CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208743Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: ***APPROVAL***

NDA 208743
Tymlos (abaloparatide) injection

Review #1

Drug Name/Dosage Form	Abaloparatide multi-dose, fixed dose, disposable pen injection
Strength	80 mcg (40 µL)
Route of Administration	Subcutaneous Injection
Rx/OTC Dispensed	Rx
Applicant	Radius Health
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original (0001)	03/30/16	All
Package Insert (0004)	07/01/16	Product
Response to IR (0009)	09/21/16	Substance, Product, CDRH
Response to IR (0010)	09/29/16	Microbiology
Response to IR (0011)	10/19/16	Product
Response to IR (0016)	11/08/16	Device
Response to IR (0018)	11/21/16	Product
Response to IR (0020)	11/29/16	Microbiology
Response to IR (0021)	11/30/16	CDRH
Response to IR (0022)	12/12/16	Product, CDRH
Labeling (0023)	12/19/16	Product
Response to IR (0024)	12/21/16	CDRH
Response to IR (0026)	01/10/17	CDRH
Response to IR (0027)	01/17/17	Substance, Product, DPA
Response (0028)	01/17/17	CDRH
Labeling (0029)	01/17/17	Product
Response to IR (0030)	01/23/17	Product
Response to IR (0031)	02/06/17	DPA
Labeling (0032)	02/08/17	Product
Response to IR (0036)	02/14/17	CDRH
Labeling (0037)	02/16/17	Product

Response to IR (0038)	02/17/17	CDRH, Product
Response to IR (0039)	02/27/17	Substance, Product and DPA

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Xavier Ysern	BII / DNDAPI /ONDP
Drug Product	Hamid Shafiei	BV / DNDPII / ONDP
Process	Yuesheng Ye	BVIII / DPAIII / OPF
Microbiology	Yeissa Rosello	BIII / DMA / OPF
Facility	Krishna Ghosh	BIII / DIA / OPF
Biopharmaceutics	-	-
RBPM	Thao Vu	BI / DRBPM I / OPRO
Application Technical Lead	Mark Seggel	BV / DNDPII / ONDP
Method Verification	Laura Pogue, Jingyue Yang	DPA /OTR / OPQ
CDRH-OC	Latoya Oliver-Powell	-
CDRH-GHDB	Robert Meyer	-
Environmental Analysis (EA)	Hamid Shafiei	BV / DNDPII / ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	N/A	Last review: 10/28/14	Adequate, with info in NDA
	Type III			N/A	Last review(s): (1) 10/20/15; (2) 09/02/11	Adequate, with info in NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Commercial IND and Associated Reviews	73176	IND for Abaloparatide submitted 12/08/05

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
CDRH-ODE	Complete	Approval	12/13/16	Robert Meyer
CDRH-OC (Facilities)	Complete	Approval	11/18/16	L. Oliver-Powell
CDRH-OC (21 CFR 820)	Complete	Approval	03/01/17	L. Oliver-Powell

Executive Summary

I. Recommendations and Conclusion on Approvability

Radius Health's 505(b)(1) New Drug Application #208743, for Tymlos (abaloparatide) Injection, is recommended for APPROVAL from the OPQ perspective.

Sufficient information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, potency and bioavailability of the drug product. As revised, the drug product labeling complies with the requirements under 21 CFR 201.

The drug substance and drug product manufacturing, packaging and testing facilities have acceptable CGMP status. CDRH-OC concluded that adequate documentation demonstrating compliance with the applicable sections of the medical device Quality System Regulation under 21 CFR 820 has been provided in the application. The application therefore complies with the requirements for a drug-device combination product under 21 CFR Part 4.

CDRH-ODE has determined that the pen injector component (i.e, Ypsomed UnoPen) of this drug-device combination product is comparable to the BD Pen II used in the Phase III clinical studies. Overall, the UnoPen is suitable for the intended use.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	Abaloparatide injection is indicated for the treatment of postmenopausal women with osteoporosis.
Duration of Treatment	Not to exceed 24 months
Maximum Daily Dose	80 µg / day
Alternative Methods of Administration	Not Applicable

Abaloparatide injection is small synthetic peptide for subcutaneous injection that was developed as an alternative to teriparatide and bisphosphonates. Reportedly, it significantly reduced major osteoporotic fractures when compared to teriparatide. It is also described as having lower rates of hypercalcemia and hypercalciuria than teriparatide. Abaloparatide is supplied in a cartridge and pen injector that is designed to

deliver 40 µL of the sterile product per daily injection. The cartridge contains sufficient sterile solution for 30 once-daily injections plus priming. Sterility and device performance are therefore critical to the safe and efficacious use of this drug-device combination product. Assurance of the stability of the peptide in the aqueous formulation is also is a significant quality consideration.

B. Quality Assessment Overview

Drug Substance:

Abaloparatide is a 34-amino acid, C-terminal amidated peptide analog of parathyroid hormone related protein (PTHrP(1-34)). The applicant describes abaloparatide as "a novel 34 amino acid peptide created to be a potent and selective activator of the PTH1 receptor (PHTR1) signaling pathway, with 41% homology to PTH(1-34) and 76% homology to PTHrP (1-34)."

Chemically, abaloparatide is [Glu^{22,25}, Leu^{23,28,31}, Aib^{29}, Lys^{26,30}] hPTHrP (1-34)-NH_2. It has the following amino acid sequence:

H-Ala-Val-Ser-Glu-His-Gln-Leu-Leu-His-Asp-Lys-Gly-Lys-Ser-Ile-Gln-Asp-Leu-Arg-Arg-Arg-Glu-Leu-Leu-Glu-Lys-Leu-Leu-Aib-Lys-Leu-His-Thr-Ala-NH2

Abaloparatide has molecular formula of $C_{174}H_{300}N_{56}O_{49}$ and a molecular mass of 3961 Daltons. (b) (4) It is freely soluble in 0.1 N acetic acid and in water.

As documented in the NDA, abaloparatide is manufactured by (b) (4) synthesis (b) (4) The (b) (4) peptide ((b) (4) (b) (4) is (b) (4) (b) (4) (b) (4) . (b) (4) indicates the presence (b) (4) have not been deduced from (b) (4) data.

Xavier Ysern, Ph.D., API reviewer concludes that, "the proposed specifications (tests and acceptance criteria) appear adequate to ensure the quality of the drug substance abaloparatide. Identification by MS, HPLC and optical activity suffice; the proven preservation of structure in solution justifies the lack of bioassay/biodentity testing as part of specifications. Consequently, Abaloparatide material conforming to these specifications is deemed safe and adequate to be used as API for the manufacture of the proposed drug product Abaloparatide SC."

Per the drug substance specification, the API is not less than (NLT) (b) (4) % and the amount of (b) (4) %, respectively. Peptide purity, by HPLC, is NLT (b) (4) %. Total impurities cannot exceed (i.e., are not more than (NMT)) (b) (4) % and the principal individual unspecified impurity is limited to NMT (b) (4) %.

Known impurities include the [redacted]. The [redacted] content is NMT [redacted] % and the sum of [redacted] %. Abaloparatide is hygroscopic, and to minimize degradation it is [redacted]. The proposed retest period of [redacted] months for the drug substance when stored under [redacted] is fully justified by the stability data provided (primary and supportive stability studies).

Dr. Ysern concludes that, "adequate information to judge the quality of the drug substance Abaloparatide has been provided by the Applicant. The quality of the described drug substance is deemed acceptable to support [] use in the manufacture of the proposed drug product [Tymlos](abaloparatide) Injection 2 mg/mL as described under Applicant's NDA 208743." See IQA Chapter 1 for details.

Drug Product: Tymlos (abaloparatide) injection (referred to throughout the application as 'abaloparatide-SC') is a sterile solution for the subcutaneous delivery of abaloparatide. The container closure system consists of a Type I [redacted] glass cartridge with [redacted] rubber septum on one end and a [redacted] rubber plunger on the other end. The cartridge has a fill volume of 1.56 mL (with no headspace). The delivery system consists of an Ypsomed AG UnoPen™, a "dial and push" type fixed-dose multi-dose disposable pen injector. Note that a Becton Dickinson BD Pen II was used during development. Data bridging this phase III device and the commercial UnoPen were provided (see Module 2.7.1). Needles are not provided with the pen, but may be obtained from a pharmacy wuith a prescription. The instructions for use specify mylife™ Clickfine® Needles, 8mm, 31-gauge.

Each milliliter of abaloparatide sterile solution contains 2.0 mg abaloparatide. Inactive ingredients include sodium acetate trihydrate and acetic acid [redacted] phenol [redacted] and water for injection. The solution has a pH of [redacted].

The regulatory drug product specification for abaloparatide injection filled in cartridges includes tests for identity, foreign particulate matter, pH, [redacted], assay [redacted] %), [redacted], a degradant in [redacted] (not more than [redacted]%), specified but unidentified impurities (not more than [redacted]% each), total impurities (not more than [redacted]%), sterility, endotoxins, and content uniformity. A test for "break loose and glide forces" (not more than [redacted] N) ensures that rubber plunger in the cartridge will move smoothly when the pen injector device is actuated.

The regulatory specification for the final assembled pen consists of a test to verify function [redacted] doses delivered) and dose accuracy (0.040 mL [redacted]%). For discussion of the latter see comments below).

Drug product (abaloparatide injection in cartridge) stability was characterized under the proposed long-term conditions (2-8°C), accelerated conditions (25°C/60% RH), and stress conditions (40°C/75% RH). In-use stability was characterized on samples stored at

2-8°C followed by puncturing 30 times followed by storage at 25°C/60% RH for 30 days. A temperature cycling study (30 days cycling between 2-8°C and ambient room temperature) was also conducted on punctured cartridges.

The degradation of abaloparatide to [redacted] (b) (4) is time and temperature dependent. The storage conditions and expiration dating period are limited primarily by this degradation.

The applicant proposed an expiration dating period of [redacted] (b) (4) However, the [redacted] (b) (4)-month period is not supported by long-term data (primarily because data from product after manufacturing scale-up are limited) and only a 24-month expiry can be granted at this time. Radius acknowledged acceptance of a 24-month expiration dating period for drug product stored at 2-8°C (January 23, 2017, 0030).

Overall, the applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product at release and throughout the expiration dating period of 24 months. Therefore, this application is recommended for approval from the drug product perspective. See IQA Chapter 2 for details.

Analytical Methods Verification: Because abaloparatide is a new molecular entity, a methods verification request was submitted to the CDER laboratories in St. Louis (OPQ/OT/DPA). Specifically, verification of the following methods was requested: drug substance analysis by RP-UPLC, drug product identity, purity and content by UPLC, and drug product identity by LC-MS. DPA determined that the methods are, "acceptable with modifications for quality control and regulatory purposes," (see Methods Verification Summary Report dated December 20, 2016). Recommendations based on the DPA evaluation were sent to the applicant on January 5, 2017. Revisions were satisfactorily implemented by the applicant.

On February 6, 2017 the applicant reported that the originally submitted [redacted] (b) (4) drug product identity test [redacted] (b) (4) had never been used and had been replaced by LC-MS procedure G1603122. It is not clear why the applicant had not report this earlier. Nevertheless, Dr. Laura Pogue, DPA, concluded that the new LC-MS method "should work as intended."

Environmental Analysis: Radius Health has requested a categorical exclusion from the environmental assessment requirements in accordance with 21 CFR 25.31(b). The environmental introductory concentration (EIC) is estimated to be below [redacted] (b) (4) ppb. This is significantly lower than the 1 ppb threshold. To the applicant's knowledge, no extraordinary circumstances exist that indicate that approval of the NDA would adversely affect the quality of the human environment. The claimed categorical exclusion for abaloparatide injection is therefore acceptable.

Labeling: The container and carton labels, as well as the package insert and instructions for use were evaluated from the CMC perspective. Deficiencies related to the declaration

of net contents, the storage conditions, identification of the manufacturer/distributor, the sterility statement, and the "prescribing information" statement have been resolved. The latest revision (February 16, 2017, 0037) to the labeling covers the addition of "the Country of Origin as Belgium for the Active Pharmaceutical Ingredient (API) as required by Customs" to the carton labels.

From the CMC perspective the labeling, as revised, meets the requirements under 21 CFR 201. See IQA Chapter IV and addendum for details.

Process: (b) (4)

(b) (4)

The NDA is, as amended, recommended for approval from the product manufacturing perspective. See IQA Chapter V for details.

Facilities: Abaloparatide drug substance is synthesized, (b) (4) (b) (4) (b) (4), by Lonza Braine S.A., Belgium. (b) (4) testing is conducted by (b) (4)
Based on file review, both facilities have acceptable CGMP status.

Vetter Pharma-Fertigung GmbH, Ravensburg, Germany, is responsible for the manufacturer of the drug product (sterile abaloparatide solution in cartridge) and final pen assembly (cartridge and device subassemblies). A PAI inspection covering drug and device GMPs was conducted in July 2016. This site is acceptable for manufacturing of the drug-device combination product.

Ypsomed AG, Switzerland, manufactures the subassemblies for the pen injector system. A medical device GMP inspection was performed in August 2016. No deficiencies were noted.

Several other Vetter Pharma sites prepare (b) (4) primary packaging (b) (4) (b) (4) also conducts (b) (4)

(b) (4) (b) (4) performs (b) (4) t. All of these facilities have acceptable CGMP status based on file review (see IQA Attachment IV, Manufacturing Facility Status).

Based on the recommendations made by CDRH-OC (see consult review dated November 18, 2016) and the OPF review (see IQA Chapter VI), the OPF Division of Inspectional Assessment concluded that the manufacturing and testing facilities for this NDA are acceptable (overall Approval recommendation entered in Panorama on December 15, 2016).

A 'desk review' of documentation submitted in accordance with the applicable sections of the medical device Quality System Regulation under 21 CFR 820 was completed by CDRH-OC on March 1, 2017. CDRH-OC concluded that the documentation, as amended, is adequate to support approval of the NDA. However, CDRH-OC now also recommends a post-approval medical device GMP inspection of the Vetter Pharma Holbeinstrasse, Ravensburg, Germany facility.

Biopharmaceutics: The drug product is a sterile solution for subcutaneous injection. There are no reference products containing abaloparatide to which it is being compared (i.e., no need for a biowaiver). Therefore review of the NDA by the ONDP Biopharmaceutics team is not required.

Microbiology: Sterile abaloparatide injection is manufactured by (b) (4) (b) (4) Numerous deficiencies were identified during the initial review of the product quality microbiology, and several information requests were sent to the applicant.

The container closure system (cartridge consisting of glass barrel, septum and plunger) is appropriately designed to maintain product sterility. Suitability of the preparation of the container closure components by (b) (4) has been demonstrated.

Holding times for solutions throughout the manufactured process have been adequately justified. The overall manufacturing process including (b) (4) has been adequately validated.

Container closure integrity testing (b) (4) While spectrophotometric detection is preferred because it is more sensitive, visual inspection is acceptable.

The regulatory drug product specification includes tests for bacterial endotoxins, sterility, and antimicrobial effectiveness testing. Radius has demonstrated that (b) (4) present in this formulation, remains effective at (b) (4)% of the label claim (acceptance criterion: (b) (4) mg/mL ((b) (4)%)).

As amended, the application is recommended for approval from the product quality microbiology perspective (see IQA Chapter VIII).

CDRH-ODE: The Ypsomed AG UnoPen device is, as designated in ISO 11608-1, Needle-based injection systems for medical use — Requirements and test methods, a Type C system (multi-dose, non-replaceable container) with a fixed, pre-set dose.

The device was reviewed by Robert Meyer, Mechanical Engineering Reviewer (see Consult review from CDRH entered into DARRTS on 12/13/2016). Deficiencies were identified in the initial submission (e.g., several reports including design specifications and design verification were not provided). The reports, including English translations from the German, were subsequently provided. CDRH notes that, "the device constituents are adequately demonstrated to function as specified after adequate pre-conditions are applied to device," and recommends approval of the application as amended.

The CDRH review noted that the dose accuracy is (b) (4)%) 0.040mL ± (b) (4)mL. This observation was conveyed to the clinical review team. Per ISO 11608-1, the dose accuracy requirement, for volumes less than mL, is the target volume (0.040 mL) ± (b) (4)mL, which is equivalent to ± (b) (4)%. This appears to be an extremely wide range. The clinical implications of such variability are unknown. This issue was raised with the applicant at the December 20, 2016 late-cycle meeting. Radius Health responded January 17, 2017 (0028). Based on the response, CDRH concluded that, "the BD pen which was used in a clinical study, and the subject pen injector manufactured by Ypsomed have the same specifications and similar dose accuracy results" (see Attachment III, email from Robert Meyer).

The ATL notes that the Ypsomed design verification summary report covering dose accuracy test results identifies 10 different dose accuracy tests performed on from 20 to 60 samples. A total of 202 individual values were obtained. Samples in only one study ((b) (4)Last-dose testing) varied from the target by as much as (b) (4)%. Results from the other studies varied from the target 0.040 mL by less than (b) (4)% to not more than (b) (4)%. These results suggest that the device is, in fact suitable for he accurate delivery of the target dose.

C. Special Product Quality Labeling Recommendations
Not Applicable

D. Final Risk Assessment (see Attachment)

OVERALL ASSESSMENT AND SIGNATURES:

Application Technical Lead Name:

Mark R. Seggel, Ph.D.
CMC Lead (acting)

Mark R. Seggel -S

Digitally signed by Mark R. Seggel -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mark R. Seggel -S, 0.9.2342.19200300.100.1.1 =1300071539
Date: 2017.03.02 16:43:30 -05'00'

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

LABELING

R Regional Information

1.14 Labeling

Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section

TRADENAME™ (abaloparatide) injection, for subcutaneous use
Initial U.S. Approval: xxxx

----------DOSAGE FORMS AND STRENGTHS ----------
Injection: 3120 mcg/1.56 mL (2000mcg/mL) in a single-patient use pre-filled pen. The pre-filled pen delivers 30 daily doses of 80 mcg abaloparatide in 40 mcL of sterile, clear, colorless solution. (**Error! Reference source not found.**)

Item	Information Provided in NDA
Drug name (201.57(a)(2))	
Proprietary name and established name	TRADENAME™ (abaloparatide) injection **Satisfactory**
Dosage form, route of administration	Injection for subcutaneous use. Injection: 3120 mcg/1.56 mL (2000mcg/mL) in a single-patient use pre-filled pen. The pre-filled pen delivers 30 daily doses of 80 mcg abaloparatide in 40 mcL of sterile, clear, colorless solution. **Satisfactory**
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (201.57(a)(8))	
Whether the drug product is scored	N/A

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths

Injection: 3120 mcg/1.56 mL (2000 mcg/mL) in a single-patient use pre-filled pen. The pre-filled pen delivers 30 doses of TRADENAME, each containing 80 mcg of abaloparatide in 40 mcL of a sterile, clear, colorless solution.

Item	Information Provided in NDA
Available dosage forms	Injection **Satisfactory**
Strengths: in metric system	3120 mcg/1.56 mL (2000 mcg/mL) in a single-patient use pre-filled pen. **Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	The pre-filled pen delivers 30 doses of TRADENAME, each containing 80 mcg of abaloparatide in 40 mcL of a sterile, clear, colorless solution. **Satisfactory**

#11: Description

TRADENAME
TYMLOS injection for subcutaneous administration contains abaloparatide, a synthetic 34 amino acid peptide. Abaloparatide is an analog of human parathyroid hormone related peptide, PTHrP1-34. It has 41% homology to hPTH(1-34) (human parathyroid hormone 1-34) and 76% homology to hPTHrP(1-34) (human parathyroid hormone-related peptide 1 34).

Abaloparatide has a molecular formula of $C_{174}\ H_{300}\ N_{56}\ O_{49}$, a molecular weight of 3961 daltons with the amino acid sequence shown below:

Ala-Val-Ser-Glu-His-Gln-Leu-Leu-His-Asp-Lys-Gly-Lys-Ser-Ile-Gln-Asp-Leu-Arg-Arg-Arg-Glu-Leu-Leu-Glu-Lys-Leu-Leu-Aib-Lys-Leu-His-Thr-Ala-NH2

TRADENAME Injection is supplied as a sterile, colorless, clear solution in a glass cartridge which is pre-assembled into a disposable single-patient use pen. The pen is intended to deliver 30 once daily doses of 80mcg abaloparatide in 40mcL. Each cartridge contains 1.56 mL of TRADENAME solution. Each mL contains 2000 mcg of abaloparatide and the following inactive ingredients: 5 mg phenol, 5.08 mg sodium acetate trihydrate, 6.38 mg acetic acid, and water for injection.

Item	Information Provided in NDA
Proprietary name and established name	TRADENAME (abaloparatide) **Satisfactory**
Dosage form and route of administration	Injection for subcutaneous administration **Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	N/A
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Each cartridge contains 1.56 mL of TRADENAME solution. Each mL contains 2000 mcg of abaloparatide and the following inactive ingredients: 5 mg phenol, 5.08 mg sodium acetate trihydrate, 6.38 mg acetic acid, and water for injection. **Satisfactory**
Statement of being sterile (if applicable)	TRADENAME Injection is supplied as a sterile, colorless, clear solution in a glass cartridge which is pre-assembled into a disposable single-patient use pen. **Satisfactory**
Pharmacological/ therapeutic class	Abaloparatide is an analog of human parathyroid hormone related peptide, PTHrP1-34 . It has 41% homology to hPTH(1-34) (human parathyroid hormone 1-34) and 76% homology to hPTHrP(1-34) (human parathyroid hormone-related peptide 1 34). **Satisfactory**
Chemical name, structural formula, molecular weight	Abaloparatide has a molecular formula of C_{174} H_{300} N_{56} O_{49}, a molecular weight of 3961 daltons with the amino acid sequence shown below: Ala-Val-Ser-Glu-His-Gln-Leu-Leu-His-Asp-Lys-Gly-Lys-Ser-Ile-Gln-Asp-Leu-Arg-Arg-Arg-Glu-Leu-Leu-Glu-Lys-Leu-Leu-Aib-Lys-Leu-His-Thr-Ala-NH_2 **Satisfactory**
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	TRADENAME Injection is supplied as a sterile, colorless, clear solution in a glass cartridge which is pre-assembled into a disposable single-patient use pen. **Satisfactory**

#16: How Supplied/Storage and Handling

TRADENAME Injection is supplied as a pre-assembled single-patient-use disposable pen packaged in a cardboard carton (NDC 70539-xxx-xx) with the Instructions for Use and Medication Guide. Each disposable pen embodies a glass cartridge that contains 3120 mcg of abaloparatide in 1.56 mL (2000mcg/mL) of sterilized, clear, colorless fluid. Each pen provides a 30-day supply for once daily injection of 80 mcg abaloparatide in 40 mcL.

Sterile needles are not included.

- Store TRADENAME in a refrigerator between 2°C to 8°C (36°F to– 46°F).
- Do not freeze.

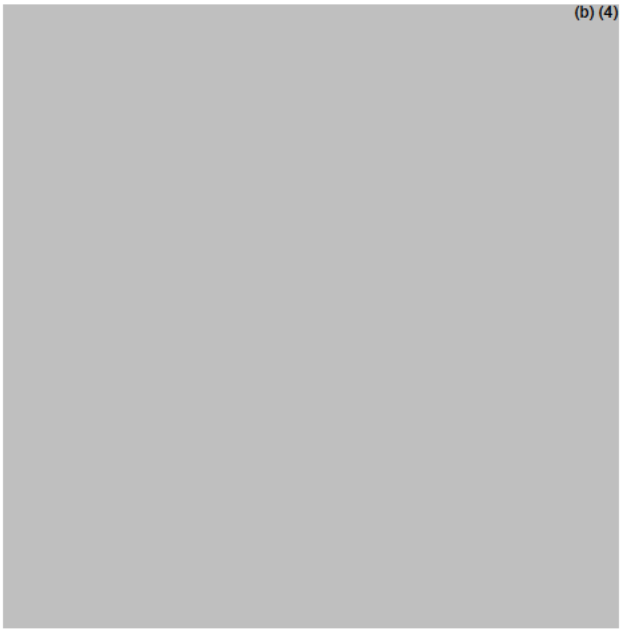
Item	Information Provided in NDA
Strength of dosage form	Each pen provides a 30-day supply for once daily injection of 80 mcg abaloparatide in 40 mcL. **Satisfactory**
Available units (e.g., bottles of 100 tablets)	a 30-day supply for once daily injection **Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	a pre-assembled single-patient-use disposable pen packaged in a cardboard carton (NDC 70539-xxx-xx) with the Instructions for Use and Medication Guide. Each disposable pen embodies a glass cartridge that contains 3120 mcg of abaloparatide in 1.56 mL (2000mcg/mL) of sterilized, clear, colorless fluid. **Satisfactory**
Special handling (e.g., protect from light)	N/A
Storage conditions	• Store TRADENAME in a refrigerator between 2°C to 8°C (36°F to– 46°F). • Do not freeze. **Satisfactory**
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured for: Radius Health, Inc. 950 Winter Street Waltham, MA 02451 **Satisfactory**

Reviewer's Assessment:

The ONDP perspective packaged insert is deemed **satisfactory.**

2. *Immediate Container Label*

(b) (4)



Item	Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Displayed. **Satisfactory**
Dosage strength	80mcg per dose **Satisfactory**
Net contents	(b) (4) It should revised to 3120 mcg/1.56 mL (2000 mcg/mL) **Unsatisfactory**
"Rx only" displayed prominently on the main panel	Displayed **Satisfactory**
NDC number (21 CFR 207.35(b)(3)(i))	Displayed **Satisfactory**
Lot number and expiration date (21 CFR 201.17)	Spaces to display lot number and expiration are allocated. **Satisfactory**
Storage conditions	Before first use, keep in refrigerator at 36°F – 46°F (2°C – 8°C). After first use, store up to 30 days at (b) (4) (b) (4) 77°F (25°C). Do not freeze or subject to heat. Should be revised to: Before first use, keep in refrigerator at 2°C – 8°C (36°F – 46°F). After first use, store for up to 30 days at 20°C – 25°C (68°F – 77°F). Do not Freeze or subject to heat. **Unsatisfactory**
Bar code (21CFR 201.25)	Displayed **Satisfactory**
Name of manufacturer/distributor	Not displayed **Unsatisfactory**
And others, if space is available	(b) (4) **Satisfactory**

Reviewer's Assessment:

The following revision should be made to the immediate container label:

- Storage condition should be change to: "Before first use, keep in refrigerator at 2°C – 8°C (36°F – 46°F). After first use, store for up to 30 days at 20°C – 25°C (68°F – 77°F). Do not Freeze or subject to heat".
- Name of manufacturer/distributor should be displayed.

- Net content should be revised from [redacted] (b) (4) to 3120 mcg/1.56 mL (2000 mcg/mL).

Conclusion: The immediate container label needs to be revised and therefore, it is **unsatisfactory**.

3. *Carton Labeling*

Item	Information Provided in NDA
Proprietary name, established name (font size, prominence)	Displayed. **Satisfactory**
Dosage strength	80mcg per dose **Satisfactory**
Net quantity of dosage form	(b) (4) It should revised to 3120 mcg/1.56 mL (2000 mcg/mL) **Unsatisfactory**
"Rx only" displayed prominently on the main panel	Displayed **Satisfactory**
Lot number and expiration date	Spaces to display lot number and expiration are allocated. **Satisfactory**
Storage conditions	Before first use, keep in refrigerator at 36°F – 46°F (2°C – 8°C). After first use, store up to 30 days at (b) (4) (b) (4) 77°F (25°C). Do not freeze or subject to heat.

	Should be revised to Before first use, keep in refrigerator at 2°C – 8°C (36°F – 46°F). After first use, store for up to 30 days at 20°C – 25°C (68°F – 77°F). Do not Freeze or subject to heat. **Unsatisfactory**
Bar code (21CFR 201.25)	Displayed **Satisfactory**
NDC number (21 CFR 207.35(b)(3)(i))	Displayed **Satisfactory**
Manufacturer/distributor's name	Displayed **Satisfactory**
Quantitative ingredient information (injectables)	Displayed **Satisfactory**
Statement of being sterile (if applicable)	Not displayed **Unsatisfactory**
"See package insert for dosage information"	Not displayed **Unsatisfactory**
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Not displayed as it is Not required. However, the following statement is displayed. "Not a child-resistant container" **Satisfactory**

Reviewer's Assessment:

The following revision should be made to the carton label:

- Storage condition should be change to: "Before first use, keep in refrigerator at 2°C – 8°C (36°F – 46°F). After first use, store for up to 30 days at 20°C – 25°C (68°F – 77°F). Do not Freeze or subject to heat".
- The statement of being sterile should be added.
- The statement "for full prescribing information see the package insert" should be added.
- Net content should be revised from (b) (4) to 3120 mcg/1.56 mL (2000 mcg/mL).

Conclusion: The carton label needs to be revised and therefore, it is **unsatisfactory**.

List of Deficiencies:

1) ***Immediate container label:***
   - *The storage condition should be revised to: "Before first use, keep in refrigerator at 2°C – 8°C (36°F – 46°F). After first use, store for up to 30 days at 20°C – 25°C (68°F – 77°F). Do not Freeze or subject to heat".*
   - *Name of manufacturer/distributor should be added to the label.*
   - *Net content should be revised from* [redacted] (b) (4) *to 3120 mcg/1.56 mL (2000 mcg/mL).*

2) ***Carton label:***
   - *The storage condition should be revised to: "Before first use, keep in refrigerator at 2°C – 8°C (36°F – 46°F). After first use, store for up to 30 days at 20°C – 25°C (68°F – 77°F). Do not Freeze or subject to heat".*
   - *The statement of being sterile should be added to the label.*
   - *The statement "for full prescribing information see the package insert" should be added to the label.*
   - *Net content should be revised from* [redacted] (b) (4) *to 3120 mcg/1.56 mL (2000 mcg/mL).*

Overall Assessment and Recommendation:

This NDA is not recommended for approval until the label/labeling issues are appropriately resolved.

Primary Labeling Reviewer: Hamid Shafiei, Ph.D., Branch V/DNDP II/ONDP 12/01/2016

Secondary Reviewer:

I agree with Dr. Shafiei's assessment of the labeling and labels, and concur with his statement that this application is not ready for approval until the issues are satisfactorily resolved.

Moo-Jhong Rhee, Ph.D.
Chief Branch V
DNDP II/ONDP

Yichun Sun

Digitally signed by Yichun Sun
Date: 12/14/2016 09:26:15PM
GUID: 507c72be00005c4494de145d79515e1f

Hamid Shafiei

Digitally signed by Hamid Shafiei
Date: 12/14/2016 05:02 29PM
GUID: 507d824300005f344cf8b5e5989f0057

MEMORANDUM DEPATMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTARTION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 07, 2017

TO: NDA 208743 CMC Labeling Review # 1

FROM: Hamid R. Shafiei, Ph.D., Drug Product Reviewer
(Branch V/DNDP II/ONDP/OPQ)

THROUGH: Moo-Jhong Rhee, Ph.D., Branch Chief
(Branch V/DNDP II/ONDP/OPQ)

SUBJECT: Final CMC Labeling Recommendation

In the Review # 1 of NDA 208743 for TYMLOS (abaloparatide) Injection for subcutaneous administration, this NDA was not recommended for approval from the CMC label/labeling perspective due to the following deficiencies:

1) Immediate container label:
   - The storage condition should be revised to: "Before first use, keep in refrigerator at 2°C – 8°C (36°F – 46°F). After first use, store for up to 30 days at 20°C – 25°C (68°F – 77°F). Do not Freeze or subject to heat".
   - Name of manufacturer/distributor should be added to the label.
   - Net content should be revised from (b) (4) to 3120 mcg/1.56 mL (2000 mcg/mL).

2) Carton label:
   - The storage condition should be revised to: "Before first use, keep in refrigerator at 2°C – 8°C (36°F – 46°F). After first use, store for up to 30 days at 20°C – 25°C (68°F – 77°F). Do not Freeze or subject to heat".
   - The statement of being sterile should be added to the label.
   - The statement "for full prescribing information see the package insert" should be added to the label.
   - Net content should be revised from (b) (4) to 3120 mcg/1.56 mL (2000 mcg/mL).

The CMC label/labeling issues have been resolved via the amendments dated December 19, 2016 and January 17, 2017 (see the review notes in the **Attachment**). Section 16 of package insert (PI) has also been updated to include the in-use storage condition. For simplicity all recommended storage conditions in the updated PI are provided below:

- Before first use, store TYMLOS in a refrigerator between 2°C to 8°C (36°F to 46°F).
- After first use, store for up to 30 days at 20°C – 25°C (68°F – 77°F).
- Do not freeze or subject to heat.

Recommendation:

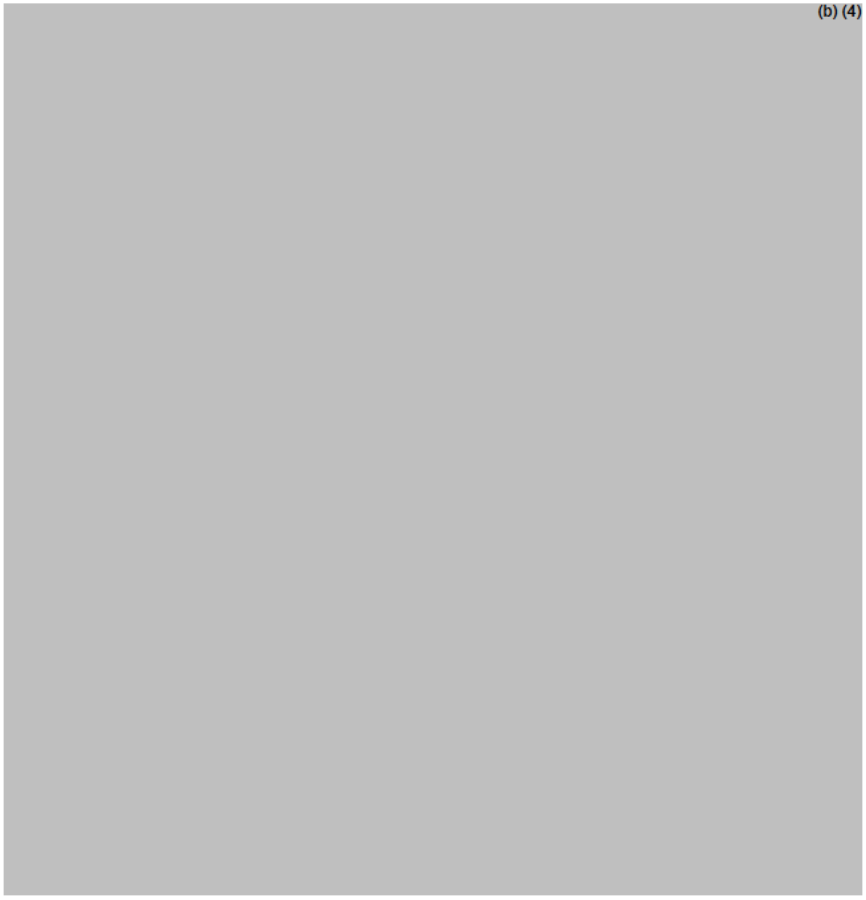
This NDA is now recommended for **approval** from the CMC label/labeling perspective.

Hamid R. Shafiei, Ph.D.
Drug Product Reviewer, Branch VDNDP II/ONDP/OPQ

Moo-Jhong Rhee, Ph.D.
Branch Chief, Branch V/DNDP II/ONDP/OPQ

Attachment: Review Notes

1. Immediate Container Label:



Reviewer Evaluation: *The immediate container label deficiencies noted in the label/labeling review # 1 have been* ***satisfactorily resolved****. The in-use storage condition of "After first use, store for up to 30 days at 20°C – 25°C (68°F – 77°F") has also been added to the section 16 of the PI.*

2. Carton Label:

Reviewer Evaluation: *The carton label deficiencies noted in the label/labeling review # 1 have been* ***satisfactorily resolved****. The in-use storage condition of "After first use, store for up to 30 days at 20°C – 25°C (68°F – 77°F)" has also been added to the section 16 of the PI.*

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 2/07/2017 02:42:35PM
GUID: 502d0913000029f9798ca689a802fa55

Hamid Shafiei

Digitally signed by Hamid Shafiei
Date: 2/07/2017 02:35:13PM
GUID: 507d824300005f344cf8b5e5989f0057

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

MICROBIOLOGY

Product Background: -

ANDA: 208743

Drug Product Name / Strength: Abaloparitide

Route of Administration: Subcutaneous injection

Applicant Name: Radius Health, Inc., 950 Winter St., Waltham, MA 02451

Manufacturing Site: Vetter Pharma-Fertigung GmbH & Co. KG, Mooswiesen 2, 88214 Ravensburg, Baden-Wuerttemberg, Germany

Method of Sterilization: (b) (4)

Review Summary: Recommended for Approval

List Submissions being reviewed: 3/30/2016, 9/29/2016 & 11/25/2016

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: No outstanding issues.

Supporting/Related Documents: N/A

Remarks Section: This is an eCTD submission and the final review document (A208743MR01.doc) will be placed in Panorama. This review includes Information Requests sent on 9/19/2016 and 11/21/2016 and the corresponding Information Request Responses sent on 9/29/2016 and 11/25/2016, respectively. Some of the tables in this review are adapted from the original submission.

S. Drug Substance

The drug substance (b) (4)

P.1 Description of the Composition of the Drug Product

Drug product is a sterile (b) (4) drug solution for multi-dose subcutaneous administration given over a period of 30 days as a daily dose of 40 µl/day.

Drug product composition:

Ingredient	Content mg/ml
Abaloparatide	2.0
Sodium acetate trihydrate USP	5.08
Acetic acid (b) (4) USP	6.38
Phenol, USP	5.0

WFI, USP	(b) (4)

Description of the container closure system:
The container closure system for the subject drug product consists of a glass cartridge loaded with the sterile drug solution (b) (4) ml) capped on one end by an aluminum crimp cap with rubber disc and a rubber plunger stopper on the other end. The glass cartridge is loaded into the pen applicator. The drug product contact parts are the glass cartridge, plunger and aluminum crimp cap (see drawing below). A rod is used to depress the plunger, but this item does not have product contact, and is considered part of the pen applicator (the device). The drug product is delivered to the patient through an externally added needle compatible with the pen applicator that inserts through the crimp cap rubber disc during use.

(b) (4)

Component	Description	Manufacturer
Cartridge (single chamber)	(b) (4) ml clear (b) (4) glass type I	(b) (4)
Crimp cap	Aluminum crimping cap (b) (4)	
Plunger	(b) (4) rubber plunger	

Acceptable

Reviewer's Assessment: Example: The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity
The firm indicated that the container closure integrity testing was performed by dye ingress test for all exhibit batches (RAOE01, RAOE02 & RAOE03). However, the studies and results could not be located.

Reviewer's Assessment: The CCIT studies could not be located. Further information was requested

Information Request:

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

Marla
Stevens Riley

Digitally signed by Marla Stevens Riley
Date: 12/08/2016 05:20:49PM
GUID: 508da70c00028f21637ed864c514d12a

Yeissa
Chabrier Rosello

Digitally signed by Yeissa Chabrier Rosello
Date: 12/08/2016 04:00:40PM
GUID: 5317ea990000ce969cecabfa83284493

ATTACHMENT I: Drug Product Risk Assessments

Initial Risk Assessment

Initial Risk Assessment for NDA 208743 Abaloparatide Injection as indicated for the Treatment of Osteoporosis in Postmenopausal Women.

Product Attribute / CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Appearance	• Process • Stability	1	3	2	6	
Identification	• CGMPs	1	5	1	5	
Assay (active) / Stability	• Formulation • Raw materials • Process • Container closure • Storage conditions	4	2	3	24	(b) (4)
Assay (b) (4)	• Formulation • Raw materials • Process	3	4	3	36	
pH	• Formulation • Raw materials • Process	2	3	1	6	
Related Substances Impurities / Degradants	• Formulation • Raw materials • Process • Container/Closure	4	3	3	36	
Leachables / Extractables	• Formulation • Raw materials • Container/Closure	2	3	4	24	
Uniformity of Dosage Fill Volume	• Process parameters	2	2	2	8	1.56 mL fill in cartridge (30 doses x 40 µL = 1.20 mL)
Dose Accuracy	• Container/Closure	2	3	3	18	Multi-dose, fixed dose, disposable pen injection system delivering 40 µL (80µg); pen injector subject to CDRH-ODE device review
Osmolality	• Formulation • Raw materials • Process	1	1	1	1	Testing not proposed
Foreign Particulate Matter	• Raw materials • Process • Container closure	3	3	3	27	
Sterility	• Raw materials • Process parameters • Hold time	4	4	5	80	Subcutaneously injected drug product. Sterility assurance is critical! (b) (4)
Endotoxins	• Raw materials	2	4	4	32	

RPN Values: Low Risk (1-25); Moderate Risk (26-60); High Risk (61-125)

Final Risk Assessment

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**
Appearance	• Process • Stability	6	(b) (4)	Acceptable	None.
Identification	• CGMPs	5		Acceptable	None
Assay (active) / Stability	• Formulation • Raw materials • Process • Container closure • Storage conditions	24		Acceptable	(b) (4) Proposed shelf-life months) not supported. 24-Month expiry granted. Extensions will need to be supported with real-time data.
Assay (b) (4)	• Formulation • Raw materials • Process	36		Acceptable	
pH	• Formulation • Raw materials • Process	6		Acceptable	
Related Substances Impurities / Degradants	• Formulation • Raw materials • Process • Container/Closure	36		Acceptable	(b) (4) Proposed shelf-life months) not supported. 24-Month expiry granted. Extensions will need to be supported with real-time data.
Leachables / Extractables	• Formulation • Raw materials • Container/Closure	24		Acceptable	
Uniformity of Dosage Fill Volume	• Process parameters	8		Acceptable	
Dose Accuracy	• Container/Closure	18		Acceptable	Any proposed changes to the pen injector should be carefully evaluated
Osmolality	• Formulation • Raw materials • Process	1		Acceptable	Testing not proposed. Small injection volume.
Foreign Particulate Matter	• Raw materials • Process • Container closure	27		Acceptable	
Sterility	• Raw materials • Process parameters • Hold time	80		Acceptable	Possible manufacturing changes that could affect the microbiological quality of the subject drug product include: change of (b) (4)
Endotoxins	• Raw materials	32		Acceptable	

ATTACHMENT II: List of Deficiencies for Complete Response

Not Applicable

ATTACHMENT III: CDRH-ODE eMail on BD Pen II and Ypsomed UnoPen

From:	Meyer, Robert
Sent:	Tuesday, January 31, 2017 3:54 PM
To:	Seggel, Mark R; Kehoe, Theresa
Cc:	Stevens, Alan M
Subject:	RE: NDA 208743 Abaloparatide Inj. - Dose Accuracy

I believe I read this report during the review. The BD pen which was used in a clinical study, and the subject pen injector manufactured by Ypsomed have the same specifications and similar dose accuracy results. Ypsomed provides reasoning which takes into account the dose accuracy, and the reproducibility of the pens, thus I believe the current specification is reasonable from a manufacturing perspective.

Thanks,

Robert Meyer, B.S. M.E.
Reviewer/ Mechanical Engineer
FDA/CDRH/ODE

Attachment IV: Manufacturing Facility Status

Facility Status	Completion Date	FEI	DUNS	Facility ID	Facility Name	Profile Code
Approve Facility	12/15/2016	3005170966	480047439	110003694	YPSOMED AG	DKA DEVICE KIT ASSEMBLER
Approve Facility	12/15/2016	3005987757	312670654	110001970	VETTER PHARMA-FERTIGUNG GMBH & CO. KG	SVL SMALL VOLUME PARENTERAL, ...
Approve Facility	11/22/2016	3005987757	312670654	110001970	VETTER PHARMA-FERTIGUNG GMBH & CO. KG	DKA DEVICE KIT ASSEMBLER
Approve Facility	9/6/2016	3002808846	344217323	110002603	VETTER PHARMAFERTIGUNG GMBH & CORPORATIO...	(b) (4)
Approve Facility	5/3/2016	3002808410	763929036	110004921	LONZA BRAINE SA	(b) (4)
Cancelled	(b) (4)				(b) (4)	SVS STERILE-FILLED SMALL VOLU...
Approve Facility	(b) (4)				(b) (4	(b) (4)
Approve Facility	(b) (4)					
Approve Facility	4/5/2016	3002270322	316126754	110002391	VETTER PHARMAFERTIGUNG GMBH & CORPORATIO...	
Approve Facility	4/5/2016	3009560142	341629292	110003135	VETTER PHARMA FERTIGUNG GMBH & CORPORATI...	
Cancelled	(b) (4)				(b) (4	
Cancelled	(b) (4)					
Approve Facility	(b) (4)				(b) (4	

Notes: Vetter Pharma, Holbeinstrasse 40, Ravensburg, Baden-Wuerttemberg, Germany (FEI 3003882331) is listed on the Form 356h and is identified as being responsible for "Visual inspection, (b) (4), (b) (4) of the filled drug product cartridges. The CDRH-OC review dated November 18, 2016 states, "No EIR was provided for review; therefore CDRH cannot attest to the compliance of the firm as it relates to 21 CFR 820. CDRH Office of Compliance defers to CDER as it relates to the approvability of the application given the lack of information for this firm."

Based on subsequent discussions, CDRH-OC and OPQ/OPF/DIA concluded that, "this site was considered to be 'No further evaluation required.'" However, in the CDRH-OC review dated March 1, 2017, it was recommended that a medical device GMP inspection of this facility be conducted post-approval.

######

Mark
Seggel

Digitally signed by Mark Seggel
Date: 3/02/2017 04:59:20PM
GUID: 507572b5000036176969356148025bae