V. Addendum – Division of Risk Management, Office of Medication Error Prevention and Risk Management, Office of Surveillance and Epidemiology

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

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To: Members of the Joint Advisory Committee of the Psychopharmacologic Drugs Advisory Committee (PDAC), and Drug Safety and Risk Management (DSaRM) Advisory Committee

From: Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)

Subject: Risk Evaluation and Mitigation Strategy (REMS)

Product: Brexanolone injection) 5 mg/mL

Application Number: NDA 211371

1 INTRODUCTION

This addendum presents FDA's proposed risk evaluation and mitigation strategy (REMS) to mitigate the risk of serious adverse events resulting from loss of consciousness/pre-syncope (LOC) associated with the use of brexanolone.

2 BACKGROUND

2.1 Brief Summary of Brexanolone

Brexanolone is a proprietary analogue of the endogenous human hormone allopregnanolone. It is a new molecular entity (NME) with the proposed indication is treatment of postpartum depression (PPD). Although its mechanism of action is unknown, it appears to be a positive allosteric modulator of $GABA_A$ receptors with a binding site distinct from benzodiazepines. Brexanolone is available as a 5 mg/mL solution, which is administered as an intravenous (IV) infusion over 60 hours. The dose is weight- and time-based as per the following:

- 4 hours at 30 μg/kg/hour
- 20 hours at 60 μg/kg/hour
- 28 hours at 90 μg/kg/hour
- 4 hours at 60 μg/kg/hour

- 4 hours at 30 μg/kg/hour

The product would be administered once per episode of PPD.

The efficacy is derived from three randomized, double-blind, placebo-controlled studies: 202A (N=21), 202B (N=138), and 202C (N=108). The participants included 247 women (18 to 44 years of age) diagnosed with PPD, of which,140 women were exposed to brexanolone. In all three studies, the primary efficacy endpoint was depression symptoms (measured by the Hamilton Depression Scale; HAM-D) at hour 60 (the end of infusion). Brexanolone statistically significantly improved the HAM-D greater than placebo in all three studies (p=0.008, p=0.03, and p=0.02, respectively). Mean, placebo-subtracted improvements on the HAM-D were clinically meaningful (and ranged from 2.5 to 12.2 points across the studies).

The adverse reactions that occurred in brexanolone-treated patients at a rate of at least 3% and at a higher rate than in the placebo-treated patients during the 60-hour treatment period and 4-week follow-up period were dry mouth, infusion site pain, fatigue, headache, sedation/somnolence, dizziness/vertigo, and loss of consciousness.

Refer to Section 2.5 of the FDA Briefing Document, Effectiveness of Brexanolone for Treatment of Postpartum Depression and Section 2.6 Safety of Brexanolone for Treatment of Postpartum Depression for detailed information on efficacy and safety results.

2.2 Brexanolone related loss of consciousness/pre-syncope

A serious risk with brexanolone is excessive sedation and loss of consciousness during the 60-hour infusion. Of the 140 brexanolone-treated patients, there were six patients (4%) who experienced LOC compared to no patients in the placebo-treated group.

The most concerning case involved a 25-year-old who reported dizziness approximately 8.5 hours after beginning the infusion. The patient was eating when she abruptly dropped her spoon and became unresponsive. After 10 minutes, the patient opened her eyes to verbal stimuli but was not responsive for 1 hour. The patient was transported to the emergency department, but no additional treatment was administered. This patient had no memory of the event. All of the LOC cases resolved 10 to 60 minutes once the infusion was interrupted. A summary of the cases of LOC are provided in Appendix 1.

Of note, during the QT study, a 55-year-old male subject receiving 150 μg/kg/h developed somnolence, confusion, and brief (<1 minute) apnea. There were no cases of apnea in the phase 3 studies.

The healthcare settings used for administration of brexanolone varied during the clinical development. Each site was required to have overnight capabilities to house subjects for approximately 72 hours, IV infusion capabilities, and per Good Clinical Practice (GCP)

requirements, a healthcare professional was required to be onsite at all times. To meet the overnight requirements, investigators at sites without overnight capabilities arranged for the infusion to occur in a variety of settings including: sleep centers, day surgery centers, a pediatric wing of a private hospital, an urgent care facility, hospital clinical research centers, and a physician outpatient office. The credentials of the onsite healthcare professionals varied by site per state regulations and ranged from emergency medical technicians to nurses or physicians. Of note, there were no ambulation restrictions during the infusion, however, subjects were not the primary caretaker of their infant or children.

Although sedation and somnolence were the most common brexanolone-related AEs (15% for brexanolone, 6% for placebo across the three efficacy studies), they did not predict LOC events. There was no pattern suggestive of LOC-risk based on age, BMI, vital signs, time since delivery, past medical history, or concurrent medications. There was no relationship observed with brexanolone blood level, dose, or timing relative to the start of the infusion or dose.

The Agency is concerned about serious adverse events resulting from the LOC. If a patient were to abruptly lose consciousness during infusion, she is at risk of injury to herself (e.g., falls, drowning, choking, aspiration, apnea or respiratory depression), and her infant (e.g., dropping, smothering) if the patient was caring for the infant during infusion. Additionally, there are no data on outcomes if the infusion is not stopped. Therefore, to mitigate these risks the Agency believes that a patient receiving brexanolone should be continuously monitored by a healthcare provider (HCP) who can recognize the symptoms of excessive sedation and interrupt the infusion to ensure her recovery as was done in the clinical development program

2.3 Risk Evaluation and Mitigation Strategy (REMS)

Section 505-1 of the Food, Drug, and Cosmetic Act (FDCA), added to the law by the Food Drug Administration Amendments Act of 2007 (FDAAA) authorizes the FDA to require pharmaceutical sponsors to develop and comply with a REMS for a drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management plan that uses risk minimization strategies beyond the professional labeling.

The elements of a REMS can include: a Medication Guide or patient package insert (PPI), a communication plan to healthcare providers, elements to assure safe use, and an implementation system. FDAAA also requires that all REMS approved for drugs or biologics under New Drug Applications (NDA) and Biologics License Applications (BLA) have a timetable for submission of assessments of the REMS. These assessments are prepared by the sponsor and reviewed by FDA.

A communication plan consists of FDA approved materials used to aid a sponsor's implementation of the REMS and/or inform healthcare providers about serious risk(s) of an approved product. This can include, for example, "Dear Healthcare Professional" letters,

collaboration with professional societies, and education pieces (such as letters, drug fact sheets) to inform prescribers of the risks and the safe use practices for the drug.

Elements to assure safe use (ETASU) can include one or more of the following requirements:

- Healthcare providers who prescribe the drug have training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be subject to monitoring
- Patients must be enrolled in a registry

Because ETASU can impose significant burdens on the healthcare system and reduce patient access to treatment, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific serious risk listed in the labeling. Accordingly, the statute [FDCA 505-1(f)(2)] specifies that ETASU:

- Must be commensurate with specific serious risk(s) listed in the labeling.
- Cannot be unduly burdensome on patient access to the drug.
- To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with REMS elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs.

3 RISK MANAGEMENT CONSIDERATIONS

A variety of strategies are used to minimize risks associated with drugs and therapeutic biologics. These strategies minimize risks in several ways. They can communicate specific risk information, as well as information about the safe use of the product. In addition, they can provide guidance and encourage, remind, or support adherence to certain prescribing, dispensing, or monitoring requirements, and/or limit use of a product to only the most appropriate patients where a favorable benefit-risk profile has been adequately demonstrated.

3.1 Applicant Risk Minimization Plan

The Applicant did not submit a REMS with the application. Because of the potential risk of injury

to the patient and the infant if the patient experiences a LOC, the Agency informed the Applicant that a REMS was likely required that ensures the patient is continuously monitored during the infusion by a health care provider that can evaluate the patient and determine if the infusion needs to be stopped or additional intervention is required.

The Applicant submitted an outline of their REMS proposal on August 24, 2018. The proposed REMS goal is to inform patients, competent companions, and healthcare professionals on how to mitigate the risk of excessive sedation during brexanolone infusion and includes certification of infusion providers (hospital pharmacies, home infusion companies, or other infusion providers) by using an authorized representative to enroll on behalf of the site. The proposal did not contain additional details about who would qualify as a competent companion.

The Applicant's proposed labeling includes information about the risk of sedation and impaired alertness and hazardous activities (e.g. driving or operating heavy machinery) in the Warnings and Precautions Section. In addition, the proposed label states that "Patients should be periodically monitored during the infusion. If the patient experiences symptoms of excessive sedation, consider interrupting the infusion until symptoms resolve. The infusion may be resumed at the same or lower dose as clinically appropriate." The proposed label does not contain language that describes the setting for the infusion or limitations of use.

3.2 Agency Proposed REMS

Should brexanolone be approved, the Agency is proposing a REMS to mitigate the risk of serious adverse events resulting from excessive sedation and loss of consciousness, to ensure the benefits outweigh the risks. The FDA's proposed REMS provides the following safeguards that ensure administration of brexanolone is only in healthcare settings that have HCPs available to monitor the patient continuously for excessive sedation and intervene if needed.

FDA is proposing the following REMS components to mitigate the risk of serious adverse events resulting from loss of consciousness associated with brexanolone:

1. Elements to assure safe use including:
    - Administration of brexanolone only in certain health care settings that ensure continuous patient monitoring by a HCP
    - Enrollment of patients who are treated with brexanolone in a registry to better characterize the risk of LOC.
2. An implementation system
3. A timetable for submission of assessments

Administration only in certain healthcare settings

Restricting the distribution of brexanolone to certain healthcare settings would ensure that the patient is continuously monitored by a HCP for excessive sedation and loss of consciousness during the administration of the 60-hour infusion and potentially following the infusion. The

healthcare providers at these sites will be able to intervene if the patient is excessively sedated or has an abrupt loss of consciousness. To become certified, the healthcare setting must attest that HCPs are available to continuously monitor for LOC.

Enrollment of Patients in a Registry

Enrollment of patients who are treated with brexanolone in a registry would allow for the collection of additional data to further characterize the risk of LOC including time to onset, dose at the time of the event, vital signs, and other symptoms and risk factors associated with the event. The advantage of this approach is that it would systematically capture information on all patients and allow for calculation of an incident rate and potentially the ability to identify factors that may increase an individual's risk for LOC.

3.3 Discussion of the Agency Proposed REMS

The Applicant is proposing a REMS and labeling that would allow administration of brexanolone in settings outside of what was studied during the clinical development program (e.g. home infusion) and the use of a competent companion to monitor for excessive sedation and LOC. Use of a competent companion was not studied nor has it been well described. The Agency's proposed REMS would restrict administration of the product to certified healthcare settings that will ensure that the patient will be continuously monitored by a healthcare provider who can adjust or interrupt the infusion in the event of excessive sedation or loss of consciousness. In addition, all patients who receive brexanolone will be enrolled in a registry to try to better characterize the risk.

4 CONCLUSION

FDA has the authority to require a REMS if additional measures beyond the labeling are necessary to ensure the benefits of a drug outweigh the risks. If brexanolone were approved, it would be in the best interest of public health to have it widely available to the relevant patient population. We do not believe infusions must be done in an inpatient hospital setting. However, we do not believe it would be safe to allow home infusions at this time.
The committee will be asked if the FDA's proposed REMS will ensure safe use of brexanolone. The committee will also be asked if FDA's proposed REMS will ensure the benefits outweigh the risks of brexanolone for the treatment of PPD.

5 APPENDIX

Appendix 1:

Subject ID (Study)	Demographics	Description of Event
(b) (6) (202B)	31 yo, AA BMI 28.1 kg/m2 78 days after delivery h/o MDD Medication -medroxyprogesterone	-Vasovagal syncope during venipuncture for PK sampling (reported fear of needles)
(b) (6) (202B)	25 yo, W BMI 40 kg/m^2	-Infusion pump malfunction, high dose -BP lability before and during the event (71/48 to

	40 days after delivery h/o anxiety Medication -labetalol -lansoprazole -promethazine -acetaminophen	140/101 mmHg) -LOC occurred 14 h after starting 90µg/kg/h (actual dose unclear) -LOC x 30 sec, "as if in deep, sound sleep" -Infusion stopped; felt well after 10 min
(b) (6) (202B)	28 yo, W BMI 35 kg/m^2 82 days after delivery Medication -none	-Infusion pump malfunction, high dose -Asked if the drug made one sleepy, then fell forward "abruptly"; snoring -No change in vitals -Infusion stopped; recovered after 14 min
(b) (6) (202B)	24 yo, W BMI 29 kg/m^2 185 days after delivery h/o anxiety, MDD Medication -ASA/acetaminophen/ caffeine	-Reported dizziness 20 h after starting 60 µg/kg/h -10 h later was extremely somnolent and unaware of surroundings -Infusion stopped; improved after 15 min, resolved after 45 min
(b) (6) (202C)	25 yo, W BMI 30 kg/m^2 189 days after delivery h/o anxiety, MDD Medication -sertraline (since 2016) -single dose ondansetron	-Reported dizziness 5 h after starting 60 µg/kg/h -Was eating Jell-O when abruptly dropped spoon and became unresponsive -Opened eyes to verbal stimuli after 10 min, but not responsive for 1 h -Sent to emergency department -No memory of event
(b) (6) (202C)	36 yo, AA BMI 51 kg/m^2 115 days after delivery h/o HTN Medication -medroxyprogesterone -methadone (since 2012) -metoprolol -naproxen -lisinopril/HCTZ	-Reported dizziness and somnolence at 30 and 60 µg/kg/h -Presyncope/vertigo 13 h after starting 90 µg/kg/h -Sat down and presyncope resolved after 10 min, vertigo after 2 h