

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202799Orig1s000

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo
NDA 202799 Omontys (Peginesatide) Injection
Date: 08-MAR-2012

Introduction

Omontys (Peginesatide) Injection is indicated for the treatment of anemia in patients with chronic renal failure who are on dialysis. It is to-be-marketed in several strengths in single use vials (preservative free), single use pre-filled syringes (also preservative free) and multiple dose vials (with preservative).

All CMC review issues have been resolved, and ONDQA recommends approval of this NDA. Please see highlighted comments at the end of this memo for inclusion in the action letter.

Administrative

The original submission of this 505(b)(1) NDA (1S type, standard review clock) was received 27-MAY-2011 from Affymax, Inc of Palo Alto, CA. Four (4) CMC amendments were also reviewed during the review cycle; the last one received 30-JAN-2012.

The NDA is supported by IND 62357 and four (4) drug master files (DMFs). All DMFs were assessed for adequacy in the chemistry review.

The following consults are complete and acceptable to support an approval recommendation: EES on 17-FEB-2012 and DMEPA 23-DEC-2011

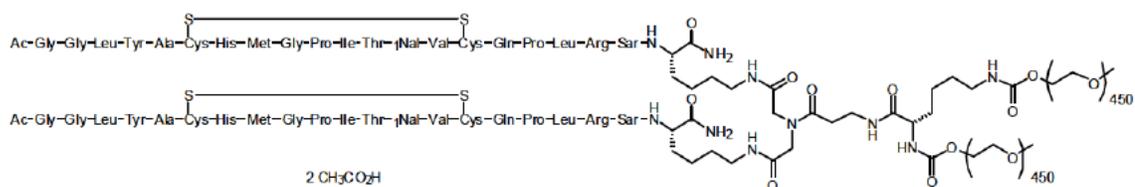
This NDA is recommended for approval from a Chemistry, Manufacturing and Controls standpoint.

Drug Substance (peginesatide acetate)

USAN: peginesatide, peginesatide acetate

CAS name: Poly(oxy-1,2-ethanediyl), α -hydro- ω -methoxy-, diester with 21N⁶,21'N⁶-[[N²,N⁶-dicarboxy-L-lysyl- β -alanyl]imino]bis(1-oxo-2,1-ethanediyl)]bis[N-acetylglycylglycyl-L-leucyl-L-tyrosyl-L-alanyl-L-cysteinyl-L-histidyl-L-methionylglycyl-L-prolyl-L-isoleucyl-L-threonyl-3-(1-naphthalenyl)-L-alanyl-L-valyl-L-cysteinyl-L-glutaminy-L-prolyl-L-leucyl-L-arginyl-N-methylglycyl-L-lysineamide] cyclic (6 \rightarrow 15),(6' \rightarrow 15')-bis(disulfide), acetate (salt)

IUPAC name: N^{6,21},N^{6,21'}-{[(N²,N⁶-bis{[ω -methoxypoly (oxyethylene)]carbonyl}-L-lysyl- β -alanyl]imino]bis(methylenecarbonyl)}bis[acetylglycyl glycyl-L-leucyl-L-tyrosyl-L-alanyl-L-cysteinyl-L-histidyl-L-methionylglycyl-L-prolyl-L-isoleucyl-L-threonyl-3-(naphthalen-1-yl)-L-alanyl-L-valyl-L-cysteinyl-L-glutaminy-L-prolyl-L-leucyl-L-arginyl-N-methylglycyl-L-lysineamide] cyclic (6-15:6'-15')-bisdisulfide, acetate (salt)



Molecular formula: C₂₀₃₁H₃₉₅₀N₆₂O₉₅₈S₆ (free base).

Molecular weight: (b) (4)

Peginesatide / Peginesatide acetate is a synthetic, PEGylated dimeric peptide comprised of two identical, covalently-linked 21 amino acid chains covalently bonded to a linker derived from iminodiacetic acid and β-alanine. The dimeric peptide acts as an erythropoiesis stimulating agent (ESA) and has MW 4,900 daltons covalently linked to a single lysine-branched bis-(methoxypoly(ethylene glycol)) (PEG) chain (approximate MW 40,000 daltons).

Peginesatide acetate is manufactured (b) (4)

Peginesatide acetate is temperature and light sensitive, therefore conservative storage conditions are required. A retest period of (b) (4) protect from light, is approved based on stability studies.

Drug Product Omontys (Peginesatide) Injection

The drug product (DP), AF37702 Injection, is provided in three drug product (DP) presentations:

Single Dose Vials (SDV) also known as Single Use Vials,
Multiple Dose Vials (MDV) also known as Multiple Use Vials, and
Pre-Filled Syringes (PFS) also known as Single Use Pre-Filled Syringes.

A total of thirteen different commercial drug product configurations (varying strength and/or fill volume) are proposed, including five SDV presentations, two MDV presentations, and six PFS presentations. The SDV and MDV drug products are manufactured by Takeda, and the PFS drug product is manufactured by (b) (4)

The **SDV and PFS** drug products are manufactured (b) (4) and both use the same formulation. In both of these cases, the formulation is an aqueous, phosphate-buffered, isotonic solution (pH approximately 6.0) containing polysorbate 20 as a (b) (4) and sorbitol for (b) (4)

The SDV drug product is packaged in USP / Ph. Eur. Type I clear glass vials with rubber stoppers and aluminum overseals. The PFS drug product is packaged in

USP/Ph.Eur. (b) (4) Type I clear glass syringes with rubber stoppers, needles, needle shields and plungers.

The MDV drug product is also manufactured (b) (4) as an aqueous, acetate-buffered, isotonic solution (pH approximately 5.4). The MDV formulation also contains methionine as an (b) (4) phenol as a (b) (4) and sorbitol for (b) (4). The MDV drug product is available in a single concentration (10 mg/mL) but at two different fill volumes (1 mL and 2 mL).

Due to the large number of strengths, batches, and storage conditions, the Applicant employed a matrixing design for the stability study. Based on a statistical analysis (refer to the statistical review, dated 18-Jan-2012) on these stability data, *an 18 month expiry, stored at 2-8 °C, protection from light, retain in carton until time of use, is granted.*

Place the following language in the action letter:

Based on the provided stability data, an expiration dating period of 18 months is granted for the drug product when stored refrigerated at 2°C to 8°C, and the storage statement indicates to protect from light and store in original carton until time of use.

Thank you,

Richard (Rik) Lostritto, Director, Division-I, ONDQA

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

/s/

RICHARD T LOSTRITTO
03/08/2012

Memorandum

To: NDA 202799
From: Sarah Pope Miksinski, Ph.D.
Date: 3/6/2012
Re: Final CMC recommendation for NDA 202799

NDA 202799 (OMONTYS®) was initially submitted on 27-MAY-2011 and was granted a standard review by the Agency. Chemistry Review #1 (dated 31-JAN-2012) recommends approval of the NDA from a CMC perspective, provided that an overall acceptable recommendation was later issued from the Office of Compliance. As of the finalized date of Chemistry Review #1, this recommendation had not been finalized by the Office of Compliance.

This memo serves to update that status. The Office of Compliance issued an overall acceptable recommendation for this application on 17-FEB-2012. This resolves the only remaining CMC issue in the previous CMC review. Chemistry Review #1 also references a potential Pharmacology/Toxicology review issue regarding the proposed acceptance criterion for (b) (4). Based on subsequent discussion with the Pharmacology/Toxicology reviewer (Dr. B. Gehrke), this issue was resolved, and no modifications to the acceptance criterion were made. Lastly, Chemistry Review #1 states that a DMEPA review is pending. This memo confirms that the DMEPA review was completed on 23-DEC-2011.

All CMC deficiencies have been resolved, there is now a final acceptable recommendation from the Office of Compliance, and there are no other outstanding CMC issues with this NDA. Therefore, approval of NDA 202799 is recommended from a CMC perspective.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

SARAH P MIKSINSKI
03/06/2012

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application: NDA 202799/000
Stamp Date: 27-MAY-2011
Regulatory: 27-MAR-2012

Action Goal:
District Goal:

Applicant: AFFYMAX
4001 MIRANDA AVE
PALO ALTO, CA 94304

Brand Name: Peginesatide
Estab. Name:
Generic Name: Peginesatide

Priority: 1
Org. Code: 161

Product Number; Dosage Form; Ingredient; Strengths
001; SOLUTION, INJECTION; PEGINESATIDE ACETATE; 2MG/.5ML
002; SOLUTION, INJECTION; PEGINESATIDE ACETATE; 3MG/.5ML
003; SOLUTION, INJECTION; PEGINESATIDE ACETATE; 4MG/.5ML
004; SOLUTION, INJECTION; PEGINESATIDE ACETATE; 5MG/.5ML
005; SOLUTION, INJECTION; PEGINESATIDE ACETATE; 6MG/.5ML
006; INJECTABLE; PEGINESATIDE ACETATE; 1MG/.5ML
007; INJECTABLE; PEGINESATIDE ACETATE; 2MG/.5ML
008; INJECTABLE; PEGINESATIDE ACETATE; 3MG/.5ML
009; INJECTABLE; PEGINESATIDE ACETATE; 4MG/.5ML
010; INJECTABLE; PEGINESATIDE ACETATE; 5MG/.5ML
011; INJECTABLE; PEGINESATIDE ACETATE; 6MG/.5ML
012; SOLUTION, INJECTION; PEGINESATIDE ACETATE; 10MG
013; SOLUTION, INJECTION; PEGINESATIDE ACETATE; 20MG

Application Comment: AF37702 IS A SYNTHETIC, DIMERIC PEPTIDE COVALENTLY LINKED TO POLYETHYLENE GLYCOL (PEG) THAT ACTS AS AN ERYTHROPOIESIS STIMULATING AGENT (ESA) (on 06-JUN-2011 by T. LAMBERT () 3017964246)

FDA Contacts:	T. LAMBERT	Project Manager	3017964246
	L. HSIEH	Review Chemist	3017961682
	J. BROWN	Team Leader	3017961652

Overall Recommendation:	ACCEPTABLE	on 17-FEB-2012	by D. SMITH	(HFD-323)	3017969643
	PENDING	on 24-JUN-2011	by EES_PROD		
	PENDING	on 15-JUN-2011	by EES_PROD		

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment Comment: (b) (4)

Profile: (b) (4) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	15-JUN-2011				BROWNJA
SUBMITTED TO DO	15-JUN-2011	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	10-AUG-2011	Product Specific			CEVERLY
INSPECTION SCHEDULED	23-NOV-2011		13-JAN-2012		CEVERLY
INSPECTION PERFORMED	20-JAN-2012		20-JAN-2012		CEVERLY
DO RECOMMENDATION	30-JAN-2012			ACCEPTABLE	CEVERLY
A PRODUCT SPECIFIC AND GMP INSPECTION WAS PERFORMED (b) (4) THE INSPECTION REVEALED TWO OBSERVATIONS:				INSPECTION	
(b) (4)					
THESE OBSERVATIONS WERE NOT SERIOUS ENOUGH TO WARRANT WITHHOLDING APPROVAL THEREFORE (b) (4) RECOMMENDS APPROVAL OF THIS APPLICATION.					
CARYN MCNAB, PRE-APPROVAL MANAGER					
OC RECOMMENDATION	02-FEB-2012			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

E. Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment Comment: DRUG PRODUCT MANUFACTURE ADN RELEASE TESTING FOR STERILITY AND BACTERIAL ENDOTOXINS FOR PRE-FILLED SYRINGE PRESENTATION. (on 06-JUN-2011 by T. LAMBERT () 3017964246)

Profile: (b) (4) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	15-JUN-2011				BROWNJA
SUBMITTED TO DO	15-JUN-2011	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	17-JUN-2011	Product Specific			PDOMINGO
DO RECOMMENDATION	22-DEC-2011			ACCEPTABLE	PDOMINGO
INSPECTION PERFORMED (b) (4) WAS CLASSIFIED NAI. FIRM IS ACCEPTABLE.				INSPECTION	
OC RECOMMENDATION	22-DEC-2011			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

E. Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER

Establishment Comment: LABELING AND SECONDARY PACKAGING SITE FOR ALL DRUG PRODUCT PRESENTATIONS (on 06-JUN-2011 by T. LAMBERT () 3017964246)

Profile: (b) (4) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	15-JUN-2011				BROWNJA
OC RECOMMENDATION	15-JUN-2011			ACCEPTABLE BASED ON PROFILE	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

E. Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: (b) (4); DRUG SUBSTANCE RELEASE AND STABILITY TESTING; DRUG PRODUCT ANALYTICAL RELEASE AND STABILITY TESTING FOR ALL DRUG PRODUCT PRESENTATIONS (on 06-JUN-2011 by T. LAMBERT () 3017964246)
 Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	15-JUN-2011				BROWNJA
OC RECOMMENDATION	15-JUN-2011			ACCEPTABLE BASED ON PROFILE	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: **CFN:** [REDACTED] **FEI:** (b) (4)

[REDACTED] (b) (4)

DMF No: [REDACTED] **AADA:** [REDACTED]

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment Comment: [REDACTED] (b) (4)

Profile: [REDACTED] (b) (4) **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	24-JUN-2011				LAMBERTTU
SUBMITTED TO DO	26-JUN-2011	Product Specific			STOCKM
DO RECOMMENDATION	01-JUL-2011			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION	01-JUL-2011			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: DRUG SUBSTANCE RELEASE TESTING FACILITY; (b) (4) (on 06-JUN-2011 by T. LAMBERT () 3017964246)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	15-JUN-2011				BROWNJA
OC RECOMMENDATION	15-JUN-2011			ACCEPTABLE BASED ON PROFILE	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment Comment: (b) (4)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	15-JUN-2011				BROWNJA
OC RECOMMENDATION	15-JUN-2011			ACCEPTABLE BASED ON PROFILE	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 9610307 FEI: 3004664162
TAKEDA PHARMACEUTICAL CO LTD

4720 TAKEDA MITSUI
MITSUI, HIKARI, YAMAGUCHI, JAPAN

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment Comment: DRUG PRODUCT MANUFACTURE, RELEASE AND STABILITY TESTING FOR SINGLE DOSE VIAL (SDV) AND MULTI DOSE VIAL (MDV) (on 06-JUN-2011 by T. LAMBERT () 3017964246)

Profile: (b) (4) **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	15-JUN-2011				BROWNJA
SUBMITTED TO DO	15-JUN-2011	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	23-JUN-2011	Product Specific			PHILPYE
INSPECTION PERFORMED	29-SEP-2011		29-SEP-2011		KHAM.PHOMMACHANH
<p>This pre-announced CGMP and Pre-Approval inspection of (b) (4) drug manufacturer was conducted as per request from CDER EES. The inspection was conducted per FACTS Assignment #7097250 covering profile class (b) (4). The inspection was conducted in accordance with Compliance Programs (CPs) 7346.832 (Pre-Approval Inspections) and CP 7356.002 (Drug Manufacturing Inspections). Abbreviated systems coverage was selected to include quality and laboratory control. Pre-approval coverage included NDA 202799 for (b) (4) Peginesatide Acetate Injection single dose vial (SDV) and multi dose vial (MDV). Compliance achievement reporting system (CARS) entered into FACTS for corrective actions to previous USFDA inspection.</p> <p>The firm was previously inspected in 10/2010 and an FDA-483 was issued (b) (4)</p> <p>The final inspectional classification was voluntary actions indicated (VAI).</p> <p>This inspection revealed that the firm corrected the previous inspectional observations and during this current inspection an FDA-483, Inspectional Observations, was issued for: (b) (4)</p>					
UNDER REVIEW	17-FEB-2012				STOCKM
DO RECOMMENDATION	17-FEB-2012			ACCEPTABLE	STOCKM
PAI CONDUCTED 9/21-9/29 PROVIDED COVERAGE FOR NDA 202799; INSPECTION CLASSIFIED VAI.				INSPECTION	
OC RECOMMENDATION	17-FEB-2012			ACCEPTABLE	SMITHDE
				DISTRICT RECOMMENDATION	

NDA 202799

Omontys[®] (Peginesatide) Injection

Affymax, Inc.

Li-Shan Hsieh, Ph. D.

Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I/Branch II**

**CMC REVIEW OF NDA 202799
For the Office of Hematology and Oncology Drug Products
Division of Hematology Products**

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CMC Review Data Sheet

CMC Review Data Sheet

- 1. NDA 202799
- 2. REVIEW #: 1
- 3. REVIEW DATE: 31-Jan-2012
- 4. REVIEWER: Li-Shan Hsieh, Ph. D

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Pre-IND meeting	04-Mar-2005
Original IND 63257 submission	25-Mar-2005
Original IND 63257 CMC review	12-Apr-2005
CMC end-of-phase-2 meeting	01-Feb-2007
CMC only pre-NDA meeting	03-Aug-2009
CMC included pre-NDA meeting	21-Oct-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	1	27-May-2011	27-May-2011
Amendment (Response to 14/10/11 CMC IR)		27-Oct-2011	27-Oct-2011
Amendment (container and carton labeling)	1	27-May-2011	27-May-2011
Amendment (Response to 01/25/12 telecon)		30-Jan-2012	30-Jan-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Affymax, Inc.
 Address: 4001 Miranda Ave, Palo Alto, CA 94304

Representative: Ann-Marie Duliege, MD, MS, Chief Medical Officer
 Telephone: 650-812-8700, Fax: 650-424-0260

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Omontys™

CMC Review Data Sheet

- b) Non-Proprietary Name: peginesatide Injection
c) Code Name/# (ONDQA only): AF37702, Hematide™,
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 1
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Erythropoiesis Stimulating Agent (ESA).

11. DOSAGE FORM: solution

12. STRENGTH/POTENCY:

SDV: 2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5 mg/mL, and 6 mg/0.5 mL

PFS: 1 mg/0.5 mL, 2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5 mg/0.5 mL, and 6 mg/0.5 mL

MDV: 10 mg/mL and 20 mg/2mL

13. ROUTE OF ADMINISTRATION: Intravenous and subcutaneous administration

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

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

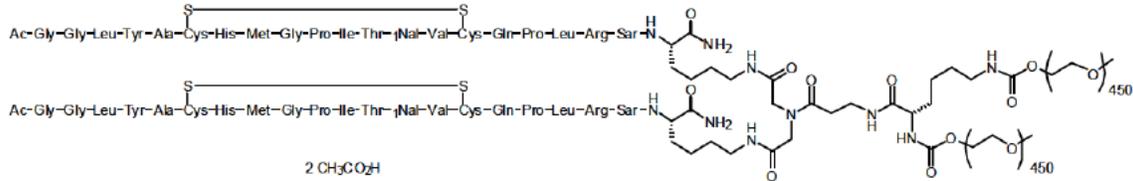
USAN: peginesatide, peginesatide acetate

CAS name: Poly(oxy-1,2-ethanediyl), α -hydro- ω -methoxy-, diester with 21N⁶,21N⁶-[[[(N²,N⁶-dicarboxy-L-lysyl- β -alanyl)imino]bis(1-oxo-2,1-ethanediyl)]bis[N-acetylglycylglycyl-L-leucyl-L-tyrosyl-L-alanyl-L-cysteinyl-L-histidyl-L-methionylglycyl-L-prolyl-L-isoleucyl-L-threonyl-3-(1-naphthalenyl)-L-alanyl-L-valyl-L-cysteinyl-L-glutaminyll-L-prolyl-L-leucyl-L-arginyl-N-methylglycyl-L-lysynamide] cyclic (6 \rightarrow 15),(6' \rightarrow 15')-bis(disulfide), acetate (salt)

IUPAC name: N^{6,21},N^{6,21}' - {[(N²,N⁶-bis {[\omega-methoxypoly (oxyethylene)]carbonyl} -L-lysyl- β -alanyl)imino]bis(methylenecarbonyl)}bis[acetylglycyl glycyl-L-leucyl-L-tyrosyl-L-alanyl-L-cysteinyl-L-histidyl-L-methionylglycyl-L-prolyl-L-isoleucyl-L-threonyl-3-

CMC Review Data Sheet

(naphthalen-1-yl)-L-alanyl-L-valyl-L-cysteinyl-L-glutaminyll-L-prolyl-L-leucyl-L-arginyl-N-methylglycyl-L-lysineamide] cyclic (6-15:6'-15')-bisdisulfide, acetate (salt)



Molecular formula: C₂₀₃₁H₃₉₅₀N₆₂O₉₅₈S₆ (free base).

Molecular weight: (b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	20-Jan-2012	(b) (4)
	III			3	Adequate	Josephine Jee 24-May-2011	
	III			3	Adequate	Dr. Marla K Stevens-Riley, 21-Jun-2011	
	III			4	Adequate	20-Jan-2012	

¹ Action codes for DMF Table:

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

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	63,257	Initial IND
IND	102,846	(b) (4)

CMC Review Data Sheet

			(b) (4)
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18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Acceptable	18-Jan-2012	Youngsook Jeon
EES	pending		
Pharm/Tox	pending		Brenda Gehrke
Biopharm	Approval	18-Jan-2012	Kareen Riviere
LNC	N/A		
Methods Validation Requested on 16-Sep-2011	Acceptable	30-Jan-2012	James M Allgire
DMEPA*	Pending		
EA	Categorical exclusion (see review)	20-Jan-2012	Li-Shan Hsieh
Microbiology	pending		Denise Miller
CDRH consult	Acceptable	25-Oct-2011	Mary Brooks, RN, BSN, MS

*DMEPA: Division of Medication Error Prevention and Analysis

Executive Summary Section

The CMC Review for NDA 202799

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This New Drug Application for Omontys® (Peginesalide) Injection,

Single use vials (preservative-free):

2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5 mg/0.5 mL, and 6 mg/0.5 mL .

Single use pre-filled syringes (preservative-free):

1 mg/0.5 mL, 2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5 mg/0.5 mL, and 6 mg/0.5 mL.

Multiple use vials (with preservative):

10 mg/mL and 20 mg/2 mL

is recommended for approval from the Chemistry, Manufacturing and Controls perspective, pending an overall acceptable recommendation from the Office of Compliance and receipt of acceptable final labeling.

Also note that there is a pending issue regarding the (b) (4) which was discussed with the Applicant on 25-JAN-2012. As a result of that teleconference, the Applicant agreed to provide additional justification for the proposed acceptance criterion. The Applicant provided additional pharmacological justification for the proposed acceptance criterion, and the adequacy of this information is currently under review by the Pharmacology/Toxicology reviewer. This is not an approvability issue from a CMC perspective, and any administrative changes (ie (b) (4)) will be captured in a subsequent CMC memo as needed.

The following language needs to be inserted into the action letter:

Based on the provided stability data, an **18-month expiration dating period** is granted for the drug product when stored at 2-8 °C, protected from light, and as retained in carton until time of use.

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

None

Executive Summary Section

II. Summary of CMC Assessments**A. Description of the Drug Product(s) and Drug Substance(s)****(1) Drug Substance**

The drug substance (DS), Peginesatide or Peginesatide acetate, also known as AF37702, is a synthetic, PEGylated dimeric peptide comprised of two identical, covalently-linked 21 amino acid chains covalently bonded to a linker derived from iminodiacetic acid and β -alanine. The dimeric peptide acts as an erythropoiesis stimulating agent (ESA) and has MW 4,900 daltons covalently linked to a single lysine-branched bis-(methoxypoly(ethylene glycol)) (PEG) chain (approximate MW 40,000 daltons).



Peginesatide is light sensitive, slightly thermal labile and extraordinary storage precautions are required. A retest period of (b) (4), protect from light, is proposed based on real-time stability studies at the recommended storage condition and at the accelerated condition. The retest interval may be extended as more data is collected.

The Peginesatide manufacturing process and process controls, materials control, critical steps and intermediates, process evaluation studies, controls; and manufacturing process development have been reviewed and found Acceptable.

(2) Drug Product

The drug product (DP), AF37702 Injection, is provided in three drug product (DP) types: Single Dose Vials (SDV) also known as Single Use Vials, Multiple Dose Vials (MDV) also known as Multiple Use Vials, and Pre-Filled Syringes (PFS) also known as Single Use Pre-Filled Syringes. A total of thirteen different commercial drug product configurations (varying strength and/or fill volume) are described, including five SDV presentations, six PFS presentations, and two MDV presentations. The SDV and MDV drug products are manufactured by Takeda, and the PFS drug product is manufactured by (b) (4).

Executive Summary Section

SDV and PFS drug products are manufactured (b) (4). The formulation for both SDV and PFS drug products is the same, and contains AF37702 (drug substance) in an aqueous, (b) (4) isotonic solution (pH approximately 6.0) for parenteral administration. The formulation also contains polysorbate 20 as a (b) (4) and sorbitol for (b) (4). The **SDV** drug product is packaged in USP / Ph. Eur. Type I clear glass vials with rubber stoppers and aluminum overseals. The **PFS** drug product is packaged in USP/Ph.Eur (b) (4) Type I clear glass syringes with rubber stoppers, (b) (4) needle shields and plungers. Because all strengths of the SDV and PFS formulations are proportionally similar and a biowaiver is granted for all strengths of the proposed products.

MDV drug product is manufactured (b) (4) and contains AF37702 drug substance in an aqueous, (b) (4) isotonic solution (pH approximately 5.4) for parenteral administration. The formulation also contains methionine as an (b) (4) phenol as a (b) (4) and sorbitol for (b) (4). The MDV drug product is available in one concentration (10 mg/mL) and two different fill volumes (1 mL and 2 mL). The SDV and MDV drug products are packaged in the same container-closure system, i.e., USP/Ph.Eur. Type I clear glass vials with rubber stoppers and aluminum overseals. Because the proposed commercial formulation for the MDV presentations differs from that used in the Phase 1 and 2 trials, a Bio-Equivalent (BE) study was conducted to bridge these two formulations. Based on Biopharmaceutics review, the BA/BE data directly supports the approval of the MDV configurations (refer to the review 18-Jan-2010).

All drug products are (b) (4) into vials or syringes. (b) (4) is a critical process and has been carefully monitored (b) (4). Based on the microbiological point of view, the sterility process is assured (Refer to the Microbiological review for additional information).

The quality of AF37702 Injection products has been assessed based on its manufacturing process, process controls, analytical procedures for identification, purity, and strength, sterility, and stability. AF37702 Injection contains an amount not less than (b) (4) of the labeled amount of AF37702.

Due to a large number of strengths, batches, and storage conditions, the Applicant employed a matrixing design for the stability study. Based on a statistical analysis (refer to the statistical review, dated 18-Jan-2012) on these stability data, ***an 18 month expiry, stored at 2-8 °C, protection from light***, retain in carton until time of use, is granted. The expiration period may be extended as more data are collected for all proposed strengths and presentations.

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

Executive Summary Section

Treatment of anemia in patients with chronic renal failure (CRF) who are on dialysis.

C. Basis for Approvability or Not-Approval Recommendation

The requirements of 21 CFR 314.50(d)(1) have been adequately met by the applicant.

All drug substance and drug product manufacturing, packaging and control facilities were submitted to EES. An overall recommendation is pending.

III. Administrative**A. Reviewer's Signature:**

(See appended electronic signature page)

Li-Shan Hsieh, Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Janice Brown, CMC Lead, Division of New Drug Quality Assessment I, Office of New Drug Quality Assessment (ONDQA)

Sarah Pope Miksinski, Ph.D., Branch Chief, Branch II, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

C. CC Block: entered electronically in DARRTS

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

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

/s/

LI SHAN HSIEH
01/31/2012

SARAH P MIKSINSKI
01/31/2012

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

NDA Number:	Supplement Number and Type:	Established/Proper Name:
202799	Original NDA	peginesatide injection
Applicant:	Letter Date:	Stamp Date:
Affymax, Inc.	23-May-2011	27-May-2011

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	PARAMETER	YES	NO	COMMENT
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

B. FACILITIES*				
	PARAMETER	YES	NO	COMMENT
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	
E. drug product (dp)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?			
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?		X	Expiry will be determined by primary reviewers in ONDQA/OBP
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	X		

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

I. Labeling				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			N.A.
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?			None

{See appended electronic signature page}

Janice Brown
Pharmaceutical Assessment Lead or CMC Lead / CMC Reviewer
Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

Date: 22-Jun-2011

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D.
Chief, Branch 2
Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

Date: 22-Jun-2011

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

/s/

JANICE T BROWN
07/06/2011

SARAH P MIKSINSKI
07/06/2011