CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208325Orig1s000

CHEMISTRY REVIEW(S)

Recommendation:
APPROVAL
(including the Overall Manufacturing Inspection Recommendation)

NDA 208325
Review #3
Review Date (see last page)

Drug Name/Dosage Form	etelcalcetide solution for IV injection
Strength	2.5 mg/0.5 mL vial, 5 mg/mL vial, 10 mg/2 mL vial
Route of Administration	IV injection
Rx/OTC Dispensed	Rx
Applicant	KAI Pharmaceuticals

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0000	8/24/2015
0002	10/16/2015
0003	11/10/2015
0004	12/2/2015
0009	3/8/2016
0019	12/9/2016

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/OFFICE
Application Technical Lead	Suong Tran	New Drug Products I/ONDP
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
Drug Substance	Joseph Leginus	New Drug API/ONDP
Drug Product	John Amartey	New Drug Products II/ONDP
Biopharmaceutics	Hansong Chen	Biopharmaceutics/ONDP
Process	Quallyna Porte	Process Assessment II/OPF
Microbiology	Peggy Kriger	Process Assessment II/OPF
Facility	Quallyna Porte Vidya Pai	Inspectional Assessment/OPF
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Assessment (EA)	N/A	

Executive Summary

I. Recommendation

The recommendation from the Office of Pharmaceutical Quality (OPQ) is for APPROVAL, including the 12/19/16 Overall Manufacturing Inspection Recommendation for "Approval".

- This recommendation is for the NDA Resubmission dated 12/9/16.
- The resubmission was submitted to address clinical deficiencies in the 8/24/16 Complete Response (CR).
- At the time of the CR action, there was no pending Quality deficiency, and the 8/4/16 OPQ review recommended for "approval".
- The resubmission does not include any new Quality information.

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues: not applicable
2. Action letter language: not applicable

II. Summary of Quality Assessment

See the 8/4/16 OPQ Review.

OVERALL ASSESSMENT AND SIGNATURE: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Suong (Su) Tran, PhD, Quality/CMC Lead, OPQ
electronic signature on the last page

Su (Suong) Tran

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Date: 1/04/2017 11:08:34AM
GUID: 508da71f00029ec8b75e233f12b15339

Recommendation:
APPROVAL
(including the Overall Manufacturing Inspection Recommendation)

NDA 208325
Review #2
Review Date (see page 2)

Drug Name/Dosage Form	etelcalcetide solution for IV injection
Strength	2.5 mg/0.5 mL vial, 5 mg/mL vial, 10 mg/2 mL vial
Route of Administration	IV injection
Rx/OTC Dispensed	Rx
Applicant	KAI Pharmaceuticals

SUBMISSION(S) REVIEWED	DOCUMENT DATE
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0002	10/16/2015
0003	11/10/2015
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0009	3/8/2016

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Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
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Drug Product	John Amartey	New Drug Products II/ONDP
Biopharmaceutics	Hansong Chen	Biopharmaceutics/ONDP
Process	Quallyna Porte	Process Assessment II/OPF
Microbiology	Peggy Kriger	Process Assessment II/OPF
Facility	Quallyna Porte	Inspectional Assessment/OPF
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Assessment (EA)	N/A	

Executive Summary

I. Recommendation

The FINAL recommendation from the Office of Pharmaceutical Quality (OPQ) is for APPROVAL.

- This recommendation replaces the 04/25/2016 recommendation that was finalized to meet the GRMP goal but the Overall Manufacturing Inspection Recommendation was still pending on that date.
- The Overall Manufacturing Inspection Recommendation for "Approval" was finalized in Panorama on 08/03/2016. The Facilities review was finalized on 08/03/2016 (attached).

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues: not applicable
2. Action letter language: not applicable

II. Summary of Quality Assessment

See the OPQ Integrated Quality Assessment/Review #1 finalized on 04/25/2016.

OVERALL ASSESSMENT AND SIGNATURE: EXECUTIVE SUMMARY

Application Technical Lead Signature:
I concur with the reviewers' conclusions.

Suong T. Tran -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Suong T. Tran -S, 0.9.2342.19200300.100.1.1=1300101829
Date: 2016.08.04 10:00:46 -04'00'

Suong (Su) Tran, PhD, Quality/CMC Lead, OPQ

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OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

A review of the application and inspectional documents of the facilities responsible for manufacturing Etelcalcedite Hydrochloride Injection has determined that there are no significant outstanding risks. These facilities are acceptable to manufacture product for NDA 208325.

Quallyna Porte
Acting QAL / Biologist, OPQ/OPF/DIA/BII
8/1/2016

Secondary Review Comments and Concurrence:

Derek Smith, Ph.D. 08/3/2016

Su (Suong) Tran

Digitally signed by Su (Suong) Tran
Date: 8/04/2016 10:28:45AM
GUID: 508da71f00029ec8b75e233f12b15339

Recommendation:

Approval

(This Recommendation is finalized to meet the GRMP goal and does not include the Facility Review/Manufacturing Inspection Recommendation, which is pending)

NDA 208325
Review #1
Review Date (see page 6)

Drug Name/Dosage Form	etelcalcetide solution for IV injection
Strength	2.5 mg/0.5 mL vial, 5 mg/mL vial, 10 mg/2 mL vial
Route of Administration	IV injection
Rx/OTC Dispensed	Rx
Applicant	KAI Pharmaceuticals

SUBMISSION(S) REVIEWED	DOCUMENT DATE
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0002	10/16/2015
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Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/OFFICE
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Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
Drug Substance	Joseph Leginus	New Drug API/ONDP
Drug Product	John Amartey	New Drug Products II/ONDP
Biopharmaceutics	Hansong Chen	Biopharmaceutics/ONDP
Process	Quallyna Porte	Process Assessment II/OPF
Microbiology	Peggy Kriger	Process Assessment II/OPF
Facility	Quallyna Porte	Inspectional Assessment/OPF
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Assessment (EA)	N/A	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	I		(b) (4)	Adequate	4/20/16	by P. Kriger
	III			Adequate information provided in the NDA. by J. Amartey/D. Christodoulou		
	III					
	III					

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	109773	

2. CONSULTS: n/a

Executive Summary

I. Recommendation

The recommendation from the Office of Pharmaceutical Quality is for Approval (this recommendation is finalized to meet the GRMP goal and does not include the Facility Review/Manufacturing Inspection Recommendation, which is pending).

- The recommendation in this Quality Review covers all CMC information submitted in the NDA.
- The Facility/Manufacturing Inspection review will be finalized at a later date, prior to the PDUFA goal, as an addendum in Panorama.

Labeling comments will be finalized during the multi-disciplinary OND-managed labeling review.

A. Recommendation and Conclusion on Approvability

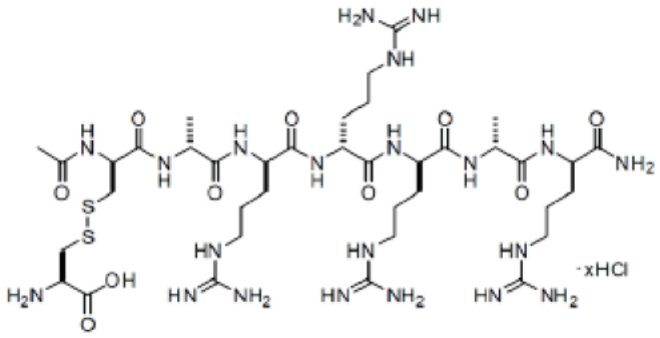
1. Summary of Complete Response issues: not applicable
2. Action letter language: not applicable

B. Recommendation on Post-Marketing Commitments, Agreements, and/or Risk Management Steps- not applicable

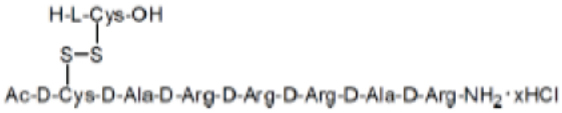
II. Summary of Quality Assessment

This NDA is a 505(b)(1) application for a New Molecular Entity.

A. Drug Substance



Also:



Molecular Formula: $C_{38}H_{73}N_{21}O_{10}S_2 \bullet$ xHCl (where x is calculated as (b) (4)

Molecular Weight: (b) (4)

1047.5 (free base)

Etelcalcetide is a relatively small synthetic peptide with 7 D-amino acids linked to L-cysteine by a disulfide bond. It is a hydrochloride salt in the form of a powder, white to off-white in color and is (b) (4) water-soluble (b) (4) amorphous, hygroscopic, with no known secondary and tertiary structures. It has a specific optical rotation of (b) (4)° and pH of (b) (4).

The manufacturing process has (b) (4) steps: (b) (4) (b) (4)

The analysis includes all batches used in pivotal and stability studies and one clinical batch manufactured at commercial (b) (4) site, and process.

The primary structure of the drug substance was confirmed by amino acid analysis, elemental analysis, mass spectrometry (MS), nuclear magnetic resonance (NMR) spectroscopy, chiral amino acid analysis and ultraviolet/visible (UV/Vis) spectroscopy. The lack of any secondary structure was confirmed by far (b) (4)

Characterization of impurities included testing for those with potential genotoxicity. The drug substance itself is Ames-positive but is not mutagenic as confirmed by in vivo studies (see details in the Pharmacology Toxicology review). (b) (4) impurities with the same functional groups are covered by toxicology studies conducted on the drug substance. Specified impurities have qualified limits, and the limit of (b) (4)% on an unspecified impurity was previously agreed upon by FDA.

The drug substance specification includes attributes standard for this type of drug substance. Identity testing by amino acid analysis and mass spectrometry is acceptable because this is a relatively small peptide. Chirality is tested using specific optical rotation. Bioassay testing is not necessary because this is a relatively small peptide (obvious structure-potency correlation), per previous FDA's agreement.

The (b) (4) with a retest period of (b) (4) months. The drug substance is sensitive to (b) (4) and light.

B. Drug Product

The product is 5 mg/mL of etelcalcetide free-base (equivalent to 5.77 mg/mL etelcalcetide hydrochloride), a sterile, preservative-free, ready-to-use solution for intravenous injection. It is packaged in a single-dose vial available in 3 fill sizes: 0.5 mL (to deliver 2.5 mg etelcalcetide, 1 mL (to deliver 5 mg etelcalcetide), and 2 mL (to deliver 10 mg etelcalcetide).

Excipients are 8.5 mg/mL (or 0.85% w/v) sodium chloride, 1.2 mg/mL (or 10 mM) succinic acid, (b) (4), and adjusted to pH 3.3 with sodium hydroxide and/or hydrochloric acid.

The manufacturing process is standard for this type of dosage form and includes: (b) (4)

The specification includes attributes standard for this type of dosage form (injectable solution). The 3 specified degradants are the same as in the drug substance specification, with qualified limits.

Container closure system: USP type 1 glass vial with an elastomeric stopper and aluminum outer seal.

Expiration Date & Storage Conditions: 24 months at 2-8 °C

C. Summary of Drug Product Intended Use

Proprietary Name	[not finalized by GRMP goal; see CDTL's memo]
Non Proprietary Name of the Drug Product	etelcalcetide
Non Proprietary Name of the Drug Substance	etelcalcetide
Proposed Indication(s)	[not finalized by GRMP goal; see CDTL's memo]
Duration of Treatment	chronic
Maximum Daily Dose	[not finalized by GRMP goal; see CDTL's memo]
Alternative Methods of Administration	not applicable

D. Biopharmaceutics Considerations

The commercial formulation is an injectable solution product that is titrated to the correct dose. The formulation was used in the open-labeled extension phase 3 studies, which also included an earlier formulation (b) (4) A biowaiver request was submitted for the

change in formulation and is found acceptable because both formulations are for intravenously administration where bioavailability is instant and self-evident. In addition, the two formulations have (b) (4) is not clinically meaningful.

E. **Novel Approaches**: not applicable
F. **Any Special Product Quality Labeling Recommendations**: not applicable
G. **Life Cycle Knowledge Information (see Attachment)**

OVERALL ASSESSMENT AND SIGNATURE: EXECUTIVE SUMMARY

Application Technical Lead Signature: I concur with the reviewers' conclusions.

Suong T. Tran -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Suong T. Tran -S, 0.9.2342.19200300.100.1.1=1300101829
Date: 2016.04.25 11:37:01 -04'00'

Su (Suong) Tran, PhD

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(b) (4)

[redacted]

OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Reviewer's Assessment and Signature:

I have so far not identified any major critical issues with the application. The application is approvable from the drug product perspective.

John K. Amartey, Ph.D. (2/4/2016)

Supervisor Comments and Concurrence:

I concur.

Environmental Assessment:

The applicant is requesting a categorical exclusion from environmental assessment for AMG 416 in accordance with 21 CFR 25.31(b). According to the applicant, the concentration of AMG 416 at the point of entry into aquatic environment is expected to below 1 part per billion. This value was estimated based on the assumption that the projected annual amount of AMG 416 produced is (b) (4) kg. The estimated introductory concentration (EIC) = (b) (4) ppb. **Acceptable**

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

NDA 208325

Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

[TRADENAME] (etelcalcetide HCl) is a synthetic peptide calcimimetic agent that activates the calcium-sensing receptor (CaSR). [TRADENAME] is a white to off-white powder with a molecular formula of $C_{38}H_{73}N_{21}O_{10}S_2 \cdot xHCl (4 \leq x \leq 5)$ and a molecular weight of 1047.5 g/mol (monoisotopic; free base). It is soluble in water. The hydrochloride salt of [TRADENAME] is described chemically as N-acetyl-D-cysteinyl-S-(L-cysteine disulfide)-D-alanyl-D-arginyl-D-arginyl-D-arginyl-D-alanyl-D-argininamide, hydrochloride.

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: [TRADENAME] Established Name: Etelcalcetide	Adequate
Dosage form, route of administration	Dosage: • 2.5 mg etelcalcetide in 0.5 mL solution (5 mg/mL) in a single-dose vial • 5 mg etelcalcetide in 1 mL solution (5 mg/mL) in a single-dose vial • 10 mg etelcalcetide in 2 mL solution (5 mg/mL) in a single-dose vial Route: intravenous Injection	Adequate
Controlled drug substance symbol (if applicable)	Not Applicable	NA
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Etelcalcetide is supplied as a sterile solution for intravenous injection in three strengths 2.5 mg in 0.5 mL solution, 5 mg in 1 mL solution, and 10 mg in 2 mL solution. (**3.2.P.1**)	Adequate

Conclusion:
The required information provided is acceptable

(b) "Full Prescribing Information" Section

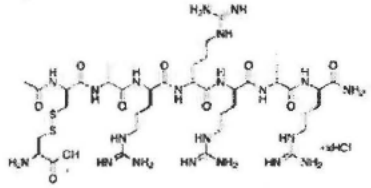
 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Injection	Adequate
Strengths: in metric system	• 2.5 mg etelcalcetide in 0.5 mL solution (5 mg/mL) in a single-dose vial • 5 mg etelcalcetide in 1 mL solution (5 mg/mL) in a single-dose vial • 10 mg etelcalcetide in 2 mL solution (5 mg/mL) in a single-dose vial	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Not Applicable	NA

Conclusion: Acceptable

#11: Description (21CFR 201.57(c)(12))

[TRADENAME] (etelcalcetide HCl) is a synthetic peptide calcimimetic agent that activates the calcium-sensing receptor (CaSR). [TRADENAME] is a white to off-white powder with a molecular formula of $C_{38}H_{73}N_{21}O_{10}S_2 \cdot xHCl (4 \leq x \leq 5)$ and a molecular weight of 1047.5 g/mol (monoisotopic; free base). It is soluble in water. The hydrochloride salt of [TRADENAME] is described chemically as N-acetyl-D-cysteinyl-S-(L-cysteine disulfide)-D-alanyl-D-arginyl-D-arginyl-D-arginyl-D-alanyl-D-argininamide, hydrochloride.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Proprietary Name: [TRADENAME] Established Name: etelcalcetide	Adequate
Dosage form and route of administration	Injection solution for intravenous injection	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	2.5 mg (equivalent to 2.88 mg etelcalcetide hydrochloride salt) 5 mg (equivalent to 5.77 mg etelcalcetide hydrochloride salt) 10 mg (equivalent to 11.54 mg etelcalcetide hydrochloride salt)	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	0.85% (w/v) sodium chloride, 10 mM succinic acid, sodium hydroxide and hydrochloric acid	Adequate
Statement of being sterile (if applicable)	Sterile (b) (4)	Adequate
Pharmacological/ therapeutic class	Synthetic peptide calcimimetic reduces serum calcium level.	Adequate
Chemical name, structural formula, molecular weight	N-acetyl-D-cysteinyl-S-(L-cysteine disulfide)-D-alanyl-D-arginyl-D-arginyl D-arginyl-D-alanyl-D-argininamide, hydrochloride.  $C_{38}H_{73}N_{21}O_{10}S_2.xHCl$. M.Wt.= 1047.5 g/mol	Adequate

If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa, solubility, or pH)	NA	NA

Conclusion: Adequate

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

<table>
<tr><th>Item</th><th>Information Provided in NDA</th><th>Reviewer's Assessment</th></tr>
<tr><td>Strength of dosage form</td><td>[TRADENAME] for injection in a single-dose vial with stopper and aluminum flip-off cover containing 5 mg/mL of etelcalcetide solution with the following strengths:
<table>
<tr><td>2.5 mg/0.5 mL</td><td>Carton of 10 single-dose vials</td><td>NDC 55513-740-10</td></tr>
<tr><td>5 mg/1 mL</td><td>Carton of 10 single-dose vials</td><td>NDC 55513-741-10</td></tr>
<tr><td>10 mg/2 mL</td><td>Carton of 10 single-dose vials</td><td>NDC 55513-742-10</td></tr>
</table></td><td>Adequate</td></tr>
<tr><td>Available units (e.g., bottles of 100 tablets)</td><td>NA</td><td>NA</td></tr>
<tr><td>Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number</td><td>NDC numbers are shown above</td><td>Adequate</td></tr>
<tr><td>Special handling (e.g., protect from light, do not freeze)</td><td>Store at 2°C to 8°C (36°F to 46°F) in a refrigerator and protected from light.</td><td>Adequate</td></tr>
<tr><td>Storage conditions</td><td>-Must not be exposed to temperatures above 25°C</td><td>Adequate</td></tr>
</table>

	(77°F). -Must be used within 7 days if stored in the original carton. -Must be used within 4 hours and not be exposed to direct sunlight if removed from the original carton.	

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	AMGEN/KAI Pharmaceuticals Inc. One Amgen center Drive, Thousand Oaks, CA 91320-1799	Adequate

Conclusion: Adequate

2. Labels

1) Immediate Container Label

A container label for the 2.5 mg/mL strength is reproduced here to represent the remaining two strengths presentations.

Reviewer's Assessment: Adequate

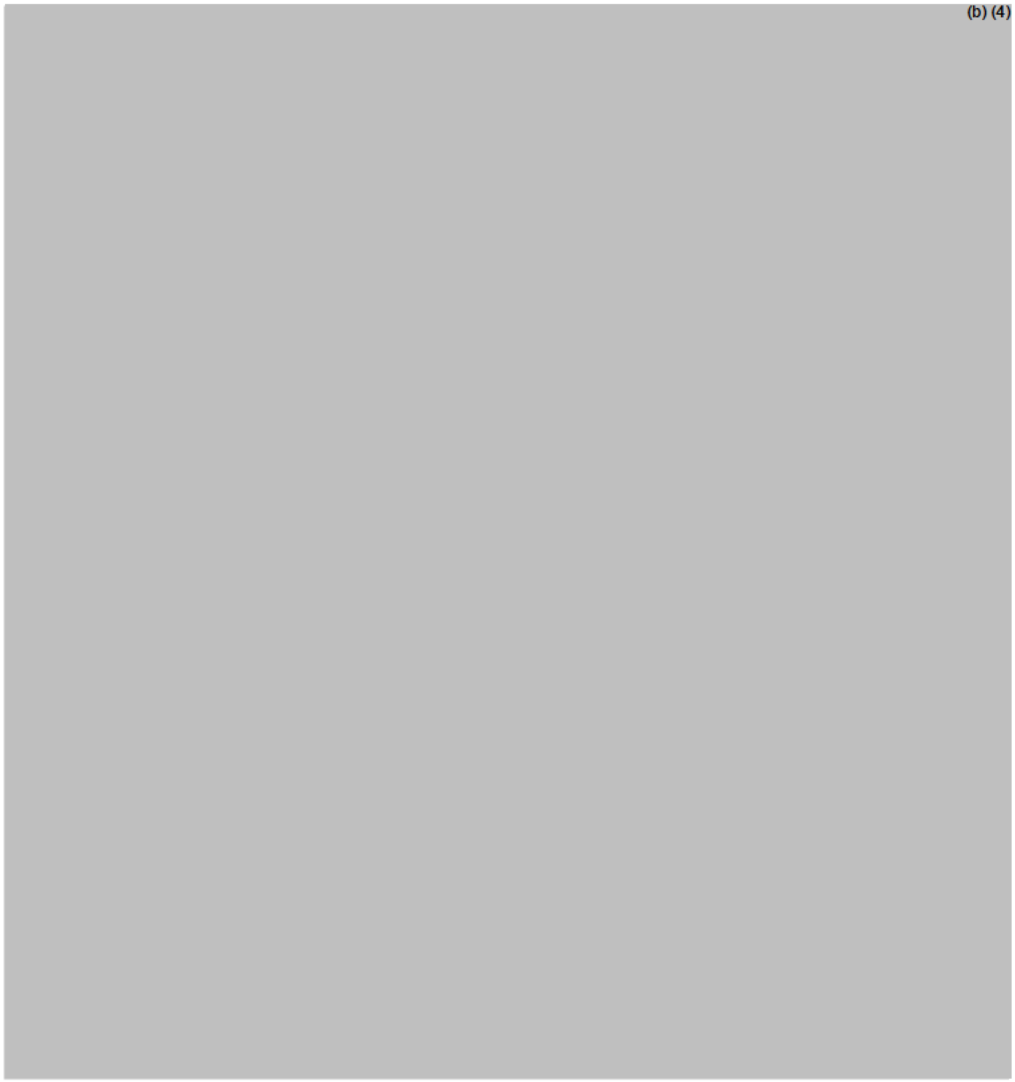
Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The proprietary name [TRADENAME] and the established name etelcalcetide satisfy the font size deferential required by 21CFR 210.10(g)(2)	Acceptable
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Three strengths are described in the application seeking approval	Adequate
Net contents (21 CFR 201.51(a))	The net quantity of the three strengths have been described in the application	Adequate
Lot number per 21 CFR 201.18	Provision is made for lot number in the label.	Adequate
Expiration date per 21 CFR 201.17	Location of expiration date is provided	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	The statement "Rx only" is indicated on the label	Adequate
Storage	Storage condition is stated	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC # is provided	Acceptable
Bar Code per 21 CFR 201.25(c)(2)**	The position of the bar code is provided	Adequate
Name of manufacturer/distributor	AMGEN/KAI Pharmaceuticals Inc. One Amgen center Drive, Thousand Oaks, CA 91320-1799	Adequate
Others	NONE	

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: The information provided is adequate

2) **Cartons**
The carton for the 2.5 mg/mL strength is reproduced below to represent the remaining two strength presentations.



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	The proprietary name [TRADENAME] and the established name Etelcalcetide satisfy the font size deferential required by 21CFR 210.10(g)(2)	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Three strengths are described in the application: 2.5 mg etelcalcetide in 0.5 mL solution (5 mg/mL) in a single-dose vial; 5 mg etelcalcetide in 1 mL solution (5 mg/mL) in a single-dose vial; 10 mg etelcalcetide in 2 mL solution (5 mg/mL) in a single-dose vial	Adequate
Net contents (21 CFR 201.51(a))	Net contents are described	Adequate
Lot number per 21 CFR 201.18	Provision for lot number is indicated	
Expiration date per 21 CFR 201.17	The expiration date is provided	Acceptable
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	0.85% (w/v) sodium chloride, 10 mM succinic acid, sodium hydroxide and hydrochloric acid	Adequate
Sterility Information (if applicable)	Sterile, preservative-free solution	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	"Rx only" indicated	Adequate
Storage Conditions	Storage condition indicated	Acceptable

NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also	NDC numbers for the three strengths have been indicated.	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	The Bar code is provided	Adequate
Name of manufacturer/distributor	AMGEN/KAI Pharmaceuticals Inc. One Amgen center Drive, Thousand Oaks, CA 91320-1799	Adequate
"See package insert for dosage information" (21 CFR 201.55)	The statement is provided	
"Keep out of reach of children" (optional for Rx, required for OTC)	Optional and was not indicated by applicant	Acceptable
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	"For intravenous Administration Only" indicated	Adequate

Conclusion: The requisite information has been provided on the carton. ADEQUATE

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Biopharmaceutics Review

Background

For Phase 3 clinical studies, Amgen developed [redacted] for etelcalcetide, which was [redacted] For commercial use, etelcalcetide is formulated as a ready-to-use (RTU) liquid product. These two formulations have the [redacted] A side-by-side comparison of the components and composition of the [redacted] and liquid drug products is shown in the following table:

Table 1. Comparison of AMG 416 [redacted] and RTU Liquid Formulations

Components	[redacted]	Liquid formulation
Etelcalcetide (AMG 416)	[redacted]	10 mg
Succinic acid	[redacted]	[redacted]
Sodium chloride	[redacted]	[redacted]
pH	[redacted]	[redacted]

[redacted]

Information Request (IR)

On 11/6/2015, the FDA sent an IR to the Applicant. On 12/2/2015, the Applicant responded to the IR. The following are the Biopharmaceutics IR, the Applicant's response, and this reviewer's comment.

IR

(b) (4)

The Applicant's response

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The differences between two formulations do not affect PK profile and safety

(b) (4)

[redacted] (b) (4)

Reviewer's comment

The Applicant's response is adequate. This reviewer also confirmed with the medical reviewer of this application that the [redacted] (b) (4) *do not affect the In Vivo PK performance and clinical outcome (efficacy/safety).*

Biowaiver

In this application, the Applicant is requesting a waiver from in-vivo bioequivalence (BE) study requirements for the liquid formulation.

Reviewer's comment:

Although the Applicant partially fulfills the requirement of 21CFR320.22 (b) (1), the biowaiver for the liquid formulation still can be granted due to the following reasons:

(1) The proposed liquid formulation contains [redacted] (b) (4) *Although two formulations have* [redacted] (b) (4) *based on the justification provided and in presence of* [redacted] (b) (4) *of* [redacted] (b) (4) *the differences* [redacted] (b) (4) *is not likely to affect the clinical performance.*

[redacted] (b) (4)

(3) Both formulations are intended solely for intravenous administration where bioavailability will be instant and self-evident.

Conclusion

Based on the above review, the Applicant's request for a waiver from in-vivo bioequivalence (BE) study requirements for the liquid formulation can be granted and overall, NDA 208325 is recommended for approval from a biopharmaceutics perspective.

Tran, Suong T

From: Chen, Hansong
Sent: Tuesday, April 19, 2016 9:42 PM
To: Tran, Suong T; Lalmansingh, Anika
Cc: Ghosh, Tapash
Subject: FW: Review for NDA 208325

Importance: High

Hi Su and Anika,

Here is my review for NDA 208325, which has been edited and concurred by Tapash.
Please let me know if you have any questions,

Thanks,

Hansong

From: Ghosh, Tapash
Sent: Tuesday, April 19, 2016 7:56 AM
To: Chen, Hansong
Cc: Chen, Tien Mien; Seo, Paul; Ghosh, Tapash
Subject: FW: Review for NDA 208325
Importance: High

With my edits. Thanks,

From: Chen, Hansong
Sent: Monday, April 18, 2016 8:10 PM
To: Ghosh, Tapash
Subject: Review for NDA 208325
Importance: High

Hi Tapash,

I have finished drafting the review for NDA208325, which is due This Thursday April 21. Albert is out of office, would you please take time to look at it as a secondary reviewer?

I will send it to Su and the PM once you edit it.

Thanks,

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Thanks,

Product Quality Microbiology Review

April 20, 2016

NDA: 208325

Drug Product Name
Proprietary: AMG 416 (Parsabiv)
Non-proprietary: Etelcalcetide Injection

Review Number: #1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
8/24/2015	8/24/2015	N/A	10/07/2015
8/25/2015	8/25/2015	N/A	N/A
11/10/2015	11/10/2015	N/A	N/A
12/02/2015	12/02/2015	N/A	N/A
3/08/2016	3/08/2016	N/A	3/08/2016

Applicant/Sponsor
Name: KAI Pharmaceuticals/Amgen
Address: One Amgen Center Drive, Thousand Oaks, CA 91320-1799
Representative: Jennifer Steinbock, Manager, Regulatory Affairs
Telephone: 805-313-4718
Fax: 805-480-1330

Name of Reviewer: Peggy Kriger, Ph.D.

Conclusion: The submission is **recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** Original NDA

2. **SUBMISSION PROVIDES FOR:** Initial marketing of sterile drug product

3. **MANUFACTURING SITE:**
(b) (4)

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile injection; IV; 5 mg/mL, packaged as 2.5 mg/0.5 mL, 5 mg/1 mL, and 10 mg/2 mL; all 3 mL/13 mm, single dose vials

5. **METHOD(S) OF STERILIZATION:** (b) (4)

6. **PHARMACOLOGICAL CATEGORY:** Treatment of secondary hyperparathyroidism in patients with chronic kidney disease on maintenance hemodialysis therapy.

B. **SUPPORTING/RELATED DOCUMENTS:**
DMF (b) (4) (Type V, (b) (4)) is referenced for the (b) (4) An LOA, dated November 13, 2015, is provided. The relevant information in DMF (b) (4) was reviewed by S. Steffen ((b) (4)mic24.doc, dated February 25, 2013) and deemed adequate.
DMF (b) (4) (Type V, (b) (4) is referenced for the (b) (4) An LOA, dated May 19, 2015, is provided. Relevant information in DMF (b) (4) was reviewed by S. Langille (Product Quality Microbiology review of DMF (b) (4) dated October 30, 2014, adequate), B. Mello (D0(b) (4)_2013_10_03_A1.DOC, dated December 11, 2013, adequate), L. Shelton (b) (4)mic1.doc, dated February 10, 2016, inadequate; (b) (4)mic1a1.doc, dated March 8, 2016, adequate) and P. Kriger ((b) (4)mic2.doc, dated April 20, 2016, adequate).

C. **REMARKS:** This is an eCTD submission. Some tables were copied from the submission. The 8/25/15 amendment is referenced for labeling and dosage information. The 11/10/15 amendment is referenced for manufacturing facility information. The 12/02/15 amendment is referenced for updated LOA information. The 3/08/2016 amendment is referenced for the response to a CMC information request sent on 2/02/2016 and an updated agent.

Filename: 208325.doc
Template version: OGD modified_AP_2014v6.doc

Executive Summary

I. **Recommendations**

A. **Recommendation on Approvability -**
The submission is **recommended** for approval on the basis of sterility assurance.

B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

II. **Summary of Microbiology Assessments**

A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -** (b) (4) drug solution is subjected to (b) (4); vials are (b) (4)

B. **Brief Description of Microbiology Deficiencies** – None identified

C. **Contains Potential Precedent Decision(s) -** ☐ **Yes** ☒ **No**

III. **Product Quality Microbiology Risk Assessment**

A. **Initial Product Quality Microbiology Risk Assessment**

CQA	Risk Factor	Prob. of Occ. (O)	Severity of Effect (S)	Detect. (D)	Risk Priority Number[6] (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
Ster.	(b) (4)	10	5	5	250	Simulations and interventions conducted during media fills, Environmental monitoring
Endo		4	4	4	64	
(b) (4)						

6 = RPN = O(after modification when applicable)×S×D
RPN <50 = Low Risk; RPN 50-120 = Moderate Risk; RPN >120 = High Risk

B. **Final Risk Assessment** – None, sufficient sterility assurance information is provided.

IV. **Administrative**

A. **Reviewer's Signature** _____

B. **Endorsement Block**
Microbiologist/Peggy Kriger, Ph.D.
Microbiology Quality Assessment Lead (acting)/Erika Pfeiler, Ph.D.

C. **CC Block** cc: Field Copy

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

Note to reviewer: A Letter of Authorization (LOA), dated May 19, 2015, is provided for DMF (b) (4) as a reference for the (b) (4) The LOA indicates the applicable information for the (b) (4) (b) (4) manufacturing process is found in (b) (4) submitted September 13, 2013. The facility manufactures (b) (4) (b) (4)

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – Clear, colorless, Ready To Use solution

- **Drug product composition** –

Ingredient	Quantity per Vial for Stated Label Strength			Function
	2.5 mg	5 mg	10 mg	
AMG 416 Hydrochloride	(b) (4)			Active Ingredient
Sodium Chloride				(b) (4)
Succinic Acid				
(b) (4)				
Hydrochloric Acid				pH adjustment
Sodium Hydroxide				pH adjustment
				(b) (4)

- **Description of container closure system** –

Configuration	Component	Description	Manufacturer
5 mg/mL, packaged as 2.5 mg/vial, 5 mg/vial, 10 mg/vial	Vial	3 mL/ 13 mm USP Type 1 clear glass (b) (4)	(b) (4)
	Stopper		
	Seal		

Acceptable

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Container-Closure and Package integrity -**

(b) (4)

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(b) (4)

[redacted]

Acceptable

- **Antimicrobial Effectiveness Testing –**

  N/A. The subject drug product is a single dose; antimicrobial effectiveness testing is not required.

Acceptable

P.3 Manufacture

P.3.1 Manufacturers

Drug product manufacturing, stability and release testing:

(b) (4)

[redacted]

Drug product packaging, labeling, storage and CCI stability testing:
Amgen Manufacturing Ltd.
Carr 31, KM 24.6, Kilometer 24.6, Juncos, Puerto Rico, USA 00777

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

[redacted]

11 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)

MODULE 1

A. PACKAGE INSERT

Storage temperature: 2-8°C, protected from light
Route of administration: IV. Do not dilute prior to administration.
Container: Single dose

Acceptable

Attachment

Lifecycle Knowledge Management

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Drug content/Assay	Formulation Process Container closure	H	stability studies in-process controls	L	none
Impurities/degradants	Formulation Process Container closure	H	stability studies in-process controls	L	none
Appearance	Formulation Process Container closure	H	stability studies	L	none
Sterility	Container closure Process	H	stability studies in-process controls	L	reference the pharmaceutical development for any change in process none
Endotoxins	Container closure Process	H	stability studies in-process controls	L	
Viscosity	Formulation	H	optimize formulation	L	reference the pharmaceutical development for any change in formulation or process
Solubility	Formulation	H	optimize formulation	L	
Particulate matter	Formulation	H	stability studies in-process controls	L	none
Osmolality	Formulation	H	optimize formulation	L	reference the pharmaceutical development for any change in formulation or process
pH	Formulation	H	optimize formulation stability studies	L	
Leachable/extractables	Formulation Container closure	H	optimize formulation qualification of packaging components	L	reference the pharmaceutical development for container closure components

OVERALL ASSESSMENT AND SIGNATURE:

Application Technical Lead Signature: I concur with the reviewers' conclusions.

Suong (Su) Tran, PhD

[See digital signature and date on page 5, Executive Summary]

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

/s/

JONATHAN T DOW
02/16/2017