CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-688

CHEMISTRY REVIEW(S)

NDA 21-688

SENSIPAR (cinacalcet hydrochloride) 30, 60, 90 mg Tablets

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Amgen, Inc.
Address: One Amgen Center Dr.
Thousand Oaks, CA

Representative:
Pamela Danagher, Manager Regulatory Affairs
(805) 447-1000

Indication: Treatment of secondary hyperparathyroidism in pts with chronic kidney disease not undergoing dialysis and for treatment of primary hyperparathyroidism when parathyroidectomy is not a treatment option

Presentations: 30, 60, 90 mg tablets in HDPE bottles of 30. [redacted]. Physician sample HDPE bottles of 7 count are also qualified. Bottles contain filler and a desiccant.

EER Status: Acceptable 26-FEB-2004

Consults: DMETS – SENSIPAR is acceptable 08-NOV-2003
Statistics – none
Biopharm – dissolution tests, acceptance criteria OK
EA – no consult - waiver requested - granted

The SENSIPAR NDA was submitted 05-SEP-2003. CMC IR letters were issued 13-NOV-2003, 23-dec-2003, AND 26-jan-2004 (EMail) and was responded to in the amendments dated 03-DEC-2003 and 12-JAN-2004, and 03-FEB-2004. The NDA was designated Priority.

The **drug substance** is manufactured by:

[redacted]

Structural characterization of the drug substance, and chirality determination was satisfactory. [redacted] was agreed at a pre-NDA

[redacted]

Conclusion
Drug substance information is acceptable.

The **drug product** is a film coated immediate release tablet in strengths of 30, 60, 90 mg.

[redacted] Submitted stability data support the proposed 24 month expiry. The stability protocol and commitment are acceptable. Labeling is acceptable.

All associated DMFs are acceptable.

Overall Conclusion
From a CMC perspective the application an approval action is recommended.

Eric P Duffy, PhD
Director, DNDC II/ONDC

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/s/

Eric Duffy
3/8/04 11:51:05 AM
CHEMIST

NDA 21-688

SENSIPAR™ (cinacalcet hydrochloride) Tablets

Amgen Inc.

Shulin Ding, Ph.D.

Division of Metabolic and Endocrine Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-688

2. REVIEW #: 1

3. REVIEW DATE: February 25, 2004

4. REVIEWER: Shulin Ding, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Presubmission	Aug. 14, 2003
Original	Sep. 5, 2003
Amendment to original[1]	Oct. 8, 2003
Amendment[2]	Dec. 3, 2003
Amendment[3]	Jan. 12, 2004
Amendment[4]	Feb. 3, 2004

[1]The 10/8/03 amendment provides for an additional testing site for raw material testing, and a correction to the address of [redacted] Laboratories.

[2]The 12/3/03 amendment provides for (1) responses to the CMC questions included in the Nov. 18, 2003, 74-day filing review letter, (2) three replacement tables (Table 5, Data Summary for Yield and Purity of AMG 073 Amide, Section 3.2.S.2.6; Table 1, Commercial Batch Formula for Cinacalcet HCl Tablets, Section 3.2.P.3.2; and Table 4, Moisture Accuracy Summary, Section 3.2.P.5.3.6), and (3) removal of [redacted] from Item 4 of NDA 21-688.

[3]The 1/12/04 amendment provides for responses to the CMC questions included in the IR letter dated Dec. 23, 2003.

[4]The 2/3/04 amendment provides for responses to the CMC questions e-mailed to Amgen on Jan. 26, 2004.

7. NAME & ADDRESS OF APPLICANT:

Name:	Amgen Inc.
Address:	One Amgen Center Drive, Thousand Oaks, CA 91320-1799
Representative:	Pamela Danagher, Manager Regulatory Affairs
Telephone:	805-447-1000

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Sensipar™
b) Non-Proprietary Name (USAN): Cinacalcet hydrochloride
c) Code Name/# (ONDC only): AMG 073, AMG 073 HCl, AMG 99073-01
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Bone/calcium-phosphorous metabolism

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 30 mg, 60 mg, and 90 mg per tablet

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x_ Rx ___OTC

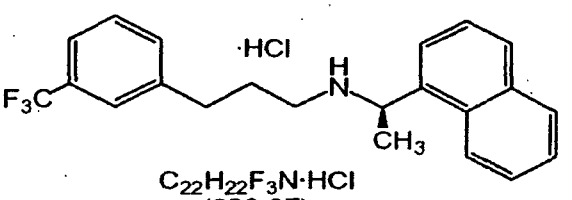
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Established (INN, USAN) Name:	Cinacalcet Hydrochloride
Chemical Name:	N-[1-(R)-(-)-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]-1-aminopropane hydrochloride
CAS Registry Number:	364782-34-3
Molecular Formula:	$C_{22}H_{22}F_3N{\cdot}HCl$
Molecular weight:	393.87 g/mole (HCl salt) 357.41 g/mole (free base)



$C_{22}H_{22}F_3N{\cdot}HCl$
(393.87)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS	DATE REVIEW COMPLETED	COMMENTS
[redacted]	IV	[redacted]	Opadry II green	1	Adequate	1/16/04	Reviewed by Sheldon Markofsky Chem Rev# 1
[redacted]	IV	[redacted]	Opacode black S [redacted] k)	1	Adequate	1/16/04	Reviewed by Sheldon Markofsky Chem Rev # 1
[redacted]	IV	[redacted]	Opadry Clear	3	Adequate	9/22/00	Reviewed by Dale Koble Chem Rev # 1
[redacted]	III	[redacted]	[redacted]	3	Adequate	9/12/00 5/09/96	Reviewed by Sharon Kelley, Chem Rev # 1 Reviewed by Mike Adams, Chem Rev # 12
[redacted]	III	[redacted]	[redacted]	3	Adequate	4/20/01	Reviewed by Donald N. Klein Chem Rev # 15
[redacted]	III	[redacted]	[redacted]	3	Adequate	10/9/03	Reviewed by Sara C. Pope Chem Rev # 23
[redacted]	III	[redacted]	[redacted]	4	Not Applicable	Not applicable	[redacted]
[redacted]	III	[redacted]	[redacted]	3	Adequate	12/6/00	Reviewed by Moo-Jhong Rhee Chem Rev # 1
[redacted]	III	[redacted]	[redacted]	3	Adequate	5/30/2003	Reviewed by Lorenzo Rocca Chem Rev # 3

[1] Action codes for DMF Table: 1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	56,010	Original IND dated May 21, 1998

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not applicable	---	
EES	Pending		Shulin Ding, Ph.D.
Pharm/Tox	Approval	2/12/04	Gemma Kuijpers, Ph.D.
Biopharm	Approvable	2/20/04	Johnny Lau, Ph.D.
LNC	Not needed	---	---
Methods Validation	Pending		
ODS	Satisfactory trade name	11-8-03	Alina Mahmud
EA*	Acceptable.	---	Shulin Ding, Ph.D.
Microbiology	Not applicable	---	---

*Amgen requests a categorical exclusion per 21 CFR 25.31(a) since the Expected Environment or Introductory Concentration (EEC or EIC) is projected to be less than 1 part per billion (ppb).

19. ORDER OF REVIEW (OGD Only): N/A

APPEARS THIS WAY ON ORIGINAL

The Chemistry Review for NDA 21-688

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 21-688 is recommended for **approval** from the standpoint of chemistry, manufacture and controls, pending a satisfactory cGMP status of the manufacturing/testing sites.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1) Drug Product

The proposed drug product, Sensipar™ is a [redacted] light green, film-coated, oval-shaped tablet for oral administration, and intended for the treatment of primary and secondary hyperparathyroidism.

Sensipar™ tablets contain 30 mg, 60 mg and 90 mg of cinacalcet free base equivalent (33 mg, 66 mg, and 99 mg as the hydrochloride salt, respectively). The active ingredient is the free base whereas the drug substance is the hydrochloride salt. The tablets also contain the following inactive ingredients: pre-gelatinized starch, microcrystalline cellulose, povidone, crospovidone, colloidal silicon dioxide, and magnesium stearate. The tablets are coated with color (Opadry® II green) and clear film-coat (Opadry® clear), carnauba wax, and printed with Opacode® black ink.

[redacted]

Long term stability data (three batches for each strength) are provided for the 30 mg and the 90 mg tablets. The batches were manufactured at the designated commercial manufacturing site, and their scale ranged from pilot to commercial scale. All stability results met the specifications with no significant trend observed for chemical assay and drug dissolution (see Chemistry Assessment for details). [redacted] Based on the data submitted, the recommended expiry period for the drug product is 24 months for the bottle configuration [redacted] when stored at controlled room temperature, 25°C (excursions permitted 15-30°C).

The clinical studies were conducted using [redacted] (Phase 1 and early Phase 2), and bioequivalent tablets (Phase 2 and Phase 3). With the exception of a [redacted] the proposed to-be-

marketed formulation is identical to the product used in Phase 3 pivotal studies for secondary hyperparathyroidism. The [redacted] has been shown not to impact the *in-vitro* dissolution and stability profiles of the finished drug product.

[redacted]

2) Drug Substance

Cinacalcet hydrochloride is the recommended International Nonproprietary Name (INN) and the United States Adopted Name (USAN) for the drug substance. Cinacalcet hydrochloride is a calcimimetic agent. It acts as an allosteric modulator of the calcium-sensing receptor on the parathyroid cell surface.

Cinacalcet hydrochloride is a secondary amine with a pKa of [redacted] It is a white to off-white, non-[redacted] crystalline powder with a melting range of [redacted] crystalline [redacted] temperature. It is slightly soluble in water, resulting in a [redacted] (25°C). It is also slightly soluble in [redacted] Cinacalcet hydrochloride is freely soluble in methanol, ethanol, [redacted]

[redacted]

The molecule of cinacalcet hydrochloride has one chiral center, and cinacalcet is the R-enantiomer. Pharmacological studies have shown that the R-enantiomer is much more potent than the [redacted]

[redacted]

B. Description of How the Drug Product is Intended to be Used

Note: The following description is based on the revised draft label submitted by Amgen on Feb. 20, 2004.

SENSIPAR™ tablets are supplied in 30, 60, and 90 mg strengths. SENSIPAR™ tablets should be taken whole and should not be divided. They should be taken with food or shortly after a meal. SENSIPAR™ dosage must be individualized. Below is dose recommendation for each group of patients:

Secondary Hyperparathyroidism in Patients with Chronic Kidney Disease

The recommended starting oral dose of Sensipar™ is 30 mg once daily. Serum calcium and serum phosphorus should be measured within 1 week and iPTH should be measured 1 to 4 weeks after initiation or dose adjustment of Sensipar™. Sensipar™ should be titrated every 2 to 4 weeks through sequential doses of 60, 90, 120 and 180 mg once daily to achieve a range consistent with the NKF-K/DOQI recommended target for iPTH:

CKD patients undergoing dialysis: 150-300 pg/mL

Sensipar™ can be used alone or in combination with vitamin D sterols; phosphate binders. During dose titration, serum calcium levels should be monitored frequently and if serum

Parathyroid Carcinoma
The recommended starting oral dose of Sensipar™ is 30 mg twice daily.
The dosage of Sensipar™ should be titrated every 2 to 4 weeks through sequential doses of 30 mg twice daily, 60 mg twice daily, 90 mg twice daily, and 90 mg three or four times daily as necessary to normalize serum calcium levels.

Special Populations
Geriatric patients: Age does not alter the pharmacokinetics of Sensipar™; no dosage adjustment is required for geriatric patients.

Patients with renal impairment: Renal impairment does not alter the pharmacokinetics of Sensipar™; no dosage adjustment is necessary for renal impairment.

Patients with hepatic impairment: 2.4- and 4.2-fold, respectively. In patients with moderate - severe hepatic impairment, PTH and serum calcium concentrations should be closely monitored throughout treatment with Sensipar™.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-688 is recommended for approval (pending Office of Compliance's recommendation regarding cGMP status for the manufacturing site of drug substance) based on the following:

- Formulation comparability of pivotal batches to the proposed to-be-marketed drug product
- Manufacturing process comparability of pivotal batches to the proposed to-be-marketed drug product
- Validated stability-indicating assay method to support lot release and stability monitoring of drug product
- Adequate stability package to support the recommended expiry period for drug product
- Adequate specifications/controls for drug substance and drug product

III. Administrative

A. Reviewer's Signature

Shulin Ding, Ph.D.

B. Endorsement Block: in DFS

C. CC Block: in DFS

A-6

86 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

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/s/

Shulin Ding
2/25/04 02:39:03 PM
CHEMIST

Please concur. Action package to be sent tomorrow.

Mamta Gautam-Basak
2/25/04 02:59:55 PM
CHEMIST
Concur

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21688/000
Org Code : 510
Priority : 1P

Sponsor: AMGEN
1840 DEHAVILLAND DR
THOUSAND OAKS, CA 913201789

Stamp Date : 08-SEP-2003
PDUFA Date : 08-MAR-2004
Action Goal :
District Goal: 08-JAN-2004

Brand Name : SENSIPAR(CINACALCET HCL)
30/60/90MG TABS
Estab. Name:
Generic Name: CINACALCET HCL
Dosage Form: (TABLET)
Strength : 30, 60, AND 90 MG

FDA Contacts:			
D. HEDIN	Project Manager	(HFD-510)	301-827-6392
S. DING	Review Chemist	(HFD-510)	301-827-6385
M. GAUTAM BASAK	Team Leader	(HFD-510)	301-827-9084

Overall Recommendation: ACCEPTABLE on 26-FEB-2004by S. ADAMS (HFD-322) 301-827-9051

Establishment : [redacted] FEI :

DMF No: AADA:

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 13-JAN-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 2026154 FEI : 2026154

AMGEN INC

ONE AMGEN CENTER DRIVE

THOUSAND OAKS, CA 91362

DMF No: AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-DEC-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : [redacted] FEI : [redacted]

[redacted]

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 25-SEP-03

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : [redacted] FEI : [redacted]

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 27-OCT-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : [redacted]

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : TCM OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 15-OCT-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : [redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 29-SEP-03

Decision : ACCEPTABLE

Reason : BASED ON FILE REVIEW

Establishment : [redacted]

DMF No: AADA:

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 25-SEP-03

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment [redacted]

[redacted]

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-FEB-04

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 3, 2004

TO: Randy Hedin, Project Manager (HFD-510)

FROM: Shulin Ding, Chemistry Reviewer (HFD-820 co-located with HFD-510)

SUBJECT: **NDA 21-688: Review of the Modified Container Label and Establishment Inspection Results**

Container Label Review

Background

Modified container label items are provided by the applicant for review as a response to the agency's recommendation on the proposed container label. The recommendation was e-mailed to the applicant by the project manager on February 13, 2004. Specifically, the agency requested the applicant to follow the standard format (Sensipar™ (cinacalcet HCl) Tablets) for the trademark printed on all labeling (carton, bottle and packaging insert). The agency also requested the applicant to further differentiate different strengths of tablets through color difference on the container label.

Reviewer's evaluation

The applicant has complied with the agency's requests. The trademark of the modified container label conforms to the standard format, and color differentiation among different strengths has been enhanced through a significant adjustment in the shade of the proposed colors. The modified container label items submitted through a letter dated Feb. 26, 2004, are acceptable.

Establishment Evaluation

Establishment inspection was completed after the signing-off the primary chemistry review of the NDA. The overall recommendation from the Office of Compliance is, therefore, not in the primary review. EER (Establishment Evaluation report) has been issued since then. Per Establishment Evaluation Summary Report dated February 27, 2004, the overall recommendation form the Office of Compliance is **acceptable**.

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/s/

Shulin Ding
3/3/04 01:40:42 PM
CHEMIST

Mamta Gautam-Basak
3/3/04 02:01:58 PM
CHEMIST
Concur