

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
210557Orig1s000

Trade Name: Vyleesi (bremelanotide) subcutaneous injection, 1.75 mg/0.3 mL

Generic Name: Bremelanotide

Sponsor: AMAG Pharmaceuticals, Inc

Approval Date: 06/21/2019

Indication: VYLEESI is 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 and is NOT due to:

- A co-existing medical or psychiatric condition,
- Problems with the relationship, or
- The effects of a medication or drug substance.

Acquired HSDD refers to HSDD that develops in a patient who previously had no problems with sexual desire. Generalized HSDD refers to HSDD that occurs regardless of the type of stimulation, situation or partner.

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APPROVAL LETTER

NDA 210557

NDA APPROVAL

AMAG Pharmaceuticals, Inc
Attention: Helen Milton
Senior Vice President, Regulatory Affairs
1100 Winter Street
Waltham, MA 02451

Dear Ms. Milton:

Please refer to your New Drug Application (NDA) dated and received March 23, 2018, and your amendments submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Vyleesi (bremelanotide) subcutaneous injection.

We acknowledge receipt of your major amendment dated September 21, 2018, which extended the goal date by three months.

This new drug application provides for the use of Vyleesi 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 and is NOT due to:

- A co-existing medical or psychiatric condition,
- Problems with the relationship, or
- The effects of a medication or drug substance.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert, and Instructions for Use) as well as annual reportable changes not included in the

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

As per your email dated, May 3, 2019, you have agreed to the following:

- **Carton Labeling**
The format to be used for the expiration date on the carton will be “YYYY-MM-DD” in numerical characters.
- **Container Labeling**
The format to be used for the expiration date on the container (autoinjector) label will be “YYYY-MM-DD” in numerical characters.

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling and submitted carton and container labeling, except with the revisions listed above, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 210557.**” Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial or significant safety or efficacy issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

We are waiving the pediatric study requirement for this application because studies would be impossible or highly impractical.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of adverse pregnancy, maternal, fetal/neonatal and infant outcomes associated with exposure to Vyleesi.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following two studies:

3635-1 A prospective, registry-based, observational cohort study that compares obstetrical, maternal, fetal/neonatal, and infant outcomes in women exposed to Vyleesi during pregnancy to an internal, unexposed cohort of pregnant women. The registry will identify major and minor congenital malformations, spontaneous abortions, elective terminations, small for gestational age, pre-term births, and any other adverse pregnancy-related outcomes. These outcomes will be adjudicated with medical chart review. Infant outcomes, including effect on post-natal growth and development, will be assessed through at least the first year of life.

3635-2 A retrospective cohort study using electronic claims data that compares maternal, fetal/neonatal, and infant outcomes in women exposed to Vyleesi during pregnancy to an internal, unexposed cohort of pregnant women. Maternal, fetal/neonatal, and infant outcomes, and adverse pregnancy-related outcomes will be adjudicated with medical chart review. Pregnant women exposed and unexposed to Vyleesi will be matched by age at pregnancy and gestational age at cohort entry. This study will complement the post marketing pregnancy registry study. To assess the extent of misclassification for Vyleesi exposure in claims data, you will conduct an evaluation of the validity of claims exposure data, compared to patient self-reported data.

The PMR 3635-2 study will collect information including, but not limited to, the following data elements (to the extent possible):

- Age, demographics, body mass index
- Exposure to smoking, alcohol, drugs
- Medical history, concomitant medications, prenatal vitamins, obstetrical history

- Current pregnancy: date of last menstrual period/gestational dating, prenatal tests and ultrasound results, pregnancy status
- Vyleesi exposure data (timing of exposure in pregnancy, dose, duration)

The timetable you submitted on April 12, 2019, states that you will conduct these two pregnancy-related studies according to the following schedule

Draft study protocol submissions:	9/2019
Final study protocol submissions:	5/2020
Study completion for both studies:	5/2030
Final report submission for both studies:	12/2030

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of adverse infant outcomes from potential exposure to Vyleesi via breastmilk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trial:

3635-3 A trial in lactating women who have received Vyleesi to assess potential adverse effects in the breastfed infant and measure bremelanotide concentrations in breast milk using a validated assay.

The timetable you submitted on April 12, 2019, states that you will conduct this study according to the following schedule:

Draft study protocol submission:	9/2019
Final study protocol submission:	5/2020
Study completion:	5/2025
Final report submission:	12/2025

Submit clinical protocol(s) to your IND 064119 with a cross-reference letter to this NDA 210557. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.³

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.⁴ Information and Instructions for completing the form can be found at FDA.gov.⁵ For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.⁶

³ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁴ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

⁶ <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

We also request that you submit quarterly safety reports based on all postmarketing adverse pregnancy and neonatal outcomes. The outcome information for these adverse events should include major and minor congenital malformations, spontaneous abortions, elective terminations, small for gestational age, pre-term births, and any other adverse pregnancy-related outcomes. If a neonate is determined to have been exposed, assessment of growth and development should be assessed through at least the first year of life. These quarterly safety reports should continue until the pregnancy registry is operational.

In addition, for the next three years we request that your quarterly safety reports include a separate section that summarizes the interval experience since the last quarterly report and cumulative experience since launch of adverse events of liver injury, including abnormal liver function and liver transplantation.

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.⁷

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

⁷ <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>

If you have any questions, contact Jeannie Roule, Regulatory Health Project Manager, at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, M.D., M.M.Sc.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
 - Prescribing Information
 - Patient Package Insert
 - Instructions for Use
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HYLTON V JOFFE
06/21/2019 04:38:35 PM

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