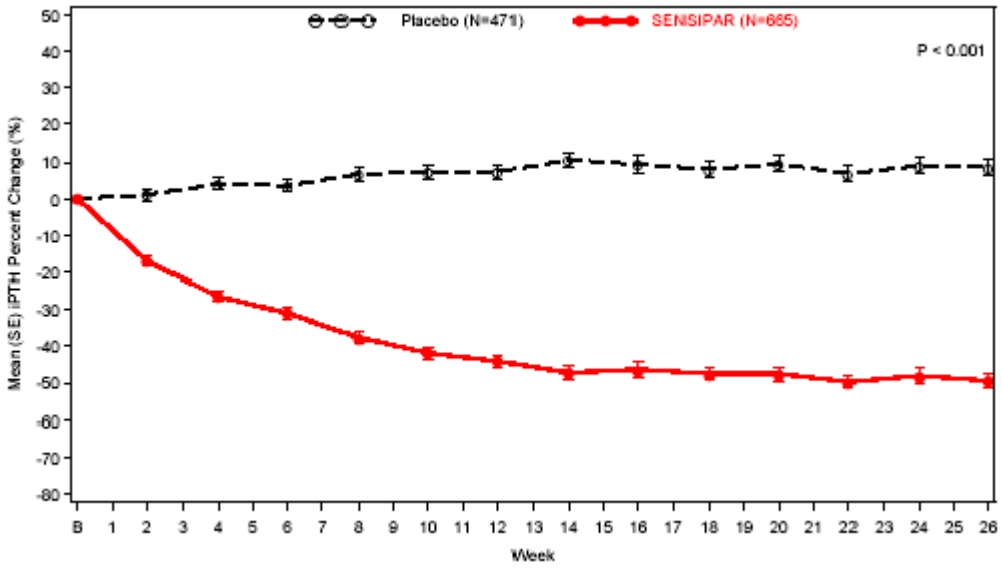
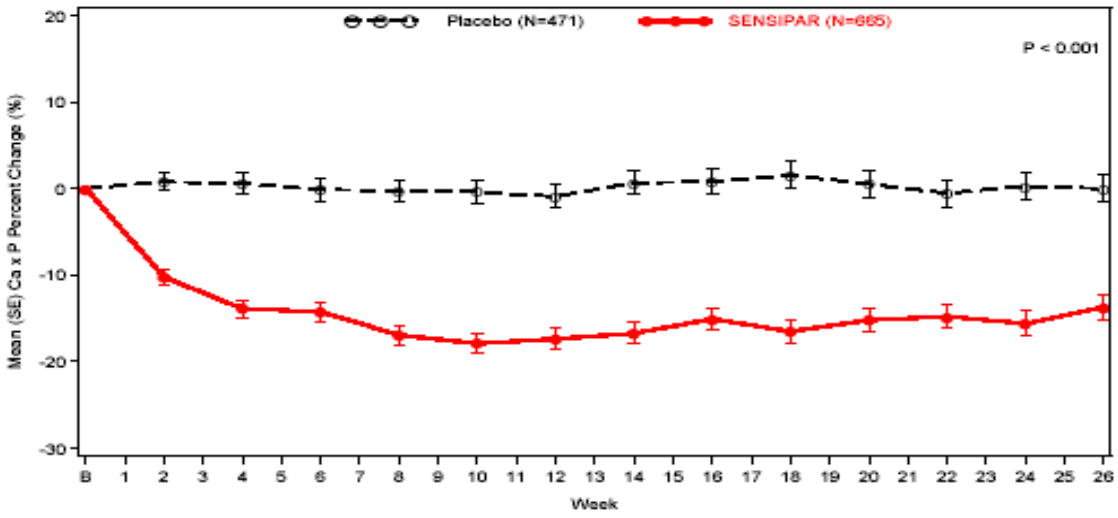


Figure 2. Mean (SE) Percent Change from Baseline in Ca x P (Pooled Phase 3 Studies)



Reductions in iPTH and Ca x P occurred within 2 weeks and were maintained for up to 12 months of treatment. Cinacalcet hydrochloride decreased iPTH and Ca x P levels regardless of disease severity (ie, baseline iPTH value), dialysis modality (PD versus HD), duration of dialysis, and whether or not vitamin D sterols were administered. Approximately 60% of patients with mild (iPTH ≥ 33 to ≤ 55 pmol/L), moderate (iPTH > 55 to 88 pmol/L), or severe (iPTH > 88 pmol/L) secondary HPT achieved a ≥ 30% reduction in iPTH levels. Cinacalcet hydrochloride treatment reduced iPTH and Ca x P regardless of pre-treatment Ca x P levels.

Bone Health

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

Cardiovascular

A randomized, double-blind placebo-controlled study of 3,883 patients with secondary HPT and CKD receiving dialysis, evaluated Cinacalcet hydrochloride vs. placebo for the reduction of the risk of all- cause mortality and cardiovascular events. The study did not meet its primary objective of demonstrating a reduction in risk of all-cause mortality or cardiovascular events including myocardial infarction, hospitalization for unstable angina, heart failure or peripheral vascular event (HR 0.93; 95% CI: 0.85, 1.02; p = 0.112).[19]

Parathyroid Carcinoma and Primary HPT for Whom Parathyroidectomy is not a Treatment Option

Forty-six patients participated in the clinical trial supporting the indications in patients with parathyroid carcinoma (29 patients) and primary HPT who had failed or had contraindications to surgery (17 patients), ie, for whom parathyroidectomy is not a treatment option. Patients were treated for as long as 3 years. The mean duration of follow-up was 328 days for patients with parathyroid carcinoma and 347 days for patients with primary HPT. Cinacalcet hydrochloride was administered at dosages ranging from 30 mg twice daily to 90 mg four times daily (13 patients received the 90 mg four times daily dosage). The primary endpoint of the study was a reduction of serum calcium of ≥ 1 mg/dL (0.25 mmol/L). Eighteen of 29 patients (62%) with parathyroid carcinoma and 15 of 17 patients (88%) with primary HPT achieved 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 at baseline to 12.4 mg/dL (3.5 mmol/L to 3.1 mmol/L) at the end of the titration phase (up to 16 weeks). In patients with primary HPT, serum calcium levels declined from 12.7 mg/dL at baseline to 10.4 mg/dL (3.2 mmol/L to 2.6 mmol/L) at the end of the titration phase (up to 16 weeks).

DETAILED PHARMACOLOGY

Preclinical Studies

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

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PART III: CONSUMER INFORMATION

PrM-CINACALCET
Cinacalcet Tablets
30 mg, 60 mg and 90 mg Cincalcet

(as Cinacalcet Hydrochloride)

This leaflet is part III of a three-part "Product Monograph" published when M-CINACALCET was approved for sale in Canada and is designed specifically-for consumers. This leaflet is a summary and will not tell you everything about M-CINACALCET. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

M-CINACALCET is used:

- to treat secondary hyperparathyroidism (high-per-pear-uh-THIGH-royd-izm) in patients with chronic kidney disease (CKD) receiving dialysis;
- to reduce high levels of calcium in the blood (hypercalcemia) in patients with parathyroid cancer;
- to reduce high levels of calcium in the blood (hypercalcemia) in patients with primary hyperparathyroidism when removal of the gland(s) is not possible.

What it does:

Four small glands located behind the thyroid gland in your neck are called parathyroid glands. They make a hormone called parathyroid hormone (PTH). Normally, PTH makes sure you have just enough calcium and phosphorus in your blood to keep your bones, heart, muscles, nerves and blood vessels working well.

Secondary hyperparathyroidism

When your kidneys are working, PTH keeps your calcium and phosphorus levels normal by moving the right amounts of calcium and phosphorus in and out of your bones. Chronic Kidney Disease (CKD) can cause a condition called secondary hyperparathyroidism.

When your kidneys aren't working properly, the calcium and phosphorus balance in your body is upset, and your parathyroid glands send out too much PTH to your body. This can cause bone disease and also may be a risk factor for heart disease and abnormal calcification of blood vessels and other parts of the body. M-CINACALCET treats secondary hyperparathyroidism by lowering PTH. This helps keep calcium and phosphorus within proper levels.

Parathyroid carcinoma/Primary hyperparathyroidism

Primary hyperparathyroidism is caused by an overactive, enlarged parathyroid gland (or glands), occasionally due to cancer of the parathyroid gland. In primary hyperparathyroidism, your parathyroid glands send out too much PTH to your body and your blood level of calcium becomes high. M-CINACALCET lowers PTH by telling your parathyroid glands to stop releasing too much PTH into your blood.

This helps lower your blood calcium levels.

When it should not be used:
You should not take M-CINACALCET if you are hypersensitive (allergic) to any of the ingredients in the tablet.
You should not take M-CINACALCET if your blood calcium level is below the normal range.

What the medicinal ingredient is:

Cinacalcet hydrochloride

What the important nonmedicinal ingredients are:

Microcrystalline cellulose, Low Substituted Hydroxy Propyl Cellulose, Lactose Monohyrate, Colloidal silicon dioxide, Magnesium stearate and Purified water. Tablets are coated with colour (Opadry® II green).

What dosage forms it comes in:
M-CINACALCET is available as small, light green tablets packaged in bottles of 30's, 100's and 500's tablets. Each tablet contains 30 mg, 60 mg, or 90 mg of cinacalcet.

WARNINGS AND PRECAUTIONS

BEFORE you use M-CINACALCET talk to your doctor or pharmacist if:

1. You have or had seizures (convulsions). The risk of having a seizure is greater if you have had seizures before.
2. You have or had heart problems (low blood pressure or worsening heart failure).
3. You have or had liver problems.
4. You have lower blood calcium levels.

5. You are pregnant, breastfeeding, or plan to do so.

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

M-CINACALCET is not recommended for patients with CKD not receiving dialysis.

M-CINACALCET should not be used in children. A death was reported in an adolescent clinical trial patient with very low calcium levels in the blood (hypocalcemia).

INTERACTIONS WITH THIS MEDICATION

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Drugs that may interact with M-CINACALCET include: ketoconazole, erythromycin, itraconazole, metoprolol, flecainide, vinblastine, thioridazine, rifampin, phenytoin, or medicines such as tricyclic antidepressants (desipramine, amitriptyline).

PROPER USE OF THIS MEDICATION

It is important to take M-CINACALCET exactly as your doctor has instructed you. Your doctor will tell you how much M-CINACALCET to take. Your doctor will order regular blood tests to measure how you are responding to M-CINACALCET and may increase or decrease your dose based on your PTH, calcium, and phosphate levels.

Usual Adult Dose:

If you have secondary hyperparathyroidism the usual starting dose for M-CINACALCET is one 30 mg tablet once daily.

If you have parathyroid cancer or primary hyperparathyroidism, the usual starting dose for M-CINACALCET is one 30 mg tablet twice daily.

M-CINACALCET is taken with food or right after a meal. M-CINACALCET tablets must be taken whole and are not to be chewed, crushed, or divided. It's best to take M-CINACALCET at the same time each day. M-CINACALCET can be used alone or in combination with vitamin D sterols and/or phosphate binders.

Overdose:

Tell your doctor or contact your regional Poison Control Centre immediately if you think you took more than the recommended dose of M-CINACALCET.

If you think you have taken too much M-CINACALCET, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

Do not take a double dose to make up for forgotten daily doses. If you have forgotten a dose of M-CINACALCET, you should take your next daily dose as normal.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

All medicines have side effects.

If you have any of the following side effects while taking M-CINACALCET, you should tell your doctor right away.

- Nausea and vomiting. These are the most common side effects seen with M-CINACALCET treatment. This may make it difficult to take your medicines.
- Diarrhea, muscle pain and back pain. These side effects also are commonly reported.
- Rash or hypersensitivity (allergic reactions). Cases of rash have been commonly reported, while cases of hypersensitivity (allergic reactions) have been uncommonly reported.
- Hives (urticaria) is very rarely reported.
- Swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing (angioedema) is also very rarely reported.
- Joint pain (pseudogout)

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/ effect		Talk with your doctor or pharmacist		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Common	Diarrhea	√		
	Hypocalcemia/ low calcium level (symptoms may include: unusually fast or pounding heart beat numbness/ tingling around mouth, muscle aches/cramps, seizures)			√
Uncommon	Seizures (convulsions)			√
	Hypersensitivity/ allergic reactions (symptoms may include: skin rash, hives, itching, difficulty breathing, swelling of face, tongue or throat)			√
Very Rare	Low blood pressure (symptoms may include: dizziness, feeling lightheaded, feeling tired)			√
	Worsening heart failure (symptoms may include: increased difficulty breathing, swelling of the legs, ankles and feet, feeling more tired)			√
	Angioedema (swelling of the face, lips, mouth, tongue or throat)			√
	Severe hypersensitivity/ allergic reactions (symptoms may include: skin rash, hives, itching, difficulty breathing or swallowing, swelling of face, tongue or throat)			√

This is not a complete list of side effects. For any unexpected effects while taking M-CINACALCET, contact your doctor or pharmacist.

HOW TO STORE IT

Store M-CINACALCET tablets at room temperature (15°C to 30°C). Keep in a safe place out of the reach and sight of children.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- **Visiting the web page on Adverse Reaction Reporting (**https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html**) for information on how to report online, by mail or by fax; or**
- **Calling toll-free at 1-866-234-2345.**

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about M-Cinacalcet:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp);, or by calling 1-877-726-2707.

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