CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-688

PHARMACOLOGY REVIEW

PHARMACOLOGY AND TOXICOLOGY REVIEW OF NDA

NDA #:	**21-688**
Product Name :	**Sensipar™ (Cinacalcet HCl)**
Sponsor:	**Amgen Inc, CA**
Indication:	**Treatment of primary and secondary hyperparathyroidism**
Division:	**HFD-510 (DMEDP)**
Reviewer:	**Gemma Kuijpers**
Date:	**February 12, 2004**

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EXECUTIVE SUMMARY

1. Recommendations

1.1 Recommendation on approvability
Pending the proposed labeling changes, Pharmacology/Toxicology recommends approval of this NDA (AP)

1.2 Recommendation for nonclinical studies
None

1.3 Recommendations on labeling
See Team Leader Memo (K.Davis-Bruno, February 10, 2004) (Appendix)

2. Summary of nonclinical findings

2.1 Overview of nonclinical findings

The current NDA is for the use of cinacalcet in the [redacted] treatment of secondary hyperparathyroidism (HPT) in patients with chronic kidney disease, and the treatment of hypercalcemia in patients with parathyroid carcinoma or patients with primary HPT. In chronic kidney disease hypocalcemia results from a disturbance in renal phosphorus handling and decreased formation of $1,25(OH)_2$-VitD. Hypocalcemia causes increased parathyroid gland secretion of PTH as primary defense of the system against lowered serum calcium. Primary HPT is a hypercalcemic disorder that results from excessive secretion of PTH and is usually caused by parathyroid adenoma or primary parathyroid hyperplasia.

A dose titration regimen is proposed with oral doses of 30 mg up to 180 mg, once daily, in secondary HPT, [redacted] The dose is titrated in each individual patient based on a target level of PTH and/or serum calcium.

The calcium sensing receptor (CaR) is a G-protein coupled receptor and plays an important role in calcium homeostasis. It regulates the release of parathyroid hormone (PTH) from the parathyroid gland in response to changes in extracellular calcium. Cinacalcet is a calcimimetic and acts at the CaR to increase its sensitivity to extracellular calcium, thereby suppressing the secretion of PTH from the parathyroid gland. Cinacalcet can also stimulate calcitonin secretion through interaction with the CaR on thyroid C-cells.

Pharmacology
In monkey, rat and mouse tissues CaR mRNA was detected primarily in the parathyroid gland but also in kidney, GI tract, thyroid, CNS, pancreatic islets, adrenal gland, thymus, testis, bone and/or bone marrow. *In vitro* pharmacology studies demonstrated a potent and concentration-dependent stimulation of the CaR by cinacalcet. Modulation of the CaR by cinacalcet led to inhibition of PTH secretion from [redacted] cells, and stimulation of calcitonin release from rat thyroid C-cells.

In intact rats, cinacalcet induced inhibition of PTH secretion resulting in a rapid and reversible reduction in serum calcium levels with half maximal effect (ED_{50}) at an oral dose of 3 mg/kg (Cmax: ————). Using *in vivo* models of secondary hyperparathyroidism, such as the partially (5/6) ———————— rat, it was demonstrated that cinacalcet causes a dose-dependent and transient reduction in serum PTH and reduces blood ionized calcium. Upon repeat dosing, cinacalcet prevented or attenuated parathyroid gland hyperplasia in the Nx rat. In one study in Nx rats, cinacalcet (15 mg/kg) suppressed bone turnover, reduced bone fibrosis and cortical porosity and increased cortical BMD and toughness. These effects were most likely mediated by the reduction in serum PTH. In parathyroidectomized (PTX) rats, cinacalcet reduced blood ionized calcium through activation of CaR-mediated thyroid calcitonin secretion. The studies identified the parathyroid and thyroid as target organs for the pharmacologic action of cinacalcet in the rat. Cinacalcet reduced hypercalcemia but had no effect on vascular mineralization in VitD-treated Nx rats. Effective oral doses (ED_{50-100}) in the *in vivo* rat studies were generally in the range of 10-30 mg/kg (Cmax ————).
In vitro receptor studies suggested that the transmembrane and/or intracellular domains of the CaR are required for sensitivity of the receptor to cinacalcet.
An animal model for primary hyperparathyroidism was not available.

Safety pharmacology

Note: Calculation of exposure multiples in nonclinical studies are based on the maximum 180 mg/day dose proposed for secondary hyperparathyroidism. Clinical PK data indicated maximal exposure (Cmax, AUC) at the 180 mg/day dose, and further exposure was not observed at doses >180 mg/day. Exposure at the maximum dose of 360 mg/day (90 mg QID) recommended for primary hyperparathyroidism is not known.

In safety pharmacology studies, single oral doses of cinacalcet had no effects on neuropharmacologic signs or body temperature, and no analgesic, anticonvulsant or proconvulsant effects in mice, at doses up to 200 mg/kg (equivalent to 6 times the human dose of 180 mg/day, based on mg/m^2). In mice, a decrease in spontaneous motor activity and an increase in gastric motility was observed at an oral dose of 200 mg/kg. In the guinea pig, an IV dose of 20 mg/kg caused a transient increase in airway resistance and bronchoconstriction. These effects may have been due to hypocalcemia or interaction of cinacalcet with central or peripheral ion channels/receptors. There were no significant cardiovascular or EKG effect in the dog at single oral doses up to 50 mg/kg (—— human Cmax @ 180 mg/day). EKG effects were also not observed in a 1-month dog toxicity study at doses up to 100 mg/kg/day (0.8x human AUC @ 180 mg/day). However, in repeat dose toxicity studies in the monkey QT and QTc interval prolongation was observed (see General Toxicity).

An *in vitro* cardiac ion channel study showed that cinacalcet at high concentrations blocked K_{ATP} channels, Kv4.3, Kv1.5 and hcNa channels. hERG channel activity were minimally affected. K_{ATP} channels are believed to be involved in the protective response of the body, e.g. the heart and the vasculature, to stress. In the heart, they mediate preconditioning in response to ischemic stress, and in blood vessels they may be involved in vasoconstriction. K_{ATP} channels may also have cardioprotecive effects through shortening of action potential and QT duration. K_{ATP} channels are known to mediate the insulin secretory response of pancreatic —

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