reduction in potency may be offset by relative increased formation. The levels of metabolites exceed parent by ≥50 times in rat and monkey. Excretion in monkeys is ~50% fecal and urinary whereas in humans 95% is urinary. Fecal excretion predominates in rat (~60%).

A number of toxicities have been identified that are of clinical concern because they occur in animals at relatively low exposure multiples. These include: hypocalcemia, cardiovascular toxicity (QTc prolongation, myocardial degeneration/necrosis, left ventricular arterial hyperplasia rat/juvenile dog, CPK increase and muscle degeneration monkey), GI toxicity, endocrine changes (decreased testosterone, testicular atrophy, T3 decrease, T4 increase, decreased Vit. D monkey), liver (minimal enzyme induction, decreased serum protein, vacuolation/necrosis rat, monkey) and renal toxicity (BUN/creatinine increase mineralization rat). A number of these nonclinical findings were observed in the clinic including: nausea, vomiting, hypocalcemia, convulsions, decreased testosterone and QTc prolongation.

In acute and chronic toxicity studies in rats, dogs and monkeys signs of hypocalcemia: hypoactivity, neuromuscular and respiratory effects, tremors, excessive salivation and convulsions were observed. In a 2 week rat study convulsions were observed at 500 mg/kg/day (23X human AUC @ 180 mg/day) in conjunction with hypocalcemia. Convulsions and CNS toxicity were observed in an acute study with a putative metabolite/degradation product ———— at 100 mg/day (exposure relative to the clinical dose is unknown). Serum calcium was not measured which further suggested that the toxicity observed may be a function of the metabolites formed and hypocalcemia. It is unclear whether the metabolites have a differential capacity to alter calcium homeostasis. Also related to the hypocalcemic effect is the QTc prolongation (maximum 80 msec) observed in the 3 and 12 month monkey studies at exposures <2X the human therapeutic. Interestingly the EKG effects appear to attenuate after 12 months of treatment compared to 6 months although the hypocalcemia (10-40%) does not. QT prolongation was not observed in a one month dog study despite a maximal serum calcium reduction of 20% at doses similar to those tested in the monkey. The QTc prolongation and convulsions may reflect at least a partial contribution of hypocalcemia or may be mediated by a direct effect of cinacalcet and/or its metabolites on CaR in these tissues. Hence the clinical relevance of hypocalcemia and the contribution of metabolites to this mechanism should be explored further.

A clinical consult from Cardio-Renal Drugs (HFD-110) recommends a thorough evaluation of QT effects including a dosing regimen that challenges tolerability, allows for production of metabolites and suggest the timing of the EKG to Cmax (parent + metabolites), external control of plasma calcium is relevant in order to delineate this confounder. Based on the in vitro data indicating significant inhibition (95% at 500 ng/ml) of K_{ATP} ion channels by cinacalcet and the relationship these channels have in cardiac preconditioning in ischemic stress; Dr. Kuijpers' pharmacology/toxicology review recommends a clinical investigation of stress EKG testing. Since secondary HPT patients may have an increased incidence of cardiovascular disease this would seem prudent.

Serum testosterone levels were decreased in the chronic monkey study at exposures ≤ 2 times the human therapeutic dose concomitant with a decrease in testicular weight only at 100 mg/kg/day. Testicular tubular atrophy/degeneration was observed in the one and 6 month rat studies at 3 and 8 times human therapeutic AUC and in a one month dog study at human therapeutic exposures. Fertility studies in male rats did not indicate a significant reduction in fertility index. A complete battery of reprotoxicity studies in rats and rabbits was performed. Dosing was limited by maternal toxicity. Cinacalcet is secreted into milk at appreciable levels and crosses the placenta in rabbit where fetal levels are ~1/10 maternal plasma levels. No fertility effects were observed in male or female rats at exposures 3 times human therapeutic. Higher doses resulted in observable maternal toxicity. In segment II studies maternal toxicity was observed at all doses although the only fetal effect was decreased body weight. Exposures in this study were less than human therapeutic. Similar studies in rabbit do not result in any fetal adverse effects (exposures less than human therapeutic) despite maternal toxicity. Segment III studies in pregnant rats show no adverse fetal/pup effects at human therapeutic exposures in the absence of maternal toxicity. Exposures twice human therapeutic exposure was accompanied by maternal mortality, parturition difficulties, litter loss and reductions in maternal and pup body weight. The maternal toxicity seen here is likely related to hypocalcemia based on the increased need for calcium during parturition. Based on the fetal body weight effects in the absence of maternal toxicity pregnancy category C was indicated as proposed by the sponsor.

The genotoxicity standard battery was negative. The rat and mouse 2-year dietary carcinogenicity studies were reviewed by ECAC, however the Committee found that there were no relevant tumor findings related to drug treatment.

Recommendation: A full complement of nonclinical pharmacology and toxicology studies have been performed in this application which have identified findings of clinical relevance. Additional nonclinical studies are not needed for further hazard identification at this time however additional clinical evaluation may be needed at the discretion of the clinical team (see HFD-110 consult). Pharmacology/ Toxicology recommends approval (AP) pending labeling comments (see memo of 2/10/04).

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/s/

Karen Davis-Bruno
2/17/04 10:11:41 AM
PHARMACOLOGIST
AP

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: February 13, 2004

To: Pamela Danagher	**From:** Randy Hedin
Company: Amgen Inc.	Division of Metabolic and Endocrine Drug Products
Fax number: 805-480-1330	**Fax number:** 301-443-9282
Phone number: 805-447-0214	**Phone number:** (301) 827-6392

Subject: Cardio Renal Consult

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES ☑ NO

From: Hedin, Durand M
Sent: Friday, February 13, 2004 4:11 PM
To: 'Danagher, Pamela'
Subject: NDA 21-688, Revised Draft Label

Dear Ms. Danagher:

Please refer to your September 5, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sensipar (cinacalcet HCl) Tablets.

We are reviewing the labeling of your submission, and have attached a word document with revised draft labeling. Please be advised that these are initial comments by the Division. Additional, comments and recommendations will be requested by the Division, and the Office.

If you have any questions, call me at (301) 827-6392.

Sincerely,

Randy Hedin

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