NDA 022526/S-009

SUPPLEMENT APPROVAL

Sprout Pharmaceuticals, Inc.
Attention: Jaye Thompson, Ph.D.
Vice President, Regulatory Affairs
4208 Six Forks Road
Suite 1010
Raleigh, NC 27609

Dear Dr. Thompson:

Please refer to your supplemental new drug application (sNDA) dated and received August 29, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ADDYI® (flibanserin) tablets.

This Prior Approval supplemental new drug application provides for proposed modifications to the approved ADDYI risk evaluation and mitigation strategy (REMS).

We have completed our review of this supplemental application, as amended. It is approved effective on the date of this letter.

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.

Because none of these criteria apply to your application, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for ADDYI was originally approved on August 18, 2015, and the most recent REMS modification was approved on April 2, 2019. The REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of the removal of the ETASU and implementation system, and the inclusion of the Medication Guide as an element of the REMS.

In accordance with section 505-1 of the FDCA, we have determined that the following REMS modifications are necessary to ensure the benefits of the drug outweigh the risks and to minimize burden on the healthcare delivery system of complying with the REMS:

Medication Guide: In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that ADDYI poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of ADDYI. FDA has determined that ADDYI is a product for which patient labeling could help prevent serious adverse effects, and that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use or continue to use ADDYI. Under section 505-1 of the FDCA, FDA has also determined that a Medication Guide is necessary to ensure the benefits of the drug outweigh the risks of concomitant use of alcohol with ADDYI.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed ADDYI.

Elements to Assure Safe Use: In addition, we have determined that elements to assure safe use (ETASU) are no longer necessary because new information from the Phase 1 studies (SPR-18-001 and SPR-18-002) of ADDYI and alcohol showed that the risk with alcohol is narrower than understood at the time of approval. Specifically, the Phase 1 studies showed that waiting at least 2 hours after drinking up to two standard alcoholic drinks prior to taking Addyi mitigates the risk for syncope and hypotension. Given this new information, the current ETASU REMS is no longer necessary and is being removed to minimize burden on the health care system.

Implementation System: In addition, because the elements to assure safe use requiring that pharmacies, practitioners, or health care settings that dispense the drug be specially certified are no longer necessary, the implementation system is also no longer necessary as an element of the REMS.

Your proposed modified REMS, submitted on August 29, 2019, amended and appended to this letter, is approved. The modified REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS.

Submit, within 30 days of this letter, the protocol for the Medication Guide comprehension study for our review and await FDA's comments before initiating the study.

The timetable for submission of assessments of the REMS must be revised to 6 months from October 9, 2019, then 18 months, 3 years, and 7 years thereafter.

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

1. REMS Operational Metrics (beginning with the 18-month assessment and cumulatively)
    a. Number of visits and unique visits to the Medication Guide from Addyi.com.
    b. Time spent viewing the Medication Guide from Addyi.com.

2. REMS Compliance (beginning with the 18-month assessment and cumulatively)
    a. Assessment of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
        i. Assessment of pharmacy's policies and procedures for distribution and dispensing of the Medication Guide (e.g. survey of pharmacists to determine if Medication Guide is dispensed)
    b. Assessment of patient's receipt of the Medication Guide (e.g. The Knowledge Evaluation survey to assess patients' understanding of the risks of Addyi will be conducted in patients who were dispensed Addyi and will also assess whether patients received the Medication Guide).

3. Medication Guide Comprehension Study (6-month assessment)
    a. If comprehension is below the prespecified threshold, Sprout will outline steps to address it to ensure adequate comprehension (e.g. revising the Medication Guide). The target level of comprehension should be a minimum of 80%, with the exception of comprehension related to the timing of consumption of alcohol and flibanserin administration/dose which should have a target level of 90% or greater.

4. Safety Surveillance (beginning with the 18-month assessment and cumulatively)
    a. Known or suspected adverse events related to hypotension and syncope associated with Addyi due to an interaction with alcohol.

5. Knowledge Evaluation (beginning with the 18-month assessment)
    a. Assess patient's understanding of the risk of hypotension and syncope associated with Addyi due to an interaction with alcohol and how to avoid it.

6. 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) of the FDCA. 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 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 that 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 REMS modifications*, 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 022526 REMS 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.

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 022526 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 022526/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 022526/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 022526/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022526/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 REVISIONS FOR NDA 022526

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, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

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.

REPORTING REQUIREMENTS

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

If you have any questions, please call Meredith Hillig, M.S., Safety Regulatory Health Project Manager, at (301) 796-1218.

Sincerely,

{See appended electronic signature page}

Christine P. Nguyen, M.D.
Deputy Director for Safety
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- REMS

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/

CHRISTINE P NGUYEN
10/09/2019 10:00:29 PM