



NDA 211371

NDA APPROVAL

Sage Therapeutics, Inc.
Attention: Daniel Soroko, MS
Director, Regulatory Affairs
215 First Street
Cambridge, MA 02142

Dear Mr. Soroko:

Please refer to your New Drug Application (NDA) dated April 19, 2018, received April 19, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zulresso (brexanolone) injection 5 mg/ml.

We acknowledge receipt of your major amendment dated November 8, 2018, which extended the goal date by three months.

This new drug application provides for the use of Zulresso (brexanolone) injection 5 mg/ml for postpartum depression.

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 text.

CONTROLLED SUBSTANCE SCHEDULING

You were previously informed that FDA intends to recommend scheduling of Zulresso under the Controlled Substances Act (CSA). The scheduling of this product in accordance with the CSA (21 U.S.C. 811) is not yet complete as of the date of this letter. Therefore, in accordance with the FDCA (21 U.S.C. 355(x)), the date of approval for Zulresso shall be the date on which the Drug Enforcement Administration (DEA) publishes a notice in the Federal Register announcing the interim final scheduling of brexanolone.

We note that, when the drug is scheduled by the DEA, you will need to make appropriate revisions to the Prescribing Information, Medication Guide, and carton and container labeling by submitting a supplement to your NDA. This would include the statements in the labeling detailing the scheduling of brexanolone as the scheduled substance in Zulresso, as required under 21 CFR 201.57(a)(2) and (c)(10)(i). Therefore, Zulresso may be marketed only after DEA has published the notice in the Federal Register announcing the interim final scheduling of

brexanolone and you submit a supplement to your NDA to revise all applicable drug labeling to reflect the drug scheduling described in the notice. For changes to the Prescribing Information, Medication Guide, carton and container labeling to describe the scheduling of brexanolone, you can submit a Changes Being Effected supplement described in 21 CFR 314.70(c)(6). Permission to use a Changes Being Effected supplement for this purpose reflects a waiver by the Agency, pursuant to 21 CFR 314.90, of the requirement to submit a Prior Approval Supplement for changes to reflect the scheduling to the Highlights of Prescribing Information for Zulresso described in 21 CFR 314.70(b)(2)(v)(C) and changes to the Medication Guide described in 21 CFR 314.70(b)(2)(v)(B).

We note that Zulresso will be listed in the Orange Book upon the date of approval in accordance with 21 U.S.C. 355(x). With respect to the submission of patent information, as required under 21 CFR 314.53(c)(2)(ii), we note that you must submit Form FDA 3542 within 30 days after the date on which DEA has published the notice in the Federal Register announcing the interim final scheduling of brexanolone.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) as well as annual reportable changes not included in the 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*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, 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 titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical*

Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5). For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 211371.**” Approval of this submission by FDA is not required before the labeling is used.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Latrice Wilson, PharmD, RAC
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 4111
10903 New Hampshire Avenue
Silver Spring, Maryland

*Use zip code **20903** if shipping via United States Postal Service (USPS).*

*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

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.

We are waiving the pediatric study requirement for males, pre-pubertal females and post-pubertal females less than 15 years, because necessary studies are impossible or highly impracticable. This is because postpartum depression (PPD) cannot occur in males or pre-pubertal females (including neonates), and the birth rate in females younger than 15 years old is too low.

We are deferring submission of your pediatric study for ages 15 to less than 18 years for this application, because this product is ready for approval for use in adults and the pediatric study have not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. This required study is listed below.

- 3535-1 Conduct a randomized, double-blind, placebo-controlled, parallel-group study evaluating efficacy and safety of brexanolone in adolescent females, 15 years to less than 18 years of age, diagnosed with postpartum depression.

Final Protocol Submission: 01/2018
Study/Trial Completion: 10/2020
Final Report Submission: 04/2021

Submit the protocol(s) to your IND 122279, with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the 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 apoptotic neurodegeneration.

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 this serious risk.

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

- 3535-2 Conduct an animal study to assess brexanolone's potential for producing apoptotic neurodegeneration when administered during the critical period of brain development for such effects at allopregnanolone levels greater than occur endogenously.

The timetable you submitted on March 15, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 12/2019
Study Completion: 8/2020
Final Report Submission: 12/2020

Submit clinical protocol(s) to your IND 122279 with a cross-reference letter to this NDA. 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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3535-3 Conduct a study to evaluate the efficacy of a lower dose of brexanolone.

The timetable you submitted on March 11, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 12 /2019
Study/Trial Completion: 07 /2022
Final Report Submission: 01 /2023

3535-4 Evaluate outpatient daytime dosing allowing for administration of brexanolone at a non-24 hour facility.

The timetable you submitted on March 11, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 12 /2019
Study/Trial Completion: 12 /2024
Final Report Submission: 06 /2025

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 122279 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **“Postmarketing Commitment Protocol,” “Postmarketing Commitment Final Report,”** or **“Postmarketing Commitment Correspondence.”**

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for ZULRESSO to ensure the benefits of the drug outweigh the risk of serious harm resulting from excessive sedation and loss of consciousness during the ZULRESSO infusion.

Your proposed REMS must include the following:

Elements to assure safe use: Pursuant to 505-1(f)(1), we have determined that ZULRESSO can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of serious harm resulting from excessive sedation and loss of consciousness during the ZULRESSO infusion, as listed in the labeling of the drug.

Your REMS includes the following elements to mitigate these risks:

- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients only in certain health care settings
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions
- Each patient using the drug is subject to certain monitoring
- Each patient using the drug is enrolled in a registry

Implementation System: The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require pharmacies, practitioners, or health care settings that dispense the drug be specially certified, the drug be dispensed to patients only in certain health care settings, and the drug be dispensed to patients with documentation of safe use conditions.

Your proposed REMS, submitted on November 1, 2018, amended and appended to this letter, is approved.

The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce ZULRESSO into interstate commerce.

The REMS assessment plan must include, but is not limited to, the following:

1. REMS Program Implementation (6-month and 1-year assessments only)
 - a. Date of first commercial distribution of Zulresso
 - b. Date when the Zulresso REMS Website went live and was fully operational
 - c. Date when healthcare settings could become certified
 - d. Date when pharmacies could become certified
 - e. Date when patients could become enrolled
 - f. Date when REMS Call Center is established and fully operational
2. Program Outreach and Communication (6-month, 1-year, and 2-year assessments only)
 - a. Sources of the distribution lists for healthcare providers
 - b. Number of healthcare providers targeted
 - c. The date(s), number, and medical specialty of healthcare providers who were sent the Letter for Healthcare Providers by the methods of distribution
 - d. The number of mailings returned or undeliverable. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients
3. REMS Program Operation and Performance Data (per reporting period and cumulatively)
 - a. REMS Website
 - i. Number of visits and unique visits to the REMS website
 - ii. Number of REMS materials downloaded or printed for each material
 - b. REMS Call Center
 - i. Number of contacts by stakeholder type (patients, healthcare providers, pharmacies, healthcare settings, wholesaler/distributors, other)
 - ii. Summary of reasons for calls (e.g., enrollment question, location of a certified healthcare setting) and by reporter (authorized representative, healthcare setting, patient/caregiver, other)
 - iii. Summary of frequently asked questions (FAQ) by stakeholder type
 - iv. Summary report of REMS-related problems identified and resulting corrective actions
4. REMS Enrollment Statistics (per reporting period and cumulatively)
 - a. Healthcare Settings

- i. Number of newly certified and active (i.e., that have received Zulresso) healthcare settings stratified by healthcare setting type (i.e. hospital, infusion center, other), authorized representative credentials, and geographic region
 - ii. Number of healthcare settings that dispensed Zulresso for administration stratified by healthcare setting type and geographic region
 - iii. Number of certified healthcare settings with an internal central pharmacy
 - iv. Number of certified healthcare settings without an internal central pharmacy
 - v. Healthcare settings that were unable to become certified and reason
 - b. Pharmacies
 - i. Number of newly enrolled and active (i.e., that have received Zulresso) pharmacies stratified by pharmacy type (i.e., specialty, specialty infusion, compounding, other), authorized representative credentials, and geographic region
 - ii. Number of pharmacies that dispensed Zulresso stratified by pharmacy type and geographic region
 - iii. Pharmacies that were unable to become certified and reason
 - c. Wholesalers/Distributors
 - i. Number of newly enrolled and active (i.e., that have shipped Zulresso) distributors
 - ii. Number of enrolled wholesalers/distributors that shipped Zulresso
 - d. Patients
 - i. Number of newly enrolled patients stratified by age, geographic region, and healthcare setting type
5. Zulresso Utilization Data (per reporting period and cumulatively)
 - a. Number of vials distributed to certified healthcare settings and certified pharmacies
 - b. Number of prescriptions dispensed to certified healthcare settings from certified pharmacies stratified by:
 - i. Pharmacy type
 - ii. Prescriber specialty, professional degree/credentials, geographic region
 - iii. Patient demographics (i.e., age and geographic region)
 - c. Number of unique patients receiving Zulresso, stratified by age, geographic region, and healthcare setting type
6. Post-Training Healthcare Setting Knowledge Assessments (per reporting period and cumulatively)
 - a. Number of completed post-training Healthcare Setting Knowledge Assessments, including number of attempts to complete per healthcare setting authorized representative and method of completion.
 - b. A summary of the most frequently missed Healthcare Setting Knowledge Assessment questions

- c. A summary of potential comprehension or perception issues identified with the Knowledge Assessments

7. REMS Compliance (per reporting period and cumulatively)

- a. Provide a summary of non-compliance identified, including but not limited to:
 - i. Provide a copy of the non-compliance plan, including the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each case, and which event lead to de-certification from the REMS.
 - ii. Provide a copy of the audit plan for each stakeholder
 - iii. Report of audit findings for each stakeholder (healthcare settings, pharmacies, wholesalers/distributors)
 - 1. The number of audits expected, and the number of audits performed.
 - 2. The number and types of deficiencies noted for each group of audited stakeholders.
 - 3. For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) plan within one month of audit.
 - 4. For any that did not complete the CAPA within one month of the audit, describe actions taken.
 - 5. Include a unique ID for each stakeholder that had deviations to track deviations by stakeholder over time.
 - 6. Documentation of completion of training for relevant staff.
 - 7. The existence of documented processes and procedures for complying with the REMS
 - 8. Verification that each audited stakeholder's site that the designated authorized representative remains the same. If different, include the number of new authorized representatives and verification of the site's recertification.
- b. Healthcare settings (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
 - i. The number and type of healthcare settings for which non-compliance with the REMS is detected
 - ii. Number of times Zulresso was administered by a certified healthcare setting prior to patient enrollment
 - iii. Number and type of non-certified healthcare setting that administered Zulresso and the number of incidents for each healthcare setting.
 - iv. Number of healthcare settings that did not enroll patients prior to administering. Include the number of patients involved.
 - v. Number of times Zulresso was distributed, transferred, or loaned from one healthcare setting to another
 - vi. Number of healthcare settings that did not provide appropriate monitoring for the duration of the infusion. Include the number of patients involved and the proportion of patients per healthcare setting.

- vii. Number of healthcare settings that did not have the necessary equipment (i.e. continuous pulse oximetry, fall precaution protocol, intravenous programmable infusion pumps with alarms). Include the number of patients involved.
 - viii. Number of patients who refused to comply with the duration of the infusion period. Include the number of healthcare settings involved and the proportion of patients per healthcare setting
 - ix. Number of patients who were not enrolled and received a Zulresso infusion in a certified healthcare setting
 - x. Number of healthcare settings de-certified for non-compliance and reasons for de-certification
- c. Pharmacies (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
- i. The number and type of pharmacies for which non-compliance with the REMS is detected
 - ii. The number and type of non-certified pharmacies that dispensed Zulresso and the number of incidents for each
 - iii. Number of times Zulresso was dispensed to healthcare setting without verifying that the healthcare setting is certified
 - iv. Number of pharmacies who were de-certified for non-compliance and reasons for de-certification.
- d. Wholesalers/Distributors (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
- i. The number of authorized wholesalers/distributors for which non-compliance with the REMS is detected
 - ii. The number and type of non-authorized wholesalers/distributors that shipped Zulresso and the number of incidents for each
 - iii. Number of times Zulresso was distributed to a non-certified healthcare setting, non-certified pharmacy, or directly to patients.
- e. Post Infusion Forms
- i. Number of Post Infusion Forms expected, received, and outstanding as of the report cut-off date
 - ii. Number of Post Infusion Forms not received within 3 calendar days. Include outreach activities performed to collect the forms.
 - iii. Number of Post-Infusion Forms not received within 15 calendar days. Include outreach activities performed to collect the forms.
 - iv. Number of Post Infusion Forms not received within 30 calendar days. Include outreach activities performed to collect the forms and corrective actions taken.
 - v. Number of Post Infusion Forms where a patient was enrolled but did not received Zulresso and reasons why this occurred.
 - vi. Results of Post-Infusion Forms outstanding from previous reporting periods (if applicable)

- vii. Any other evidence that safe use was not demonstrated (patient was not monitored for sufficient period or appropriate monitoring was not done).
- f. Excessive Sedation and Loss of Consciousness Adverse Event Forms
- i. Number of Excessive Sedation and Loss of Consciousness Adverse Event Forms expected, received, and outstanding as of the report cut-off date
 - ii. Number of Excessive Sedation and Loss of Consciousness Adverse Event Forms not received within 15 calendar days. Include outreach activities performed to collect the forms.
 - iii. Number of Excessive Sedation and Loss of Consciousness Adverse Event Forms not received within 30 calendar days. Include outreach activities performed to collect the forms.
 - iv. Results of Excessive Sedation and Loss of Consciousness Adverse Event Forms outstanding from previous reporting periods (if applicable)
8. Safety Surveillance (per reporting period and cumulatively)
- a. Known, or suspected adverse events related to excessive sedation or loss of consciousness are to be reported regardless of outcome. Root cause analyses of whether REMS processes for patient monitoring were followed are to be included. Sources of the reports are to include but not be limited to:
 - i. Post Infusion Form
 - 1. Number of cases of excessive sedation and loss of consciousness reported on the Post Infusion Form, including a calculation of the event incidence.
 - 2. Number of patients who experienced more than one event.
 - 3. Trend analysis of whether adverse events decrease or increase over time
 - ii. Excessive Sedation and Loss of Consciousness Adverse Event Form
 - iii. Adverse events reported in the REMS registry
 - iv. Spontaneous adverse event reports
 - 1. Include the search strategy used to identify cases (via safety database) and specific MedDRA terms used to identify cases of interest
 - 2. Include a line listing of all cases that includes: manufacturer control number, narrative, assessment of causality, and source of the report
 - v. Literature searches
 - vi. Social Media
 - b. Include an overall summary and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication.

9. The requirements for assessments of an approved REMS under section 505-1(g)(3) include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c) *If the new, proposed indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.
- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification, provide a rationale for why the REMS does not need to be modified.*

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous

REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 211371 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT
METHODOLOGY**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 211371 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 211371/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 211371/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 211371/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING
CHANGES SUBMITTED IN SUPPLEMENT XXX**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 211371/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR NDA 211371

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

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 (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

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 <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

SPECIAL REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). In addition, we request that you expedite cases (i.e., submit these cases as 15-day Alert reports) of all serious adverse event reports for brexanolone. Every effort should be made to obtain thorough and complete follow-up for each case of serious adverse events for brexanolone. The clinical information collected will enhance the quality of adverse event reports submitted to FDA and facilitate our assessment of these reports. We also request that you include a summary and analysis of all serious adverse events for brexanolone in the submission of the periodic reports for brexanolone for each reporting period.

REPORTING REQUIREMENTS

You must comply with the reporting requirements described in 21 CFR 314.80(c)(1) (e.g., 15-day alert reports) beginning on the date of **this** letter. The due dates for the periodic (including quarterly) adverse drug experience reports described in 21 CFR 314.80(c)(2) should be calculated from the date of this letter. Annual reports described in 21 CFR 314.81(b)(2) are due within 60 days of the anniversary of the date of approval in accordance with 21 U.S.C. 355(x).

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

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.

If you have any questions, contact Latrice Wilson, PharmD, Regulatory Project Manager, at latrice.wilson@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
Deputy Center Director for Clinical Science
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
- Prescribing Information
- Medication Guide
- Carton and Container Labeling
- REMS

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/s/

ELLIS F UNGER on behalf of ROBERT TEMPLE
03/19/2019 05:00:11 PM