

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**210557Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Division of Risk Management (DRISK)**  
**Office of Medication Error Prevention and Risk Management (OMEPRM)**  
**Office of Surveillance and Epidemiology (OSE)**  
**Center for Drug Evaluation and Research (CDER)**

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| <b>Application Type</b>         | NDA   |
| <b>Application Number</b>       | 210557  |
| <b>PDUFA Goal Date</b>          | June 23, 2019   |
| <b>OSE RCM #</b>                | 2018-633  |
| <b>Reviewer Name(s)</b>         | Theresa Ng, PharmD, BCPS, CDE   |
| <b>Team Leader</b>              | Laura Zendel, PharmD, BCPS  |
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| <b>Review Completion Date</b>   | June 14, 2019   |
| <b>Subject</b>                  | Evaluation of Need for a REMS   |
| <b>Established Name</b>         | Bremelanotide   |
| <b>Trade Name</b>               | Vyleesi   |
| <b>Name of Applicant</b>        | AMAG Pharmaceuticals, Inc. (AMAG)   |
| <b>Therapeutic Class</b>        | Melanocortin receptor (MCR) agonist   |
| <b>Formulation(s)</b>           | Subcutaneous injection: 1.75 mg in 0.3 ml solution in (b) (4)<br>disposable pre-filled auto-injector pen  |
| <b>Dosing Regimen</b>           | 1.75 mg subcutaneous into the abdomen or thigh, based on patient preference, as-needed at least 45 mins before anticipated sexual activity. Patients should not administer more than one dose within 24 hours. Patients can administer up to 8 doses per month. |

## Table of Contents

|   |    |
|---|----|
| EXECUTIVE SUMMARY .....                                     | 3  |
| 1 Introduction.....   | 3  |
| 2 Background .....  | 3  |
| 2.1 Product Information .....                               | 3  |
| 2.2 Regulatory History.....                                 | 4  |
| 3 Therapeutic Context and Treatment Options .....           | 5  |
| 3.1 Description of the Medical Condition .....              | 5  |
| 3.2 Description of Current Treatment Options .....          | 6  |
| 4 Benefit Assessment.....                                   | 6  |
| 5 Risk Assessment & Safe-Use Conditions .....               | 8  |
| 5.1 Adverse Events of Special Interest.....                 | 9  |
| 5.1.1 Hepatotoxicity.....                                   | 9  |
| 5.1.2 Hyperpigmentation.....                                | 9  |
| 5.1.3 Blood Pressure (BP) elevations.....                   | 9  |
| 5.1.4 Misuse.....   | 11 |
| 6 Expected Postmarket Use.....                              | 12 |
| 7 Risk Management Activities Proposed by the Applicant..... | 12 |
| 8 Discussion of Need for a REMS.....                        | 12 |
| 9 Conclusion & Recommendations.....                         | 13 |
| 10 References .....   | 13 |

## EXECUTIVE SUMMARY

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This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Vyleesi (bremelanotide) is necessary to ensure the benefits outweigh its risks. AMAG Pharmaceuticals, Inc. (AMAG) submitted a New Drug Application (NDA) 210557 for bremelanotide with the proposed indication for the treatment of premenopausal women with acquired, generalized hypoactive sexual disorder (HSDD).

The risks associated with bremelanotide are transient elevations in blood pressure (BP) and potential for misuse (i.e., dosing more frequently than instructed to enhance effects of sexual desire) which may increase the risk for adverse events. The Applicant did not submit a proposed REMS or risk management plan with this application. Considering that the product is taken intermittently (dosage limited to once daily and no more than 8 doses per month), DRISK and the Division of Bone, Reproductive and Urologic Products (DBRUP) agree that a REMS is not necessary to ensure the benefits of bremelanotide outweigh its risks. Both elevations in BP and misuse can be mitigated through product labeling.

## 1 Introduction

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This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Vyleesi (bremelanotide) is necessary to ensure the benefits outweigh its risks. AMAG Pharmaceuticals, Inc. (AMAG) submitted a New Drug Application (NDA) 210557 for bremelanotide (BMT) with the proposed indication for the treatment of premenopausal women with acquired, generalized hypoactive sexual disorder (HSDD). This application is under review in the Division of Bone and Reproductive Products (DBRUP). The Applicant did not submit a proposed REMS or risk management plan with this application.

## 2 Background

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### 2.1 PRODUCT INFORMATION

Bremelanotide (BMT), a 505(b)(1) NME<sup>a</sup>, is a synthetic heptapeptide and nonselective melanocortin receptor (MCR) agonist. At the therapeutic doses of BMT, binding of MC1R and MC4 receptors are most relevant. MC1R receptors affect melanin expression and increase pigmentation; MC4R receptors are found in many regions of the central nervous system (CNS). (b) (4)

(b) (4)

The Applicant proposes BMT for the treatment of premenopausal women with acquired, generalized HSDD<sup>b</sup> as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is

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<sup>a</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

<sup>b</sup> 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.

NOT due to: (1) A co-existing medical or psychiatric condition, (2) Problems with the relationship, or (3) The effects of a medication or drug substance. Limitations of use include the treatment of HSDD in postmenopausal women or in men or to enhance sexual performance. The proposed dosage of BMT is 1.75 mg subcutaneous (SC) injection via an autoinjector into the abdomen or thigh, based on patient preference. The product is intended for use prior to each sexual encounter (i.e., on an as-needed bases) at least 45 minutes before anticipated sexual activity.<sup>c</sup> Patients should not administer more than one dose within 24 hours. Patients can administer up to 8 doses per month. At the time of this NDA submission, BMT is not approved in any jurisdiction.

## 2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for Bremelanotide NDA 210557 relevant to this review:

- 3/23/2018: AMAG submitted NDA 210557 for the treatment of premenopausal women with acquired HSDD.
- 9/12/2018: In the mid-cycle meeting with the Applicant, the Agency expressed concern for increased BP and potential impact on cardiovascular risk. Data from pre-NDA studies appear to show that BMT is associated with clinically significant increases in both systolic and diastolic blood pressures (SBP and DBP). The Agency also noted potential for blunting of the evening dip in BP, which is an indicator of increased cardiovascular risk.
- 11/7/2018: The Agency conducted a post mid-cycle teleconference with the Applicant and requested that the Applicant complete an ambulatory blood pressure monitoring (ABPM) study to fully characterize the extent and duration of the BP effect from repeated BMT dosing to aid in appropriately labeling the product. The Applicant agreed to conduct the ABPP study.<sup>2d</sup>
- 11/20/2018: Applicant submitted a phase 1 clinical study protocol assessing ABPM in premenopausal women.
- 12/13/2018: Major amendment acknowledgment letter sent to the Applicant; PDUFA goal date extended by 3 months to 6/23/2019.
- 1/14/2019: The Agency issued an information request (IR) to the Applicant with comments and recommendation for the ABPM protocol amendment from the review teams.<sup>e</sup>

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<sup>c</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

<sup>d</sup> Roule, J. Email communication, dated 11/7/2018.

<sup>e</sup> Roule, Jeannie. Email communication dated 1/14/2019

- 1/17/19: The Agency issued an IR to the Applicant to clarify that the analysis of the ABPM study should include the use of the upper bound of the 2-sided 95% CI to rule out a 4 mmHg increase in daytime SBP.<sup>f</sup>
- 1/28/2019: AMAG submitted an amendment for the APBM study protocol and agreed with the comments and recommendations as proposed by the Agency on 1/14/2019 and 1/17/2019.
- 2/4/2019: The Agency approved the ABPM protocol as amended by AMAG on 1/28/2019.
- 4/3/2019: In the late cycle teleconference with the Applicant, the Agency informed AMAG, at this time, the Agency does not anticipate the need for a REMS. AMAG provided a top-line report of the results from Study AMAG-BMT-HSDD-101, the ABPM study.
- 4/23/2019: AMAG submitted an amendment to the NDA with the final clinical study report and datasets for AMAG-BMT-HSDD-101 [REDACTED] (b) (4)  
[REDACTED]

### 3 Therapeutic Context and Treatment Options

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#### 3.1 DESCRIPTION OF THE MEDICAL CONDITION

HSDD is the most common type of female sexual disorder (FSD).<sup>3</sup> The Diagnostic and Statistical Manual 4<sup>th</sup> edition text revision (DSM-4 TR) defined HSDD and female sexual arousal disorder (FSAD) as abnormalities of female sexual desire or arousal, occurring as an acquired condition reflecting loss of prior function, not associated with depression, relationship dysfunction, or other identifiable causes and accompanied by distress.<sup>4</sup>

In the United States (US), approximately 43% of adult women experience some form of sexual difficulty with approximately 12% of these women reporting being distressed by their sexual dysfunction.<sup>5</sup> An estimate of one in 10 women or approximately 7 million adult US women may have symptoms of HSDD at some point in her life.<sup>6g</sup> HSDD is a common condition that often goes undiagnosed because of reluctance by patients and healthcare providers to initiate a discussion of sexual issues and is associated with poor quality of life.<sup>7h</sup> The etiology of sexual dysfunction is often multifactorial and may include psychological problems such as depression or anxiety, conflict within a relationship, fatigue, stress, lack of privacy, issues relating to prior physical or sexual abuse, medications, or physical problems that make sexual activity uncomfortable, such as endometriosis and genitourinary syndrome of menopause.<sup>8</sup>

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<sup>f</sup> Roule, Jeannie. Email communication dated 1/17/2019

<sup>g</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

<sup>h</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

### 3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Psychotherapy involving sexual therapy and education presently forms the basis of treatment for HSDD. Addyi (flibanserin), a serotonin 1A receptor agonist and a serotonin 2A receptor antagonist, is the only product approved in the US and worldwide for HSDD in premenopausal women. Flibanserin includes both a Boxed Warning (BW) and contraindication (CI) for severe hypotension and syncope from an interaction with alcohol, interactions with moderate or strong CYP 3A4 inhibitors, and in patients with hepatic impairment. Furthermore, at the time of approval, FDA required a REMS consisting of prescriber and pharmacy certifications to mitigate the risk of severe hypotension and syncope associated with the Addyi-alcohol interaction.<sup>9</sup> Therefore, given the paucity of available pharmacological treatments, additional therapeutic options are needed for women with HSDD.

## 4 Benefit Assessment

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The efficacy of BMT for the treatment of HSDD in premenopausal women is supported by two phase 3 randomized, double-blind, placebo-controlled trials with identical study design conducted in the US and Canada: BMT-301 (NCT02333071) and BMT-302 (NCT02338960). Additional studies evaluating safety of BMT include: Study 54 (NCT01382719), a phase 2 dose finding study, [REDACTED] (b) (4) [REDACTED] Study AMAG- BMT-HSDD-101, a phase 1 ambulatory BP study in premenopausal females.

Both BMT-301 and BMT-302 included premenopausal women with acquired, generalized HSDD of at least 6 months duration (with or without decreased arousal). In BMT-301 and BMT-302, 74% and 67% of subjects reported HSDD with decreased arousal while 26% and 32% reported HSDD without decreased arousal, respectively. The studies consisted of two parts: A Core Study Phase (24-week placebo-controlled, double blind treatment period) and an Open-Label Extension (OLE) Study Phase (52-week open label treatment period).

Both studies had the same co-primary efficacy endpoints:

- Change from Baseline to end of study (EOS) in the desire domain from the Female Sexual Function Index (FSFI), and
- Change from Baseline to EOS in the score for feeling bothered by low sexual desire as measured by the Female Sexual Distress Scale – Desire/Arousal/Orgasm Question 13 (FSDS-DAO Q13).

The key secondary endpoint was change from Baseline to EOS in the number of satisfying sexual events (SSEs) associated with study drug administration<sup>i</sup> and reported within 72 hours. Results from the Core

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<sup>i</sup> Key secondary endpoint change from Baseline to EOS is defined as an SSE that begins within 16 hours after dosing

Study Phases for both studies were pooled for analysis; however, the results from the OLE phases were not pooled.

Study participants were randomized (1:1) to either BMT 1.75 mg SC (n= 635) or placebo (n= 632), self-administered by an autoinjector on an as-needed basis. Subjects were encouraged to administer the drug approximately 45 minutes prior to anticipated sexual activity. The mean age of study participants was 39 years old (range 19 to 56 years old); the mean duration in a monogamous relationship was 12 years, and the mean duration of HSDD was approximately 4 years. The median number of injections in subjects in the BMT 1.75 mg treatment group and the placebo-treated subjects was 10.0 and 12.5 (Core Study Phase) respectively, and 12.0 during the OLE Study Phase (BMT 1.75 mg treatment group).

The following tables summarize the key co-primary endpoint results.<sup>10</sup>

**Table 1: Efficacy Results for the FSFI-Desire Domain Score in Premenopausal HSDD Subjects in Studies 1 and 2 (MITT\* Population)**



(b) (4)

**Table 2: Efficacy Results for the FSDS-DAO Q 13 Score in Premenopausal HSDD Subjects in Studies 1 and 2 (MITT\* Population)**

(b) (4)



The clinical reviewer concluded that BMT 1.75 mg met statistical significance, although the magnitude of effect is modest for the two co-primary endpoints of improving desire (improved FSFI) and reducing distress (improved FSDS-DOA Q13) associated with low desire.<sup>l</sup> The clinical meaningfulness of the observed treatment effects were supported by anchor analyses with designated responders at 1.2 or greater points for change in Desire domain (34-36% for BMT; 22% for placebo) and 1 or greater points for change in Distress domain (51-56% for BMT; 36-42% for placebo). The key secondary endpoint, however, failed to meet statistical significance between treatment groups.<sup>11</sup>

## 5 Risk Assessment & Safe-Use Conditions

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The primary evaluation of safety for BMT for HSDD is based on the analysis of the pivotal studies (BMT-301 and BMT-302) and their respective OLE phases with total of 1057 subjects who received BMT. Data from Study 54, (b) (4) Study AMAG- BMT-HSDD-101 were also used in the analysis.

The most common adverse events (AEs) occurring at > 2% comparing BMT to placebo were nausea (39.9%, 1.1%, respectively), flushing (20.3%, 0.5%), injection site reaction (18%, 9.8%), and headache (11.2%, 2.1%). In the phase 3 and extension studies, there were 12 subjects with treatment emergent severe adverse events (TEAEs) compared with 4 subjects in the placebo group. The most common TEAEs (> 2%) were nausea, flushing, injection site reactions, headache, and vomiting. One death occurred in the clinical development program (CDP) due to pedestrian injury which was determined by the Applicant

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as unrelated to study treatment. Adverse reactions leading to study drug discontinuation occurred in 17.5% of BMT subjects and 2.3% of placebo subjects. The most common AEs leading to discontinuation were: nausea (8%), headache (2%), vomiting (1%), flushing (1%), and injection site reactions (1%).

## **5.1 ADVERSE EVENTS OF SPECIAL INTEREST**

### **5.1.1 Hepatotoxicity**

The Applicant reported one hepatotoxicity case in the CDP (BMT 301 Extension); the liver function tests returned to normal 4 months after study drug discontinuation. There were no further cases of liver injury seen in the CDP. After extensive evaluation, the Applicant's and the Agency's liver experts were unable to identify the cause and concluded that the association between BMT and hepatocellular injury is not probable but could not be definitively ruled out.<sup>12</sup> This information will be included in Section 6 of the labeling.<sup>k</sup>

### **5.1.2 Hyperpigmentation**

Hyperpigmentation and skin discoloration AEs occurred at a higher rate in BMT treated subjects, especially in Black subjects (4.1%) versus Caucasian subjects (0.6%), and only half of these subjects had resolution of hyperpigmentation. No malignant melanomas or other cutaneous malignancies were reported. Due to this observation, DBRUP consulted the Division of Dermatology and Dental Products (DDDP) to assess potential risk of skin cancer with BMT. The DDDP reviewer concluded that no biomarkers capable of detecting early malignancy of pigmented lesions currently exist, and no information on whether diffuse or localized hyperpigmentation of the skin could mask a cutaneous malignancy and delay diagnosis. Thus, routine skin examination may be adequate for monitoring cutaneous malignancies in a promelanogenic state. The DDDP reviewer recommends that a Warning and Precaution for hyperpigmentation be added in labeling to educate patients on this risk and that routine postmarketing pharmacovigilance is adequate to assess for potential skin malignancy.<sup>13</sup> The DBRUP clinical reviewer concurs with DDDP's conclusion and recommendations.

### **5.1.3 Blood Pressure (BP) elevations**

The clinical reviewers from DBRUP and the Division of Cardiovascular and Renal Products (DCRP) identified an elevation in BP and blunting of the evening dip in BP (which are associated with an increased risk of cardiovascular (CV) events) from (b) (4) phase 2 (Study 54) studies.<sup>7,14,15</sup> Of note, there were no major adverse cardiovascular events (MACE) reported in the BMT core studies (BMT-301 and BMT-302) and one event of myocardial infarction in placebo group. In the extension studies there was one cerebrovascular event (BMT-301 Extension) and one event of angina (BMT-302 Extension).

The Applicant initially submitted ABPM results from primarily sporadic use of BMT in Study 54 (b) (4). There were no data for continuous daily use of BMT and BP effects. Additionally, the proposed labeling recommending subjects not administer more than one dose within 24 hours (instead of sporadic use only) potentially increasing the patient's risk for elevations in BP and cardiovascular events.

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<sup>k</sup> Whitaker, M. Internal Mid-cycle presentation, dated August 20, 2018

The Agency informed AMAG during the application review of the requirement for an ABPM trial with randomized withdrawal to facilitate the review and labeling of BMT.<sup>1</sup> The following summarizes the findings from the ABPM studies submitted by the Applicant.

Study 54 is a phase 2 dose finding study in patients with FSAD, HSDD or mixed FSAD/HSDD. The study consisted of a 4-week no treatment period, a single dose in-clinic single-blind placebo (followed by 24-hour ABPM), a 4-week single-blind outpatient period (baseline), a 2-week period with two single in-clinic doses (followed by 24-hour ABPM following each dose), and a 12 week double-blind period in which patients were randomized 1:1:1:1 to placebo, BMT 0.75 mg, BMT 1.25 mg, or BMT 1.75 mg. The BP increase in the active arms was greatest within the first 4 hours and was in the magnitude of mean maximum increase of 3.1 mmHg SBP and 3.2 mmHg DBP, and a mean maximum decrease in heart rate (HR) of 6.6 bpm (placebo-subtracted).



The phase 3 studies (BMT-301 and BMT-302) did not conduct ABPM. Therefore, as all the BMT studies that assessed BP had a highly selective study population (as they were phase 1 and 2 trials) and may not be generalizable to patients with CV risks,

Study AMAG- BMT-HSDD-101, the most recent ABPM study, was an open label, phase 1, placebo-controlled double-blind, parallel arm randomized withdrawal ABPM in premenopausal women evaluating daily administration of BMT (1.75 mg SC) for 8 days, followed by randomized (1:1), placebo-controlled withdrawal (Days 9 to 16). (b) (4)

The primary endpoint of the study was the

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<sup>1</sup> Roule, J. Email communication with AMAG, dated 11/7/2018

intra-subject mean change in SBP from Baseline (Day-1) during the daytime period following 8 days of BMT treatment during the Open-Label Period; the change from Baseline in the SBP measurements recorded during the daytime using a 2-sided 95% CI was set with priori upper bound threshold at 4 mmHg.

The Applicant concluded that daily administration of BMT of 8 and 16 days demonstrated a similar BP and HR profile as single/ acute/ intermittent dosing, similar to the results seen in Study 54. Overall, less than 2 mmHg increases in SBP were observed in 24 hours with peak effects 3 to 4 hours post-dose that attenuated by 8 hours post-dose. These BP increases were accompanied by small to no reductions in the HR of 1 bpm or less. The primary outcome was met with mean change in SBP less than 4 mmHg (mean change of 2.7 mmHg in daytime SBP from Baseline). There were no increases in night time BP following 8 days of consecutive therapy. For subjects that were randomized to the withdrawal period (Days 9- 16) of consecutive daily administration of either BMT 1.75 mg or placebo, no cumulative increases in BP or reductions in HR were observed in those receiving BMT compared with Baseline or to Day 8. In subjects who received placebo, small reductions (2 mmHg) in daytime SBP were seen following day 8 and resultant BPs were similar to those at Baseline. The Applicant contends BMT did not exhibit cumulative effect of extended daily and sequential dosing. The small increases in BP observed with BMT were found to be transient and reversible.<sup>18</sup>

DBRUP and DCRP agree with the conclusions from the AMAG- BMT-HSDD-101 study. DCRP reanalyzed the data from Study AMAG- BMT-HSDD-101. The results demonstrated that the increase in BP is largest in the first 4 to 8 hours post dose and for HR, the largest decrease is in the first 8 hours. These results are consistent with the results in Study 54 and suggest that the peak increase in systolic and diastolic BP is 2 to 3 mmHg. This study demonstrated that the increase in BP with BMT after 16 days of dosing is similar to 8 days of dosing, and that increase in BP is transient during the day and returns to baseline before the expected next dose.<sup>20</sup> Increases in BP and decreases in HR shortly after dosing usually resolves within 12 hours without the need for treatment.<sup>1</sup>

#### **5.1.4 Misuse**

The Applicant proposes BMT to be used as-needed with a dosing frequency not more than one dose per 24-hours and not more than 8 doses per month.<sup>1</sup> The frequency of BMT use in the CDP was an average of 1 time per week and 2-3 times per month. However, the clinical reviewer noted some instances of misuse: 16.8% of subjects administered 2 doses within 24 hours (12.9% within 20 to < 24 hours; 4.4% within 12 to < 20 hours; 3.9% within < 12 hours apart, as short as 5 minutes). No deaths or serious adverse events were reported in patients with misuse (defined as two doses < 24 hours apart). There were no differences in the adverse event profiles reported in subjects who had repeated injections < 20 hours apart and those who had taken BMT as instructed. The clinical reviewer concluded that most cases of misuse were non-intentional, but there were concerns for intentional misuse by subjects to potentially enhance the effects of BMT which may increase risk for nausea, hyperpigmentation, and transient hypertension. The Applicant was unable to provide further elaboration on the misuse seen in the CDP. The Applicant's proposed dosing limitations and packaging that limits the number of doses

dispensed (1.75 mg in 0.3ml in single use, disposable prefilled autoinjector provided in a carton of 4 autoinjectors) may help mitigate misuse.

## **6 Expected Postmarket Use**

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BMT is likely to be utilized in the outpatient setting primarily by gynecologists and specialists involved in women's health, although internists and family care providers may also prescribe BMT.

## **7 Risk Management Activities Proposed by the Applicant**

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The Applicant did not propose any risk management activities for BMT beyond routine pharmacovigilance and labeling. However, DBRUP informed AMAG that a postmarketing requirement (PMR) for pregnancy (an observational pregnancy registry and retrospective epidemiology) and lactation is required given use in women of childbearing potential of the patient population, exposure and subsequent pregnancy is anticipated.

## **8 Discussion of Need for a REMS**

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The clinical reviewer recommends approval of BMT on the efficacy and safety information currently available.

HSDD is the most common type of FSD affecting an estimated one in 10 women or approximately 7 million adult US women. HSDD is often undiagnosed, is associated with poor quality of life, and may negatively affect relationships with partners. There is currently only one product (Addyi) approved in the US and worldwide for HSDD. Safety concern with the Addyi-alcohol interaction resulted in the requirement for a BW, CI, and a REMS. Therefore, alternative therapeutic options for HSDD are needed.

The pivotal phase 3 trials, BMT-301 and BMT-302, support the efficacy of BMT showing statistically significant improvements in their primary co-endpoints of improving desire (improved FSFI with medium increase in desire score of 0.6) and reducing distress associated with low desire (improved FSDS-DOA Q13 with decrease score of -1). While the results are modest, the effect is considered clinically meaningful to patients. Approval of BMT would add another medical treatment option to women with HSDD.

The most common adverse events include nausea, flushing, injection site reaction, and headache. There was one case of hepatotoxicity in the CDP, but extensive evaluation by liver experts concluded that although not probable, drug induced liver injury (DILI) could not be ruled out. Therefore, this concern will be included in section 6, adverse reaction in labeling, and will reflect that the possibility of liver injury with BMT could not be definitively excluded. Hyperpigmentation also occurred at a higher rate, especially in Black subjects in the CDP. The DDDP reviewer concluded, and the medical reviewer

concluded that routine monitoring is adequate to monitor the risk for melanoma and recommend including this risk in labeling under warnings and precautions.

Safety concerns identified in the application assessment include transient elevations in BP and potential for intentional misuse. The Applicant conducted an ABPM study to further characterize the change in BP measurements during the NDA application review. The study showed that the increase in BP with corresponding decreases in HR is transient and usually resolves within 12 hours without the need for treatment. Furthermore, there were no cumulative effects with daily dosing. Therefore, the review team concluded that the safety profile of BMT is acceptable for an as-needed use treatment, however, BMT should not be used in patients with uncontrolled hypertension or known cardiovascular disease due to expected increases in BP. Concern for intentional misuse by subjects to potentially enhance the effects of BMT, increasing risks such as nausea, hyperpigmentation, and transient hypertension, were observed. However, the frequency of BMT use in the CDP (average of 1 time per week and 2-3 times per month) was low. Therefore, both risks for transient increase in BP and potential for misuse can be communicated through labeling.

Based on the currently available data, DRISK and DBRUP concur that a REMS is not necessary to ensure the benefits of BMT outweigh the risks. No additional risk management interventions beyond professional labeling, instructions for use, and pharmacovigilance are required. The risk of transient elevations in BP and misuse will be communicated with product labeling.

## 9 Conclusion & Recommendations

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Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for BMT to ensure the benefits outweigh the risks. The safety concerns of transient elevations in BP and corresponding decreases in HR as well as misuse will be communicated in labeling via warnings and precautions. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

## 10 References

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[REDACTED]
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