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

N21688
ıge Insert 2 13 ;

18 page(s) of revised draft labeling has been redacted from this portion of the review.

A-16

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/s/

Randy Hedin
2/13/04 04:32:03 PM
CSO

1 page(s) of revised draft labeling has been redacted from this portion of the review.

A-16

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/s/

Karen Davis-Bruno
2/10/04 01:23:47 PM
PHARMACOLOGIST
P/T label comments

From: Hedin, Durand M
Sent: Monday, February 09, 2004 3:31 PM
To: 'Danagher, Pamela'
Subject: RE: NDA 21-688

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 clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Pooled Data from Studies 172, 183, and 188

- For the Cinacalcet group, please provide a histogram of the doses of drug that patients were receiving at the ends of the Titration and Efficacy-Assessment phases.

- What were the mean and median doses for patient who achieved a iPTH < 250 pg/ml?

- What was the association between risk for hypocalcemia (< 8.4 mg/dl) and dose of Cinacalcet?

- If available, please provide follow up information on the SGPT levels of patients 16302 and 13910.

Studies 236 and 239

- For 236, please provide the mean and median doses for the patients in the Cinacalcet group who achieved a iPTH < 65 pg/ml.

- For 239, please provide the mean and median doses for the patients in the Cinacalcet group who achieved a iPTH reduction of $\geq$ 30% from baseline.

Study 120

- Please provide the percentage of patients in each group who developed a serum calcium level of < 8.4 mg/dl on at least one occasion during the trial.

- Please provide the percentage of patients in each group who developed a serum calcium level < 7.4 mg/dl on at least one occasion during the trial.

- Please provide a histogram of the changes from baseline to Week 52 in iPTH and

calcium levels for the two groups.

- Please provide the mean and median doses of Cinacalcet at Week 52 of the study.

- We are concerned that you may have "enriched" the population of patients enrolled into Study 120 by including 22 patients who previously participated in Study 980125. Please explain.

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

Sincerely,

Randy Hedin

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/s/

Randy Hedin
2/9/04 03:52:15 PM
CSO

From: Hedin, Durand M
Sent: Wednesday, February 04, 2004 2:18 PM
To: 'Danagher, Pamela'
Subject: RE: NDA 21688
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 clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Please provide the PTH assays that were used in each of the phase 2 and 3 clinical studies included in the Cinacalcet NDA submission. This information should include:

- Name of the study
- Dates the assay(s) was used
- Trade name of the assay
- Methodological description of the assay

Because [redacted] performed the PTH assays, we believe it is important that [redacted] verify in writing the above information.

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

Sincerely,

Randy Hedin

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/s/

Randy Hedin
2/4/04 02:40:15 PM
CSO

From: Hedin, Durand M
Sent: Thursday, January 22, 2004 4:29 PM
To: 'pamelad@amgen.com'
Cc: 'jfellows@amgen.com'
Subject: NDA 21-688
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 clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

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

Sincerely,

Randy Hedin

For the following questions, please provide answers or reference the appropriate section(s) of the NDA where the answers can be found.

From the Entire Clinical Development Database (phase 1- 3):

1. Please provide all WHOART primary adverse event terms that could reasonably be associated with increased acid secretion in the stomach or duodenum.

2. Based on the WHOART terms in question 1, please provide the number of patients and treatment assignment who experienced symptoms that could reasonably be associated with increased acid secretion in the stomach or duodenum.

Using the pooled data from studies 172, 183, and 188:

3. Based on the WHOART terms in question 1, please provide the number of patients in the cinacalcet and placebo groups who experienced symptoms that could reasonably be associated with increased acid secretion in the stomach or duodenum.

4. Please provide the number of patients in the cinacalcet and placebo groups that received, on at least one occasion, a medication to treat an increased stomach acidity, GERD, gastritis, etc.

For studies 990126, 990740 and 20010141:

5. Please provide end of study values and analysis for the bone turnover parameters: mineralization lag time, osteoid thickness and osteoid surface

For study 20000188:

6. For the data provided in Tables 8 and 11 of the Internal Report on the Assessment of Hormone Levels, please provide appropriate statistical analyses of the comparison between the placebo and cinacalcet groups for the mean changes in total and free testosterone from baseline to Weeks 16 and 26.

7. For the data provided in Tables 10 and 13 of the Internal Report on the Assessment of Hormone Levels, please provide appropriate statistical analyses of the comparison of the proportion of subjects in the placebo and cinacalcet groups with normal baseline and below normal range levels of total and free testosterone at Weeks 16 and 26.

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/s/

Randy Hedin
1/22/04 04:49:51 PM
CSO

From: Hedin, Durand M
Sent: Wednesday, January 14, 2004 1:47 PM
To: 'Danagher, Pamela'
Cc: 'jfellows@amgen.com'
Subject: NDA 21-688

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 clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

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

Sincerely,

Randy Hedin

Using the pooled data from studies 172, 183, and 188:

1. Please provide the number of patients in the cinacalcet and placebo groups that received, on at least one occasion, a medication to treat an episode of nausea or vomiting.

2. Please provide the reference range for normal serum calcium used by the ——— laboratory.

3. Please provide the number and % of patients in each treatment group who had at least one serum calcium level < 8.4 mg/dl; the number and % of patients who were instructed to increase their calcium intake; the number and % of patients who had their dose of vitamin D increased; and the number and % of patients who had their study drug withheld. Please present data in total and stratified, based on treatment, treatment period and strata.

4. Please provide the baseline heart rates in the placebo and cinacalcet groups along with the mean changes from baseline to Week 26.

5. Please provide the mean percent change from baseline to Week 26 for all of the parameters listed in section 2.7.4.3.1.1 of the Clinical Summary, Summary of Clinical Safety.

6. Please provide the number and % of patients in the placebo and cinacalcet groups

who developed SGPT values that were > 1x ULN, > 2 x ULN, and > 3 x ULN. Please also provide the absolute value for the largest increase in SGOT in the placebo and cinacalcet groups. In addition to providing the overall results of these analyses, please present data stratified, by treatment group, treatment period (titration, efficacy assessment) and all of the pre-defined subgroup strata.

7. Was body weight systematically measured during the trials? If so, please provide the mean percent change from baseline to Week 26 for the placebo and cinacalcet groups.

8. Please provide the modified WHO lab ranges used and precise definitions of the derived levels used to define the various grades for abnormal laboratory values used in the shift tables.

9. Please provide the number of all protocol deviations and eligibility deviations, stratify by study, treatment group, treatment period (titration, efficacy assessment), and all pre-defined subgroup strata.

Using pooled data from studies 236 and 239:

10. Please provide the number and % of patients in each treatment group who had at least one serum calcium level < 8.4 mg/dl; the number and % of patients who were instructed to increase their calcium intake; the number and % of patients who had their dose of vitamin D increased; and the number and % of patients who had their study drug withheld.

11. Please provide the mean baseline serum calcium levels for the cinacalcet and placebo groups and the mean percent change from baseline to Week 16 (with min and max values).

From the Entire Clinical Development Database (phase 1- 3):

12. Please provide the number of patients who experienced a seizure during participation in any of the phase 1 – 3 clinical studies. Please also indicate which clinical study and treatment group (cinacalcet or placebo) the patients were assigned to.

13. Are there WHOART primary adverse event terms in addition to convulsions, convulsions local, and status epilepticus that could indicate seizure activity?

14. Please provide the number of patients who experienced esophagitis, gastritis, or upper GI bleed during participation in any of the phase 1 – 3 clinical studies. Please also indicate which clinical study and treatment group (cinacalcet or placebo) the patients were assigned to.

Clinical Study 240:

15. What determined whether a patient entered study 240?

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/s/

Randy Hedin
1/14/04 03:40:40 PM
CSO

MEMORANDUM OF TELECON

DATE: January 7, 2004

APPLICATION NUMBER: NDA 21-688, Sensipar (cinicalcet HCl) Tablets

BETWEEN:

Name: Pamela Danagher, Manager, Regulatory Affairs
Phone: 805-447-0214
Representing: Amgen Inc.

AND

Name: Randy Hedin, Senior Regulatory Management Officer
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Request QT and PK Information

I called Ms. Danagher and requested the following information:

- Submit a very brief summary of the multiple-dose PK data including T_{max} and T_{nadir} serum calcium.
- Submit all QT data for phases 1-3 and include a description of patient populations and indicate the time ECGs were obtained relative to the most recent dose of drug.

Ms. Danagher stated that Amgen would try to get this information to us in a week, but, they try to turn-around all information requests in two weeks.

/S/

Randy Hedin
Senior Regulatory Management Officer

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/s/

Randy Hedin
1/7/04 04:06:12 PM
CSO

12/23/03

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-688

INFORMATION REQUEST LETTER

Amgen Inc.
Attention: Pamela Danagher
Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

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 also refer to your submission dated December 3, 2003.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance:

1. If you plan to recycle any of the solvents involved in the drug substance manufacturing, provide the protocol for the procedure.

2. Provide typical storage temperatures, and duration, for the storage of the intermediates used in the synthesis of the drug substance, cinacalcet HCl.

3. Inform us if "pooling" multiple lots of an intermediate may occur. If so, what is your protocol for "pooling?"

4. The values of LOD and LOQ reported in the analytical procedure for impurities (p. 74 of the Method Validation Package, Volume 1 of 3) are not consistent with those values reported in the validation report (p. 100 of the Method Validation Package, Volume 1 of 3 and p. 24 of NDA CMC section 3.2.S.4). Provide clarification for this discrepancy.

5. Your acceptance criteria should include a specific identity test (e.g. by IR) for the packaging component which directly contacts the drug substance. Therefore, provide an ID test for your [redacted].

6. Your primary stability studies for the drug substance are performed at 25°C. Therefore, the proposed storage statement in the NDA should be revised.

7. Concerning your proposal for the primary reference standard (PRS) specification limits (Table 1, page 8, Response to CMC questions, NDA 21-688 Amendment 3), the acceptance criteria of future PRS lots should be at least the same as those for the first PRS lot. In order to adequately characterize each future PRS, your protocol for this purpose should also include a [redacted] for the new standard.

Drug Product:

In Section 3.2.P.2.2.1 (Formulation Development), [redacted]

If you have any questions, call Randy Hedin, Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Randy Hedin
12/23/03 03:28:17 PM
Signing for Kati Johnson

11/18/03

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-688

74-day ltr

Amgen Inc.
Attention: Pamela Danagher
Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

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 have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on November 7, 2003 in accordance with 21 CFR 314.101(a). Our filing review is only a preliminary review and deficiencies may be identified during substantive review of your application.

In our filing review, we have identified the following potential review issues:

Drug Substance:

1. [redacted]

2. Please provide an executed batch record for a representative commercial lot of the drug substance.

3. Describe any remedial actions you take, prior to the final step, in the manufacture of the drug substance, when any in-process acceptance criteria are not met.

4. [redacted]

Drug Product:

1. In section 3.2.P.3, you state that [redacted] substance prior to use in manufacturing the drug product. Is this [redacted] the same as that performed by [redacted] for their release of the drug substance? If not, describe the differences.

2. Please indicate whether or not any reprocessing, in the manufacture of your drug product, may be carried out. If there is any reprocessing during manufacture, describe the procedures that may be carried out.

3. Your acceptance criteria should include specific identity tests (e.g. by IR) for those packaging components that may contact the drug product. Consequently, provide specific identity tests for your [redacted] bottles, the appropriate surface of your [redacted] filler, and relevant seals on your child-resistant-closure.

4. Your release and stability data for the batches of manufactured drug product show total impurities at much lower levels than your proposed acceptance criteria of [redacted] Accordingly, your specification for total impurities in the drug product should have a lower limit.

5. Provide your justification for not including a test for amorphous cinacalcet HCl in your drug product specification.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

David Orloff
11/18/03 09:44:15 AM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-688	Efficacy Supplement Type SE-	Supplement Number	
Drug: Sensipar		Applicant: Amgen Inc.	
RPM: Randy Hedin		HFD- 510	Phone # 827-6392
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	( ) Standard (X) Priority
• Chem class (NDAs only)	1
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	March 8, 2004
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity (approvals only)	
• Exclusivity summary	March 8, 2004
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of*	( ) Yes, Application #_____ (X) No

sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	PM Review: October 30, 2003 ADRA, March 5, 2004
General Information	
❖ Actions	
• Proposed action	(X) AP NDA 21-688 (X) AE NDA 21-688/S-001 NDA 21-688/S-002
• Previous actions (specify type and date for each action taken)	None
• Status of advertising (approvals only)	(X) Material requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None (X) Press Release (X) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	March 5, 2004
• Original applicant-proposed labeling	September 5, 2003
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMETS, November 8, 2003 March 5, 2004
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NA
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	September 5, 2003 February 26, 2004
• Reviews	Chemistry, February 26, 2004 March 3, 2004
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	March 3, 2004
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	December 19, 2001
• Pre-NDA meeting (indicate date)	July 29, 2003
• Pre-Approval Safety Conference (indicate date; approvals only)	February 11, 2004
• Other	Filing: October 30, 2003
❖ Advisory Committee Meeting	
• Date of Meeting	None
• 48-hour alert	

9/22/03

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-688

Amgen Inc.
Attn: Pamela Danagher
Manager, Regulatory Affairs
One Amgen Center Drive, Mail Stop 17-2-A
Thousand Oaks, CA 91320-1799

Dear Ms. Danagher:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Sensipar™ (cinacalcet HCl) Tablets
Review Priority Classification:	Priority (P)
Date of Application:	September 5, 2003
Date of Receipt:	September 8, 2003
Our Reference Number:	NDA 21-688

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 7, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be March 8, 2004.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6429.

Sincerely,

/S/

{See appended electronic signature page}

Randy Hedin, R.Ph.
Senior Regulatory Management Officer
Division of Metabolic & Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Valerie Jimenez
9/22/03 03:19:18 PM
Signing for Randy Hedin, R.Ph.

NDA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

NDA #	21-688
Trade Name:	Sensipar
Generic Name:	cinacalcet HCl
Strengths:	30, 60, and 90 mg
Applicant:	Amgen Inc.
Date of Application:	September 5, 2003
Date of Receipt:	September 8, 2003
Date clock started after UN:	N/A
Date of Filing Meeting:	October 15, 2003
Filing Date:	November 7, 2003
User Fee Goal Date:	March 8, 2004
Indication(s) requested:	Treatment of primary and secondary hyperparathyroidism.

Type of Original NDA: (b)(1) ____X_____ (b)(2) _____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____
NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S _____ P ____X_____
Resubmission after withdrawal? ___No__ Resubmission after refuse to file? ____No__
Chemical Classification: (1,2,3 etc.) ____1_____
Other (orphan, OTC, etc.) Not at this time.

User Fee Status: Paid ___X_____ Exempt (orphan, government) _____
Waived (e.g., small business, public health) _____

Form 3397 (User Fee Cover Sheet) submitted: YES NO
User Fee ID # ____4596_____
Clinical data? YES___X_____ NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES NO X

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? YES NO X

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

Is the application affected by the Application Integrity Policy (AIP)? YES NO X
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? N/A

- Does the submission contain an accurate comprehensive index? YES X NO
- Was form 356h included with an authorized signature? YES X NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES X NO
  If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A YES X NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?
  All parts are submitted in electronic format.

  Additional comments:
- If in Common Technical Document format, does it follow the guidance? N/A YES X NO
- Is it an electronic CTD? N/A YES X (NO)
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?
  All parts are submitted in electronic format.

  Additional comments:
- Patent information submitted on form FDA 3542a? YES X NO
- Exclusivity requested? YES, ___5___years NO
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES X NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., *"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application."* Applicant may not use wording such as "To the best of my knowledge . . . ."
- Financial Disclosure forms included with authorized signature? YES X NO
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES X NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES X NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers: IND 56,010

- End-of-Phase 2 Meeting(s)? Date(s) _November 9, 2001
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _July 20, 2003
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?

  DDMAC will come to labeling meetings.

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES X NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A X YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A X YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?
  N/A X YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO
  If no, did applicant submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO

- If a parenteral product, consulted to Microbiology Team (HFD-805)? N/A

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #:

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

  YES NO

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  ____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

  ____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

  IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

  ____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

  ____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:

  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES NO

  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    YES NO

  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    N/A YES NO

  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

    N/A YES NO

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    YES NO

  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    YES NO

  - EITHER
    The number of the applicant's IND under which the studies essential to approval were conducted.

    IND # _____ NO

    OR

    A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

    N/A YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

  YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 15, 2003

BACKGROUND:
(Provide a brief background of the drug, e.g., it was already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES:

ASSIGNED REVIEWERS:

Discipline	Reviewer
Medical:	Patricia Beaston
Secondary Medical:	Eric Colman
Statistical:	Joy Mele
Secondary Statistical:	Todd Sahlroot
Pharmacology:	Gemma Kuijpers
Secondary Pharmacology:	Karen Davis-Bruno
Chemistry:	Shulin Ding
Secondary Chemistry:	Mamta GAutam-Basak
Biopharmaceutical:	Johnny Lau
Secondary Biopharmaceutical:	Hae-Young Ahn
DSI:	Andrea Slavin
Regulatory Project Management:	Randy Hedin

Per reviewers, are all parts in English or English translation? YES X NO

CLINICAL FILE __X_ REFUSE TO FILE____

- Clinical site inspection needed: YES X NO
- Advisory Committee Meeting needed? YES, date if known _____ NO X
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A X YES NO

CLINICAL MICROBIOLOGY NA _X____ FILE _____ REFUSE TO FILE _____

STATISTICS FILE ___X___ REFUSE TO FILE _____

BIOPHARMACEUTICS FILE ___X___ REFUSE TO FILE _____

- Biopharm. inspection needed: YES NO X

PHARMACOLOGY NA _____ FILE ___X__ REFUSE TO FILE _____

- GLP inspection needed: YES NO X

CHEMISTRY FILE ___X___ REFUSE TO FILE _____

- Establishment(s) ready for inspection? YES X NO
- Microbiology (NA) YES NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

___X___ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

___X____ No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

- Goal to finish reviews with team leader sign-off is January 15, 2004.
- Action Package should start circulating on January 25, 2004.
- Action Package should go to the Division Director on February 1, 2004.
- Action package should go to ODEII on February 15, 2004
- Pre-Approval Safety Conference should be scheduled the week of February 2, 2004.
- Internal labeling meeting should be scheduled the week of January 2, 2004

ACTION ITEMS:

- Document filing issues/no filing issues conveyed to applicant by Day 74.

{See appended electronic signature page}

Regulatory Project Manager, HFD-510

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Randy Hedin
10/30/03 09:33:24 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-688

8/26/03

Amgen Inc.
Attn: Pamela Danagher
Manager Regulatory Affairs
One Amgen Center Drive, Mail Stop 24-1-C
Thousand Oaks, CA 91320-1799

Dear Ms. Danagher:

We have received your presubmission of nonclinical and Chemistry, Manufacturing, and Controls information for the following:

Name of Drug Product:	Sensipar™ (cinacalcet HCl) Tablets
Date of Submission:	August 14, 2003
Date of Receipt:	August 15, 2003
Our Reference Number:	NDA 21-688

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete. Please cite the NDA number assigned to this application at the top of the first page of every communication concerning this application.

Address all additional presubmissions as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

Send the submission that completes this application and is intended to start the review clock to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Ave.
Rockville, Maryland 20852-1833

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

Sincerely,

/S/

{See appended electronic signature page}

Randy Hedin, R.Ph.
Senior Regulatory Management Officer
Division of Metabolic & Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Julie Rhee
8/26/03 02:39:56 PM
Signed for Randy Hedin

NDA 21-688
Sensipar (cinacalcet HCl) Tablets

No Advisory Committee meeting was held.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

See Instructions on Reverse Side Before Completing This Form

ompleted form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320

2. TELEPHONE NUMBER *(Include Area Code)*

(805) 447-1000

3. PRODUCT NAME
SENSIPAR (Cinacalcet HCl)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
N021-688

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER
4596 12 AUG 2003

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?
☐ YES ☒ NO
(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	VP Regulatory Affairs	8/21/03

FORM FDA 3397 (1/03)

PSC Media Arts (301) 443-1090 EF

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning SEE ATTACHED LIST OF INVESTIGATORS, who participated as a clinical investigator in the submitted study SEE ATTACHED LIST OF STUDIES, is submitted in accordance with 21 CFR part

Name of clinical investigator

Name of clinical study

54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

any proprietary interest in the product tested in the covered study held by the clinical investigator;

any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Dawn Viveash, MD	Vice President, Regulatory Affairs
FIRM / ORGANIZATION: Amgen, Inc.	
SIGNATURE: Dr Viveash	DATE: 8/11/03

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

NDA 21-688
Sensipar (cinacalcet HCl) Tablets

Introductory promotional materials requested in action letter.

23 page(s) of revised draft labeling has been redacted from this portion of the review.

A-17

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: May 9, 2003 **DATE OF DOCUMENT:** April 15, 2003	**DESIRED COMPLETION DATE:** July 9, 2003	**ODS CONSULT #:** 03-0109

TO:

David Orloff, MD
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH:

Randy Hedin
Project Manager
HFD-510

PRODUCT NAME: Sensipar (Cinacalcet HCl Tablets) 30 mg, 60 mg, and 90 mg **NDA#:** 21-688	**NDA SPONSOR:** Amgen

SAFETY EVALUATOR: Nora Roselle, PharmD

SUMMARY: In response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name, Sensipar, to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:

1. DMETS has no objections to the use of the proposed proprietary name Sensipar provided that only one name Sensipar (NDA 21-688) or [redacted] is approved. [redacted] Sensipar, which was discovered on the internet. According to a publicly available database, the Sensipar trademark was filed with the Patent and Trademark Office on January 26, 2001 by Amgen, Inc. We have suggested that [redacted] contact Amgen before proceeding with any marketing plans [redacted] FDA will not allow these two names to co-exist in the marketplace due to their similarity.

2. DMETS recommends implementation of the label and labeling recommendations outlined in section III of this review.

3. DDMAC finds the proprietary name, Sensipar, acceptable from a promotional perspective.

/S/ /S/

Carol Holquist, RPh
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION

An Expert Panel Discussion was held by DMETS to gather professional opinions on the safety of the proprietary names Sensipar. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. Several product names were identified in the Expert Panel Discussion (EPD) and as a result of a consult completed with a similar name, that were thought to have potential for confusion with Sensipar. These products are listed in Table 1 (see below) along with the dosage forms available and usual FDA-approved dosage.

2. DDMAC did not have concerns about the name Sensipar with regard to promotional claims.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other
Sensipar	Cinacalcet HCl Tablets, 30 mg, 60 mg, and 90 mg	Secondary Hyperparathyroidism: 30 mg/day; maximum recommended dose is 180 mg/day Primary Hyperparathyroidism: 30 mg BID	
			Look-alike, Sound-alike
Fansidar	Sulfadoxine 500 mg/ Pyrimethamine Tablets: 25 mg	Malaria prophylaxis for adults: The first dose should be taken 1 or 2 days before departure to an endemic area; administration should be continued during the stay and for 4 to 6 weeks after return (1 tablet once weekly, then 2 tablets once every 2 weeks) Acute Attack of Malaria: A single dose of 2-3 tablets used in sequence with quinine or alone.	Look-alike, Sound-alike
Zanosar	Streptozocin Powder for Injection: 1 g vials	IV: 500 mg/m^2 of body surface area for 5 consecutive days every six weeks until maximum benefit or until treatment-limiting toxicity is observed	Look-alike, Sound-alike
Sinequan	Doxepin HCl Capsules: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg Oral Concentrate: 10 mg/mL	Initial: 75 mg/day, up to 150 mg/day	Look-alike
			Look-alike
			Sound-alike

Product Name	Dosage form(s), Established name	Usual adult dose*	Other
Sensipar	Cinacalcet HCl Tablets, 30 mg, 60 mg, and 90 mg	Secondary Hyperparathyroidism: 30 mg/day; maximum recommended dose is 180 mg/day Primary Hyperparathyroidism: 30 mg BID	
Zinecard	Dexrazoxane Powder for Injection, lyophilized: 250 mg and 500 mg vials	Administer less than 30 minutes before the doxorubicin injection. The recommended dosage ration of dexrazoxane:doxorubicin is 10:1.	Sound-alike
Zemplar	Paricalcitol Injection: 5 mcg/mL in 1 mL and 2 mL single dose vials	Inject 0.04 mcg/kg to 0.1 mcg/kg as an intravenous bolus every other day during dialysis.	Sound-alike
*Frequently used, not all-inclusive. ***NOTE: This review contains proprietary and confidential information that should not be released to the public.***			

B. DMETS' Phonetic and Orthographic Analysis (POCA) database

DMETS' Phonetic and Orthographic Analysis (POCA) database was unavailable to search at the time of this review.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary names to determine the degree of confusion of Sensipar with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 128 health care professionals (pharmacists, physicians, and nurses) for each name. These exercises were conducted in an attempt to simulate the prescription ordering process. Inpatient orders and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Sensipar (see below). These prescriptions were optically scanned and were delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

Sensipar

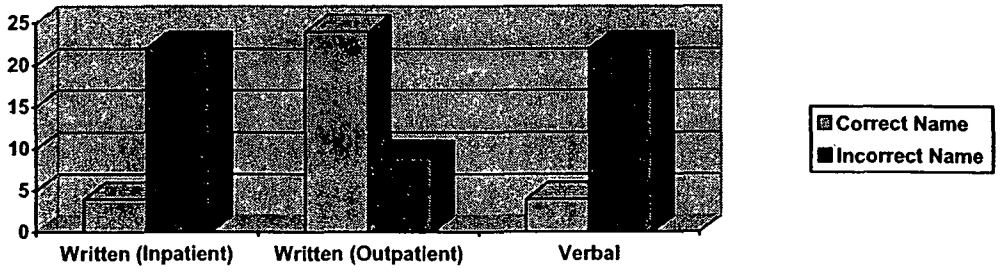
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Sensipar 60mg 1 po qd #30	Sensipar 60 mg Take one by mouth daily. Dispense number thirty.
Inpatient RX: Sensipar 60mg 1 po QD #30	

2. Results:

The results for **Sensipar** are summarized in Table 2.

Table 2

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	42	26 (62%)	4 (15%)	22 (85%)
Written Outpatient	43	33 (77%)	24 (73%)	9 (27%)
Verbal	43	26 (60%)	4 (15%)	22 (85%)
Total	128	85 (66%)	32 (38%)	53 (62%)



Among the written inpatient prescription study participants for Sensipar, 22 of 26 (85%) participants interpreted the name incorrectly. The incorrect responses were *Sensipan (5), Sinsipan (4), Sensupar (2), Sinspan (2), Sinsipar (2), Sinsupan (1), Sinsupar (1), Sensypan (1), Sinsyun (1), Sinsypan (1), Senspan (1),* and *Sinsipa (1),* none of which are names of currently marketed drug products. One respondent commented that the name "looks like Sinequan".

Among the written outpatient prescription study participants for Sensipar, 9 of 33 (27%) participants interpreted the name incorrectly. The incorrect responses were *Sensipac (7), Senipar (1),* and *Sensipae (1).* None of the incorrect responses are names of currently marketed drug products.

Among the verbal prescription study participants for Sensipar, 22 of 26 (85%) of the participants interpreted the name incorrectly. The incorrect responses were *Sensapar (9), Sensopar (7), Censapar (2), Censpar (1), Sensabar (1),* and *Sensepar (1),* none of which are names of currently marketed drug products.

D. SAFETY EVALUATOR RISK ASSESSMENT:

In reviewing the proposed proprietary name "Sensipar", the primary concerns raised were related to eight look-alike and/or sound-alike names. The products considered to have potential for name confusion with Sensipar were [redacted] Fansidar, Zanosar, Sinequan, [redacted] Zinecard, and Zemplar.

We conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Sensipar could be confused with [redacted] Fansidar, Zanosar, Sinequan, [redacted] Zinecard, or Zemplar. However, negative findings are not always predicative as to what may occur once the drug is

NOTE: This review contains proprietary and confidential information that should not be released to the public.

widely prescribed, as these studies have limitations primarily due to sample size. In the written outpatient study, one respondent interpreted the prescription as [redacted] which looks almost identical to [redacted]

1. [redacted] was identified to have look and sound-alike potential with Sensipar.

[redacted]

Both products share six letters common in both names. Both products begin with the letter 'S' and end with the letters [redacted]

Sensipar [redacted]

Although the first syllable is spelled differently ([redacted] vs. SEN), when pronounced both syllables are phonetically similar bearing the sound of [redacted] In addition, [redacted] and Sensipar end with the same 'EE-PAR' sound. These similarities contribute to the sound and look-alike characteristics of Sensipar and [redacted] The only phonetic and orthographic difference in the names is the second syllable in which [redacted] sound and Sensipar has the 'SI' sound. Sensipar [redacted] characteristics. In addition, these products will be available as tablets. It should be noted that in the written outpatient study, one respondent interpreted the prescription as [redacted] which looks almost identical to [redacted] There are different characteristics such as the strengths and indication of use but the commonalties between these two names strongly contribute to their look-alike and sound-alike characteristics of the two products. Additionally, the potential for confusion is compounded by [redacted]

NOTE: This review contains proprietary and confidential information that should not be released to the public.

[redacted] There is a high potential for name confusion especially if both products are introduced into the marketplace in close proximity to each other. Given the look-alike and sound-alike similarities between [redacted] and Sensipar, DMETS believes that the names may not co-exist in the marketplace. DMETS has no objections to the used of the proposed proprietary name Sensipar provided that only one name, Sensipar (NDA 21-688) or [redacted], is approved. The acceptability of the proposed proprietary name Sensipar depends on which application, Sensipar or [redacted], receives approval first, as these two names may not co-exist due to their similarities.

2. Fansidar has a look and sound-alike similarity to Sensipar. Fansidar is indicated for the treatment of P. falciparum malaria for those patients in whom chloroquine resistance is suspected. For treatment of acute attack of malaria, a single dose of 2 to 3 tablets of Fansidar is taken in sequence with quinine or alone. For malaria prophylaxis, Fansidar should be taken 1 to 2 days before departure to an endemic area and administration should be continued during the stay and for 4-6 weeks after return (take one tablet weekly then 2 tablets once every 2 weeks). Fansidar is supplied in unit dose package of 25, each tablet containing 500 mg sulfadoxine and 25 mg pyrimethamine. Both product names share rhyming characteristics with each having 3 syllables. Additionally, depending on the way the letter 'F' is scripted, 'FANSI' and 'SENSI' can potentially look-alike.

Fansidar Sensipar

Both names also share the last two letters 'AR'. Fansidar has a dosing regimen that is unique and distinguishes it from the usual once or twice daily dosing of Sensipar. Also, based on the dosing regimen for Fansidar, the quantity to be dispensed will be small compared to Sensipar which is likely to be ordered for a month supply at a time. Therefore, DMETS believes there is minimal risk for confusion between the two names.

3. Zanosar may have a look and sound-alike similarity to Sensipar. Zanosar is indicated for the treatment of metastatic islet cell carcinoma of the pancreas. It is available in 1 gram injectable vials. The recommended daily intravenous dose is 500 mg/m^2 of body surface area for five consecutive days every six weeks until maximum benefit or until treatment-limiting toxicity is observed. The names have rhyming suffixes ('SAR' vs. 'PAR') and the prefixes, 'ZAN' and 'SEN', may look similar when scripted.

Zanosar Sensipar

However, there are differences between the two products that may decrease potential name confusion. Each product has a different dosage form (injectable vs. tablet), strength (1 g vs. 30 mg, 60 mg, and 90 mg), indication for use (carcinoma vs. hyperparathyroidism), and route of administration (intravenous vs. oral). In addition, Zanosar should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. A patient does not need to be hospitalized but should have access to a facility with laboratory and supportive resources sufficient to monitor drug tolerance, and protect and maintain a patient compromised by drug toxicity. Sensipar, on the other hand, can be dispensed on an outpatient basis without the supervision of a healthcare practitioner. Also, Zanosar will have detailed intravenous dosing

instructions as the dosage is based on the body surface area (BSA) of the patient. Although there are some look and sound-alike similarities between Zanosar and Sensipar, we believe the above-mentioned differences will help minimize the potential for name confusion between the two products.

4. Sinequan was identified to have a look-alike similarity with Sensipar. Sinequan is a tricyclic antidepressant. Sinequan is available as 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg oral tablets and as a 10 mg/mL oral concentrate. The usual dose of Sinequan in the treatment of depression is 75 mg to 150 mg per day. Doses up to 300 mg/day have been used with more severe anxiety or depression. One respondent from the written inpatient study commented that the name "looks like Sinequan". The two names share some similar look-alike characteristics such as the prefixes 'SIN' and 'SEN'. In addition, each name contains a downstroke letter ('Q' vs. 'P') in the middle and ends with similar looking letters ('AN' vs. 'AR') if the name trails off at the end. The handwriting sample provided in the study is shown below.

Sinequan 60mg 1 po QD #30

Besides slight look-alike similarities, the two drugs share an overlapping route of administration (oral), dosage form (tablet), and dosing regimen (once daily). However, there are other characteristics that may help differentiate Sinequan from Sensipar. The two products have different indications for use, strengths (30 mg, 60 mg, and 90 mg vs. 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, and 10 mg/mL), and usual daily doses (30 mg or 60 mg vs. 75 mg or 150 mg). Even though there are some similarities between the two names, the differences in strength and daily dose will help minimize the risk for confusion.

5. [redacted] may have look-alike potential with Sensipar. [redacted]

[redacted]

Sensipar

However, there are many characteristics that help differentiate between the two products. The two products each have a different indication for use [redacted] vs. hyperparathyroidism), dosage form ([redacted] tablet), route of administration ([redacted] oral), and strength ([redacted] 30 mg, 60 mg, and 90 mg). Furthermore, the use of [redacted] will be limited [redacted] whereas Sensipar will not. [redacted]

contributes to the verbal similarities between the names. However, Zemplar contains two syllables and Sensipar contains three syllables, which causes the names to have a different rhyming quality when spoken. The second syllable of Sensipar ('SI') also helps to differentiate the names. Moreover, differences such as the dosage form (injectable vs. tablet), route of administration (intravenous vs. oral), and strength (5 mcg/mL and 5 mcg/2 mL vs. 30 mg, 60 mg, and 90 mg) further differentiate the two products. Although it is likely that Sensipar prescriptions can be called into an outpatient pharmacy, Zemplar orders will be restricted to an institution or hospital setting for patients with chronic renal failure receiving dialysis. Even though there are some similarities in the phonetic characteristics between Zemplar and Sensipar, the above-mentioned differences will help minimize the potential for confusion between the two products.

III. PACKAGING, LABELING, AND SAFETY RELATED ISSUES:

Additionally, DMETS reviewed the physician sample labels and labeling, container labels and insert labeling for Sensipar and has identified the following areas of possible improvement.

A. CONTAINER LABELS (Physician Sample and 30-count bottles)

1. We recommend increasing the prominence of the established name. While the 'HCl' portion of the established name is ½ the size of the proposed name, the 'Cinacalcet' is not. Revise accordingly.

2. Relocate the strength to appear in conjunction with the proprietary and established name. In addition, place the 'mg' on the same line as the numbered strength.

3. We recommend relocating the net quantity statement to appear away from the product strength and de-bolding the font especially since the net quantity overlaps with an existing strength.

4. We are unable to determine from the materials provided if the 30-count bottle is packaged with a Child Resistant Closure (CRC). If appropriate, please revise accordingly as a 30-count bottle may be dispensed on an outpatient basis as a "unit of use" bottle.

B. CARTON LABELING (Physician Sample)

See comments A1 – A3.

C. INSERT LABELING

No comments at this time.

IV. RECOMMENDATIONS:

A. [redacted]

B. [redacted]

C. [redacted]

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

/S/

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