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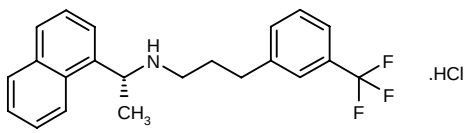
Cinacalcet Hydrochloride

Treatment of Hyperparathyroidism

USAN

AMG-073.HCl

N-[1(*R*)-(1-Naphthyl)ethyl]-*N*-[3-[3-(trifluoromethyl)phenyl]propyl]amine hydrochloride



$C_{22}H_{22}F_3N.HCl$

Mol wt: 393.8777

CAS: 364782-34-3

CAS: 226256-56-0 (as free base)

EN: 302362

Abstract

Hyperparathyroidism is characterized by high levels of circulating calcium due to an increased secretion of parathyroid hormone (PTH) by one or more of the parathyroid glands. It is estimated that 28 out of every 100,000 people in the U.S. will develop this disorder. A standard treatment for hyperparathyroidism is surgical removal of the affected gland(s). However, pharmacological intervention with vitamin D analogs of calcimimetics is an option for those patients with mild cases or secondary hyperparathyroidism. The extracellular calcium sensing receptor (CaR), a low affinity G-protein-coupled receptor, is found in high levels on the surface of parathyroid cells, where in response to small changes in extracellular calcium, they regulate secretion of PTH. The CaR is an attractive therapeutic target for the design of novel calcimimetics for the treatment of hyperparathyroidism because alterations in CaR expression are thought to be responsible for inherited forms of hypercalcemia and hyperparathyroidism, and acquired alterations in this receptor could be responsible for the pathogenesis of primary hyperparathyroidism and secondary hyperparathyroidism due to renal failure. Cinacalcet hydrochloride is a novel second-generation calcimimetic that modulates the CaR by making it more sensitive to the calcium suppressive effects on PTH secretion. It has a high oral bioavailability and has been chosen for further development as a treatment for primary and secondary hyperparathyroidism.

Synthesis

Reaction of 1(*R*)-(1-naphthyl)ethylamine (I) with 3-[3-(trifluoromethyl)phenyl]propionaldehyde (II) by means of titanium tetraisopropoxide gives the corresponding imine (III), which is finally reduced with $NaBH_3CN$ in ethanol (1). Scheme 1.

Introduction

The parathyroid glands produce parathyroid hormone (PTH) which is involved in maintaining blood calcium homeostasis. When circulating calcium levels are too low, PTH induces release of calcium from bone, reduces renal calcium excretion and increases calcium absorption from food. Hyperparathyroidism is an endocrine disorder in which one or more of the four parathyroid glands becomes enlarged and produces too much PTH, resulting in high levels of circulating calcium. Because bones are the main source of calcium, hyperparathyroidism can lead to osteoporosis. Hyperparathyroidism may be primary or secondary (*e.g.*, resulting from kidney failure); those patients with renal failure suffering from secondary hyperparathyroidism have an increased risked of renal bone disease, soft-tissue calcifications and vascular disease. The majority of cases of hyperparathyroidism reported (about 85%) occur due to dysfunction of a single parathyroid gland which develops into a benign adenoma; hyperplasia of two or more glands is responsible for only 15% of all cases, while primary hyperparathyroidism due to cancer or an inherited disorder (*e.g.*, familial endocrine neoplasia type I, familial hypocalciuric hypercalcemia) is rare. It is estimated in the U.S. that 28 out of every 100,000 people will suffer from the disorder, with women outnumbering men by 2 to 1. An increase in risk for developing the disorder is seen with age so that it is estimated that 2 out of 1000 women 60 years of age or older will develop hyperparathyroidism. Treatment for hyperparathyroidism includes surgical removal of the affected gland(s). However, pharmacological intervention with vitamin D analogs or, more recently, calcimimetics, is an

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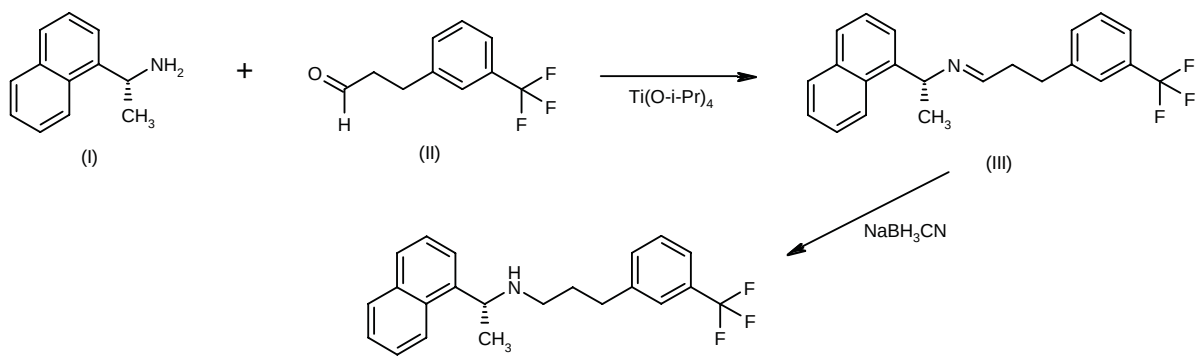
Scheme 1: Synthesis of Cinacalcet Hydrochloride



option for those patients with mild cases or secondary hyperparathyroidism (2, 3).

The extracellular calcium sensing receptor (CaR) is a low- affinity G-protein-coupled receptor with a large extracellular domain (approximately 700 amino acids), 7 membrane-spanning segments and a cytoplasmic carboxyl terminal segment (about 200 amino acids). CaR can be activated by small changes in extracellular calcium and its activation contributes to the control of calcium homeostasis of the body. The receptor is not specific so that it can be stimulated by other divalent cations (*e.g.*, Mg^{2+}), the trivalent elements gadolinium and lanthanum and polycationic compounds (*e.g.*, neomycin and spermine). There is a strong inverse relationship between plasma PTH levels and changes in serum calcium levels and the marked rise in urinary calcium that occurs when serum calcium rises slightly above threshold levels (4, 5).

CaRs are found in high levels on the surface of parathyroid cells where small changes in extracellular calcium regulate secretion of PTH. Activation of CaR in the kidney may be involved in the organ's response to hypercalcemia which includes the lowering glomerular filtration rates, decreasing renal cortical calcitriol synthesis, increasing urinary calcium and magnesium and increasing volume of dilute urine. CaR has also been localized on bone cells where it is thought to regulate bone metabolism (*i.e.*, stimulating bone formation and inhibiting bone resorption) and in the lungs and brain where its function has not yet been fully elucidated (6-9).

Alterations in CaR are responsible for several disorders, including familial hypocalciuric hypercalcemia, severe infantile hyperparathyroidism and hereditary forms of hyperparathyroidism, and acquired alterations in the receptor could be responsible for the pathogenesis of primary hyperparathyroidism in addition to secondary hyperparathyroidism due to renal failure (10-14). For example, it appears that parathyroid cells from uremic patients with secondary hyperparathyroidism may have reduced levels of CaR expression (15). In addition, some patients with parathyroid adenoma or carcinoma exhibit reduced CaR expression in the parathyroid.

Thus, the CaR is a particularly attractive therapeutic target for the design of compounds, known as calcimimetics, that enhance the affinity of the receptor for calcium (i.e., negative feedback) and decrease the secretion of PTH. Calcimimetics directly inhibit PTH secretion via activation of the CaR receptor on parathyroid cells and have a potential efficacy in the treatment of primary and secondary hyperparathyroidism. The first generation calcimimetic was R-568. However, it was discontinued due to poor bioavailability and the high variability of pharmacokinetics between patients (16). Since then, the second-generation phenylalkylamine cinacalcet hydrochloride (AMG-073) was synthesized. Cinacalcet exhibited calcimimetic properties similar to R-568 although it possessed a higher bioavailability after oral administration and more consistent interpatient pharmacokinetics. Cinacalcet was chosen for further development as a treatment for primary and secondary hyperparathyroidism.

Pharmacokinetics

The population pharmacokinetics of cinacalcet were determined from results of 2 randomized, double-blind, placebo-controlled trials involving patients with secondary hyperparathyroidism. The first fixed-dose study involved both a single-dose (25, 50, 75 and 100 mg) and multiple-dose (10, 25 or 50 mg, 8 doses/day) phase, while in the second study patients were titrated to a possible maximum dose of 50 mg after which they were maintained on their maximum dose for 6 weeks. The pharmacokinetics obtained fit a 2-compartment open model with first-order absorption. An absorption rate constant (Ka) was estimated to be 1.48 ± 0.25 h^{-1} while oral clearance was 321 ± 69 l/h and found to be 28% higher in men. The peripheral volume of distribution increased with body weight. Estimated values for central and peripheral

volume of distribution and intercompartmental clearance were 2630 ± 255, 8700 ± 1630 l and 150 ± 23 l/h, respectively (17).

Clinical Studies

Treatment of primary hyperparathyroidism

The safety and efficacy of cinacalcet as a treatment for primary hyperparathyroidism has been demonstrated in several clinical trials. The results of these trials are summarized in Table I.

The efficacy of cinacalcet (65 mg p.o. b.i.d. for 4 weeks) in reducing serum calcium was shown in a prospective, randomized, double-blind, placebo-controlled, 5-week trial involving 10 patients with moderate to severe primary hyperparathyroidism (serum calcium levels = 11 mg/dl or higher). Treatment was generally well tolerated. Of the 6 patients randomized to receive cinacalcet, serum calcium levels were decreased to normal levels (10.3 mg/dl or less) in 5 patients as compared to only 1 patient receiving placebo. Serum calcium levels returned to baseline in all patients during the 1-week follow-up when no drug/placebo was administered. Maximum decreases (about –39%) in PTH levels in cinacalcet-treated patients were seen 2-4 h postdosing. On day 28, PTH levels decreased by –14.5 ± 7.62% (from 189.9 ± 89.6 pg/ml at baseline) at 12 h postdosing as compared to an increase of +10.6 ± 7.57% (from 92.7 ± 25.3 pg/ml at baseline) (18).

The efficacy of cinacalcet (30, 40 or 50 mg p.o. b.i.d. for 15 days) in reducing serum calcium and PTH levels and its safety were shown in a pilot, placebo-controlled clinical trial involving 22 patients with primary hyperparathyroidism. Treatment was generally well tolerated with the majority of the infrequent adverse advents reported were considered mild and related to low total serum calcium levels. It was suggested for future studies that low total serum calcium be avoided by utilizing dose titration protocols. Total serum calcium levels were reduced by day 15 in all cinacalcet dose groups (30, 40 and 50 mg) from baseline levels of 10.5 ± 0.79, 10.6 ± 0.76 and 10.7 ± 1.12 mg/dl, respectively, to 9.4 ± 0.76, 8.6 ± 0.75 and 8.9 ± 0.27 mg/dl, respectively; no changes were noted in placebo. Mean intact PTH was also reduced by about 45% in cinacalcet-treated patients at 2-4 h postdosing as compared to only 2% in placebo (19).

The long-term effects (24 and 52 weeks) and safety of cinacalcet (30 mg p.o. b.i.d. titrated to a maximum dose of 50 mg) in reducing serum calcium and PTH levels were shown in two prospective, randomized, double-blind, placebo-controlled trials involving 78 patients with primary hyperparathyroidism (serum calcium = 10.3-12.5 mg/dl). In both studies, patients were first treated over 12 weeks after which they were administered a fixed dose for 12 or 40 weeks in a maintenance phase. Treatment was well tolerated with similar adverse events seen in both treatment and placebo groups. After 24 weeks of treatment, 88% of the cinacalcet-treated patients displayed a reduction in serum calcium of at least 0.5 mg/dl as compared to only 5% of the patients on placebo. Cinacalcet-treated patients also displayed a maximum decrease in PTH levels at 2-4 h postdosing of about 50%. Moreover, during the 12-week maintenance phase, a –7.6 ± 22.9% decrease in mean PTH levels was seen 12 h postdosing as compared to an increase of +7.7 ± 26.6% seen with placebo. No changes in the 24-h urine calcium/creatinine ratios were seen in any of the patients (20). Similarly, after 1 year of treatment during which 90% of the patients were maintained on 30 mg cinacalcet while the rest were titrated to a maximum dose of 40 mg, serum calcium (–9.8 ± 6.8 *vs.* +1.4 ± 5%) and PTH (–11.4 ± 17 *vs.* +2.3 ± 28.4%) levels were significantly reduced as compared to placebo. No changes in urine calcium/creatinine ratios were observed. Treatment with cinacalcet for 1 year was also well tolerated with similar adverse events seen in both placebo and treatment groups. Administration of the agent for 1 year also resulted in significantly increased bone-specific alkaline phosphatase (+33.3 ± 30.1 *vs.* +4.2 ± 28.5%) and serum N-telopeptide (+20.4 ± 30.1 *vs.* –2.7 ± 28.1%) levels as compared to placebo; levels of $1,25(OH)_2D_3$ and bone mineral density were similar for both treatment and placebo groups. It was concluded that cinacalcet may be an effective alternative to nonsurgically managed primary hyperparathyroidism (21).

Treatment of secondary hyperparathyroidism

Several clinical trials have demonstrated the safety and efficacy of cinacalcet as a treatment for secondary hyperparathyroidism. The results of these studies are also summarized in Table I.

The efficacy and safety of cinacalcet were clearly demonstrated in a multicenter, randomized, double-blind, placebo-controlled trial including a single-dose phase (5, 10, 25, 50, 75 or 100 mg p.o. within 3 h of completing a regular dialysis session) and multiple-dose phase (10, 25 or 50 mg/day for 8 consecutive days). The trial involved 52 patients with end-stage renal disease and secondary hyperparathyroidism who were undergoing thrice-weekly hemodialysis (plasma PTH = 250-1500 pg/ml; serum calcium = about 10 mg/dl) and who continued on stable-dose phosphate binders and vitamin D analogs. Treatment with 25, 50, 75 or 100 mg cinacalcet resulted in dose-dependent decreases (43 ± 29, 40 ± 36, 54 ± 28 and 55 ± 39%, respectively) in plasma PTH levels so that nadir was reached within 2 h postdosing; plasma PTH levels were unaltered on placebo. A reduction of serum calcium levels was only observed in those patients receiving 75 or 100 mg cinacalcet whose levels decreased modestly (–8.3 and –9.4%, respectively) to a nadir of about 9 mg/dl at 8-12 postdosing; calcium levels returned to predose values by 48 h postdosing. No patients experienced episodes of hypocalcemia (22, 23).

Table I: Clinical studies of cinacalcet (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Hyperparathyroidism	Randomized, double-blind, multicenter	Cinacalcet, 65 mg p.o. b.i.d. x 4 wk (n=6) Placebo (n=4)	10	Cinacalcet was well tolerated and effective in reducing serum calcium levels in 83% of patients and parathyroid hormone in patients with moderate to severe primary hyperparathyroidism	18
Hyperparathyroidism	Randomized, double-blind, multicenter	Cinacalcet, 30 mg p.o. b.i.d. x 15 d (n=5) Cinacalcet, 40 mg p.o. b.i.d. x 15 d (n=6) Cinacalcet, 50 mg p.o. b.i.d. x 15 d (n=5) Placebo (n=6)	22	Cinacalcet was safe, well tolerated and effective in reducing serum calcium and parathyroid hormone compared to placebo in patients with primary hyperparathyroidism	19
Hyperparathyroidism	Randomized, double-blind, multicenter	Cinacalcet, 30 mg p.o. b.i.d. [dose titration to normal Ca levels] x 12 wk → fixed dose x 12 wk Placebo	78	Cinacalcet was well tolerated and effective. Compared to placebo cinacalcet produced a significant reduction in serum calcium (88% patients) and parathyroid hormone, without changing urine calcium/creatinine ratio, and an increase in bone-specific alkaline phosphatase and serum N-telopeptide in patients with primary hyperparathyroidism. No changes were observed in $1,25(OH)_2D_3$ levels and bone mineral density, suggesting an effective nonsurgical therapy	20, 21
Hyperparathyroidism, hemodialysis	Randomized, double-blind multicenter	Cinacalcet, 5 mg p.o. s.d. (n=8) Cinacalcet, 10 mg p.o. s.d. (n=8) → x 8 d (n=8) Cinacalcet, 25 mg p.o. s.d. (n=6) → x 8 d (n=6) Cinacalcet, 50 mg p.o. s.d. (n=6) → x 8 d (n=9) Cinacalcet, 75 mg p.o. s.d. (n=6) Cinacalcet, 100 mg p.o. s.d. (n=6) Placebo s.d. (n=12) → x 8 d (n=7)	52	Cinacalcet was safe, well tolerated and effective in reducing PTH and phosphorus levels and calcium X phosphorus product in a dose-dependent manner with doses higher than 25 mg in hemodialysis patients with secondary hyperparathyroidism	22
Hyperparathyroidism, hemodialysis	Randomized, double-blind, multicenter	Cinacalcet, 10 mg/d p.o. x 8 d + phosphate binders + vitamin D analogs (n=8) Cinacalcet, 25 mg/d p.o. x 8 d + phosphate binders + vitamin D analogs (n=6) Cinacalcet, 50 mg/d p.o. x 8 d + phosphate binders + vitamin D analogs (n=9) Placebo + phosphate binders + vitamin D analogs (n=7)	30	Cinacalcet was safe, well tolerated and effective in reducing PTH, calcium and phosphorus levels, indicating that it could be useful in the treatment of hemodialysis patients with secondary hyperparathyroidism	24
Hyperparathyroidism, hemodialysis	Multicenter	Cinacalcet, up to 50-100 mg/d p.o. x 12 wk (n=141) Placebo (n=74)	215	Cinacalcet was well tolerated and effective in reducing serum Ca X phosphorus product and parathyroid hormone (in 83% of patients) in patients with secondary hyperparathyroidism in this combined analysis of preliminary data from 3 clinical trials	25
Hyperparathyroidism, hemodialysis	Randomized, double-blind, multicenter	Cinacalcet, 25 mg/d p.o. [dose titrated up to 100 mg/d] x 12 wk → fixed dose x 6 wk Placebo	71	Cinacalcet was well tolerated and effective in reducing PTH and calcium X phosphorus product compared with placebo in hemodialysis patients with secondary hyperparathyroidism, regardless of whether they were receiving concomitant vitamin D therapy	26
Hyperparathyroidism multicenter	Randomized, double-blind,	Cinacalcet, 20 mg/d p.o. [dose titrated up to 50 mg/d] x 12 wk → fixed dose x 6 wk Placebo	77	Cinacalcet was safe, well tolerated and effective in reducing PTH (in 38.5% of the patients), as well as phosphorus and Ca X P product compared with placebo in hemodialysis patients with secondary hyperparathyroidism	26

Cinacalcet was also shown to be safe and effective in the multiple-dose phase of this trial that involved 30 of the patients who participated in the single-dose phase. Cinacalcet was well tolerated. Frequency of adverse events did not differ between any of the treatment groups and placebo. The most common adverse events were nausea, vomiting, headache and hypertension prior to regular dialysis sessions. The cinacalcet dose for 3 patients initially given 50 mg was reduced to 25 mg for nausea in 1 patient and for transient reductions of serum calcium to below 8 mg/dl in 2 others. Maximum reductions in PTH (–39.6 ± 33.1 and –44.5 ± 30.8%, respectively) occurred in patients treated with 25 and 50 mg cinacalcet at 2 h postdosing. Similar reductions in plasma PTH were seen on day 8 (–42 and –32%, respectively, at 4 h postdosing) in patients treated with the 25 and 50 mg doses; no changes in PTH were observed in patients treated with the 10 mg dose or placebo. Only the 50 mg dose of cinacalcet resulted in a decrease in serum calcium levels to 5-10% below baseline between days 5 and 8 of the treatment period; a slight reduction in serum calcium was seen in the 25 mg dose group on day 8 but no changes occurred in patients given the 10 mg dose or placebo. A reduction in serum phosphorus of about 10% was also seen in these patients that was concluded to probably be due to increased compliance with diet and phosphorus binders during the study period (22, 24).

Pooled data collected from 3 trials involving a total of 215 hemodialysis patients with secondary hyperparathyroidism (PTH = 300 pg/ml or greater; serum calcium between 8.8 and 11 mg/dl; calcium X phosphorous product = less than 70) confirmed the efficacy and safety of short-term (12 weeks) treatment with cinacalcet (titrated from 10 mg/day up to 50 or 100 mg/day p.o. every 3 weeks). Treatment was well tolerated with similar adverse events reported for treatment and placebo groups. Cinacalcet treatment resulted in decreases in levels of plasma mean intact PTH levels (–20 to –30 *vs.* + 16% in placebo) and mean calcium X phosphorus product (–7.1 ± 28 *vs.* +14.3 ± 30.6%). Within the first weeks, 83% of the cinacalcet-treated patients had a decrease in baseline intact PTH of 30% or greater (25).

The safety and efficacy of cinacalcet (20 mg titrated every 3 weeks over 12 weeks to a maximum of 50 mg/day p.o. and subsequently treated with a fixed dose in a 6-week maintenance phase) were shown in a prospective, randomized, double-blind, placebo-controlled, 18-week trial conducted in 77 hemodialysis patients with end-stage renal disease and secondary hyperparathyroidism (plasma PTH = 300 pg/ml or greater) on concurrent phosphate binder and vitamin D analog therapy. Treatment was safe and well tolerated and only 3 of the 38 patients treated with the compound experienced transient asymptomatic hypocalcemia; other reported side effects were similar for both treatment and placebo groups. A significant reduction (–26%) in mean PTH of cinacalcet-treated patients was observed in the maintenance phase as compared to an increase (+22%) seen with placebo. During this phase, significantly more patients treated with the agent (38.5%) had a decrease in mean PTH of 30% or greater as compared to placebo (7.7%). Cinacalcet-treated patients also exhibited a decrease in serum calcium of about 6% from baseline during the maintenance phase. In addition, by 18 weeks the calcium X phosphorous product decreased by –16.9% from baseline as compared to an increase of +11.4% seen in placebo; serum phosphorus were reduced by –14.4% in the cinacalcet group (26).

Due to the excellent safety profile obtained, the above study by Linberg et al. was repeated in another prospective, randomized, double-blind, placebo-controlled, 18-week trial involving 71 hemodialysis patients (PTH = 300 pg/ml or greater), some of whom were also taking phosphate binders (61 and 66% in the active drug group and placebo, respectively) and/or vitamin D analogs (100 and 94%, respectively). In this study cinacalcet administered starting at 25 mg/day p.o., titrated up to 100 mg/day and subsequently given at a fixed dose for 6 weeks in a maintenance phase. The drug was well tolerated with no difference in adverse events seen between groups. Cinacalcet effectively reduced PTH and calcium levels regardless of whether patients were receiving vitamin D therapy. Significant reductions in mean PTH (–32.5 *vs.* +3% in placebo) and calcium X phosphorus product (–7.9 *vs.* +11% in placebo) were observed during the maintenance phase in the cinacalcet group as compared to placebo; 83% of the cinacalcet-treated patients had a decrease of 30% or greater in mean PTH. While serum calcium levels in the cinacalcet groups were decreased from a baseline of 9.6 ± 0.7 mg/dl to 9.1 ± 1 mg/dl (–4.6%), these levels increased from 9.7 ± 0.8 mg/dl to 10 ± 0.7 mg/dl in placebo during the maintenance phase. Serum phosphorus levels also decreased by 2.6% in the cinacalcet group (27).

Cinacalcet hydrochloride continues to undergo phase III development for the treatment of primary and secondary hyperparathyroidism (28).

Source

Discovered by NPS Allelix Corp. (CA); licensed to Amgen Inc. (US) and Kirin Brewery Co., Ltd. (JP).

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