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/s/

S.W. Johnny Lau
2/20/04 05:20:51 PM
BIOPHARMACEUTICS

Hae-Young Ahn
2/20/04 05:25:42 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-688

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-688

NAME OF APPLICANT / NDA HOLDER
Amgen Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
SENSIPAR™

ACTIVE INGREDIENT(S)	STRENGTH(S)
N-[1-(R)-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]-1-aminopropane hydrochloride	30mg, 60mg and 90mg strengths

DOSAGE FORM
Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

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FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6211244	4/3/2001	10/23/2015

d. Name of Patent Owner	Address *(of Patent Owner)*	
NPS Pharmaceuticals, Inc.	420 Chipeta Way	
	City/State: Salt Lake City, Utah	
	ZIP Code: 84108	FAX Number *(if available)*: (801) 583-4961
	Telephone Number: (801) 583-4939	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
☞ N/A	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)*: 21, 26, 30-31 — Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use. *(Submit indication or method of use information as identified specifically in the approved labeling.)* See the copy of sections of the proposed label for the drug product in EXHIBIT 1 (9 pages) attached hereto.	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes	

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
Frank Ungemach	2/25/04

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Frank Ungemach, Assoc. General Counsel	
Address One Amgen Center Drive	City/State Thousand Oaks, CA
ZIP Code 91320-1799	Telephone Number (805) 447-1000
FAX Number *(if available)*	E-Mail Address *(if available)*

Department of Health and Human Services
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1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6031003	2/29/2000	12/14/2016

d. Name of Patent Owner	Address *(of Patent Owner)*	
NPS Pharmaceuticals, Inc. and	420 Chipeta Way	
	City/State: Salt Lake City, Utah	
	ZIP Code: 84108	FAX Number *(if available)*: (801) 583-4961
	Telephone Number: (801) 583-4939	E-Mail Address *(if available)*:

	Address *(of Patent Owner)*	
The Brigham and Women's Hospital	75 Francis Street	
	City/State: Boston, MA	
	ZIP Code: 02115	FAX Number *(if available)*:
	Telephone Number: (617) 732-5500	E-Mail Address *(if available)*:

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) N/A	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?	☐ Yes	☒ No
g If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	☐ Yes	☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
1-2, 4, 9, 13-14, 16-17, 19, 31-32, 34-37, 40-45, 51-52, 82-86, 89-93, 99-109, 115-116, 131, 132, 138, 142-145	☒ Yes	☐ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*

EXHIBIT 1 (9 pages) attached hereto.

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

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Frank Ungemach

Date Signed: 2/25/04

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Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name: Frank Ungemach, Assoc. General Counsel

Address: One Amgen Center Drive	City/State: Thousand Oaks, CA
ZIP Code: 91320-1799	Telephone Number: (805) 447-1000
FAX Number *(if available)*	E-Mail Address *(if available)*

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

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a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6313146	11/6/2001	12/14/2016

d. Name of Patent Owner	Address *(of Patent Owner)*	
NPS Pharmaceuticals, Inc. and	420 Chipeta Way	
	City/State Salt Lake City, Utah	
	ZIP Code 84108	FAX Number *(if available)* (801) 583-4961
	Telephone Number (801) 583-4939	E-Mail Address *(if available)*

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	ZIP Code 02115	FAX Number *(if available)*
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e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) N/A	Address *(of agent or representative named in 1.e.)*	
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f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?	☐ Yes	☒ No
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2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3.**		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

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4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

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Address: One Amgen Center Drive	City/State: Thousand Oaks, CA
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Department of Health and Human Services
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6011068	1/4/2000	12/14/2016

d. Name of Patent Owner	Address *(of Patent Owner)*	
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	City/State: Salt Lake City, Utah	
	ZIP Code: 84108	FAX Number *(if available)*: (801) 583-4961
	Telephone Number: (801) 583-4939	E-Mail Address *(if available)*:

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The Brigham and Women's Hospital	75 Francis Street	
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2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No

4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*		

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*

Frank Ungemach.

Date Signed: 2-25-04

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Frank Ungemach, Assoc. General Counsel	
Address One Amgen Center Drive	City/State Thousand Oaks, CA
ZIP Code 91320-1799	Telephone Number (805) 447-1000
FAX Number *(if available)*	E-Mail Address *(if available)*

Regional Administrative Information
Patent Information

1 Patent Information

1.1 Introduction

Provided here is patent information described under 21 CFR 314.53 for cinacalcet and salts thereof, including the hydrochloride salt thereof.

1.2 Drug Substance Patent

1.2.1 Detailed Drug Substance Patent Information

Presented in Table 1 are the U.S. patents that claim the drug substance cinacalcet and salts thereof, including the hydrochloride salt thereof, which is the subject of this present application.

Table 1. Drug Substance Patents for Cinacalcet HCl

Patent No.	Owner	Patent Type	Expiration
6,313,146	NPS Pharmaceuticals, Inc. & The Brigham and Women's Hospital	Drug Substance	December 14, 2016
6,211,244	NPS Pharmaceuticals, Inc.	Drug Substance	October 23, 2015
6,011,068	NPS Pharmaceuticals, Inc. & The Brigham and Women's Hospital	Drug Substance	December 14, 2016

1.3 Formulation and Composition Patent

Presented in Table 2 are U.S. patents that claim drug product forms of cinacalcet and salts thereof, including the hydrochloride salt thereof, which is the subject of this present application.

Table 2. Formulation and Composition Patents for Cinacalcet HCl

Patent No.	Owner	Patent Type	Expiration
6,313,146	NPS Pharmaceuticals, Inc. & The Brigham and Women's Hospital	Drug Product	December 14, 2016
6,211,244	NPS Pharmaceuticals, Inc.	Drug Product	October 23, 2015
6,011,068	NPS Pharmaceuticals, Inc. & The Brigham and Women's Hospital	Drug Product	December 14, 2016

1.4 Method of Use Patent

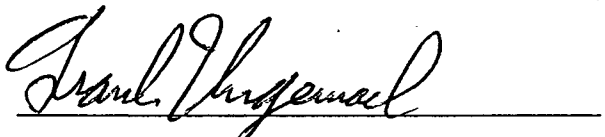
Presented in Table 3 are U.S. patents that claim methods of using the drug substance cinacalcet and salts thereof, including the hydrochloride salt thereof, and/or drug product forms thereof, which is the subject of this present application.

Table 3. Formulation and Composition Patents for Cinacalcet HCl

Patent No.	Owner	Patent Type	Expiration
6,211,244	NPS Pharmaceuticals, Inc.	Method of Use	October 23, 2015
6,031,003	NPS Pharmaceuticals, Inc. & The Brigham and Women's Hospital	Method of Use	December 14, 2016

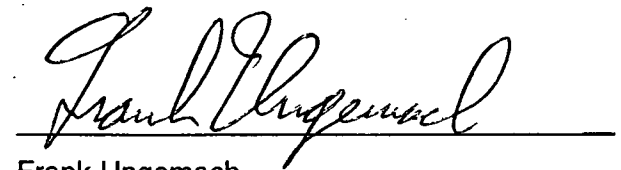
1.5 Declarations

The undersigned declares that that U.S. Patent Nos. 6,313,146; 6,211,244; 6,031,003; and 6,011,068 claim the formulation, composition, and/or method of use of cinacalcet and salts thereof, including the hydrochloride salt thereof. This product is the subject of this application for which approval is being sought under section 505 of the Federal Food, Drug, and Cosmetic Act.



Frank Ungemach
Associate General Counsel

The undersigned certifies that the above listed patents are solely owned by NPS Pharmaceuticals, Inc., or jointly owned by NPS Pharmaceuticals, Inc. and The Brigham and Women's Hospital, Inc. The undersigned further certifies that Applicant is licensed under each of the above U.S. Patents with respect to cinacalcet and salts thereof, including the hydrochloride salt thereof, which is the subject of this present application.



Frank Ungemach
Associate General Counsel

EXCLUSIVITY SUMMARY for NDA # 21-688

Trade Name Sensipar **Generic Name** Cinacalcet HCl

Applicant Name Amgen Inc. HFD-510

Approval Date XXX

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/ X / NO / /

   b) Is it an effectiveness supplement? YES / / NO / X /

      If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES / X / NO / /

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) **Did the applicant request exclusivity?**

YES / X / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request? 5 Years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / / NO / X /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES / / NO / X /

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / X /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO / X /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III:

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON** Page 9:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ ! NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) **Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study?** (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____
Signature of Preparer Date
Title:

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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
3/8/04 03:43:11 PM

David Orloff
3/8/04 04:42:31 PM

Exclusivity Statement

Pursuant to 21 CFR § 314.50(j) and § 314.108(b)(2), Amgen submits this statement claiming five years of marketing exclusivity for its new drug product, cinacalcet HCl. To the best of Amgen's knowledge or belief, the Food & Drug Administration has not previously approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act any drug containing the active moiety cinacalcet HCl.

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-688 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: September 8, 2003 **Action Date:** March 8, 2004

HFD-510 **Trade and generic names/dosage form:** Sensipar (cinacalcet HCl) Tablets

Applicant: Amgen Inc. **Therapeutic Class:** 1P

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: Treatment of secondary hyperparathyroidism in patients with chronic kidney disease undergoing dialysis

Is there a full waiver for this indication (check one)?

X **Yes: Please proceed to Section A.**

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- X **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____ **kg**____ **mo.**____ **yr.**____ **Tanner Stage**____
Max____ **kg**____ **mo.**____ **yr.**____ **Tanner Stage**____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____ kg____ mo.____ yr.____ Tanner Stage_____
Max____ kg____ mo.____ yr.____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____ kg____ mo.____ yr.____ Tanner Stage_____
Max____ kg____ mo.____ yr.____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Treatment of hypercalcemia in patients with parathyroid carcinoma

Is there a full waiver for this indication (check one)?

X Yes: Please proceed to Section A.

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
X Too few children with disease to study
☐ There are safety concerns
☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min	**kg**	**mo.**	**yr.**	**Tanner Stage**	
Max	**kg**	**mo.**	**yr.**	**Tanner Stage**	

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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
3/8/04 04:17:57 PM

AMGEN

SENSIPAR™ (cinacalcet HCl)
NDA 21-688

Debarment Certification Statement

Amgen Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.

Dawn Viveash, M.D.
Vice President, Regulatory Affairs

8/19/03
Date

Office Director's Sign-Off Memorandum

Date:	Monday, March 08, 2004
NDA:	21-688
Sponsor:	Amgen
Proprietary Name:	Sensipar (cinacalcet hydrochloride) Tablets

Introduction: The review for Sensipar (cinacalcet hydrochloride), a new molecular entity, is on its first cycle and was performed on a priority basis. Cinacalcet is a calcimimetic agent that increases the sensitivity of the calcium-sensing receptor to activation by extracellular calcium, proposed for the treatment of hyperparathyroidism. The thrust of the development program was towards the treatment of secondary hyperparathyroidism (particularly in patients on chronic dialysis), but the sponsor is proposing labeling for _____, _____ hypercalcemia resulting from parathyroid carcinoma. The reasoning behind the priority review is that the population of secondary hyperparathyroidism with chronic renal failure (CRF) does not have adequate treatment options at this time. They are managed by vitamin D, phosphate binders and calcium supplementation. Yet, ultimately, many end up with an elevated calcium-phosphorus product and metastatic calcification due to the elevation in this product. Cinacalcet would represent a major advance in therapy.

The molecule is a calcimimetic at the parathyroid (but not in other metabolic sites, including bone), effectively resetting the parathyroid calcium receptor to be more sensitive to serum calcium, thereby lowering PTH secretion for any given serum calcium level. In secondary hyperparathyroidism, one must strike a balance between appropriate lowering of the PTH (thereby preserving bone) and excessive lowering, which can result in adynamic bone disease. A direct consequence of cinacalcet's actions on PTH is to lower serum calcium (though the resetting of calcium sensing) and one of the issues with the drug is the induction of hypocalcemia. That is discussed below.

I am recommending approval of the drug for secondary hyperparathyroidism in CRF patients on dialysis and for parathyroid carcinoma. [redacted]

CMC: The drug is available in 3 dosage strengths (film-coat tablets) of 30, 60 and 90 mg. The pills are all the same color, but are of somewhat different shapes and sizes. There are no outstanding issues with the drug at this time. The ONDC reviewers have found the information on drug substance and product to be satisfactory.

Final recommendations from Compliance on the EERs is that the various sites involved in the production and testing of this product are acceptable as of February 26th, 2004.

Pharm/Tox: This drug was extensively and appropriately studied preclinically and there are notable findings. These include hypocalcemia (a direct pharmacologic effect);

cardiovascular toxicity (QT effects will be further discussed), including myocardial degeneration and vacuolization; GI toxicity, mostly consisting of intolerance; CNS toxicity – notably convulsions and, in rats only, catarracts; endocrine effects apart from PTH – including decreases in serum testosterone; liver toxicity and renal toxicity. At least some of the toxicities – QT and convulsions notably – may relate to the hypocalcemia. Generally, though, the safety margins for these above noted toxicities were acceptable.

Genotoxicity assays, in vitro and in vivo, were negative. The carcinogenicity studies in rats and mice were essentially negative for significant findings.

The reproductive toxicology studies were relatively unremarkable. The sement I studies showed little effect on fertility, segment II studies showed no overt teratogenesis, and the segment III studies showed only some minor dentition effects in F1 rabbits.

QT effects: The sponsor performed a standard hERG channel assay, aiming to identify an IC50 for the channel. They used a positive control of dofetelide which, in this assay, showed 100% hERG inhibition. Cinacalcet was tested at only one dose – 500 ng/ml. This resulted in approximately a 12% block of the hERG current. Since the sponsor felt that modeling suggested the IC50 would be about 4000 ng/ml and the this exceeded the maximum serum concentrations seen clinically (318 ng/ml), the sponsor elected not to test higher concentrations to establish the definitive IC50. The sponsor also provided data supporting that there was not an accumulation of cinacalcet in cardiac tissue relative to plasma, suggesting that serum levels were adequate indicators of tissue levels. While there was no apparent QT effect in dogs, there was some QT prolongation seen in monkeys (in the three month study, not the 12-month). These monkeys also were hypocalcemic, so it cannot be known if this represents a primary effect of the drug, a secondary effect due to calcium, or both.

Biopharmaceutics: Cinacalcet is dose-titrated to effect, with a range of doses between 30 mg to 180 mg daily in secondary hyperparathyroidism patients on dialysis. Cinacalcet is well absorbed (more than 80% bioavailable), with a high volume of distribution, and a high binding to serum proteins. The terminal half-life is 30 – 40 hours. The Cmax at steady state on 50 mg was approximately 20 ng/ml. There was a significant food effect seen, with food increasing bioavailability (68% greater AUCs after a fatty meal). The drug is metabolized via multiple hepatic enzymes – notably CYP450 3A4, 2D6, and 1A2. The drug itself inhibits 2D6 strongly in vitro. The major metabolites have not all been characterized for activity, although the glucuronides are active, but at 333 fold less potency than parent drug. The biopharm team has recommended two post-approval commitments with which I concur and to which Amgen has agreed - one to examine the effects of cinacalcet on desipramine levels (an in vivo assessment of 2D6 effects) and an in vitro assessment of metabolic enzyme induction to see if the increase in seizures seen clinically may have any relation to effects of cinacalcet on the clearance of the anticonvulsants (though one would not have to invoke this considering the preclinical effects suggesting a primary or secondary effect of the drug).

Clinical / Stastical: As above, the development program for cinacalcet appears to have focused primarily on the indication of secondary hyperparathyroidism in patients on dialysis for chronic renal failure. Clinically, this is the group most affected by secondary hyperparathyroidism (as opposed to CRF patients who are not yet dialysis-dependant). Primary hyperparathyroidism is primarily a surgical disease.

Efficacy: The sponsor performed three trials in the dialysis population (trials 172, 183, 188) in patients with CRF on dialysis with serum PTH levels (Nichols IRMA assay) of > 300 pg/ml and normal to high serum calcium levels. These studies randomized a total of 1,136 patients, 665 of whom were randomized to the drug, the remainder to placebo. The primary endpoint was the percent of patients achieving a serum iPTH level of <= 250 pg/ml. The patients were started on 30 mg daily and titrated upwards as needed and tolerated to achieve either the maximal dose of 180 mg daily or the desired effect. Forty percent of cinacalcet patients achieved PTH levels below 250, while only 5% of placebo patients did so. For secondary analyses, the effect of drug on achieving consensus targets for this population on serum calcium, phosphorus, calcium-phosphorus (Ca x P) product and both the target PTH and target lowering of Ca x P were all higher with treatment than placebo (along with usual care approaches). At the end of titration, the full range of doses was represented from 30 mg a day to 180, with a reasonable spread across the doses, though relatively few were on the 30 mg dose and a full 40% were receiving the 180 mg daily dose.

Smaller, phase-2 studies were done for secondary hyperparathyroidism patients not on dialysis.

The effect of cinacalcet in primary hyperparathyroidism

Parathyroid carcinoma was studied in 10 patients in an open-labeled trial for 3 years. Interim results were supplied to the NDA. Patients had parathyroid carcinoma and hypercalcemia (Ca> 12.5 mg/dl). Patients were again dose-titrated from 30 mg twice-daily to effect, with a maximum of 90 mg QID. Seven of 10 patients with parathyroid CA were able to have their serum calcium levels lowered significantly (>= 1.0 mg/dl) with a durable lowering out to 16 weeks. While this is clearly a small database,

considering the medical options and the clinical condition of parathyroid cancer with hypercalcemia, it is justified to approve the drug for this limited population as well based on these efficacy data and the overall safety database.

Safety: Besides nausea and vomiting, which were the predominant drug-related AEs, there are a few other, notable adverse events. First is hypocalcemia. While there were relatively few occurrences of clinically evident hypocalcemia in any of the populations/trials, there were clearly drug-related instances documented by laboratory Ca levels, many of which required some intervention (i.e., calcium supplementation, vitamin D supplementation and/or withholding doses of the drug). This was particularly prominent in the secondary hyperparathyroidism patients without dialysis-dependency. Labeling regarding hypocalcemia and careful monitoring of patients, particularly during titration, will be very important. There was an excess number of seizures seen in cinacalcet-treated patients, compared to placebo (1.7% vs. 0.4%). Seizures were also noted preclinically. While this may be secondary to calcium effects and not a primary action of the drug, it is notable nonetheless and deserving of precautionary labeling. As above, the sponsor will also further explore if the drug induces metabolism of anti-seizure drugs, though not all the seizures seen were in patients with pre-existing history on therapy. Finally, as in the preclinical studies, a fall in serum testosterone was seen in dialysis patients in study 188, though the clinical consequences of this are not clear. It will be noted in the labeling, however, so that this can be monitored by prescribers.

The clinical QT effects of this drug were not studied in a definitive QT clinical pharmacology study. The Cardiorenal consult on this matter stated that there was likely a QT effect of cinacalcet (whether primary or secondary to calcium lowering) and this needs to be further explored. However, the sponsor has pointed out, correctly, that it would be very hard to design such a study so that it would not be confounded by the calcium effects of the drug. The sponsor did do ECGs approximately timed to C_{max} (about 4 hours post-dose) with manual readings in both phase 1 and phase 3 trials. In the phase 3 trials, it appears that there is an approximate a mean increase in QTc (Bazett's correction) of 2.1 msec, with a median of 6.0 msec relative to placebo. In categorical analyses of patients increasing their QTc by 30 – 60 msec or > 60 msec, and of patients exceeding 500 msec, there was very little difference between drug and placebo, though there were small excesses with drug, particularly in the patients showing a rise between 30 – 60 msec (maximum value seen feel into this category in 140/586 or 24% of cinacalcet patients vs. 80/426 or 19% of placebo patients). From the data available, it is not possible to determine if this is a primary effect of the drug or secondary. However, either way, it is a small effect. While cinacalcet does have issues related to metabolic inhibition, even with strong 3A4 inhibitors, the exposure to cinacalcet does not rise dramatically (only roughly 2.5 fold). Given the clinical consequences of secondary hyperparathyroidism in patients on dialysis and relatively poor treatment options, the risk implied by these preclinical and clinical data (which argue for a small, if any, risk of clinically significant repolarization effects) is offset in this population and the carcinoma population by the benefits.

Labeling and nomenclature: Satisfactory labeling was negotiated with the sponsor prior to action, based on the indications of secondary hyperparathyroidism in chronic kidney disease patients on dialysis and for the treatment of hypercalcemia secondary to

hyperparathyroid carcinoma. There is mention in the clinical trials portion of the labeling of the phase 2 clinical experience with secondary hyperparathyroidism in patients not on dialysis along with a caveat that the drug has not been found safe or effective for such use. This mention is there to inform practitioners who may wish to use the drug off label that this population generally seems to need lower doses to achieve the effect AND is more prone to hypocalcemia than are the dialysis population.

DMETs has found the name for cinacalcet to be acceptable – Sensipar.

Regulatory Conclusions:

Cinacalcet should be approved for use in patients with chronic kidney disease on dialysis and patients with parathyroid carcinoma and resultant hypercalcemia.

/S/

Robert J. Meyer, MD
Director,
Office of Drug Evaluation II

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/s/

Robert Meyer
3/8/04 03:33:46 PM
MEDICAL OFFICER

Demographic Worksheet

plication Information ***(Enter all identifying information for the submission pertaining to this summary)***

NDA Number: 21-688 **Submission Type:** N/A (pilot) **Serial Number:** N/A (pilot)

Populations Included In Application *(Please provide information for each category listed below from the primary safety database excluding PK studies)*

Category		Number Exposed To Study Drug		Number Exposed To Study Drug		Number Exposed To Study Drug
Gender	Males	591	All Females	407	Females >50	258
Age:	0-• 1 Mo.	0	>1 Mo.-• 2Year	0	>2-• 12	0
	12-16	0	17-64	744	• 65	254
Race:	White	502	Black	371	Asian	32
	Other	93				

Gender-Based Analyses *(Please provide information for each category listed below.)*

Category	Was Analysis Performed?		If no is checked, indicate which applies or provide comment below		Was gender-based analysis included in labeling? Yes	No
Efficacy	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☐	☒
Safety	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☐	☒

Is a dosing modification based on gender recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☒ Sponsor ☒ FDA

Age-Based Analyses *(Please provide information for each category listed below)*

Category	Was Analysis Performed?		If no is checked, indicate which applies or provide comment below		Was age-based analysis included in labeling? Yes	No
Efficacy	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☒	☐
Safety	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☒	☐

Is a dosing modification based on age recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☒ Sponsor ☒ FDA

Race-Based Analyses *(Please provide information for each category listed below)*

Category	Was Analysis Performed?		If no is checked, indicate which applies or provide comment below		Was race-based analysis included in labeling? Yes	No
Efficacy	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☐	☒
Safety	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☐	☒

Is a dosing modification based on race recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☒ Sponsor ☒ FDA

In the comment section below, indicate whether an alternate reason (other than "inadequate numbers" or "disease absent") was provided for why a subgroup analysis was NOT performed, and/or if other subgroups were studied for which the metabolism or excretion of the drug might be altered (including if labeling was modified).

Comment:

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/s/

Theresa Kehoe
3/8/04 04:36:41 PM
MEDICAL OFFICER

ADRA Review #1 of Action Package for NDA 21-688, Sensipar (cinacalcet HCl) Tablets

Reviewer: Lee Ripper, HFD-102
Date received: March 2, 2004
Date original NDA received: September 8, 2003
UF GOAL DATE: March 8, 2004

Indications: Approval - (1) Tx of 2° hyperparathyroidism in patients with chronic kidney disease on dialysis and (2) Tx of hypercalcemia in patients with parathyroid carcinoma. Approvable (3) —— Tx of 2° hyperparathyroidism in patients with chronic kidney disease not on dialysis, and (4) —— Tx of 1° hyperparathyroidism when parathyroidectomy is not a treatment option

Action type: 2 indications AP; another 2 indications (——————————
————AE
RPM: Randy Hedin
Drug Classification: 1P
505(b)(1) application

Randy Hedin confirmed that a signed, paper copy of the administrative forms was received.
Patent Info: Received on form 3542a
Debarment Certification: AC
Safety Update: 12/24/03, review on page 61 of MOR
Clinical Inspection Summary: 3 sites audited, all AC
ODS/DMETS Review of Trade Name: AC, final update review pending as of 3/3/04.
DSRCS Review of PPI/MedGuide: No PPI or MedGuide
DDMAC Review: No written review
EA: Categorical exclusion AC
EER: AC 2/26/04
Financial Disclosure: Addressed in MOR, page 15; see comment below

CMC section to Eric Duffy, 3/3/04
P/T section to Ken Hastings, 3/3/04

1. Division Director needs to sign Exclusivity Checklist
2. Demographic Worksheet is being revised per statistician; copy in DFS to be removed and revised copy entered.
3. DMETS final review of trademark is pending.
4. I talked with Pamela Danagher, Laura McCary, and Beverly Smith (last 2 names may be misspelled) at Amgen on 3/5/04 about 4 issues regarding the submitted financial disclosure information. Their responses are in italics, also see submission dated 3/5/04:

- 23 principal investigators (and 129 subinvestigators) in clinical trials the applicant categorized as "covered clinical trials" did not provide financial disclosure information. All studies appear to have begun after 2/1/99.
  Amgen confirmed that all the studies with at least one principal investigator not providing financial disclosure information started after 2/1/99. The non-reporting investigators listed for studies 172, 183, 188, and 204 (essential studies for indications being approved) did not enter any patients.
- The submission is not clear as to whether or not Amgen is certifying, based on its own files, that these investigators did not have any SPOOS, proprietary interests, or outcome payments.
  Amgen clarified that the certification statement included in section 1.2.1.1 applies to the investigators in Appendix 2 (both tables).
- Would they clarify the statement on page 10 that "Reasons for not providing information upon request by Amgen Inc. include the following: Investigator did not respond to at least one request by the Sponsor . . . ." Due diligence requires more than one attempt.
  Amgen stated that in addition to obtaining financial disclosure information before the investigator begins to participate in the study, they request follow-up information twice at the end of the study.
- A number of investigators who did report SPOOS or equity interests did not provide a dollar amount. I clarified that specific amounts should be declared and suggested they look at the form they use for collecting FD information to ensure investigators understand this requirement.

/S/

Lee Ripper
ADRA, ODE II
3/5/04

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/s/

Leah Ripper
3/5/04 07:17:10 PM
CSO

MEMORANDUM
March 5, 2004

TO: File
FROM: Kenneth L. Hastings, Dr.P.H.

SUBJECT: NDA 21-688

I have reviewed the Pharmacology/Toxicology section of the action package for Sensipar™ (cinacalcet hydrochloride) and the proposed label. I concur with the primary reviewer (Dr. Gemma Kuijpers) and the supervisor (Dr. Karen Davis-Bruno) that the package is approvable. The proposed label is acceptable.

/S/

Kenneth L. Hastings, Dr.P.H.
Associate Director for Pharmacology and Toxicology
Office of Drug Evaluation II

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/s/

Kenneth Hastings
3/5/04 11:27:51 AM
PHARMACOLOGIST

MEMORANDUM
March 5, 2004

TO: File
FROM: Kenneth L. Hastings, Dr.P.H.

SUBJECT: NDA 21-688

I have reviewed the Pharmacology/Toxicology section of the action package for Sensipar™ (cinacalcet hydrochloride) and the proposed label. I concur with the primary reviewer (Dr. Gemma Kuijpers) and the supervisor (Dr. Karen Davis-Bruno) that the package is approvable. The proposed label is acceptable.

/S/

Kenneth L. Hastings, Dr.P.H.
Associate Director for Pharmacology and Toxicology
Office of Drug Evaluation II

Office of Drug Safety

Memo

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

From: Charlie Hoppes, R.Ph., M.P.H.
Safety Evaluator, Division of Medication Errors and Technical Support
HFD-420

Through: Alina Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support
HFD-420

Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
HFD-420

Jerry Phillips, R.Ph.
Associate Director, Office of Drug Safety
HFD-400

CC: Randy Hedin
Project Manager, Division of Metabolic and Endocrine Drug Products
HFD-510

Date: February 26, 2004

Re: ODS Consult 03-0109-2; Sensipar (Cinacalcet HCl Tablets), 30 mg, 60 mg, and 90 mg; NDA 21-688.

This memorandum is in response to a February 11, 2004, request from your Division for a re-review of the proprietary name, Sensipar. In our last review, dated October 14, 2003, (ODS Consult # 03-0109), DMETS had concerns with the potential for confusion between Sensipar And [redacted]. However, since that review, the proprietary name [redacted] was withdrawn by the sponsor and thus the potential for confusion was minimized. The DMETS Expert Panel has also identified one additional proposed proprietary name as having the potential to cause name confusion with Sensipar. The Panel identified [redacted] to have sound-alike and look-alike similarities to Sensipar.

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

Sensipar may sound-alike when spoken and look-alike when scripted (see writing sample below). Each name has [redacted] The names have orthographic similarities especially when the [redacted] prominence.

Sensipar

Additionally, both products share an [redacted] Sensipar differ in strength [redacted] vs. 30 mg, 60 mg, and 90 mg). However, the strength [redacted] from [redacted] may look similar to the 30 mg strength of Sensipar if [redacted] when written. DMETS envisions scenarios where "30 mg twice a day" may be misinterpreted [redacted] DMETS believes that the sound-alike and strong look-alike similarities between [redacted] and Sensipar along with other overlapping product characteristics may cause these names to be confused in the marketplace, leading to medication errors.

In summary, DMETS has no objection to the use of the proposed proprietary name, Sensipar provided that only one name Sensipar (NDA 21-688) or [redacted] is approved. These names should not co-exist in the marketplace due to their similarity. DMETS currently recommends against the use of the proprietary name, [redacted] However, the acceptability of the name will ultimately depend on the Review Division. DDMAC continues to find the proprietary name, Sensipar, acceptable from a promotional perspective.

DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact the medication errors project manager, Sammie Beam at 301-827-3242.

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/s/

Charles Hoppes
3/5/04 03:35:30 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/5/04 03:40:34 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: February 25, 2004

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-688
Sensipar (Cinacalcet HCl)
Amgen

SUBJECT: NDA review issues and recommended action

Background

Sensipar (cinacalcet) is a calcimimetic agent that has been studied in various forms of hyperparathyroidism. It interacts with the cell-surface calcium receptor (CaR), a seven-transmembrane-domain, G-protein linked molecule that regulates a variety of intracellular second-messenger systems. Its mechanism of action is to increase the sensitivity of the parathyroid cell calcium sensor to calcium. As such, it essentially fools the "calcistat" by augmenting the extent of calcium-dependent "feedback" inhibition of PTH secretion relative to that normally achieved by a given ambient serum calcium concentration alone. In hyperparathyroid states, either primary due to glandular dysregulation, or secondary to ongoing hypocalcemic diatheses, cinacalcet has the potential to provide a therapeutic alternative to current therapies and to permit independent titration of plasma concentrations of PTH and calcium. Heretofore, this has not been possible, and it is the inverse physiological relationship between these two that ultimately renders the "no-win" of medical management of hyperparathyroid states.

Primary HPTH (either adenomatous, due to pan-parathyroid hyperplasia or carcinoma), is, ultimately a surgical disease, with the timing of intervention guided by evidence of renal or skeletal disease. Medical management of primary HPTH is never fully effective. Estrogen supplementation in post-menopausal women with mild disease can remedy the hypercalcemia but does not affect PTH levels. Oral phosphate therapy reduces plasma calcium, but can stimulate parathyroid hormone secretion and exacerbate bone disease. Bisphosphonates have been used in some cases. Currently, the place for medical therapy is to palliate and stabilize serious disease prior to surgery. Thus, run-away hypercalcemia is addressed emergently with saline diuresis and plicamycin.

In secondary hyperparathyroid states, the most common being that associated with chronic renal failure, vitamin D and calcium supplementation (and adjustment of the serum calcium by dialysis) as well as intestinal phosphate binders are the mainstays of therapy. In secondary

HPTH in patients on dialysis, efforts to control PTH secretion with calcium and vitamin D, in order to spare bone, are limited by increases in calcium-phosphate ion product, as above.

In primary hyperparathyroid

In secondary hyperparathyroidism associated with renal insufficiency or failure, current therapeutic regimens trade off lower PTH with elevated calcium, and in particular an elevated calcium-phosphate ion product. Thus, efforts to obviate the bone disease that contributes to significant morbidity in CRF only exacerbate the systemic (particularly vascular) consequences of calcium-phosphate deposition. Indeed, longitudinal observational cohort studies as well as epidemiological data support a continuous and graded relationship between PTH level, as well as calcium-phosphate product, and risk for cardiovascular disease in patients with chronic renal failure, atherosclerotic CV disease being the most common immediate cause of death in CRF.

The sponsor originally proposed study of cinacalcet in patients with secondary HPTH and CRF on hemodialysis, and studies in this population form the majority of the clinical experience with the drug. Additionally, a relatively small number of patients with HPTH and chronic renal insufficiency (CRI) not on dialysis have been studied with, most significantly, an increased risk of treatment-associated hypocalcemia (expected due to less severe HPTH and greater sensitivity to the PTH suppressive effects of the drug). A small number of patients with parathyroid carcinoma have been studied with evidence of variable responsiveness. And finally, a small number of patients with "intractable" primary HPTH (apparently not related to carcinoma) have been studied.

This review will briefly summarize the essential efficacy findings related to each population studied (and indication sought) as well as the major potential safety issues related to hypocalcemia, seizures, and possible QT effects that direct the Division's recommendations for regulatory action. Drs. Colman, Beaston, and Kehoe and Ms. Mele have exhaustively reviewed the clinical trial data, and their documents contain detailed information for reference.

Clinical

Secondary HPTH: CRF on dialysis

The pivotal phase 3 trials in this population included 665 and 471 patients randomized to cinacalcet and placebo, respectively. The trials were all similarly designed with a q2week titration scheme from a starting dose of 30 mg, through (as needed to achieved goal PTH of $\leq$ 250 pg/mL) doses of 60, 90, 120, and 180 mg.

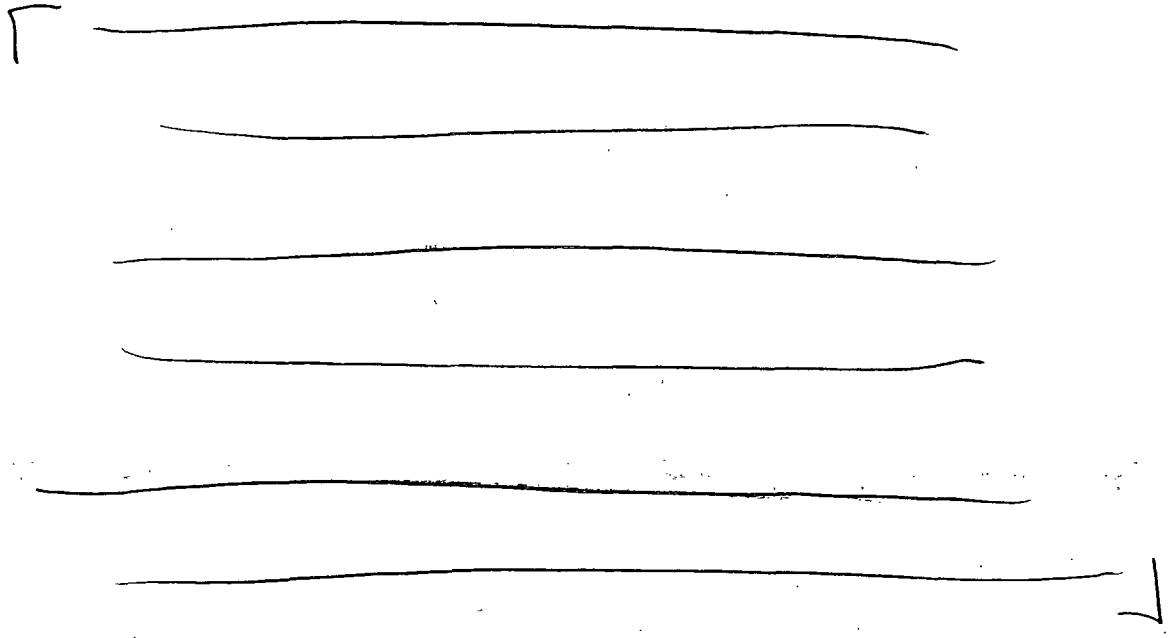
The efficacy results from trials 172, 183, and 188 are summarized in table 21 of Joy Mele's review. From baseline mean PTH levels ranging between ~550 and 850 pg/mL, across the three studies, fewer than 10% of placebo patients achieved target PTH of $\leq$ 250 pg/mL compared to ~35-50% of cinacalcet patients, with response rate inversely related to disease severity (i.e., baseline PTH). The completers' analysis in figure 4 of Ms. Mele's review shows that, relative to

placebo, PTH levels in patients on cinacalcet fell steadily throughout the titration phase and were relatively stable during the maintenance treatment phases of the studies.

Significantly, relative to placebo, cinacalcet treatment was associated with stable decreases in serum calcium and phosphorous. Indeed, ~30-40% of cinacalcet patients had combined reductions from baseline in Ca X P and end-of-treatment PTH $\leq$ 250 pg/mL compared to fewer than 5% of placebo patients.

With regard to doses required for this degree of control of disease, across all three studies, approximately 30-40% of patients were taking the highest dose studied (180 mg) at the end of the trial, suggesting perhaps that in some patients, higher doses still might be required to achieve control of the HPTH state.

Secondary HPTH: CRI not on dialysis



Primary HPTH: "refractory" non-malignant disease, parathyroid carcinoma

A total of 109 patients with primary HPTH (including 10 with carcinoma) treated in controlled and open-label trials with follow up of a few patients out to 3 years are included in the original NDA submission database. This includes approximately 45 patients with pre-operative disease, approximately 15 patients with disease persistent after parathyroidectomy, and, as above, 10 patients with parathyroid carcinoma. As expected, this last group had the highest mean baseline calcium levels, in the range of 14 mg/dL. In the single, open-label study that included patients with so-called "refractory" disease, the 5 patients so labeled had mean baseline calcium between 12 and 13 mg/dL.

In protocols in which patients were titrated with a goal of lowering serum calcium toward normal, cinacalcet was more effective than placebo in patients with primary HPTH whether they had had previous surgery or not. Categorical response rates for achievement of calcium $\leq$ 10.3

mg/dL or ≥ 1 mg/dL reduction from baseline were in the range of 50-100% in the cinacalcet groups and between 25 and 65% in the placebo groups. In the largest study that included pre-operative patients and patients with persistent disease post-operatively, response rates were ~90% for both categories in the cinacalcet group and 25% in the placebo groups. In this study, calcium response on cinacalcet was stable over time, with, as above, follow up of a handful of patients to 3 years. The response in patients with carcinoma was more variable across patients, less consistent over time, and normal calcium was not achieved in any patient. This is consistent with the variable degree of differentiation (and thus responsiveness to calcium) of such tumors.

Safety issues

The risks associated with cinacalcet appear all to be mechanism-of-action related. No toxic effects *per se* of the drug have been noted in the clinical trials. The drug does cause nausea and vomiting in up to ~30% of patients treated in the large phase 3 trials in patients with CRF on dialysis. These adverse reactions appear to be dose related by patient. In the trials, no action was required for 50% of the patients experiencing nausea and/or vomiting. In 25% of cases, dose was altered, and in 20% of cases (5-6% of cinacalcet-treated patients), drug was discontinued.

Hypocalcemia

The risk of hypocalcemia appears related to severity of disease at baseline, and dose-related by patient. In the pooled studies in patients with HPTH on dialysis, ~65% of cinacalcet patients versus ~25% of placebo patients had at least one serum calcium below 8.4 mg/dL. ~5% of cinacalcet patients versus 0.9% of placebo patients had two consecutive serum calcium levels below 7.5. In patients with renal insufficiency, not on dialysis, in the first trial (236), aggressive dose escalation resulted in high rates of hypocalcemia (~50% cinacalcet, 0% placebo). These were dramatically reduced (as were the response rates for control of HPTH and Ca X P product in study 239, a follow up study in patients with more significant HPTH and less aggressive treatment goals in which dose escalation was more gradual (hypocalcemia occurred in about 15% of patients treated with cinacalcet and in only a single placebo patient).

Hypocalcemia: seizures

While there were very few serious adverse events clearly attributable to hypocalcemia, a signal of the clinical significance of the increased tendency toward excessive lowering of serum calcium due to enhanced effectiveness in lowering PTH by cinacalcet is the imbalance in seizures seen in the phase 3 trials. As discussed in the MOR, 5% of patients in both treatment groups in the combined phase 3 CRF trials had a history of a previous seizure. Out of 11 cinacalcet patients who had seizures on treatment, 5 had a previous history. Two patients treated with placebo had seizures during on-treatment follow up.

Hypocalcemia: QT prolongation

An examination of the potential for cinacalcet to prolong cardiac repolarization was undertaken preclinically, with little compelling evidence consistent with a potential clinically significant effect in patients. In the phase 3 trials, mean changes and categorical changes in QT (Bazett's corrected) were not clearly different between treatment groups, nor were the numbers of patients with absolute QT on treatment > 500 msec. That said, as above, for obvious reasons, use of cinacalcet in patients with primary or secondary HPTH increases the risk of hypocalcemia

beyond that with currently available therapy. The sponsor's analysis of the EKG data from their trials suggests an approximate 10 msec prolongation of QT interval for every 1 mg/dL reduction in serum calcium (adjusted for the albumin concentration). As such, cinacalcet-treated patients are at greater risk for hypocalcemia-associated QT prolongation with potential arrhythmogenic consequences.

PTH oversuppression: adynamic bone

Finally, again because of the enhanced efficacy for lowering PTH with cinacalcet compared to placebo (i.e., standard of care), the risk of engendering a state of adynamic bone is increased with the drug. Table 32 of Ms. Mele's review summarizes the data on cinacalcet patients with PTH values below certain cutoffs at endpoint of phase 2 and 3 trials in secondary HPTH in patients with CRF on dialysis and in patients with CRI not on dialysis. In short, up to 18% of patients with CRF on dialysis had PTH levels of < 100 pg/mL and up to nearly 30% of CRI patients not on dialysis had PTH levels < 35 pg/mL. This is an issue to be addressed in overall risk management and obviously parallels the risk for hypocalcemia associated with cinacalcet use.

Biopharmaceutics

Cinacalcet is well absorbed via the oral route. The terminal half-life of the drug is 30-40 hours and steady state is reached in 4 days of once daily dosing. The drug is metabolized by the P450 system, by isozymes 3A4, 2D6, and 1A2. It is an inhibitor of 2D6. The calcimimetic activities of the major metabolites are not fully characterized. There is enhanced bioavailability with food as compared to fasting.

Drug interaction studies suggest a doubling of cinacalcet exposure with potent inhibitors of 3A4.

OCPB recommends specific dissolution specifications for the product. In addition, OCPB recommends a thorough clinical QT study as well as further investigations of interactions with 2D5 substrate drugs. Finally, further in vitro studies of induction of drug metabolizing enzymes are recommended. The sponsor has addressed this issue in a recent submission and further OCPB comment is anticipated.

Pharmacology/Toxicology

The pharmacology of cinacalcet is summarized above and reviewed in detail by Dr. Kuijpers. Of note, in monkey, rat, and mouse, CaR mRNA is found in parathyroid gland, kidney, GI tract, thyroid, CNS, pancreatic islets, adrenal gland, thymus, testis, bone and/or bone marrow. The major systemic effects of cinacalcet in animals appear related to changes in calcium levels in the blood. The drug is neither genotoxic nor obviously carcinogenic in animals. An effect on QT interval was noted in monkey, likely related to hypocalcemia.

High concentrations of drug in vitro block K-ATP channels with minimal effects on HERG channels in vitro.

The primary reviewer has no recommendations for further preclinical studies.

Chemistry/ Microbiology

NDA #21-688
Drug: Sensipar (cinacalcet)
Proposal: treatment of secondary HPTH in CRF and parathyroid CA
03/08/04

The chemistry, manufacturing, and controls are satisfactory and approval is recommended by ONDC.
The establishment inspections were all acceptable.

No phase 4 commitments are recommended.

A categorical exclusion from the requirement for an environmental assessment was requested by the sponsor and granted by the Agency.

DSI/Data Integrity
Three clinical sites were audited, involved in studies 159, 172, and 239, respectively. Data from all three sites were deemed acceptable.

Financial disclosure
The financial disclosure information is in order and is summarized beginning on page 15 of the MOR. There are no concerns regarding neither data reliability nor overall integrity of the clinical package related to conflict of interest.

ODS/nomenclature
The proprietary name, Sensipar, is acceptable to DDMAC.

Conclusions
Cinacalcet is a true "magic bullet" drug for the treatment of hyperparathyroid states. By directly suppressing parathyroid hormone secretion, ——————— secondary HPTH, the use of cinacalcet at last affords the tool to address separately the hyperfunction of the parathyroid glands themselves and the metabolic derangements that are the direct result (in the case of ——————— or the more complex cause and effect (in the case of secondary disease) of the hyperparathyroidism. In this manner, it is theoretically possible to obviate the bone disease of hyperparathyroidism without relying solely on manipulations of calcium, phosphate, and vitamin D, which themselves lead inexorably to acute and chronic complications related to calcium phosphate deposition, particularly in the kidneys and in the arterial tree.

The bulk of the clinical experience with the drug thus far is in patients with secondary HPTH on dialysis, a group with severe disease in whom cinacalcet represents a major breakthrough therapy. The phase 3 trials employed a sequential dose escalation scheme to titrate to control of PTH and Ca X P product. While hypocalcemia clearly was a greater risk for cinacalcet patients compared to placebo, the former achieved significantly better control of their metabolic disease. These patients are intensively cared for within the context of chronic hemodialysis, and the data presented and reviewed permit labeling with regard to expected benefits and risks in accordance with a rational, well-studied method of use.

In patients with renal insufficiency not on dialysis, the clinical experience is far less, and the proposed method of use based on the efficacy and safety results from a single trial which included approximately 30 patients treated with cinacalcet. Medical management of these patients with currently available tools (calcium, vitamin D, and phosphate binders) is acceptably efficacious pending more extensive controlled study in this patient population. Indeed, further

experience with long term management (the maintenance phase of study 239 was only one month long) to inform durability and stability of response and safety with regard to hypocalcemia risk is needed. It seems reasonable to expect that, in time, calcimimetic agents will become integral to the management of pre-dialysis renal patients. Indeed, if accelerated calcification of the arterial tree in the setting of an elevated Ca X P product is directly causative of the increased cardiovascular risk in renal failure patients (above and beyond diabetes-related risk, DM2 being the most common cause of chronic renal failure in developed nations), then, among other studies, investigation of the effect of a cinacalcet-containing regimen on the progression of atherosclerosis in these patients will be extremely important.

The sponsor has also proposed approval for use in patients with "refractory" primary HPTH or those in whom surgery is not an option. [redacted]

Finally, although the clinical trials database is severely limited, patients with parathyroid carcinoma represent a population with life-threatening disease associated with severe hypercalcemia, often refractory to medical management. The use of cinacalcet either as a temporizing measure while awaiting surgery or in patients who have residual tumor and persistent HPTH post-operatively is well rationalized based on significant risk of the underlying disease, coupled with expectation of reasonable, if variable benefit, and low risk of the cardinal adverse effect of cinacalcet, hypocalcemia.

With regard to safety, as discussed above, the potential for cinacalcet-induced reductions in serum calcium to predispose to seizures must be addressed in risk management of cinacalcet use. Likewise, the observed reductions in serum testosterone, summarized in the MOR, must also direct risk management and potentially further studies. Any clinically meaningful effects of cinacalcet on QT interval, if they exist, appear most likely related to reduction in serum calcium. That said, exclusion of a calcium-independent effect on QT would help alleviate concerns of a cinacalcet-specific risk for cardiovascular death in patients on the drug. As reductions in serum calcium in response to cinacalcet take days to manifest, it seems reasonable to consider a formal QT study with EKG at peak serum drug concentrations in patients treated short term with high doses of drug prior to the manifestation of reductions in serum calcium.

Recommendation

Four separate indications are proposed by the sponsor, with recommended regulatory action as follows:

1. Secondary HPTH due to CRF on dialysis: approve

2. Secondary HPTH due to CRI not on dialysis: approvable
   Deficiency:

3. Primary HPTH where surgery is not an option: approvable
   Deficiency:

4. Primary HPTH due to parathyroid carcinoma: approve

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

/s/

David Orloff
3/8/04 01:24:09 PM
MEDICAL OFFICER

Robert Meyer
3/8/04 03:27:08 PM
MEDICAL OFFICER

Pharmacology/Toxicology Supervisory Memo

To: NDA 21-688 Sensipar (cinacalcet) Amgen
From: Karen Davis-Bruno; Ph.D. Supervisory Pharmacologist; HFD-510
Date: 2/17/04

Related documentation: Pharmacology/Toxicology Review NDA 21-688; Supervisor's Memo on labeling recommendations 2/10/04

Cinacalcet is a calcimimetic that dose dependently increases the sensitivity of the calcium sensing receptor (CaR) to extracellular calcium, suppressing the secretion of PTH from the parathyroid. Cinacalcet can stimulate calcitonin release through its action on the CaR on thyroid C-cells. The pharmacologically active oral dose in rats is an ED_{50-100}=10-30 mg/kg (Cmax= ——— An animal model for primary HPT is unavailable; however a nephrectomized rat serving as a model for secondary HPT shows a similar effective, therapeutic dose range.

Cinacalcet is indicated for the ——— treatment of secondary hyperparathyroidism in patients with chronic kidney disease and treatment of hypercalcemia in patients with parathyroid carcinoma ——— ——— Therapeutic dose titration is proposed with oral doses of 30-180 mg/day for secondary HPT and 30 mg BID up to 90 mg QID in primary HPT based on a target level of PTH and/or serum calcium. Clinical PK data indicate maximal exposure at 180 mg/day. Exposure at the maximal proposed dose 90 mg QID for ——— ——— is not known. Clinical doses greater than 180 mg/day did not result in higher exposures hence safety margins in animals have been based on a clinical dose of 180 mg/day.

Toxicology assessments include oral 6-month rat and one year monkey studies. Dosing in animals has been limited by the confounding hypocalcemic effects of the drug and GI toxicity (abnormal feces, food consumption, emesis, intestinal mucosa hyperplasia/inflammation). Exposures established in chronic toxicity studies in rat and monkey provide safety margins of 8 and 2 times respectively the therapeutic dose of 180 mg/day. The hypocalcemic effects may be partially mediated by the metabolites. The parent compound is well absorbed (95%) but has a relatively low oral bioavailability (rat <10%, human 20%) which probably relates to its extensive first pass metabolism. N-dealkylation results in carboxylic acid metabolites (M5-M8) and oxidation of the naphthalene ring produces dihydrodiols (M2, M3). There are no unique human metabolites. M5 is the major and M6 and M2-glucuronide are the minor circulating human metabolites. M6 appears to undergo conversion to M7. Monkeys produce M5, M7 and M2-glucuronide whereas rats produce M7 and M5. Based on in vitro studies, dog metabolic profiles are quantitatively different from other species tested since the major metabolite in the dog appears to be a minor one in rat and monkey. This may explain in part the absence of QTc prolongation in dog whereas this effect was observed in the monkey and human. In general the metabolites were considered much less pharmacologically active than the parent, however based on the extensive metabolism the