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Cinacalcet Hydrochloride

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Contents

Abstract

▲ Oral cinacalcet hydrochloride (HCl) [Sensipar®, Mimpara®] is the first in a new class of therapeutic agents, the calcimimetics, and has a novel mechanism of action. It directly modulates the principal regulator of parathyroid hormone (PTH) secretion, namely the calcium-sensing receptor (CaR) on the chief cells in the parathyroid gland. Cinacalcet HCl reduces circulating PTH levels by increasing the sensitivity of the CaR to extracellular calcium.

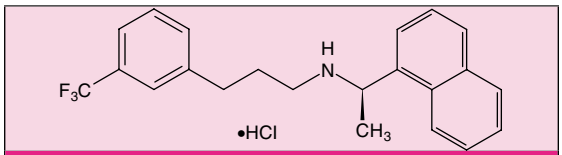
▲ In three pivotal phase III, 26-week, randomised, double-blind, multicentre trials in chronic kidney disease (CKD) patients (n = 1136) on dialysis with uncontrolled secondary hyperparathyroidism (HPT), a significantly higher proportion of oral cinacalcet HCl 30–180 mg/day than placebo recipients achieved a reduction in intact PTH levels to ≤250 pg/mL. Cinacalcet HCl treatment also simultaneously lowered serum calcium and phosphorus, and calcium-phosphorous product levels.

▲ Notably, cinacalcet HCl proved effective in a broad range of CKD patients on dialysis with uncontrolled secondary HPT, regardless of disease severity, duration of dialysis treatment, dialysis modality, race, age, gender, or concurrent phosphate binder or vitamin D sterol use.

▲ Cinacalcet HCl (60–360 mg/day) also reduced elevated serum calcium levels by ≥1 mg/dL in 15 of 21 (71%) patients with parathyroid carcinoma in an open-label, multicentre, dose-titration trial.

▲ Cinacalcet HCl was generally well tolerated in clinical trials. Most treatment-emergent adverse events were mild to moderate in severity.

Features and properties of cinacalcet hydrochloride (Sensipar®, Mimpara®, AMG 073, KRN 1493, NPS 1493)	
Indications	
Secondary hyperparathyroidism (HPT) in patients with chronic kidney disease on dialysis; hypercalcaemia in patients with parathyroid carcinoma	
Mechanism of action	
Allosteric modulator of the calcium-sensing receptor (CaR); calcimimetic	Binds to CaR, increasing sensitivity of the CaR to extracellular calcium, and thereby reducing parathyroid hormone secretion and serum calcium and phosphorous levels
Recommended dosage (oral)	
Secondary HPT	30mg titrated sequentially to 60, 90, 120 or 180mg once daily
Parathyroid carcinoma	30mg twice daily (bid) titrated sequentially to 60 or 90mg bid or 90mg three or four times daily as necessary to normalise serum calcium level
Pharmacokinetic profile (oral)	
Median maximum plasma concentration (25–200 mg/day for 7 days)	7.2–78.3 ng/mL
Mean time to maximum plasma concentration (25–100mg single dose)	2–6h
Treatment-emergent adverse events (>2% difference vs placebo)	
Nausea, vomiting	
Laboratory abnormalities (>2% difference vs placebo)	
Hypocalcaemia (serum calcium <8.4 mg/dL)	



Cinacalcet hydrochloride

Secondary hyperparathyroidism (HPT) is a frequent complication associated with chronic kidney disease (CKD) that is characterised by elevations in circulating parathyroid hormone (PTH), excessive parathyroid gland hyperplasia and abnormalities in bone mineral metabolism (e.g. in serum calcium, phosphorous and/or calcium-phosphorous product [Ca × P] levels). The disease is associated with significant morbidity and mortality, including renal osteodystrophy (characterised by bone disease, bone pain and hip fractures), and vascular and soft tissue calcification.[1,2] Elevated Ca × P levels, which occur in 50% of dialysis patients,[3] are associated with an increased risk of vascular calcification and cardiovascular mortality.[4] Indeed, cardiovascular mortality is significantly higher in dialysis patients than in the general population, accounting for nearly 50% of deaths in dialysis patients.[5] Traditional therapies for secondary HPT, namely calcium-containing phosphate binders and vitamin D sterols, may contribute to hypercalcaemia and/or hyperphosphataemia.[6] As a consequence, physicians must often balance the use of these traditional therapies with the potential for increased morbidity and mortality.[6]

In light of the significant impact that disturbances in bone and mineral metabolism due to secondary HPT have in CKD patients, the US National Kidney Foundation Disease Outcome Quality Initiative (NKF-K/DOQI™)[7] recommends individual integrated clinical management plans for patients with stage 3 (glomerular filtration rate [GFR] 30–59 mL/min/1.73m^2), stage 4 (GFR 15–29 mL/min/1.73m^2) or stage 5 CKD (GFR <15 mL/min/1.73m^2 or on dialysis). For instance, in secondary HPT patients with stage 5 CKD, the established target levels for the various biochemical markers of secondary PTH are: intact PTH (iPTH) 150–300 pg/mL, calcium 8.4–9.5 mg/dL, phosphorous 3.5–5.5 mg/dL and Ca × P <55 mg^2/dL^2. Despite the availability of traditional phosphate binders and vitamin D sterol therapies, very few patients achieve these recommended target levels. A recent retrospective analysis of more than 4000 stage 5 CKD patients on dialysis receiving traditional therapies showed that only 8% of patients achieved all four key K/DOQI™ targets during the first 6 months' follow-up and only 1% met all four targets over the entire 12-month analysis period.[8] These findings suggest that new treatment strategies may be required for the adequate management of secondary HPT.

Parathyroid carcinoma, a rare but devastating malignancy, is also associated with markedly elevated serum calcium and PTH levels.[9] Management of parathyroid carcinoma is challenging, with limited treatment options.[9] Surgical resection is the primary therapy for treating hypercalcaemia in patients with parathyroid carcinoma, but the carcinoma tends to recur within 3 years. In addition, chemotherapy and radiation therapy also often yield poor results.[9] Thus, there is a need for new calcium-lowering agents for managing hypercalcaemia in these patients.

Calcimimetics are a new class of agents that potentiate the effect of extracellular calcium on the calcium-sensing receptor (CaR), thereby reducing PTH levels. The secretion of PTH is regulated by the level of ionised calcium in the blood that, in turn, is regulated via a G-protein-coupled transmembrane cell surface calcium receptor, the CaR, which is located primarily on the chief cells of the parathyroid gland.[10] Activation of this receptor by increased levels of extracellular calcium inhibits PTH secretion by transiently increasing intracellular calcium levels.[6] The CaR is also involved in enhancing urinary calcium excretion and regulating parathyroid cell proliferation.[6] As the primary mechanism regulating PTH secretion, the CaR represents an attractive new target for treatment of diseases associated with high levels of PTH and calcium, such as secondary HPT and parathyroid carcinoma, as well as primary HPT.

Oral cinacalcet hydrochloride (HCl) [Sensipar®, Mimpara®][1] is the first calcimimetic approved in the US,[11] Canada[12] and Europe[13] for the treatment of secondary HPT in CKD patients on dialysis (stage 5 CKD). It is also approved in the US[11] and Europe[13] for the treatment of hypercalcaemia in those with parathyroid carcinoma. This review focuses on the pharmacological properties, efficacy and tolerability of oral cinacalcet HCl for the treatment of secondary HPT in CKD patients on dialysis and its use in the treatment of hypercalcaemia in those with parathyroid carcinoma. In addition, its use in patients with primary HPT and in secondary HPT patients with stage 3 or 4 CKD is briefly discussed.

1. Pharmacodynamic Profile

In Vitro and Animal Studies

- In the presence of physiological levels of extracellular calcium (5 mmol/L), cinacalcet HCl produced a dose-dependent, positive, allosteric modification of the sensitivity of the CaR to extracellular calcium, thereby resulting in dose-dependent decreases in PTH and concomitant reductions in Ca × P.[14] Cinacalcet HCl increased the concentration of cytoplasmic calcium in cultured human embryonic kidney (HEK 293) cells.[14]
- The R-enantiomer is approximately 75-fold more active than the S-enantiomer.[14] Respective mean concentrations required to produce a 50% increase (EC_{50}) in cytoplasmic calcium with each enantiomer were 51 and 3800 nmol/L in cultured HEK 293 cells expressing the human parathyroid CaR.
- In HEK 293 cells treated with cinacalcet HCl 10 or 100 nmol/L, the EC_{50} value for calcium was reduced from 0.87 nmol/L in the absence of cinacalcet HCl to 0.74 and 0.58 mmol/L.[14]
- Addition of cinacalcet HCl 10 or 100 nmol/L to cultured bovine parathyroid cells reduced the concentration of extracellular calcium required to produce a 50% inhibition of PTH secretion from 1.01 mmol/L in the absence of cinacalcet HCl to 0.60 and 0.41 mmol/L.[14]
- Cinacalcet HCl 10 or 100 nmol/L also decreased the EC_{50} of extracellular calcium required to stimulate calcitonin secretion in rat medullary thyroid carcinoma cells (2.03 mmol/L reduced to 1.63 and 1.07 mmol/L).[14]
- Oral calcimimetics, including R-568 and cinacalcet HCl (administered by gavage), inhibited hyperplasia in the parathyroid gland and reduced circulating PTH and serum calcium levels compared with control animals in rat models of chronic renal insufficiency.[15-18] Furthermore, in a rat model of CKD and secondary HPT, cinacalcet HCl reduced parathyroid cell proliferation and caused regression of established parathyroid hyperplasia (abstract presentation).[19]
- Moreover, oral cinacalcet HCl 1 or 10 mg/kg/day for 26 days did not induce aortic calcification in a rat model of secondary HPT, whereas treatment with subcutaneous vitamin D_3 0.1 μg/day resulted in aortic calcification.[20]

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

- In early single- and multiple-dose studies in secondary HPT patients with CKD and on dialysis, cinacalcet HCl treatment provided a rapid, dose-dependent reduction in elevated plasma PTH levels from baseline levels that persisted for up to 24 hours.[21] Maximum PTH reductions of 57%, 59%, 59% and 72% were observed following single oral doses of cinacalcet 25, 50, 75 or 100mg, respectively (n = 6–8 per active treatment group), compared with no change in mean plasma PTH level throughout the 24-hour assessment period in placebo recipients (n = 12). The PTH nadir occurred approximately 4 hours after dose administration.[21] Subsequent studies have confirmed that the PTH nadir occurs 2–6 hours after administration of cinacalcet HCl (see section 5).[11]
- In this same report, recipients of once-daily cinacalcet HCl 25 or 50mg for 8 days experienced an approximately 30% reduction in plasma PTH levels

1 The use of trade names is for identification purposes only and does not imply endorsement.

from mean baseline levels of 527–824 pg/mL, whereas there was no change in those who received placebo or cinacalcet HCl 10mg once daily (both cinacalcet HCl groups $p < 0.05$ vs placebo).[21] At day 8, serum calcium levels were also reduced from baseline levels (mean 9.5–10.2 mg/dL) by approximately 10% in cinacalcet HCl 50 mg/day recipients and were slightly reduced from baseline in the cinacalcet HCl 25 mg/day group. Serum calcium levels remained unchanged from baseline in the cinacalcet HCl 10 mg/day and placebo groups.[21]

For further data regarding longer-term treatment with oral cinacalcet in patients with secondary HPT on dialysis or parathyroid carcinoma see section 3.

2. Pharmacokinetic Profile

The pharmacokinetic properties of oral cinacalcet HCl have been investigated in healthy volunteers,[22,23] in CKD patients on dialysis[23-25] and in patients with liver dysfunction;[22] some data are based on the manufacturer's prescribing information.[11]

- Cinacalcet HCl is rapidly and extensively absorbed, with maximum plasma concentrations achieved after approximately 2–6 hours after a single dose of 25–100mg.[11] Steady-state plasma concentrations of cinacalcet HCl are achieved within 7 days.[11]
- In a 7-day, randomised, double-blind, dose-escalating, placebo-controlled study in CKD patients on haemodialysis, absorption of cinacalcet was dose-dependent over the range 25–200 mg/day (n = 11–16 per group).[24] No further increases in plasma levels of cinacalcet HCl occurred at higher dosages of up to 300 mg/day (n = 7–12 per group). After 7 days' treatment with cinacalcet HCl 25–200 mg/day, median maximum plasma concentration (C_{max}) values ranged from 7.2 to 78.3 ng/mL and median area under the plasma concentration-time curve (AUC) from 0 to 24 hours values ranged from 76.8 to 900 ng • h/mL.[24]
- The accumulation ratio of cinacalcet HCl after multiple doses is approximately 2 with once-daily administration and approximately 2–5 with twice-daily administration.[11]
- Cinacalcet HCl has a high volume of distribution (approximately 1000L), indicating extensive distribution.[11] The drug is approximately 93–97% bound to plasma proteins.[11] The ratio of blood : plasma concentration is 0.80 at a blood concentration of cinacalcet HCl 10 ng/mL.[11]
- Systemic exposure to cinacalcet is increased in the fed state compared with the fasted state (see also section 5).[11] C_{max} and AUC from zero to infinity (AUC_∞) values increased by 82% and 68% when cinacalcet HCl was administered with a high-fat meal and by 65% and 50% when administered with a low-fat meal.[11]
- Cinacalcet HCl is rapidly and extensively metabolised in the liver, mainly by the cytochrome P450 (CYP) isoenzymes CYP3A4, CYP2D6 and CYP1A2, to several metabolites (including *N*-dealkylation and β-oxidation derivatives) with little or no activity.[11] The primary route of elimination of these metabolites is in the urine, with approximately 80% of a single 75mg radiolabelled dose recovered in the urine and 15% in the faeces.[11]
- After absorption, cinacalcet HCl concentrations decline in a biphasic manner, with a terminal elimination half-life ($t_{1/2}\beta$) of 30–40 hours.[11]
- After 7 days' treatment with cinacalcet HCl 25–200mg once daily, median oral clearance of the drug ranged from 222 to 325 L/h.[24]

Special Patient Populations

- After a single 50mg dose of cinacalcet HCl, there were no clinically relevant differences in the pharmacokinetics of cinacalcet HCl in six adults with mild hepatic impairment (Child Pugh score 5–6) versus six healthy adult volunteers.[22] However, in those with moderate (Child Pugh score 7–9; n = 6) or severe (10–15; n = 6) hepatic impairment, mean AUC_∞ values were 2.4 and 4.2 times higher (442 and 769 vs 184 ng • h/mL) and mean $t_{1/2}\beta$ values were 33% and 70% longer than in healthy volunteers (65.3 and 83.6 vs 49.2 hours). Although systemic exposure was increased in those with moderate or severe hepatic impairment, no additional dosage adjustments are required, as the drug is titrated to optimal effect (see section 5).[22]

- In other studies, there were no clinically relevant effects on the pharmacokinetics of cinacalcet HCl based on the degree of renal impairment,[11] the dialysis modality (haemodialysis or continuous ambulatory peritoneal dialysis [CAPD])[25] or whether the drug was administered on haemodialysis or nonhaemodialysis days.[25]
- In addition, no clinically relevant differences in the pharmacokinetic profile of cinacalcet HCl have been observed in adults based on age.[11] There are no pharmacokinetic data available in those <18 years of age.[11]
- There are no well controlled studies of the pharmacokinetics of cinacalcet HCl in pregnant women.[11]

Drug Interactions

- Data from *in vitro* studies demonstrated that cinacalcet HCl is a strong inhibitor of CYP2D6, but shows no activity against CYP1A2, CYP2C9, CYP2C19 or CYP3A4.[11] Thus, when coadministered with cinacalcet HCl, dosage adjustments may be required for medications that are predominantly metabolised by CYP2D6 and have a narrow therapeutic index (e.g. flecainide, vinblastine, thioridazine and most tricyclic antidepressants).[11]
- In extensive CYP2D6 metabolisers, coadministration of cinacalcet HCl 25 or 100mg with amitriptyline 50mg increased exposure to amitriptyline and its active metabolite nortriptyline by approximately 20%.[11] The clinical relevance of these findings has not been determined.
- As discussed above, cinacalcet HCl is metabolised by several CYP enzymes (predominantly CYP3A4, CYP2D6 and CYP1A2). Coadministration of a single 90mg dose of cinacalcet HCl on day 5 in recipients of ketaconazole (700mg twice daily), a strong CYP3A4 inhibitor, resulted in an approximately 2-fold increase in systemic exposure to cinacalcet HCl.[11] Thus, dosage adjustments of cinacalcet HCl may be required, and PTH and serum calcium levels should be closely monitored if a patient initiates or discontinues therapy with a strong CYP3A4 inhibitor (e.g. ketoconazole, itraconazole or erythromycin).[11]
- In healthy adult volunteers, no significant pharmacokinetic interactions occurred when cinacalcet HCl (single 90 or 100mg dose) was coadministered with calcium carbonate (single 1500mg dose), pantoprazole (after 80mg daily for 3 days) or the phosphate binder sevelamer (after a single dose of 800mg; volunteers continued receiving sevelamer 2400 mg/day for 2 days).[23]
- Similarly, coadministration of cinacalcet 30mg twice daily with a single dose of warfarin 25mg did not affect the pharmacokinetics of either warfarin enantiomer.[11]

3. Therapeutic Efficacy

In Secondary HPT Patients with CKD and on Dialysis

The clinical efficacy and tolerability of oral cinacalcet HCl for the treatment of secondary HPT in CKD patients on dialysis has been evaluated in several randomised, double-blind, placebo-controlled, multicentre trials, including phase II studies[26-29] and three pivotal phase III trials.[11,30] Pooled data from two of the phase III trials are available in a fully published paper,[30] with combined data from all three phase III trials reported in the manufacturer's prescribing information.[11] Some data are available as abstract and/or poster presentations.[28,29,31,32]

A total of 1136 patients were enrolled in the three pivotal phase III studies.[11,30] All patients were receiving haemodialysis or CAPD and had uncontrolled secondary HPT, with plasma iPTH levels of ≥300 pg/mL despite treatment with phosphate binders and/or vitamin D sterols. Phosphate binders and vitamin D sterols, if already prescribed at study entry, were continued during treatment with cinacalcet HCl or placebo. Phosphate binders could be adjusted freely, while changes in vitamin D sterols were based on protocol-specified criteria.

Trials consisted of a 12- or 16-week dose-titration phase and a subsequent 14- or 10-week efficacy assessment phase. Cinacalcet HCl was initiated at a starting dosage of 30mg once daily and titrated sequentially to 60, 90, 120 or 180 mg/day to achieve

target iPTH levels. Dosages were titrated every 3 to 4 weeks during the titration phase if plasma iPTH remained above 200 pg/mL, unless serum calcium was <7.8 mg/dL and/or symptoms of hypocalcaemia were present. Cinacalcet HCl dosage was reduced if mean iPTH was <100 pg/mL.[11,30]

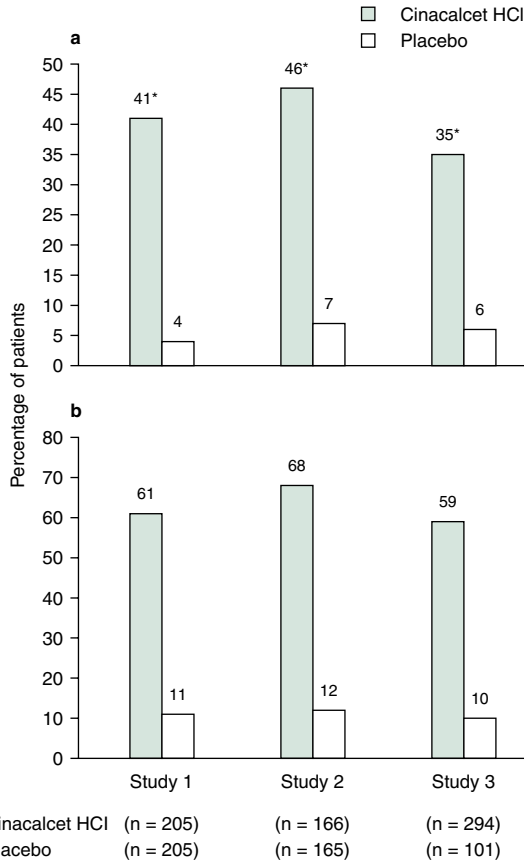


Fig. 1. Efficacy of oral cinacalcet hydrochloride (HCl) for the treatment of secondary hyperparathyroidism in chronic kidney disease patients on dialysis in three phase III, randomised, double-blind, multicentre trials.[11] Percentage of patients achieving (**a**) plasma intact parathyroid hormone (iPTH) levels of ≤250 pg/mL (primary endpoint) and/or (**b**) a ≥30% reduction from baseline in plasma iPTH level (secondary endpoint; no statistical data reported). Patients received oral cinacalcet HCl (titrated dosages of 30–180mg once daily) or placebo for 26 weeks. Plasma iPTH values were based on the average value during the evaluation phase (defined as weeks 13–26 in studies 1 and 2 and weeks 17–26 in study 3). Range of baseline values: iPTH 535–703 pg/mL; calcium 9.8–10 mg/dL; phosphorous 6–6.3 mg/dL; calcium-phosphorous product 59–62 mg^2/dL^2. * $p < 0.001$ vs placebo.

The primary endpoint was the percentage of patients who had a mean plasma iPTH level of ≤250 pg/mL during the efficacy assessment phase. Secondary endpoints included a ≥30% decrease from baseline in mean plasma iPTH levels, as well as changes from baseline in serum calcium, phosphorous and Ca × P levels during the efficacy assessment phase.[11,30]

- Significantly more cinacalcet HCl than placebo recipients achieved target plasma iPTH levels (≤250 pg/mL) in all three phase III trials (primary endpoint) [figure 1].[11] In addition, a higher proportion of patients in the cinacalcet HCl group achieved a ≥30% reduction from baseline levels in plasma iPTH (secondary endpoint; no statistical analyses reported) [figure 1].[11]

- In all trials, cinacalcet HCl treatment consistently decreased plasma iPTH and serum calcium, phosphorus and Ca × P levels, whereas these values showed minimal changes in placebo recipients (no statistical data were reported for these secondary endpoints) [figure 2].[11] Plasma iPTH levels decreased by 48.2–54.1% in cinacalcet HCl recipients, whereas levels increased by 2.3–8.4% in placebo recipients.[11]

- Pooled data from two identically designed phase III trials confirmed these findings, with significantly (both $p < 0.001$) more cinacalcet HCl-treated than placebo-treated patients achieving a mean plasma iPTH level of ≤250 pg/mL (43% vs 5%) and/or at least a 30% reduction from baseline level in mean plasma iPTH (64% vs 11%).[30] The mean percentage changes during the efficacy assessment phase in plasma iPTH (−38% vs 23%), serum calcium (−6.8% vs 0.4%), serum phosphorous (−8.4% vs 0.2%) and Ca × P level (−14.6% vs 0.5%) were also significantly (all $p < 0.001$) greater in cinacalcet than in placebo recipients.[30] Respective baseline values for these parameters were 326 and 337 mg/dL, both 9.9 mg/dL, both 6.2 mg/dL, and 61 and 62 mg^2/dL^2 in the cinacalcet (n = 371) and placebo groups (n = 370).[30]

- In several subgroup analyses of these phase III trials, decreases in plasma iPTH levels were achieved regardless of concurrent vitamin D sterol

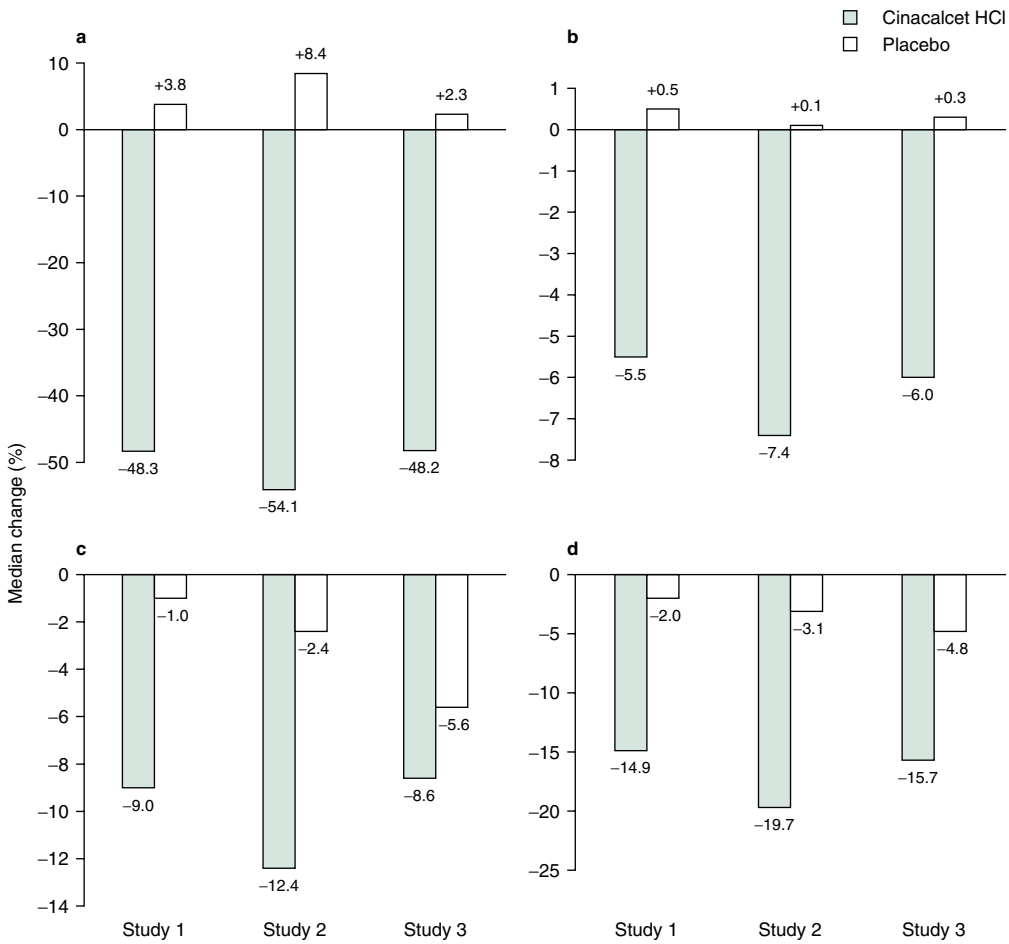


Fig. 2. Efficacy of oral cinacalcet hydrochloride (HCl) for the treatment of secondary hyperparathyroidism in chronic kidney disease patients on dialysis in three phase III, randomised, double-blind, multicentre trials.[11] Median percentage change from baseline in (**a**) plasma intact parathyroid hormone (iPTH), (**b**) serum calcium, (**c**) serum phosphorous and (**d**) calcium-phosphorus product (Ca × P) levels (secondary efficacy endpoints). Patients received oral cinacalcet HCl (titrated dosages of 30–180mg once daily; n = 205, 166 and 294 in studies 1, 2 and 3, respectively) or placebo (n = 205, 165 and 101) for 26 weeks. Plasma iPTH values were based on the average value during the evaluation phase (defined as weeks 13–26 in studies 1 and 2 and weeks 17–26 in study 3). Range of baseline values: iPTH 535–703 pg/mL; calcium 9.8–10 mg/dL; phosphorous 6–6.3 mg/dL; Ca × P 59–62 mg^2/dL^2. No statistical data reported.

or phosphate binder administration,[30,33] age,[30] gender,[30] ethnicity,[30] duration of dialysis,[30] dialysis modality,[34] presence of diabetes[30] or severity of secondary HPT.[11]

- Furthermore, in these phase III trials, significantly (all $p < 0.001$) more patients receiving cinacalcet HCl achieved equal to or below the upper limits of the four key K/DOQI™ secondary HPT targets than placebo-treated patients: iPTH level ≤300 pg/mL 57% vs 10%; Ca × P level ≤55 mg^2/dL^2 65% vs 36%; serum calcium level ≤9.5 pg/mL 69% vs 25%; and serum phosphorous level ≤5.5 mg/dL 54% vs 36%.[31] All patients were allowed concurrent therapy with traditional therapies (vitamin D sterols and phosphate binders).

- In phase III trials, reductions in plasma iPTH and Ca × P levels were maintained for up to 12 months with cinacalcet HCl treatment.[11]

- Reductions in plasma iPTH were sustained for up to 3 years without detrimental effects on serum

calcium, phosphorous or Ca × P levels in 59 evaluable patients during a 100-week extension phase of a phase II trial (1-year double-blind study with a 2-year open-label extension phase).[32] Mean serum calcium (9.7 mg/dL at the initiation of the extension phase vs 9.7 mg/dL after 100 weeks), phosphorous (5.8 vs 5.7 mg/dL) and Ca × P levels (56.4 vs 55.1 mg^2/dL^2) were maintained during this 100-week extension phase in patients treated with cinacalcet HCl ≤180 mg/day.[32]

- Phase II trial data also suggest that the iPTH reductions achieved after cinacalcet HCl treatment for 1 year may have beneficial effects on bone histology in CKD patients on dialysis with secondary HPT.[28] At 12 months, a greater proportion of cinacalcet HCl-treated (n = 30) than placebo-treated (n = 23) patients achieved a ≥30% reduction from baseline in PTH levels (47% vs 26%). Corresponding median bone-specific alkaline phosphatase (BALP) levels were reduced by 24.1% in the cinacalcet HCl group versus a 9.2% reduction in the placebo group, with decreases in BALP significantly ($p < 0.001$) correlated with reductions in mean baseline PTH levels. Reductions in PTH levels also correlated (both $p < 0.02$) with increases in total body bone mineral density (BMD; median change 0.5% vs −1.6%) and femoral BMD (2.0% vs 0.2%).[28]
- In another phase II study, treatment with cinacalcet HCl (n = 32) resulted in a 51% reduction in iPTH, an 18% reduction in serum BALP and a 24% reduction in *N*-telopeptide; no data were presented for the 16 placebo recipients.[29] Recipients of cinacalcet HCl also experienced reductions in bone turnover parameters such as the activation frequency (−0.51/y), bone formation rate/bone surface (−1.88 $mm^3/cm^2/y$), marrow fibrosis (−1.99%) and the number of osteoclasts (−64/100mm) and osteoblasts (−202/100mm). The activation frequency (−0.12/y) and number of osteoclasts (−61/100mm) were reduced in the placebo group.[29]

In Parathyroid Carcinoma

- Oral cinacalcet HCl reduced serum calcium levels in hypercalcaemic patients with parathyroid carcinoma in an open-label, multicentre study (baseline serum calcium level 14.8 mg/dL).[11,35] Patients were treated for 2–16 weeks during an initial dose-titration phase (n = 10) and then for 16–48 weeks in a subsequent maintenance phase (n = 3), with maintenance dosages ranging from 70mg twice daily to 90mg four times daily. Serum calcium changes ranged from −7.5 to +2.7 mg/dL during the titration phase and −7.4 to +0.9 mg/dL during the maintenance phase; however, no patients experienced a normalisation of calcium levels. Cinacalcet HCl treatment reduced elevated serum calcium levels by ≥1 mg/dL in six of eight evaluable patients.[11,35]
- In an open-label, multicentre, dose-titration trial in 21 patients with parathyroid carcinoma, 71% of patients achieved a target reduction of ≥1 mg/dL in serum calcium with cinacalcet HCl (30mg twice daily to 90mg four times daily) [abstract presentation].[36] At the end of the titration phase (i.e. when serum calcium was ≤10 mg/dL or after 16 weeks' treatment, whichever occurred first), mean serum calcium levels were reduced from a baseline of 14.5 mg/dL to 12.4 mg/dL; reduced serum calcium levels were maintained for up to 3 years. Furthermore, at this timepoint, there was also a modest reduction in pre-dose mean iPTH levels from baseline (856 vs 719 pg/mL), with more marked reductions observed 2 and 4 hours postdose (mean iPTH 630 and 610 pg/mL).[36]

In Primary HPT

One study in patients with primary HPT is fully published,[37] with remaining data available as abstract and/or poster presentations.[35,38]

- In a 24-week, randomised, double-blind trial in patients with mild-to-moderate primary HPT, 73% of patients receiving cinacalcet HCl achieved the primary endpoint of at least a 0.5 mg/dL reduction in serum calcium level and a mean serum calcium level of ≤10.3 mg/dL during the maintenance phase (weeks 13–24) versus 5% of placebo recipients ($p < 0.001$).[37] Seventy-eight patients received cinacalcet HCl 30mg twice daily or placebo, with the dosage of cinacalcet increased to 40 or 50mg twice daily, if necessary, to achieve serum calcium levels in the

normal range. During the maintenance phase, cinacalcet HCl recipients had an 8% reduction in mean plasma PTH level versus an 8% increase in the placebo group ($p < 0.01$). Plasma PTH levels were measured 12 hours post-dose.[37]

- In this same study in patients with mild-to-moderate primary HPT, 87% of recipients (n = 39) had serum calcium levels within the normal range after 3 years' treatment with cinacalcet HCl.[38]
- Four of five patients with intractable primary HPT achieved a mean reduction in serum calcium level of ≥1 mg/dL after 16 weeks' treatment with cinacalcet HCl 30mg twice daily titrated to 90mg four times daily.[35] The mean predose serum calcium level (12.4 mg/dL) was reduced by 1.5 mg/dL during this 16-week, open-label, dose-titration study. Intractable primary HPT is defined as severe hypercalcaemia in patients contraindicated for parathyroidectomy or with persistent hypercalcaemia and elevated PTH after parathyroidectomy.

In Secondary HPT Patients with Stage 3 or 4 CKD

- In a randomised, double-blind, phase II study in stage 3 or 4 CKD patients not on dialysis and with secondary HPT, significantly more patients receiving cinacalcet HCl 30–180mg once daily (n = 19) than placebo-treated patients (n = 21) achieved a decrease in mean iPTH of ≥30% (56% vs 19%; p = 0.01) [primary endpoint; abstract presentation].[39] Cinacalcet HCl treatment reduced mean iPTH levels by 32% versus a 6% increase with placebo treatment ($p < 0.001$; n = 21). Respective baseline mean iPTH levels were 236 and 243 pg/mL.[39]

4. Tolerability

- In 26-week phase III trials discussed in section 3, there were generally no statistical differences between the cinacalcet (n = 656) and placebo (n = 470) groups in the frequency and nature of treatment-emergent adverse events.[11] Nausea (31% in the cinacalcet HCl group vs 19% in the placebo group) and vomiting (27% vs 15%) were the most common adverse events that occurred with a >2% difference versus placebo.[11] In two identically designed phase III trials, less than 5% of cinacalcet-HCl recipients and less than 1% of placebo recipients permanently discontinued treatment because of nausea or vomiting, with events generally being mild-to-moderate in intensity and transient.[30]
- In the phase III trials, 66% of cinacalcet HCl-treated patients experienced at least one episode of hypocalcaemia (defined as serum calcium level <8.4 mg/dL) compared with 25% of placebo-treated patients.[11] Episodes of hypocalcaemia were generally asymptomatic and transient, and responded to modifications in phosphate-binding agents, vitamin D sterols and/or cinacalcet HCl.[30] Less than 1% of patients in each treatment group permanently discontinued treatment because of hypocalcaemia.[11]
- During a 6-month open-label extension phase of two of the three phase III studies (total of 1 years' treatment), the incidence of adverse events was similar in the cinacalcet HCl and placebo groups and similar to that observed during the first 6-month phase.[11] Cinacalcet HCl treatment for up to 3 years was generally well tolerated in an open-label extension phase of double-blind trials, with the nature and incidence of adverse events being similar to those reported during the double-blind phase.[32]

5. Dosage and Administration

For the treatment of secondary HPT in CKD patients on dialysis, the recommended starting dosage of oral cinacalcet HCl is 30mg once daily, taken with food or shortly after a meal.[11] Serum calcium and phosphorus should be determined within 1 week, and plasma PTH levels determined within 4 weeks after starting treatment or adjusting dosage. The dosage should be titrated no more frequently than every 2–4 weeks from a starting dosage of 30 mg/day to 60, 90, 120 or 180mg once daily to achieve target PTH levels. Because the PTH nadir occurs approximately 2–6 hours after dose administration, PTH should be measured at least 12 hours after dosing. Cinacalcet may be used alone or in combination with vitamin D sterols and/or phosphate binders.[11]

For patients with parathyroid carcinoma, the recommended starting dosage of cinacalcet HCl is

30mg twice daily.[11] The dosage should be titrated sequentially to 60 or 90mg twice daily or 90mg three or four times daily as required, to normalise serum calcium levels.

For comprehensive dosage and administration information, and indications for individual countries, local prescribing information should be consulted.

6. Cinacalcet Hydrochloride: Current Status

Oral cinacalcet HCl is the first and currently the only calcimimetic approved in the US, Canada and Europe. Unlike traditional therapies for secondary HPT, cinacalcet HCl demonstrates a novel mechanism of action in acting directly at CaR in the parathyroid gland, resulting in a reduction in plasma iPTH and serum Ca × P, calcium and phosphorous levels. Several large randomised, double-blind trials have confirmed that cinacalcet HCl is efficacious and generally well tolerated for the treatment of secondary HPT in CKD patients on dialysis. Moreover, significantly more cinacalcet HCl-treated patients achieved the four key K/DOQI™ secondary HPT goals than recipients of traditional treatment.

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