

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**210557Orig1s000**

**CHEMISTRY REVIEW(S)**

**Memorandum**

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

**Date:** June 21, 2019

**From:** Mark R. Seggel, Ph.D.  
Application Technical Lead  
Office of New Drug Products  
Branch V/DNDP II

**Through:** Moo-Jhong Rhee, Ph.D.  
Chief, Branch V  
Office of New Drug Products  
Branch V/DNDP II

**To:** OPQ IQA #1 for NDA 210557  
VYLEESI (bremelanotide injection)

**Subject:** Final Recommendation - APPROVAL

**Summary:**

The OPQ Integrated Quality Assessment (IQA) #1 dated April 10, 2019 concluded that this 505(b)(1) NDA was Not Ready for Approval in its present form per 21 CFR 314.125(b)(8). It was noted that labeling (prescribing information (PI), container (autoinjector) label, and carton label) negotiations had not been completed, and in its present form, the labeling did not comply with the requirements under 21 CFR 201. The NDA was otherwise complete and adequate from the OPQ perspective.

Deficiencies noted in IQA #1 included inadequate presentation of dosage form, strength, and route of administration, inadequate equivalency statement, and inadequate pharmacologic/therapeutic class information (see Chapter 4, Labeling, of the April 10, 2019 OPQ IQA for details).

Revised labeling was submitted April 15, 2019 (sn 0052) and April 26, 2019 (sn 0054). The revised labeling was found acceptable from the ONDP review perspective (see the attached labeling review addendum for details).

Additional revisions to the PI, container (autoinjector), carton and PPI were subsequently made, including changing the description of the autoinjector from [REDACTED] <sup>(b) (4)</sup> to “single dose” in accordance with the October 2018 Guidance for Industry, Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use.

In their June 17, 2019 Patient Label Review of the Patient Package Insert (PPI) and Instructions for Use (IFU), DMPP / OPDP recommended that the USP room temperature range 68°F to 77°F (20°C to 25°C) be added to the PI so that it could be included in the PPI. However, the Applicant demonstrated adequate product stability at 5°C and at 25°C/60% RH, and it is not incorrect to label as follows:

Store at or below 25°C (77°F). Do not freeze. Protect from light.

The revised labeling (PI, PPI, pen injector and carton) submitted on June 21, 2019 is acceptable from the ONDP perspective.

**Additional Comments:**

To address concerns (see June 12, 2019 Information Request) raised by the Nonclinical review team regarding qualification of degradation products in the drug product (Deg A, Deg B, Deg C, Deg (b) (4) and Deg D), Amag submitted clarifying information (06/17/2019, sn 0057). Amag confirmed that the material (batch 701504) used in nonclinical study 996-041, a 91-day subcutaneous toxicity study of degraded bremelanotide in mice, had been degraded by heat treatment at (b) (4) rather than for (b) (4). Amag also confirmed that some of the chromatograms of degraded drug product were mislabeled. This does not impact the conclusions made in OPQ IQA Chapter 2, Drug Product.

Per the Panorama ‘Submission Facility Status View,’ all manufacturing, packaging and testing facilities associated with this NDA remain “Compliant.”

#####

APPEARS THIS WAY ON  
ORIGINAL

**Recommendation:**

This NDA is now recommended for **Approval** from the OPQ perspective.

**Application Technical Lead Signature:**

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

*{see digital signature page}*



Mark  
Seggel

Digitally signed by Mark Seggel

Date: 6/21/2019 04:14:16PM

GUID: 507572b5000036176969356148025bae

**Memorandum**

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

**Date:** April 29, 2019

**From:** Caroline Strasinger, Ph.D.  
Reviewer, Branch V  
Division of New Drug Products II  
Office of New Drug Products

**Through:** Moo-Jhong Rhee, Ph.D.  
Chief, Branch V  
Division of New Drug Products II  
Office of New Drug Products

**To:** Labeling Review #1 of NDA 210557

**Subject:** Final Recommendation

Labeling Review #1 had noted the following pending issues with Highlights, and Sections 3, 11 and 16 and the Carton:

**A. Regarding PI**

Extensive edits to the content and format of each of the below sections is recommended. For ease of reference the below visuals have been compiled to aid in communicating the deficiencies:

**a) Highlight Section**

-----DOSAGE FORMS AND STRENGTHS-----  
• Subcutaneous injection: 1.75 mg (b) (4) in 0.3 mL solution (b) (4)  
(b) (4)

**b) Full Prescribing Information**

**#3: Dosage Forms and Strengths**

3 DOSAGE FORMS AND STRENGTHS  
Subcutaneous injection: 1.75 mg (b) (4) in 0.3 mL solution (b) (4) in a (b) (4)  
(b) (4) autoinjector (b) (4)

- Strength should be revised to “1.75mg/0.3ml clear solution in (b) (4) autoinjector”

## #11: Description

### II DESCRIPTION

VYLEESI (bremelanotide) injection contains bremelanotide, a melanocortin receptor agonist (b) (4) for subcutaneous administration via an autoinjector.

Bremelanotide acetate is a synthetic, cyclic heptapeptide (b) (4) with a free acid at the carboxyl terminus and an acetylated amino group at the amino terminus of the peptide with the following structure:



The molecular formula of bremelanotide acetate is  $\text{C}_{50}\text{H}_{68}\text{N}_{14}\text{O}_{10} \bullet x\text{CH}_3\text{COOH}$  ( $1 \leq x \leq 2$ ) and the molecular weight of 1025.16 (free base).

(b) (4)

VYLEESI (bremelanotide) injection is supplied as a sterile, clear solution in a pre-filled syringe contained in a (b) (4) autoinjector for subcutaneous administration. Each pre-filled syringe contains 1.75 mg of bremelanotide (equivalent to 1.89 mg bremelanotide acetate) in 0.3 mL solution. Inactive ingredients consist of 2.5% glycerin, sterile water for injection, and hydrochloric acid or sodium hydroxide is added to adjust the pH (b) (4)

- **The active moiety is bremelanotide. The API is an acetate of bremelanotide which results in the theoretical equivalency statement, 1.75 mg of bremelanotide theoretically equivalent to 1.89 mg bremelanotide acetate.**
- (b) (4)  
The API used in the formulation is actually bremelanotide acetate and its USAN name needs to be secured.
- **Include injection as part of the established name**
- **Pharmacologic class should be included**

## #16: How Supplied/Storage and Handling

### 16 HOW SUPPLIED / STORAGE AND HANDLING

VYLEESI (bremelanotide) is (b) (4) supplied as:

1.75 mg bremelanotide in 0.3 mL solution in a (b) (4) disposable prefilled autoinjector;

(b) (4) Carton of 4 autoinjectors (NDC 64011-701-04).

#### Storage

Store at or below 25°C (77°F). Do not freeze. Protect from light.

- **The dosage form, and strength need to be revised to “1.75mg/0.3ml clear solution in (b) (4) autoinjector”**

### **Carton Container**

- **Include parentheses around the nonproprietary name**
- **Remove [REDACTED] <sup>(b) (4)</sup> from the inactive ingredients list on the carton.**

On April 29, 2019, the above deficiencies were agreed to by the applicant and an updated PI and Carton Container were submitted. Relevant updated sections of the PI and the Carton Container are included as Attachments below.

### **OVERALL ASSESSMENT AND RECOMMENDATION:**

**NDA 210557 is now recommended for approval from the labeling perspective. The Applicant provided updated Prescribing Information and Carton Container on April 29, 2019.**

## Attachment 1: Final PI

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VYLEESI™ safely and effectively. See full prescribing information for VYLEESI™

VYLEESI™ (bremelanotide injection), for subcutaneous use  
Initial U.S. Approval: 2019

#### -----DOSAGE FORMS AND STRENGTHS-----

- Subcutaneous injection: 1.75 mg/0.3 mL solution (**Error! Reference source not found.**)

APPEARS THIS WAY ON ORIGINAL

### 3 DOSAGE FORMS AND STRENGTHS

Subcutaneous injection: 1.75 mg/0.3 mL clear solution in a (b) (4) autoinjector.

### 11 DESCRIPTION

VYLEESI (bremelanotide injection) contains bremelanotide, a melanocortin receptor agonist for subcutaneous administration via an autoinjector. Bremelanotide acetate is a synthetic, cyclic heptapeptide with a free acid at the carboxyl terminus and an acetylated amino group at the amino terminus of the peptide with the following structure:



The molecular formula of bremelanotide acetate is  $\text{C}_{50}\text{H}_{68}\text{N}_{14}\text{O}_{10} \bullet x\text{CH}_3\text{COOH}$  ( $1 \leq x \leq 2$ ) and a molecular weight of 1025.2 (free base).

VYLEESI (bremelanotide injection) is supplied as a sterile, clear solution in a pre-filled syringe contained in a (b) (4) autoinjector for subcutaneous administration. Each pre-filled syringe contains 1.75 mg of bremelanotide (equivalent to 1.89 mg bremelanotide acetate) in 0.3 mL solution. Inactive ingredients consist of 2.5% glycerin, sterile water for injection, and hydrochloric acid or sodium hydroxide added to adjust the pH.

### 16 HOW SUPPLIED/STORAGE AND HANDLING

VYLEESI (bremelanotide) is supplied as:

1.75 mg bremelanotide in 0.3 mL solution in a (b) (4), disposable prefilled autoinjector (NDC 64011-701-01) provided in a carton of 4 autoinjectors (NDC 64011-701-04).

Storage

Store at or below 25°C (77°F). Do not freeze. Protect from light.

**Attachment 2: Final Carton**

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS)  
immediately following this page



Caroline  
Strasinger

Digitally signed by Caroline Strasinger  
Date: 4/29/2019 02:30:06PM  
GUID: 5051dfdd000013b995075b4d54108ed8



Moo Jhong  
Rhee

Digitally signed by Moo Jhong Rhee  
Date: 4/30/2019 08:30:16AM  
GUID: 502d0913000029f9798ca689a802fa55



Mark  
Seggel

Digitally signed by Mark Seggel

Date: 6/21/2019 04:19:45PM

GUID: 507572b5000036176969356148025bae

Recommendation: *As of this review, this 505(b)(2) NDA is Not Ready for Approval in its present form per 21 CFR 314.125(b)(8).*

**NDA 210557  
Review # 1**

**VYLEESI™ (bremelanotide) injection**

Drug Name/Dosage Form	Bremelanotide Injection
Strength	1.75 mg / 0.3 mL in a single use autoinjector
Route of Administration	Subcutaneous Injection
Rx/OTC Dispensed	Rx
Applicant	AMAG Pharmaceuticals, Inc.
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original (0002)	03/23/18	Multidisciplinary
Amendment (0009)	06/11/18	Drug Substance, Drug Product, Process
Amendment (0014)	07/10/18	Drug Substance
Amendment (0015)	07/19/18	Device (CDRH-ODE)
Amendment (0016)	07/30/18	Drug Product
Amendment (0019)	08/06/18	Microbiology
Amendment (0023)	08/24/18	Device (CDRH-ODE)
Amendment (0027)	09/07/18	Microbiology
Amendment (0030)	10/12/18	Device (CDRH-ODE)
Amendment (0032)	10/24/18	Process
Amendment (0033)	10/30/18	Device (CDRH-ODE)
Amendment (0034)	11/09/18	Facilities
Amendment (0035)	11/13/18	Device (CDRH-ODE)
Amendment (0042)	01/22/19	Product

**Quality Review Team**

<b>DISCIPLINE</b>	<b>REVIEWER</b>	<b>BRANCH/DIVISION</b>
Drug Substance	Joe Leginus	NDBII / DNDAPI / ONDP
Drug Product / Labeling / Environmental Analysis (EA)	Caroline Strasinger	NDPBV / DNDPII / ONDP
Process / Facility	Youmin Wang	PABV / DPAII / OPF
Microbiology	Avital Shimanovich	MABIII / DMA / OPF
Biopharmaceutics	Not Applicable	-
RBPM	Florence Aisida, Grafton Adams	BI / DRBPM I / OPRO
Application Technical Lead	Mark Seggel	NDPBV / DNDPII / ONDP
Laboratory (OTR)	Not Applicable	-

## Quality Review Data Sheet

### 1. RELATED/SUPPORTING DOCUMENTS

#### A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	3		(b) (4)	N/A	-	<i>see note below</i>
	3		N/A	-		
	3		N/A	-		

N/A: There is enough data in the application, therefore the DMF did not need to be reviewed.

*Note: The applicant provided Letters of Authorization to reference the DMFs for the container closure components, however, sufficient information regarding the composition, manufacturing and quality control of the primary container closure has been provided in this NDA application (see IQA Chapter 2, Drug Product).*

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND submissions and associated reviews	IND 64119	AMAG commercial IND for treatment of (b) (4) with bremelanotide

### 2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	na			
Pharmacology/ Toxicology	na			
CDRH - ODE		This device constituent is Approvable	12/12/18	Sapana Patel
CDRH - OC		Approvable as it relates to device GMP	11/04/18	F. Brayboy; N. Mezu-Nwaba
Clinical	na			
Other	na			

na: not applicable

## Executive Summary

### I. Recommendations and Conclusion on Approvability

In its present form, AMAG Pharmaceuticals' 505(b)(1) New Drug Application #210557, for Vyleesi (bremelanotide) injection, 1.75 mg/0.3 mL, is not ready for approval. Labeling (prescribing information and container/carton labels) negotiations have not been completed, and in its present form, the labeling does not comply with the requirements under 21 CFR 201.

Vyleesi (bremelanotide) injection is supplied as a disposable single-dose prefilled syringe assembled into an (b) (4) Autoinjector, and is thus a drug-device combination product.

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.

CDRH-ODE has determined that the autoinjector component (b) (4) of this drug-device combination product is comparable to the (b) (4) autoinjector used in the Phase III clinical studies. Adequate device performance requirements have been established. Overall, the (b) (4) is suitable for the intended use.

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.

The claimed categorical exclusion from the requirement for preparation of an environmental assessment in accordance with 21 CFR 25.31(b) is acceptable based on a calculated Expected Introduction Concentration (EIC-aquatic) significantly below 1 ppb.

### POSTMARKETING COMMITMENTS

Not Applicable

### II. Summary of Quality Assessments

#### A. Product Overview

<b>Proposed Indication(s) including Intended Patient Population</b>	Bremelanotide Injection is a melanocortin (b) (4) receptor (b) (4) agonist indicated for the treatment of premenopausal women with acquired, generalized
---	--

	hypoactive sexual desire disorder (HSDD) as characterized by low sexual desire that causes marked distress or interpersonal difficulty.
<b>Duration of Treatment</b>	As needed prior to menopause.
<b>Maximum Daily Dose</b>	One dose (1.75 mg / 0.3 mL) subcutaneously per 24 hour period; not more than 8 times per month.
<b>Alternative Methods of Administration</b>	Not applicable

To date there is only one FDA-approved drug product available for the treatment of female sexual dysfunction. ADDYI (flibanserin) tablets, 100 mg was approved August 18, 2015 for the treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD) as characterized by low sexual desire that causes marked distress or interpersonal difficulty. Use of flibanserin may cause somnolence and may cause severe hypotension and syncope especially when taken with alcohol. ADDYI is currently available only through a restricted program called the ADDYI REMS Program.

While some other marketed drug products are used off-label for the treatment of female sexual dysfunction, there is a need for additional safe and efficacious products approved for the treatment of female sexual dysfunction.

The subject of this NDA, VYLEESI (bremelanotide) injection, is an alternative treatment of HSDD. Bremelanotide is a synthetic heptapeptide melanocortin <sup>(b) (4)</sup>receptor <sup>(b) (4)</sup> agonist. It will be supplied as a sterile 1.75 mg/0.3 mL solution in a glass syringe with staked ½” 29 gauge needle, assembled in a <sup>(b) (4)</sup>, disposable autoinjector. The product is intended to be marketed in a 4-pack that can be stored at or below at or below 25°C (77°F), although not frozen. Although bremelanotide is not photosensitive and the autoinjector housing and the cartons provide protection from light, it is recommended that the drug product be labeled ‘protect from light.’ No extraordinary or unique risks associated with drug product manufacturing and quality have been identified.

VYLEESI (bremelanotide) injection is a drug-device combination product and is therefore subject to 21 CFR Part 4. The device component consists of an <sup>(b) (4)</sup> autoinjector. Device performance was evaluated by CDRH-ODE while compliance with device manufacturing GMPs was assessed by CDRH-OC. Product usability (i.e., human factors) was evaluated by CDER/OSE/DMEPA. No extraordinary or unique risks have been identified with device manufacturing, performance or use.

An obvious shortcoming of Vyleesi is self-administration by subcutaneous injection. A solid oral dosage form would be more convenient but is not feasible for this 7 amino acid synthetic peptide. Potential drawbacks with Vyleesi include safety concerns (e.g., effect on blood pressure) that may limit use to once in a 24-hour period and to not more than 8 doses per month. Nevertheless, Vyleesi provides a potentially important option for the treatment of women with HSDD.

## B. Quality Assessment Overview

Note: During the initial clinical review, it was determined that the Applicant needed to conduct an additional safety study. A Deficiencies Preclude Discussion letter was issued November 9, 2018. That study was recently completed and is under review.

### Drug Substance:

The chemistry, manufacture and control of bremelanotide acetate drug substance by (b) (4), is documented in NDA 210557.

Bremelanotide is a synthetic cyclic heptapeptide. The chemical name of bremelanotide is 2,7-anhydro(N-acetyl-L-2-aminohexanoyl-L-aspartyl-L-histidyl-D-phenylalanyl-L-arginyl-L-tryptophyl-L-lysine. The amino acid sequence is Ac – Nle – cyclo (Asp – His – D-Phe – Arg – Trp – Lys – OH). The counter-ion free molecule has a molecular weight of 1025.2. Bremelanotide is isolated as the (b) (4)

Bremelanotide acetate is freely soluble in water, methanol, and DMSO. It is soluble in ethanol. It is insoluble in acetone, acetonitrile, and other organic solvents.

Bremelanotide is synthesized using an (b) (4)  
(b) (4)

The structure of bremelanotide has been confirmed by (b) (4)

The regulatory specification includes a battery of tests to confirm the identity of the drug substance. Tests for assay, purity, related substances, acetic acid, water content, (b) (4) content, residual solvents, (b) (4) content, microbial burden and endotoxins, and solid-state form are also performed. The latter is not critical as the drug product is an aqueous solution. The regulatory analytical procedures have been adequately validated and are suitable for the intended use.

(b) (4) related impurities resulting from the starting materials, manufacturing process, and degradation have been characterized. Other organic impurities (e.g., reagents, solvents) and elemental impurities in the drug substance were also characterized.

While numerous potential (b) (4) impurities may be predicted based on the starting materials and (b) (4) process, only four related substances, reported as Imp A, Imp B,

Imp C and Imp D, are detected at levels above (b) (4)%. Acceptance criteria for controlling these 4 related substances, along with limits for unspecified related substances of not more than (b) (4)% each, and a specified bremelanotide purity of not less than (b) (4)%, are supported by pharmacology/toxicology qualification as confirmed by Dr. Leslie McKinney.

(b) (4) were identified as Class 3 potential genotoxic impurities. The applicant has identified the source of each and has developed suitable control strategies to ensure levels that are acceptable for a drug product intended for use at a daily dose of 1.75 mg.

A retest period of (b) (4) months has been established for drug substance stored at (b) (4)°C.

From the drug substance / API review perspective the information on the drug substance is Adequate to support APPROVAL of the NDA (see IQA Chapter 1, Drug Substance for additional details).

#### Drug Product:

Vyleesi (bremelanotide) injection is a drug-device combination product designed to allow self-administration of bremelanotide by subcutaneous injection. Each disposable single-dose system consists of an (b) (4) autoinjector and a prefilled syringe containing a 0.3 mL solution of 1.75 mg bremelanotide (b) (4) in a 2.5% glycerin in water solution that is adjusted to pH (b) (4) with hydrochloric acid and/or sodium hydroxide.

The (b) (4) syringe consists of a (b) (4) 1-mL Type (b) (4) glass barrel with a (b) (4) stopper/piston (b) (4), a (b) (4) stainless steel ½” 29 gauge needle, and a rigid needle shield. A leachables / extractables study and toxicologic evaluation confirmed the compatibility of all components.

The drug product manufacturing process consists of (b) (4)

The regulatory product specification includes tests conducted on prefilled syringes (PFS) and on the assembled autoinjector (AAI). The identity, quality, purity, and potency of the PFS at release is ensured by chromatographic analysis, measurement of pH (b) (4) and osmolality (b) (4) tests for content uniformity, tests for foreign particulate matter, and tests for bacterial endotoxins and sterility. Tests on the AAI are conducted at release and on stability. The tests include an assay (b) (4)% LC), purity (NLT (b) (4) %), related substances (Deg A, Deg B, Deg C, Deg D and Deg (b) (4)), particulate matter, and sterility.

Degradation products Deg A, Deg B, Deg C, Deg D and Deg Csh are (b) (4) [see section 3.2.P.5.5 of the NDA for characterization of these impurities], and controlled at not more than (b) (4) respectively. Each unspecified impurity is not more than (b) (4)% and total unspecified impurities is not more than (b) (4)%. Both specified and unspecified degradation products have been qualified by a 91-toxicology study.

As requested by the CDRH-ODE reviewer, essential performance tests verifying the delivered volume, ejection time, needle shield removal function, audible device trigger function, needle shield lockout function, viewing window occlusion post-triggering, and cap removal force, are performed on the AAI on stability.

The registration stability studies were performed on assembled autoinjectors. Samples were stored at 5°C for up to 30 months, at 25°C/60% RH for up to 36 months, at 30°C/65% RH for up to 12 months, and at 40°C/75% RH for up to 6 months. Based on the data provided, an expiration dating period of 36 months for finished product stored at or below 25°C is granted.

Overall, the applicant has provided the specifications necessary to ensure the identity, strength, quality, purity, potency, and performance of the prefilled syringe and assembled autoinjector at release and through the expiration dating period.

This application is recommended for APPROVAL from the drug product perspective (see IQA Chapter 2, Drug Product for the detailed assessment). See also Dr. Sapana Patel's CDRH-ODE review of the device component.

#### Environmental Analysis:

A categorical exclusion from the requirements of an Environmental Impact Analysis is claimed based on an estimated concentration of the substance at the point of entry into the aquatic environment (EIC-aquatic) that is below 1 part per billion. No extraordinary circumstances exist. As a small peptide it is expected to be readily degraded before entry into the aquatic environment. The claim for a categorical exclusion is in accordance with 21 CFR 25.31(b) and is accepted (see IQA Chapter 2, Drug Product).

#### Labeling:

Deficiencies in and recommendations for the labeling (prescribing information (PI), and container/carton labels) have been identified (see IQA Chapter 4, Labeling). Labeling negotiations with the applicant have not been completed. An addendum to this IQA will be filed upon receipt of final labeling.

Of note is application of the USP salt policy and the requirement for USAN designations for the active ingredient and the active moiety. In this case, the active ingredient is bremelanotide acetate and the active moiety is bremelanotide. Bremelanotide was adopted by the USAN Council in 2006. At our request, the applicant has submitted a

request for USAN designation for the acetate salt. This will undoubtedly be ‘bremelanotide acetate.’ In this regard, as well as for inclusion in product labeling the number of equivalents of acetate present in the salt, on average, was re-evaluated. At this time the recommended text for the PI is: “The molecular formula of bremelanotide acetate is  $C_{50}H_{68}N_{14}O_{10} \cdot xCH_3COOH$  ( $1 \leq x \leq 2$ ) and a molecular weight of 1025.16 (free base),” and “Each pre-filled syringe contains 1.75 mg of bremelanotide (equivalent to 1.89 mg bremelanotide acetate) in 0.3 mL solution.” The salt equivalency statement will also appear on the product carton.

#### Process:

The drug product (prefilled syringe containing aqueous bremelanotide) manufacturing process consists of [REDACTED] (b) (4).  
[REDACTED] Finally, the product is packaged.

From the process review perspective, the applicant has provided adequate documentation of the batch formula and the commercial process flow. Suitability of the process equipment and components so as not to adversely impact product quality has been demonstrated. In-process controls ensure that the [REDACTED] (b) (4).  
[REDACTED]

Overall, the product manufacturing process and in-process controls are adequately defined and are suitable for the manufacture of product with the requisite quality. This NDA is recommended for APPROVAL from the manufacturing process review perspective (see IQA Chapter 5, Process, for details).

#### Facilities:

The drug substance manufacturing site, [REDACTED] (b) (4), was found acceptable based on the District’s profile review. Three drug substance test facilities were found acceptable based on file review.

[REDACTED] (b) (4), is responsible for the [REDACTED] (b) (4). The facility was recently inspected for both drug GMPs and medical device GMPs. Several observations were noted on the FDA Form 483 including deficiencies associated with [REDACTED] (b) (4).  
[REDACTED] These deficiencies were adequately resolved

subsequent to the inspection. No 483 observations were made in regard to medical device GMPs.

(b) (4) is responsible for (b) (4) testing of the (b) (4). It is also an alternative test site for (b) (4) of the (b) (4). (b) (4) A pre-approval inspection resulting in several 483 observations was recently completed. The firm's subsequent responses were found acceptable. All other finished product test and packaging facilities were found acceptable based on file review.

CDRH-OC determined that the manufacturer of the autoinjector components, (b) (4) did not need to be inspected.

An Overall Manufacturing Inspection Recommendation of APPROVE was issued on November 26, 2018. See IQA Chapter 6, Facilities, for details.

#### Biopharmaceutics:

Not applicable for this formulation (aqueous solution) and route of administration (subcutaneous injection).

#### Microbiology:

As a product for subcutaneous injection, assurance of sterility is critical for safe use by patients. As already noted, bremelanotide injection is prepared by sterile (b) (4).

The product microbiology assessment covered sterilization of the (b) (4) and environmental monitoring, process parameters and validation, container closure integrity testing (dye ingress), and sterility and endotoxin testing.

Overall, the applicant has adequately demonstrated that the manufacturing process is robust and suitable for ensuring the sterility of the product. The syringe is suitable for maintaining the sterility of the product over the shelf-life.

From the product quality microbiology review perspective this NDA is recommended for APPROVAL (see IQA Chapter 8, Microbiology, for details).

#### Analytical Methods Verification:

Because the analytical methods for the drug substance and drug product are relatively straightforward, verification of the methods by the CDER/OPQ/OTR St. Louis laboratory was not requested.

### CDRH Medical Device Assessment:

Dr. Sapana Patel's CDRH-ODE review of the (b) (4) autoinjector focused on device performance, biocompatibility of patient contacting components, the release specifications, and autoinjector stability. Her review did not cover the primary container closure syringe (i.e., the prefilled syringe), compatibility of the drug with device materials, or human factors.

During the review cycle critical issues related to demonstration of the comparability of the (b) (4) used in the pivotal clinical studies and the commercial (b) (4) autoinjectors and establishment of essential device performance criteria (delivered volume, ejection time, and others as noted above) were resolved. Issues related to device stability (including under shipping conditions) were also resolved. Device stability through the expiration dating period of the drug product component has been demonstrated. Appropriate studies for the ongoing assessment of device stability were established.

Design verification tests, biocompatibility tests, essential performance tests, and device stability tests are all adequately documented in the NDA. Overall, the applicant has provided adequate information to support use of the (b) (4) for the administration of bremelanotide injection. The NDA is recommended for APPROVAL from the CDRH device engineering perspective (see the CDRH-ODE device dated December 12, 2018 for details).

The CDRH-OC assessment consisted of a document review to determine compliance with Quality Systems Requirements under 21 CFR 820 and a determination of manufacturing facilities requiring inspection from the medical device GMP perspective.

Based on the document review, (b) (4), has adequately addressed the requirements of 21 CFR 820.20, 820.30, 820.50, and 820.100. As noted above, an inspection of the (b) (4) product manufacturing facility was performed as recommended by CDRH-OC. No other facilities were identified for device GMP inspections.

From the CDRH-OC perspective this NDA is recommended for APPROVAL (see the CDRH-OC review dated November 4, 2018).

### **C. Special Product Quality Labeling Recommendations**

Not Applicable

### **D. Final Risk Assessment (see Attachment I)**

**OVERALL ASSESSMENT AND SIGNATURES:*****Application Technical Lead Name:***

Mark R. Seggel, Ph.D.

CMC Lead (acting)

April 10, 2019

*{see electronic signature page}*

## CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

CHAPTER II: Drug Product

CHAPTER III: Environmental Assessment (*See Chapter II*)

CHAPTER IV: Labeling

CHAPTER V: Process

CHAPTER VI: Facilities

CHAPTER VII: Biopharmaceutics (*Not Applicable*)

CHAPTER VIII: Microbiology

CHAPTER IX: Additional Quality Discipline (*Not Applicable*)

Attachment I: Final Risk Assessment / Life Cycle Management

Attachment II: List of Deficiencies for Complete Response Letter (*Not Applicable*)

## ATTACHMENT I: Final Risk Assessments

### A. Final Risk Assessment and Lifecycle Knowledge Management

#### a) Drug Product

NDA 210557 Bremelanotide Injection as indicated for the Treatment of Generalized Hypoactive Sexual Desire Disorder (HSDD).

From Initial Risk Identification			Review Assessment		
Product Attribute / CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
Appearance	<ul style="list-style-type: none"> <li>Process</li> <li>Stability</li> </ul>	12		Acceptable	
Identification	<ul style="list-style-type: none"> <li>CGMPs</li> </ul>	5		Acceptable	
Assay (active) / Stability	<ul style="list-style-type: none"> <li>Formulation</li> <li>Raw materials</li> <li>Process</li> <li>Container closure</li> <li>Storage conditions</li> </ul>	24	(b) (4)	Acceptable	(b) (4)
pH	<ul style="list-style-type: none"> <li>Formulation</li> <li>Raw materials</li> <li>Process</li> </ul>	6		Acceptable	
Related Substances Impurities / Degradants	<ul style="list-style-type: none"> <li>Formulation</li> <li>Raw materials</li> <li>Process</li> <li>Container/Closure</li> <li>Storage</li> </ul>	36		Acceptable	
Leachables / Extractables	<ul style="list-style-type: none"> <li>Formulation</li> <li>Raw materials</li> <li>Container/Closure</li> </ul>	24		Acceptable	
Uniformity of Dosage Fill Volume	<ul style="list-style-type: none"> <li>Process parameters</li> </ul>	8		Acceptable	
Dose Accuracy	<ul style="list-style-type: none"> <li>Container/Closure</li> </ul>	18		Acceptable	
Osmolality	<ul style="list-style-type: none"> <li>Formulation</li> <li>Raw materials</li> <li>Process</li> </ul>	1		Acceptable	
Foreign Particulate Matter	<ul style="list-style-type: none"> <li>Raw materials</li> <li>Process</li> <li>Container closure</li> </ul>	27		Acceptable	
Sterility	<ul style="list-style-type: none"> <li>Raw materials</li> <li>Process parameters</li> <li>Hold time</li> </ul>	80		Acceptable	
Endotoxins	<ul style="list-style-type: none"> <li>Raw materials</li> </ul>	32		Acceptable	

#####



Mark  
Seggel

Digitally signed by Mark Seggel

Date: 4/10/2019 12:51:34PM

GUID: 507572b5000036176969356148025bae

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

The post-approval stability protocol is adequate.

## R Regional Information

### *Environmental Analysis*

Pursuant 21 CFR 25.31 (b) categorical exclusion from the requirements of an Environmental Impact Analysis is claimed because the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion and no extraordinary circumstances exist. The projected amounts of drug substance (DS) produced per year over a five-year period are shown in the below table.

Expected Introduction Concentration (EIC) of Bremelanotide				
Year	Sales – Units (1.75 mg/unit)	A=Production (kg)	B x C x D	EIC-Aquatic (ppb) (b) (4)
2019				
2020				
2021				
2022				
2023				

**Reviewer’s Assessment: ADEQUATE**

The Applicant’s claim for categorical exclusion is acceptable. Calculation of estimated entry into aquatic environment was provided in the submission and is below 1 ppb, therefore qualifies for a categorical exclusion under 21 CFR 25.31. Additionally, the DS is a peptide which is readily broken down via metabolism and sewage treatment.

### *Methods Verification Package*

**Reviewer’s Assessment: ADEQUATE**

The Applicant has provided the appropriate documentation of validations and verifications established for the bremelanotide drug product. No Method Verification Request was deemed to be needed by OPQ for this application.

### *Comparability Protocols*

**Reviewer’s Assessment: Not Applicable**

### *Post-Approval Commitments*

**Reviewer’s Assessment: None**

### *Lifecycle Management Considerations*

**Reviewer's Assessment: None****List of Deficiencies**

None

**Primary Drug Product Reviewer Name and Date:**

*Caroline Strasinger, PhD*

*Office of New Drug Product, Branch V*

*August 15, 2018*

**Secondary Reviewer Name and Date:**

The proposed drug product, Vyleesi (bremelanotide) injection, 1.75mg, is a drug-device combination product to treat hypoactive sexual desire disorder (HSDD) in premenopausal women. The device is to deliver subcutaneously 0.3ml of the drug containing 1.75mg of bremelanotide. This new active ingredient, bremelanotide, is a synthetic cyclic heptapeptide melanocortin which is to bind to melanocortin 4 receptor, thereby stimulating dopamine activity in the hypothalamus and restoring sexual desire in women with HSDD.

The injectable drug formulation contains 1.75mg of the bremelanotide peptide and 7.5mg of glycerine in water for injection (q.s.to 0.3ml). It has minute amounts of hydrochloric acid and sodium hydroxide for pH adjustment to pH 5, and it is supplied as a sterile prefilled syringe. The prefilled syringe is housed in a single use autoinjector which will eventually activate the prefilled syringe to deliver the drug subcutaneously to the patient.

I agree with Dr. Strasinger's assessment on the overall control strategy for the drug-device product including; 1) defining the peptide content that exists as an acetate salt where the amount of acetate is varying depending upon its production; 2) drug product specification including the levels of impurities and degradants; 3) container closure system including capability of its light protection as well as in conjunction with CDRH's functionality evaluation of the auto injector; 4) extractables/leachables including elemental impurities from the glass syringes; and 5) determination of the expiration dating period based on the submitted stability data.

Therefore, I concur with her recommendation for approval of this application from the drug product perspective with an expiration dating period of 36 months.

***Moo-Jhong, Rhee, Ph.D.***

***Chief, Branch V***

***Division of New Drug Product II***

***ONDP/OPQ***



Caroline  
Strasinger

Digitally signed by Caroline Strasinger  
Date: 9/13/2018 02:55:23PM  
GUID: 5051dfdd000013b995075b4d54108ed8



Moo Jhong  
Rhee

Digitally signed by Moo Jhong Rhee  
Date: 9/13/2018 03:04:21PM  
GUID: 502d0913000029f9798ca689a802fa55

## LABELING

### R. Regional Information

#### 1.14 Labeling

The target fill of each vial is 0.3 mL and contains 1.75 mg of bremelanotide theoretically equivalent to 1.89 bremelanotide acetate. The theoretical salt equivalency is derived from a calculation of the (b) (4) that was based on four batches of API which contained on average (b) (4)

### I. Package Insert (provided December 21, 2018)

#### 1. HIGHLIGHTS OF PRESCRIBING INFORMATION

##### 1) Title

These highlights do not include all the information needed to use VYLEESI™ safely and effectively. See full prescribing information for VYLEESI™

VYLEESI™ (bremelanotide) injection, for subcutaneous use  
Initial U.S. Approval: XXXX

##### -----DOSAGE FORMS AND STRENGTHS-----

- Subcutaneous injection: 1.75 mg (b) (4) in 0.3 mL solution (b) (4)

##### -----CONTRAINDICATIONS-----

- None (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Vyleesi Established Name: (bremelanotide) injection	ADEQUATE
Dosage form, route of administration	Dosage: injection Route: subcutaneous use	ADEQUATE
Controlled drug substance symbol (if applicable)		NA
Dosage Forms and Strengths (201.57(a)(8))		INADEQUATE 1.75mg/0,3ml clear solution in (b) (4) autoinjector
Summary of dosage form and strength	Subcutaneous Injection: 1.75 mg in 0.3 mL solution	INADEQUATE. The formatting and changes listed above should be made for accuracy and clarity

--	--	--

Reviewer Assessment: **INADEQUATE**

Applicant should modify the text of the dosage forms and strengths of the highlights for clarity as noted above. The following comment was communicated to OND labelling review team on 13-FEB-2019.

Dosage form and strength should be revised to "1.75mg/0,3ml clear solution in (b) (4) autoinjector"**FULL PRESCRIBING INFORMATION**

### #3: DOSAGE FORM AND STRENGTHS

#### 3 DOSAGE FORMS AND STRENGTHS

Subcutaneous injection: 1.75 mg (b) (4) in 0.3 mL solution (b) (4)  
 (b) (4) autoinjector (b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Available dosage forms	Subcutaneous Injection	Adequate
Strengths: in metric system	1.75 mg in 0.3 mL	INADEQUATE 1.75mg/0.3ml clear solution in (b) (4) autoinjector
Active moiety expression of strength with equivalence statement (if applicable)	NOT Present  (1.75 mg of bremelanotide theoretically equivalent to 1.89 bremelanotide acetate)	Adequate Although no equivalency statement is made, since that statement is made in the Description section as well as (b) (4) carton labels, it is deemed acceptable.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	In a (b) (4) auto injector (b) (4)	INADEQUATE Should be revised as noted above for simplification

#### Reviewer Assessment: **Inadequate**

Applicant should modify the text of the dosage forms and strengths for clarity as noted above. The following comment was communicated to OND labelling review team on 13-FEB-2019.

- Strength should be revised to "1.75mg/0.3ml clear solution in (b) (4) autoinjector"

## #11: DESCRIPTION

### 11 DESCRIPTION

VYLEESI (bremelanotide) injection contains bremelanotide, a melanocortin receptor agonist (b) (4) for subcutaneous administration via an autoinjector.

Bremelanotide acetate is a synthetic, cyclic heptapeptide (b) (4) with a free acid at the carboxyl terminus and an acetylated amino group at the amino terminus of the peptide with the following structure:



The molecular formula of bremelanotide acetate is  $\text{C}_{50}\text{H}_{68}\text{N}_{14}\text{O}_{10} \bullet x\text{CH}_3\text{COOH}$  ( $1 \leq x \leq 2$ ) and ~~the~~ a molecular weight of 1025.16 (free base).

(b) (4)

VYLEESI (bremelanotide) injection is supplied as a sterile, clear solution in a pre-filled syringe contained in a (b) (4) autoinjector for subcutaneous administration. Each pre-filled syringe contains 1.75 mg of bremelanotide (equivalent to 1.89 mg bremelanotide acetate) in 0.3 mL solution. Inactive ingredients consist of 2.5% glycerin, sterile water for injection, and hydrochloric acid or sodium hydroxide is added to adjust the pH (b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name and established name	VYLEESI bremelanotide	INADEQUATE Include injection as part of the established name
Dosage form and route of administration	subcutaneous	INADEQUATE Add injection
Active moiety expression of strength with equivalence statement (if applicable)	1.75 mg of bremelanotide in 0.3 mL.	INADEQUATE Add equivalency statement
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	0.3 mL 2.5% glycerin, sterile water	ADEQUATE
Statement of being sterile (if applicable)	Sterile	Adequate
Pharmacological/ therapeutic class	melanocortin	INADEQUATE Melanocortin receptor agonist
Chemical name, structural formula, molecular weight	Inadequate	The drug substance is bremelanotide acetate, though the USAN name is bremelanotide
If radioactive, statement of important nuclear characteristics.	NA	Adequate
Other important chemical or physical properties (such as pKa or pH)	clear solution, pre-filled syringe, (b) (4) autoinjector	Adequate

**Reviewer Assessment: INADEQUATE**

Applicant should include the established name, dosage form, pharmacological class, acetate equivalency statement and address the additional edits noted above of the Description for clarity. The following comments were communicated to OND labelling review team on 13-FEB-2019.

- The active moiety is bremelanotide. The API is an acetate of bremelanotide which results in the theoretical equivalency statement, 1.75 mg of bremelanotide theoretically equivalent to 1.89 bremelanotide acetate.
- (b) (4)
- Include injection as part of the established name
- Pharmacologic class should be included

**#16: HOW SUPPLIED/STORAGE AND HANDLING**

**16 HOW SUPPLIED / STORAGE AND HANDLING**

VYLEESI (bremelanotide) is (b) (4) supplied as:

-1.75 mg bremelanotide in 0.3 mL solution in a (b) (4) disposable prefilled autoinjector;

(b) (4) Carton of 4 autoinjectors (NDC 64011-701-04).

Storage

Store at or below 25°C (77°F). Do not freeze. Protect from light.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Strength of dosage form	1.75 mg	INADEQUATE Need to be revised to "1.75mg/0.3ml clear solution in (b) (4) autoinjector"
Available units (e.g., bottles of 100 tablets)	0.3 mL	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Single use, disposable prefilled autoinjector	Adequate
Special handling (e.g., Dispense in tight and light resistant container as defined in USP)	Do not freeze. Protect from light.	Adequate
Storage conditions	Store at or below 25°C (77°F)	Adequate
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured for: AMAG Pharmaceuticals, Inc 1100 Winter Street Waltham, MA 02451	Adequate

**Reviewer Assessment: INADEQUATE**

Applicant should modify the text of the How Supplied and Storage and Handling for clarity as noted above. This information was communicated to OND labelling review team on 13-FEB-2019.

- The dosage form, and strength need to be revised to "1.75mg/0.3ml clear solution in a (b) (4) autoinjector"

**II. Labels (provided February 1, 2019)**

**1. IMMEDIATE CONTAINER LABEL**

The immediate container label is applied to the auto injector as shown in the photo below. The applicant provided revised labels on February 1, 2019.



(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Vyleesi (bremelanotide) injection	INADEQUATE Parentheses need to be included around the nonproprietary name.
Dosage strength Active moiety expression of strength with equivalence statement (if applicable), if space is available	1.75 mg/0.3mL	Adequate. The applicant has justified there is insufficient space to include an equivalency statement on the primary container. A statement is included on the carton.
Net contents	0.3 mL	Adequate
"Rx only" displayed prominently on the main panel	Rx only	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Present	Adequate
Lot number and expiration date (21 CFR 201.17)	Location present	Adequate
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Store at or below 25°C (77°F). Do not Freeze. Protect from light.	Adequate
Bar code (21CFR 201.25)	Present	Adequate
Name of manufacturer/distributor	Distributor is present	Adequate
And others, if space is available		

The following should be communicated to the Applicant:

- Include parentheses around the nonproprietary name
- USAN name for the API needs to be established.

On February 1, 2019 the applicant provided revised labels which included a bar code. In addition to the revised label shown above, the applicant stated due to size constraints an equivalency statement is not included on the immediate container label. The applicant does include an equivalency statement on the carton as discussed below.

## 2. CARTON LABELS:

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	Vyleesi (bremelanotide) injection	INADEQUATE  Parentheses need to be included in the labels.
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	1.75 mg/0.3 mL Active Ingredient: Bremelanotide (equivalent to 1.89 mg of bremelanotide acetate).  Inactive ingredients: 2.5% glycerin (b) (4) HCl or NaOH to adjust pH. (b) (4)	INAdequate Equivalency information is correct, DMEPA has concurred that the proposed format on the carton does not introduce error. (b) (4) should be removed from the inactive ingredient list.
Net quantity of dosage form	4 (b) (4) autoinjector (b) (4)	Adequate
"Rx only" displayed prominently on the main panel	Displayed on front;	Adequate
Lot number and expiration date	Side flap	Adequate
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Store at or below 25°C (77°F). Do not Freeze. Protect from light.	Adequate
Bar code (21CFR 201.25)	Side panel	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Side panel	Adequate
Manufacturer/distributor's name	Displayed on front	Adequate
Quantitative ingredient information (injectables)	Ingredients should be listed in alphabetical order (quantity not necessary)	Adequate
Statement of being sterile (if applicable)	Present	Adequate
"See package insert for dosage information"	Back panel	Adequate

"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Keep out of reach of children;	Adequate
---	--------------------------------	----------

The following should be communicated to the Applicant:

- Include parentheses around the nonproprietary name in the label.
- Remove (b) (4) from the inactive ingredient list.

### III. LIST OF DEFICIENCIES:

#### A. Regarding PI

Extensive edits to the content and format of each of the below sections is recommended. For ease of reference the below visuals have been compiled to aid in communicating the deficiencies:

##### a) Highlight Section

-----DOSAGE FORMS AND STRENGTHS (b) (4)  
 • Subcutaneous injection: 1.75 mg (b) (4) in 0.3 mL solution (b) (4)  
 (b) (4)

##### b) Full Prescribing Information

###### #3: Dosage Forms and Strengths

3 DOSAGE FORMS AND STRENGTHS  
 Subcutaneous injection: 1.75 mg (b) (4) in 0.3 mL solution (b) (4)  
 (b) (4) autoinjector (b) (4)

- Strength should be revised to "1.75mg/0.3ml clear solution in (b) (4) autoinjector"

###### #11: Description

## II DESCRIPTION

VYLEESI (bremelanotide) injection contains bremelanotide, a melanocortin receptor agonist (b) (4) for subcutaneous administration via an autoinjector.

Bremelanotide acetate is a synthetic, cyclic heptapeptide (b) (4) with a free acid at the carboxyl terminus and an acetylated amino group at the amino terminus of the peptide with the following structure:



The molecular formula of bremelanotide acetate is  $\text{C}_{50}\text{H}_{68}\text{N}_{14}\text{O}_{10} \bullet x\text{CH}_3\text{COOH}$  ( $1 \leq x \leq 2$ ) and the molecular weight of 1025.16 (free base).

(b) (4)

VYLEESI (bremelanotide) injection is supplied as a sterile, clear solution in a pre-filled syringe contained in a (b) (4) autoinjector for subcutaneous administration. Each pre-filled syringe contains 1.75 mg of bremelanotide (equivalent to 1.89 mg bremelanotide acetate) in 0.3 mL solution. Inactive ingredients consist of 2.5% -glycerin, sterile water for injection, and hydrochloric acid or sodium hydroxide is added to adjust the pH (b) (4)

- The active moiety is bremelanotide. The API is an acetate of bremelanotide which results in the theoretical equivalency statement, 1.75 mg of bremelanotide theoretically equivalent to 1.89 bremelanotide acetate.
- (b) (4)  
(b) (4) The API used in the formulation is actually bremelanotide acetate and its USAN name needs to be secured.
- Include injection as part of the established name
- Pharmacologic class should be included

## #16: How Supplied/Storage and Handling

### 16 HOW SUPPLIED / STORAGE AND HANDLING

VYLEESI (bremelanotide) is (b) (4) supplied as:

-1.75 mg bremelanotide in 0.3 mL solution in a (b) (4) disposable prefilled autoinjector;

(b) (4) Carton of 4 autoinjectors (NDC 64011-701-04).

#### Storage

Store at or below 25°C (77°F). Do not freeze. Protect from light.

- The dosage form, and strength need to be revised to “1.75mg/0.3ml clear solution in [REDACTED] (b) (4) autoinjector”

#### **Carton and Container**

- Include parentheses around the nonproprietary name
- Remove [REDACTED] (b) (4) from the inactive ingredients list on the carton.

#### **IV. OVERALL ASSESSMENT AND RECOMMENDATION:**

The Label and Labeling of NDA 210557 is inadequate due to the deficiencies noted above for Highlights, Section 3, 11 and 16 of the PI and the Carton and Container. This information was communicated to OND labeling review team on February 13, 2019.

**This application is not deemed ready for approval in its present form per 21CFR 314.125(b)(6) from the label/labeling perspective until the deficiencies noted above are satisfactorily resolved.**

#### ***Primary Labeling Reviewer Name and Date:***

***Caroline Strasinger, PhD 5-APR-2019  
OPQ, ONDP, DNDP II, BV***

#### ***Secondary Reviewer Name and Date (and Secondary Summary, as needed):***

I agree with Dr. Strasinger’s assessment on the labeling and labels and concur with her recommendation that this application is *not* deemed ready for approval as of this review.

***Moo-Jhong Rhee, Ph.D. 05-APR-2019  
Chief, Branch V  
DNDP II/ONDP***



Moo Jhong  
Rhee

Digitally signed by Moo Jhong Rhee

Date: 4/05/2019 11:50:47AM

GUID: 502d0913000029f9798ca689a802fa55



Caroline  
Strasinger

Digitally signed by Caroline Strasinger

Date: 4/05/2019 11:44:59AM

GUID: 5051dfdd000013b995075b4d54108ed8

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

**MICROBIOLOGY**[IQA Review Guide Reference](#)**Product Background:****NDA/ANDA:** N210557**Drug Product Name / Strength:** VYLEESI (Bremelanotide injection), 1.75 mg/0.3 mL in a 1 mL syringe autoinjector for (b) (4)**Route of Administration:** subcutaneous**Applicant Name:** AMAG Pharmaceuticals**Manufacturing Site:**

(b) (4)

**Method of Sterilization:**

(b) (4)

***Review Recommendation: Adequate******Review Summary:***

(b) (4)

**List Submissions Being Reviewed:** 03/23/2018, 08/03/2018 (IR response to labeling), 8/06/2018 (Quality IR response/Microbiology), 09/07/2018 (Quality IR response/Microbiology)**Highlight Key Outstanding Issues from Last Cycle:** N/A**Remarks:** N/A**Concise Description Outstanding Issues Remaining:** None.**Supporting Documents:**

- Type III DMF (b) (4) (Holder: (b) (4))
- (u) (4) dated 04/26/2018 (V-drive), for the (b) (4)
- (u) (4) dated 08/02/2017 (V-drive), for the (b) (4)

- (b) (4), dated 12/14/17 (V-drive), for the (b) (4).

**List Number of Comparability Protocols (ANDA only): N/A**

**S Drug Substance**

The drug substance is not reviewed in this application as the final drug product is subject (b) (4)

**P.1 Description of the Composition of the Drug Product**

Section P.1, "Description and Composition of the Drug Product"

- **Description of drug product** – Clear, colorless sterile solution.
- **Drug product composition** –

Ingredient	Function	Quantity/unit
Bremelanotide	API	1.75 mg
Glycerin	(b) (4)	(b) (4)
Hydrochloride acid	Adjust pH	
Sodium hydroxide	Adjust pH	
Water for Injection	(b) (4)	

- **Description of container closure system** – Pre-filled syringes and stoppers are ready-to-use and placed in an autoinjector device (b) (4)

Syringe unit	Description
Syringe	(b) (4)
Stopper	

**Reviewer's Assessment: Adequate**

The applicant's description of the drug product and container is consistent with regulatory expectations.

**P.2 Pharmaceutical Development**

**P.2.5 Microbiological Attributes**



25 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

**P.7 Container Closure – N/A**

**P.8 Stability**

**P. 8.1 Stability Summary and Conclusion**

Microbiological stability tests and acceptance criteria are identical to the release specification provided in Section P.5.1 on the autoinjector assembled units.

Specification	Test	Criteria
Sterility*	USP <71>	“sterile”
Bacterial endotoxin test*	USP <85>	NMT (b) (4) EU/mL

The proposed shelf life is 3 years. Sterility and endotoxins tests are performed at 0, 12, 24, and 30 months on long term storage at 5±3°C, at 12, 24, 30, and 36 months on long term storage at 25±2°C/60±5% RH, 12 at months on accelerated storage at 30±2°C/65±5% RH, and at 6 month on accelerated stability at 40±2°C/75±5% RH.

**Reviewer’s Assessment: Adequate**

The applicant has met regulatory expectations with regard to the design of the stability testing program to support the drug product’s microbiological quality throughout its shelf life.

**P. 8.2 Post-Approval Stability Protocol and Stability Commitment**

The applicant committed to place one batch annually and the first three batches on stability. Sterility and endotoxins tests are performed at 0, 12, 24, and 30 months on long term storage at 5±3°C, at 12, 24, 30, and 36 months on long term storage at 25±2°C/60±5% RH, 12 at months on accelerated storage at 30±2°C/65±5% RH, and at 6 month on accelerated stability at 40±2°C/75±5% RH.

**Reviewer’s Assessment: Adequate**

The applicant has met regulatory expectations with regard to the design of the stability testing program to support the drug product’s microbiological quality throughout its shelf life.

**P.8.3 Stability Data**

The applicant provides stability data for the three registration batches, (b) (4) B007A, (b) (4) B009, (b) (4) B010 and supportive stability clinical batches (b) (4) B014, (b) (4) B015, (b) (4) B017. The three registration batches were sterile and (b) (4) EU/mL at all time points. The supportive stability batches were sterile and (b) (4) EU/mL at 0 and 12 months at

5±2°C, 12 months at 25±2°C/60±5% RH, 12 months at 30±2°C/65±5% RH, 6 months at 40±2°C/75±5% RH.

**Reviewer's Assessment:** *Adequate*

The applicant has met regulatory expectations with regard to the design of the stability testing program to support the drug product's microbiological quality throughout its shelf life.

**A Appendices – N/A**  
**R Regional Information**  
*Executed Batch Records*

Supportive stability/clinical batch was manufactured, (b) (4)

**Reviewer's Assessment:** *Adequate*

The applicant has met regulatory requirements sterilization processes used in the production of the batch.

*Comparability Protocols*

**Reviewer's Assessment:** N/A, no CPs were submitted with the application.

**2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q)**  
**MODULE 1**

**2.A. Package Insert**

- **Post-dilution/constitution hold time**  
Drug product is stored at or below 25°C, single use, and not diluted.

**Reviewer's Assessment:** *Adequate*

The applicant provides adequate patient instructions with regard to microbiology.

*Post-Approval Commitments – N/A*

*List of Deficiencies:* None

**Primary Microbiology Reviewer Name and Date:** *Avital Shimanovich, Ph.D., 10/22/2018*

**Secondary Reviewer Name and Date (and Secondary Summary, as needed):** *Marla Stevens-Riley, Ph.D., 10/22/2018*



Avital  
Shimanovich

Digitally signed by Avital Shimanovich  
Date: 2/27/2019 07:55:48AM  
GUID: 598ca8f5005723e97e9300810ca9b31a



Marla  
Stevens Riley

Digitally signed by Marla Stevens Riley  
Date: 2/27/2019 09:12:53AM  
GUID: 508da70c00028f21637ed864c514d12a



Mark  
Seggel

Digitally signed by Mark Seggel

Date: 4/10/2019 01:02:22PM

GUID: 507572b5000036176969356148025bae