



NDA 022526

**NDA APPROVAL**

Sprout Pharmaceuticals, Inc.  
Attention: Amy Moore  
Director, Regulatory Affairs  
4208 Six Forks Road, Suite 1010  
Raleigh, NC 27609

Dear Ms. Moore:

Please refer to your New Drug Application (NDA) dated and received October 27, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Addyi (flibanserin) Tablets.

We acknowledge receipt of your amendments dated November 20, December 17, 18, and 23, 2009, January 21, and 26, February 5, 19, 24, March 3, 9, 12, 16, April 13, 26, 28, 30(2), May 7, 12(2), 13, 14, 19, 25, 26, 27, June 8, 15, 16(2), 17, July 2, and 8, 2010, August 8, September 20, December 29, 2011, January 20, August 23, 2012, April 10, May 6, 17, 22, June 14, July 17, 18, August 1, 5, and September 12, October 1 and 21, December 3 and 12, 2013; February 12, 19, 20, and 21, March 31, April 2 and 17, July 7, August 12, 2014; February 18, March 3, 13 and 20, April 13, 21 and 22, May 4, 6, 20 and 29, June 18 and 29, July 2, 21, 29, and August 5, 6, 7, 11, 12, 14, 17, and 18, 2015.

The February 18, 2015, submission constituted a complete response to our September 27, 2013, action letter.

This new drug application provides for the use of Addyi (flibanserin) Tablets for the treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD), as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is NOT due to:

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

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

## **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.

### **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 package insert and Medication Guide). 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 IMMEDIATE CONTAINER LABELS**

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on August 14, 2015, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 022526.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

### **MARKET PACKAGE**

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

Jennifer Mercier  
Food and Drug Administration

Center for Drug Evaluation and Research  
White Oak Building 22, Room: 5390  
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, 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the 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 assess signals of serious risks of 1) severe hypotension and syncope, accidents or injuries, and fatal outcomes associated with Addyi, 2) risk of appendicitis and 3) risk of adverse pregnancy-related outcomes and birth defects.

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

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

2939-1 Enhanced Pharmacovigilance Study to Assess and Analyze the Risks of Hypotension, Syncope, Accidents or Injuries, and Fatal Outcomes with Use of Addyi (flibanserin).

The timetable you submitted on August 18, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	10/15
Study Completion:	10/20
Interim Reports:	04/16, 10/16, 04/17, 10/17, 04/18, 10/18, 04/19, 10/19, 04/20
Study Reassessment Report Submission:	04/21
Final Study Report Submission:	04/24

2939-2 Prospective Observational Study to Evaluate the Risk of Appendicitis with the Use of Addyi (flibanserin) in Women Aged 18 to 44.

The timetable you submitted on August 17, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/16
Study Completion:	03/19
Final Report Submission:	09/19

2939-3 Pregnancy Registry Study to Evaluate Adverse Pregnancy Outcomes and Birth Defects in Pregnancies Exposed to Addyi (flibanserin).

The timetable you submitted on August 18, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/16
Study Completion:	06/21
Interim Reports:	06/17, 06/18, 06/19, 06/20
Final Report Submission:	12/21

2939-4 Maternal-Fetal Outcome Study to Evaluate Adverse Pregnancy Outcomes and Birth Defects in Pregnancies Exposed to Addyi (flibanserin).

The timetable you submitted on August 18, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 03/16  
Study Completion: 06/21  
Interim Reports: 06/17, 06/18,  
06/19, 06/20

Final Report Submission: 12/21

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious increased risk of severe hypotension and syncope due to an interaction between Addyi (flibanserin) and alcohol intake.

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

2939-5 Alcohol Interaction Trial in the Target Female Population (Between Ages 18 and 44) to Evaluate the Interaction Between Addyi (flibanserin) and Alcohol Through a “Worst Case Scenario” with Varying Quantities of Alcohol Intake.

The timetable you submitted on August 18, 2015, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 11/15  
Trial Completion: 08/16  
Final Report Submission: 12/16

2939-6 Alcohol Interaction Trial in the Target Female Population (Between Ages 18 and 44) to Evaluate the Interaction of the Timing of Alcohol Intake Relative to Addyi (flibanserin) Dosing.

Dose(s) to be evaluated in this trial will be selected based on the findings from PMR 2939-5.

The timetable you submitted on August 18, 2015, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 01/17  
Trial Completion: 10/17  
Final Report Submission: 02/18

2939-7 Alcohol Interaction Trial in the Target Female Population (Between

Ages 18 and 44) to Evaluate the Interaction Between Addyi (flibanserin) and Alcohol Intake in a “Typical Real World Use” Setting.

Dose(s) to be evaluated in this trial will be selected based on the findings from PMR 2939-5.

The timetable you submitted on August 18, 2015, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	01/17
Trial Completion:	10/17
Final Report Submission:	02/18

Submit the protocol(s) to your IND 101912, with a cross-reference letter to this NDA. Submit 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.

### **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 [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Addyi to ensure the benefits of the drug outweigh the increased risk of severe hypotension and syncope associated with Addyi due to an interaction with alcohol.

Your proposed REMS must include the following:

**Elements to assure safe use:** Pursuant to 505-1(f)(1), we have determined that Addyi can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the increased risk of severe hypotension and syncope associated with Addyi due to an interaction with alcohol listed in the labeling. In addition, we have determined that a Medication Guide and a communication plan are not sufficient to mitigate the serious risk. The elements to assure safe use will require prescribers and pharmacies, who prescribe and dispense Addyi, to be specially certified so that they understand they are required to counsel patients about the increased risk of severe hypotension and syncope associated with Addyi due to an interaction with alcohol.

Your REMS includes the following elements to mitigate these risks:

- Healthcare providers have particular experience or training, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified

**Implementation System:** The REMS must include an implementation system to monitor and evaluate 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. Include an intervention plan to address any findings of non-compliance with elements to assure safe use and to address any findings that suggest an increase in risk.

Your proposed REMS, submitted on August 18, 2015, 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.

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

**A. REMS Program implementation and operational metrics**

All metrics will include the current reporting period and cumulative data. Whenever appropriate, data will be provided in tabular format.

1. *Stakeholders (prescribers, pharmacies, and distributors) utilization*
  - a. Numbers of each stakeholder, status of certification, and method of certification.
  - b. Distribution of certified prescribers by degree, clinical specialty, practice setting, geographic region.
  - c. Distribution of certified pharmacies by pharmacy type (inpatient, outpatient multiple location, outpatient individual location), geographic region, title of authorized representative.
  - d. Distribution of authorized distributors and wholesalers by geographic region.

- e. Listing and categorization of reasons enrollment is incomplete for each stakeholder group (e.g., pharmacy unable to configure a pharmacy management system, missing information on enrollment form, incomplete knowledge assessment).
2. *Addyi utilization*
    - a. Total number of orders (bottles or packages) shipped to pharmacies stratified by pharmacy type.
    - b. Number of outpatient prescriptions dispensed stratified by method of dispensing authorization (PMS or non-electronic) and prescriber specialty.
    - c. Based upon available third-party patient audits a summary of ages of patients who are dispensed product and the duration of use; A description of the source of audits will be provided in each assessment.
  3. *REMS Support Center report*
    - a. Number of contacts by stakeholder type (patient, prescriber, pharmacy, other).
    - b. Summary of frequently asked questions (FAQ) by stakeholder type.
    - c. Listing and categorization of REMS-related problems (e.g., technical, process, inability to find certified prescriber) by stakeholder type and a description of any corrective actions resulting from issues identified.
  4. *REMS Program Compliance (beginning at the 12-month assessment)*
    - a. Audits: Summary of audit findings for audits conducted during the reporting period, including any corrective actions taken to address findings, the status of corrective actions, and any resulting preventative actions taken.
    - b. Number of prescriber, pharmacy and distributors de-certified and reasons for de-certification.
    - c. Number of Addyi prescriptions dispensed that were written by non-certified prescribers and any action taken and outcome of action (e.g., provision of educational program materials, prescriber becoming certified).
    - d. Number of prescriptions dispensed by non-certified outpatient pharmacies and the actions taken to prevent future occurrences.
    - e. Number of shipments sent to non-certified pharmacies, sources of report, and actions taken to prevent future occurrences.
    - f. Number of times an Addyi prescription was dispensed because a pharmacy bypassed REMS, and if any event occurred, a description of how the events were identified and any corrective actions taken.
    - g. Non-compliance with safe use, source of report, and any corrective action or resolution from reports to the REMS Support Center or the Applicant directly.
  5. *Barriers or delays in patient access*
    - a. Number of times all entities are certified, but system generated a prescription rejection notice.
    - b. Lack of certified prescribers and/or pharmacies in a patient's local area (based on reports to the Addyi REMS Support center or to the Applicant directly).

- c. Unintended system interruptions and resolutions.
- d. For electronic verification: number of times a “back up” system was used to validate a prescription and source of problem (e.g., switch level, pharmacy level, REMS database).

6. *Inappropriate patient access*

- a. Number of times inpatient pharmacy dispenses Addyi for outpatient use (as identified through audits or reports to the Addyi REMS Support Center).
- b. Number of times one or all entities were not certified but system verified dispensing and generated an authorization code.

**B. Evaluation of knowledge through Knowledge, Attitude and Behavior (KAB) surveys**

1. Prescribers

- a. An evaluation of knowledge of certified prescribers of the increased risk of severe hypotension and syncope associated with Addyi due to an interaction with alcohol and knowledge of Addyi REMS program requirements.
- b. An evaluation of prescriber practice or behavior with regards to counseling patients about the increased risk of severe hypotension and syncope associated with Addyi due to an interaction with alcohol.

2. Pharmacies

- a. An evaluation of knowledge of authorized representatives and staff pharmacists in certified pharmacies of the increased risk of severe hypotension and syncope associated with Addyi due to an interaction with alcohol and knowledge of Addyi REMS program requirements.
- b. For staff pharmacists: An evaluation of pharmacist practice or behavior with regards to counseling patients about the increased risk of severe hypotension and syncope associated with Addyi due to an interaction with alcohol.

3. Patients

- a. An evaluation of knowledge of patients of the increased risk of severe hypotension and syncope associated with Addyi due to an interaction with alcohol.
- b. An evaluation of patients' recall of counseling by prescriber, pharmacist, or both, on the increased risk of severe hypotension and syncope associated with Addyi due to an interaction with alcohol.

**C. Overall REMS evaluation**

As required for assessments of an approved REMS under section 505-1(g)(3) the Applicant will 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.

**D. Knowledge Assessments at time of enrollment (to be provided in the 6 and 12 month assessments only)**

1. Numbers of certified prescribers, authorized pharmacy representatives, and staff pharmacists who successfully completed the knowledge assessment, including the method of completion (web or paper), and the number of attempts to successfully complete the knowledge assessment.
2. Summary of the most frequently missed *Addyi REMS Knowledge Assessment* questions, stratified by prescriber and pharmacy type.
  - a. Description of any potential comprehension or perception issues identified.
  - b. Proposed REMS materials revisions to address comprehension or perception issues identified, if necessary

**E. REMS Program implementation (to be provided in 6 and 12 month assessments only)**

1. Product Launch Date
2. Date when REMS materials became available to healthcare providers (HCPs) on the website and via the call center
3. The dates HCPs could become certified online, by mail, by fax
4. Addyi REMS website utilization
5. Date when the Addyi REMS website went live
6. Number of unique site visits

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 of 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 022526 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 022526 REMS ASSESSMENT**

**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 LABEL CHANGES  
SUBMITTED IN SUPPLEMENT XXX**

**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 REVISION 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, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

## **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 package insert, Medication Guide, and patient PI (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 package insert, 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>.

## **REPORTING REQUIREMENTS**

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

## **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>.

If you have any questions, call Jennifer Mercier, Chief, Project Management Staff, at (301) 796-0957.

Sincerely,

*{See appended electronic signature page}*

Julie Beitz, M.D.  
Director  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosures:

Content of Labeling  
Physician Insert  
Medication Guide  
Carton and Container Labeling  
REMS

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JULIE G BEITZ  
08/18/2015