

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### ***APPLICATION NUMBER:***

**22526Orig1s009**

***Trade Name:*** ADDYI  
***Generic or Proper Name:*** flibanserin

***Sponsor:*** SPROUTS PHARMS

***Approval Date:*** October 9, 2019

***Indication:*** ADDYI is indicated 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.

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22526Orig1s009

## CONTENTS

### Reviews / Information Included in this NDA Review.

<b>Approval Letter</b>	<b>X</b>
<b>Other Action Letters</b>	
<b>Labeling</b>	<b>X</b>
<b>REMS</b>	<b>X</b>
<b>Summary Review</b>	
<b>Officer/Employee List</b>	
<b>Office Director Memo</b>	
<b>Cross Discipline Team Leader Review</b>	
<b>Clinical Review(s)</b>	<b>X</b>
<b>Product Quality Review(s)</b>	
<b>Non-Clinical Review(s)</b>	
<b>Statistical Review(s)</b>	
<b>Clinical Microbiology / Virology Review(s)</b>	
<b>Clinical Pharmacology Review(s)</b>	
<b>Other Reviews</b>	<b>X</b>
<b>Risk Assessment and Risk Mitigation Review(s)</b>	<b>X</b>
<b>Proprietary Name Review(s)</b>	
<b>Administrative/Correspondence Document(s)</b>	<b>X</b>

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22526Orig1s009**

**APPROVAL LETTER**



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:

**U.S. Food and Drug Administration**  
Silver Spring, MD 20993  
[www.fda.gov](http://www.fda.gov)

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](http://Addyi.com).
  - b. Time spent viewing the Medication Guide from [Addyi.com](http://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](mailto: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

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**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.**  
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/s/  
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CHRISTINE P NGUYEN  
10/09/2019 10:00:29 PM

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22526Orig1s009**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ADDYI safely and effectively. See full prescribing information for ADDYI.

**ADDYI (flibanserin) tablets, for oral use**  
Initial U.S. Approval: 2015

### WARNING: HYPOTENSION AND SYNCOPE IN CERTAIN SETTINGS

See full prescribing information for complete boxed warning.

- Use of ADDYI and alcohol together close in time increases the risk of severe hypotension and syncope. Counsel patients to wait at least two hours after consuming one or two standard alcoholic drinks before taking ADDYI at bedtime or to skip their ADDYI dose if they have consumed three or more standard alcoholic drinks that evening. (4, 5.1)
- Severe hypotension and syncope can occur when ADDYI is used with moderate or strong CYP3A4 inhibitors or in patients with hepatic impairment; therefore, ADDYI use in these settings is contraindicated. (4, 5.2, 5.5)

### RECENT MAJOR CHANGES

Boxed Warning, Hypotension and Syncope in Certain Settings 10/2019  
Contraindications, Alcohol (4) Removed 10/2019  
Warnings and Precautions, Hypotension and Syncope due to an Interaction with Alcohol (5.1) 10/2019  
Warnings and Precautions, ADDYI REMS Program (5.2) Removed 10/2019

### INDICATIONS AND USAGE

ADDYI is indicated 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. (1)

### Limitations of Use:

- ADDYI is not indicated for the treatment of HSDD in postmenopausal women or in men. (1)
- ADDYI is not indicated to enhance sexual performance. (1)

### DOSAGE AND ADMINISTRATION

- Recommended dosage is 100 mg taken once daily at bedtime (2.1)
- ADDYI is dosed at bedtime because administration during waking hours increases risks of hypotension, syncope, accidental injury, and central nervous system (CNS) depression (2.1)
- Discontinue treatment after 8 weeks if no improvement (2.3)

### DOSAGE FORMS AND STRENGTHS

Tablets: 100 mg (3)

### CONTRAINDICATIONS

- Moderate or strong cytochrome P450 3A4 (CYP3A4) inhibitors (4, 5.2)
- Hepatic impairment (4, 5.5)

### WARNINGS AND PRECAUTIONS

- **Hypotension and Syncope due to an Interaction with Alcohol:** After taking ADDYI at bedtime, advise patients to avoid alcohol until the following day. (5.1)
- **Hypotension and Syncope with ADDYI Alone:** Patients with pre-syncope should immediately lie supine and promptly seek medical help if symptoms do not resolve. (5.4)
- **Central Nervous System (CNS) Depression (e.g., Somnolence, Sedation):** Can occur with ADDYI alone. Exacerbated by other CNS depressants, and in settings where flibanserin concentrations are increased. Patients should avoid activities requiring full alertness (e.g., operating machinery or driving) until at least six hours after each dose and until they know how ADDYI affects them. (5.3)

### ADVERSE REACTIONS

Most common adverse reactions (incidence  $\geq 2\%$ ) are dizziness, somnolence, nausea, fatigue, insomnia, and dry mouth. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sprout Pharmaceuticals, Inc. at 1-844-746-5745, or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- **Oral Contraceptives and Other Weak CYP3A4 Inhibitors:** Increases flibanserin exposures and incidence of adverse reactions (6.1, 7)
- **Strong CYP2C19 Inhibitors:** Increases flibanserin exposure which may increase risk of hypotension, syncope, and CNS depression (7)
- **CYP3A4 Inducers:** Use of ADDYI not recommended; flibanserin concentrations substantially reduced (7)
- **Digoxin:** Increases digoxin concentrations, which may lead to digoxin toxicity. Increase monitoring of digoxin concentrations (7)

### USE IN SPECIFIC POPULATIONS

- **Nursing Mothers:** ADDYI is not recommended. (8.2)
- **CYP2C19 Poor Metabolizers:** Increases flibanserin exposure which may increase risk of hypotension, syncope, and CNS depression (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2019

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### WARNING: HYPOTENSION AND SYNCOPE IN CERTAIN SETTINGS

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

- 5.1 Hypotension and Syncope due to an Interaction with Alcohol
- 5.2 Hypotension and Syncope with CYP3A4 Inhibitors
- 5.3 Central Nervous System Depression
- 5.4 Hypotension and Syncope with ADDYI Alone
- 5.5 Syncope and Hypotension in Patients with Hepatic Impairment
- 5.6 Mammary Tumors in Female Mice

#### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

#### 7 DRUG INTERACTIONS

#### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use

8.6 Hepatic Impairment

8.7 CYP2C19 Poor Metabolizers

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### 14 CLINICAL STUDIES

- 14.1 Studies in Premenopausal HSDD Patients
- 14.2 Effects on Driving

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

### WARNING: HYPOTENSION AND SYNCOPE IN CERTAIN SETTINGS

#### **Interaction with Alcohol**

The use of ADDYI and alcohol together close in time increases the risk of severe hypotension and syncope [see *Warnings and Precautions (5.1)*]. Counsel patients to wait at least two hours after consuming one or two standard alcoholic drinks before taking ADDYI at bedtime or to skip their ADDYI dose if they have consumed three or more standard alcoholic drinks that evening.

#### **Contraindicated with Strong or Moderate CYP3A4 Inhibitors**

The concomitant use of ADDYI and moderate or strong CYP3A4 inhibitors increases flibanserin concentrations, which can cause severe hypotension and syncope [see *Warnings and Precautions (5.2)*]. Therefore, the use of moderate or strong CYP3A4 inhibitors is contraindicated in patients taking ADDYI [see *Contraindications (4)*].

#### **Contraindicated in Patients with Hepatic Impairment**

The use of ADDYI in patients with hepatic impairment increases flibanserin concentrations, which can cause severe hypotension and syncope [see *Warnings and Precautions (5.5)*]. Therefore, ADDYI is contraindicated in patients with hepatic impairment [see *Contraindications (4)*].

## 1 INDICATIONS AND USAGE

ADDYI is indicated 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.

#### **Limitations of Use**

- ADDYI is not indicated for the treatment of HSDD in postmenopausal women or in men.
- ADDYI is not indicated to enhance sexual performance.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dosage

The recommended dosage of ADDYI is 100 mg administered orally once per day at bedtime. ADDYI is dosed at bedtime because administration during waking hours increases the risks of hypotension, syncope, accidental injury, and central nervous system (CNS) depression (such as somnolence and sedation).

### 2.2 Missed Dose

If a dose of ADDYI is missed at bedtime, instruct the patient to take the next dose at bedtime on the next day. Instruct the patient to not double the next dose.

### 2.3 Discontinuation of ADDYI

Discontinue ADDYI after 8 weeks if the patient does not report an improvement in her symptoms.

## 2.4 Initiation of ADDYI Following Moderate or Strong CYP3A4 Inhibitor Use

If initiating ADDYI following moderate or strong CYP3A4 inhibitor use, start ADDYI 2 weeks after the last dose of the CYP3A4 inhibitor.

If initiating a moderate or strong CYP3A4 inhibitor following ADDYI use, start the moderate or strong CYP3A4 inhibitor 2 days after the last dose of ADDYI [see *Warnings and Precautions (5.2)*].

## 3 DOSAGE FORMS AND STRENGTHS

Tablets: 100 mg, oval, pink, debossed on one side with “f100” and blank on the other side.

## 4 CONTRAINDICATIONS

ADDYI is contraindicated:

- With concomitant use with moderate or strong CYP3A4 inhibitors [see *Boxed Warning and Warnings and Precautions (5.2)*].
- In patients with hepatic impairment [see *Boxed Warning and Warnings and Precautions (5.5)*].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypotension and Syncope due to an Interaction with Alcohol

Taking ADDYI within two hours after consuming alcohol increases the risk of severe hypotension and syncope. To reduce this risk, counsel patients to wait at least two hours after drinking one or two standard alcoholic drinks before taking ADDYI at bedtime [see *Boxed Warning and Adverse Reactions (6.1)*]. Patients who drink three or more standard alcoholic drinks should skip their ADDYI dose that evening. One standard alcoholic drink contains 14 grams of pure alcohol and is equivalent to one 12-ounce regular beer (5% alcohol), 5-ounces wine (12% alcohol), or 1.5 ounces of distilled spirits/shot (40% alcohol).

After taking ADDYI at bedtime, advise patients to not use alcohol until the following day.

### 5.2 Hypotension and Syncope with CYP3A4 Inhibitors

#### Moderate or Strong CYP3A4 Inhibitors

The concomitant use of ADDYI with moderate or strong CYP3A4 inhibitors significantly increases flibanserin concentrations, which can lead to hypotension and syncope [see *Adverse Reactions (6.1)*]. The concomitant use of ADDYI with a moderate or strong CYP3A4 inhibitor is contraindicated. If the patient requires a moderate or strong CYP3A4 inhibitor, discontinue ADDYI at least 2 days prior to starting the moderate or strong CYP3A4 inhibitor. In cases where the benefit of initiating a moderate or strong CYP3A4 inhibitor within 2 days of stopping ADDYI clearly outweighs the risk of flibanserin exposure related hypotension and syncope, monitor the patient for signs of hypotension and syncope. Discontinue the moderate or strong CYP3A4 inhibitor for 2 weeks before restarting ADDYI [see *Drug Interactions (7)*].

#### Multiple Concomitant Weak CYP3A4 Inhibitors

Concomitant use of multiple weak CYP3A4 inhibitors that may include herbal supplements (e.g., ginkgo, resveratrol) or non-prescription drugs (e.g., cimetidine) could also lead to clinically relevant increases in flibanserin concentrations that may increase the risk of hypotension and syncope [see *Drug Interactions (7)*].

### 5.3 Central Nervous System Depression

ADDYI can cause CNS depression (e.g., somnolence, sedation). In five 24-week, randomized, placebo-controlled, double-blind trials of premenopausal women with HSDD, the incidence of somnolence, sedation or fatigue was 21% and 8% in patients treated with 100 mg ADDYI once daily at bedtime and placebo,

respectively [see *Adverse Reactions (6.1) and Clinical Studies (14.1)*]. The risk of CNS depression is increased if ADDYI is taken during waking hours, or if ADDYI is taken with alcohol or other CNS depressants, or with medications that increase flibanserin concentrations, such as CYP3A4 inhibitors [see *Contraindications (4), Warnings and Precautions (5.1, 5.2), Adverse Reactions (6.1), and Drug Interactions (7)*].

Patients should not drive or engage in other activities requiring full alertness until at least 6 hours after taking ADDYI and until they know how ADDYI affects them [see *Clinical Studies (14.2)*].

#### **5.4 Hypotension and Syncope with ADDYI Alone**

The use of ADDYI – without other concomitant medications known to cause hypotension or syncope – can cause hypotension and syncope. In five 24-week, randomized, placebo-controlled, double-blind trials of premenopausal women with HSDD, hypotension was reported in 0.2% and <0.1% of ADDYI-treated patients and placebo-treated patients, respectively; syncope was reported in 0.4% and 0.2% of ADDYI-treated patients and placebo-treated patients, respectively. The risk of hypotension and syncope is increased if ADDYI is taken during waking hours or if higher than the recommended dose is taken [see *Warnings and Precautions (5.1, 5.3), Adverse Reactions (6.1), Drug Interactions (7), and Use in Specific Populations (8.7)*]. Consider the benefits of ADDYI and the risks of hypotension and syncope in patients with pre-existing conditions that predispose to hypotension. Patients who experience pre-syncope should immediately lie supine and promptly seek medical help if the symptoms do not resolve. Prompt medical attention should also be obtained for patients who experience syncope.

#### **5.5 Syncope and Hypotension in Patients with Hepatic Impairment**

The use of ADDYI in patients with any degree of hepatic impairment significantly increases flibanserin concentrations, which can lead to hypotension and syncope. Therefore, the use of ADDYI is contraindicated in patients with hepatic impairment [see *Contraindications (4), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

#### **5.6 Mammary Tumors in Female Mice**

In a 2-year carcinogenicity study in mice, there was a statistically significant and dose-related increase in the incidence of malignant mammary tumors in female mice at exposures 3 and 10 times the recommended clinical dose. No such increases were seen in male mice or in male or female rats [see *Nonclinical Toxicology (13.1)*]. The clinical significance of these findings is unknown.

### **6 ADVERSE REACTIONS**

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Hypotension and syncope [see *Warnings and Precautions (5.1, 5.2, 5.4, 5.5)*]
- CNS depression [see *Warnings and Precautions (5.3)*]

#### **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The approved 100 mg ADDYI dosage at bedtime was administered to 2,997 premenopausal women with acquired, generalized HSDD in clinical trials, of whom 1672 received treatment for at least 6 months, 850 received treatment for at least 12 months, and 88 received treatment for at least 18 months [see *Clinical Studies (14)*].

## Data from Five 24-Week, Randomized, Double-Blind Placebo-Controlled Trials in Premenopausal Women with HSDD

The data presented below are derived from five 24-week randomized, double-blind, placebo-controlled trials in premenopausal women with acquired, generalized HSDD. In these five trials, the frequency and quantity of alcohol use was not recorded. Three of these trials (Studies 1 through 3) also provided efficacy data [see *Clinical Studies (14.1)*]. One of these trials (Study 5) did not evaluate the 100 mg bedtime dose.

In four trials, 100 mg ADDYI at bedtime was administered to 1543 premenopausal women with HSDD, of whom 1060 completed 24 weeks of treatment. The clinical trial population was generally healthy without significant comorbid medical conditions or concomitant medications. The age range was 18-56 years old with a mean age of 36 years old, and 88% were Caucasian and 9% were Black.

Serious adverse reactions were reported in 0.9% and 0.5% of ADDYI-treated patients and placebo-treated patients, respectively.

### Adverse Reactions Leading to Discontinuation

The discontinuation rate due to adverse reactions was 13% among patients treated with 100 mg ADDYI at bedtime and 6% among patients treated with placebo. Table 1 displays the most common adverse reactions leading to discontinuation in four trials of premenopausal women with HSDD.

**Table 1. Adverse Reactions\* Leading to Discontinuation in Randomized, Double-blind, Placebo-controlled Trials in Premenopausal Women with HSDD**

	Placebo (N=1556)	ADDYI (N=1543)
Dizziness	0.1%	1.7%
Nausea	0.1%	1.2%
Insomnia	0.2%	1.1%
Somnolence	0.3%	1.1%
Anxiety	0.3%	1%

\*Adverse reactions leading to discontinuation of  $\geq 1\%$  of patients receiving 100 mg ADDYI at bedtime and at a higher incidence than placebo-treated patients.

### Most Common Adverse Reactions

Table 2 summarizes the most common adverse reactions reported in four trials of premenopausal women with HSDD. This table shows adverse reactions reported in at least 2% of patients treated with ADDYI and at a higher incidence than with placebo [see *Warnings and Precautions (5.3)*]. The majority of these adverse reactions began within the first 14 days of treatment.

**Table 2. Common Adverse Reactions\* in Randomized, Double-blind, Placebo-controlled Trials in Premenopausal Women with HSDD**

	Placebo (N=1556)	ADDYI (N=1543)
Dizziness	2.2%	11.4%
Somnolence	2.9%	11.2%
Nausea	3.9%	10.4%
Fatigue	5.5%	9.2%
Insomnia	2.8%	4.9%
Dry mouth	1.0%	2.4%

\* Adverse reactions reported in  $\geq 2\%$  of patients receiving 100 mg ADDYI at bedtime and at a higher incidence than placebo-treated patients.

### Less Common Adverse Reactions

In four trials in premenopausal women with HSDD treated with 100 mg ADDYI at bedtime, less common adverse reactions (reported in  $\geq 1\%$  but  $< 2\%$  of ADDYI-treated patients and at a higher incidence than with placebo) included:

- Anxiety (ADDYI 1.8%; placebo 1.0%),
- Constipation (ADDYI 1.6%; placebo 0.4%),
- Abdominal pain (ADDYI 1.5%; placebo 0.9%),
- Metrorrhagia (ADDYI 1.4%; placebo 1.4%),
- Rash (ADDYI 1.3%; placebo 0.8%),
- Sedation (ADDYI 1.3%; placebo 0.2%), and
- Vertigo (ADDYI 1%; placebo 0.3%).

### Appendicitis

In the five trials of premenopausal women with HSDD, appendicitis was reported in 6/3973 (0.2%) flibanserin-treated patients, while there were no reports of appendicitis in the 1905 placebo-treated patients.

### Accidental Injury

In five trials of premenopausal women with HSDD, accidental injury was reported in 42/1543 (2.7%) ADDYI-treated patients and 47/1905 (2.5%) placebo-treated patients. Among these 89 patients who experienced injuries, 9/42 (21%) ADDYI-treated patients and 3/47 (6%) placebo-treated patients reported adverse reactions consistent with CNS depression (e.g., somnolence, fatigue, or sedation) within the preceding 24 hours.

### Adverse Reactions in Patients Who Reported Hormonal Contraceptive Use

In four trials of premenopausal women with HSDD, 1466 patients (43%) reported concomitant use of hormonal contraceptives (HC) at study enrollment. These trials were not prospectively designed to assess an interaction between ADDYI and HC. ADDYI-treated patients who reported HC use had a greater incidence of dizziness, somnolence, and fatigue compared to ADDYI-treated patients who did not report HC use (dizziness 9.9% in HC non-users, 13.4% in HC users; somnolence 10.6% in HC non-users, 12.3% in HC users; fatigue 7.5% in HC non-users, 11.4% in HC users). There were no meaningful differences in the incidence of these adverse reactions in placebo-treated patients who reported or did not report HC use [*see Drug Interactions (7)*].

### **Data from Other Trials**

One death occurred in a 54 year-old postmenopausal woman treated with 100 mg ADDYI taken at bedtime (ADDYI is not approved for the treatment of postmenopausal women with HSDD) [*see Indications and Usage (1)*]. This patient had a history of hypertension and hypercholesterolemia and baseline alcohol consumption of 1-3 drinks daily. She died of acute alcohol intoxication 14 days after starting ADDYI. Blood alcohol concentration on autopsy was 0.289 g/dL. The autopsy report also noted coronary artery disease. A relationship between this patient's death and use of ADDYI is unknown [*see Boxed Warning and Warnings and Precautions (5.1)*].

### **Hypotension, Syncope, and CNS Depression in Studies of Healthy Subjects**

*Hypotension, Syncope, and CNS Depression with Alcohol*

Alcohol and ADDYI Administration at the Same Time

The first alcohol interaction study was conducted in 25 healthy subjects (23 men and 2 premenopausal women). The study excluded subjects who drank fewer than five alcoholic drinks per week and those with a history of orthostatic hypotension, or syncope. A single dose of 100 mg ADDYI was administered concurrently with 0.4 g/kg or 0.8 g/kg alcohol in the morning; alcohol was consumed over 10 minutes. Hypotension or syncope requiring therapeutic intervention (ammonia salts and/or placement in supine or Trendelenberg position) occurred in 4 (17%) of the 23 subjects co-administered 100 mg ADDYI and 0.4 g/kg alcohol (equivalent to two 12 ounce cans of beer containing 5% alcohol content, two 5 ounce glasses of wine containing 12% alcohol content, or two 1.5 ounce shots of 80-proof spirit in a 70 kg person). In these four subjects, all of whom were men, the magnitude of the systolic blood pressure reductions ranged from 28 to 54 mmHg and the magnitude of the diastolic blood pressure reductions ranged from 24 to 46 mmHg. In addition, 6 (25%) of the 24 subjects co-administered 100 mg ADDYI and 0.8 g/kg alcohol (equivalent to four 12 ounce cans of beer containing 5% alcohol content, four 5 ounce glasses of wine containing 12% alcohol content, or four 1.5 ounce shots of 80-proof spirit in a 70 kg person) experienced orthostatic hypotension when standing from a sitting position. The magnitude of the systolic blood pressure reduction in these 6 subjects ranged from 22 to 48 mmHg, and the diastolic blood pressure reductions ranged from 0 to 27 mmHg. One of these subjects required therapeutic intervention (ammonia salts and placement supine with the foot of the bed elevated). There were no events requiring therapeutic interventions when ADDYI or alcohol were administered alone.

In this study, somnolence was reported in 67%, 74%, and 92% of subjects who received ADDYI alone, ADDYI in combination with 0.4 g/kg alcohol, and ADDYI in combination with 0.8 g/kg alcohol, respectively. [see *Boxed Warning, Warnings and Precautions (5.1, 5.3 and 5.4)*].

In the second alcohol interaction study, 96 healthy premenopausal women received a single dose of 100 mg ADDYI concurrently with 0.2 g/kg, 0.4 g/kg, or 0.6 g/kg alcohol (equivalent to one, two or three alcoholic drinks in a 70 kg person, respectively) in the morning. The study excluded subjects with a history of syncope, orthostatic hypotension, hypotensive events, and dizziness, and those with a resting systolic blood pressure less than 110 mmHg or diastolic blood pressure less than 60 mmHg.

In this study, no subjects experienced syncope or hypotension requiring therapeutic intervention. However, subjects who were already hypotensive (blood pressure below 90/60 mmHg) or symptomatic (e.g., dizzy) while in the semi-recumbent position were not permitted to stand for orthostatic measurements, and those with blood pressures below 90/40 mmHg while in the semi-recumbent position had blood pressures repeated until it was deemed safe for them to change position. More subjects had missing or delayed orthostatic measurements (in general, due to hypotension or dizziness) when receiving ADDYI and alcohol, compared to those who received alcohol alone or ADDYI alone. This pattern of missing or delayed orthostatic measurements is concerning for a risk of hypotension and syncope if those subjects had been allowed to stand.

In this study, somnolence was reported in 81-89% of subjects administered ADDYI with alcohol, compared to 25-41% of subjects administered alcohol alone and 84% of subjects taking ADDYI alone. Dizziness was reported in 27-40% of subjects administered ADDYI with alcohol, compared to 6-20% of subjects administered alcohol alone and 31% of subjects taking ADDYI alone. [see *Warnings and Precautions (5.1, 5.3, 5.4)*].

#### Alcohol Use at Various Time Intervals Before ADDYI Administration

In a third alcohol interaction study, 64 healthy premenopausal women consumed 0.4 g/kg alcohol (equivalent to 2 alcoholic drinks in a 70 kg person) two, four or six hours prior to receiving ADDYI 100 mg or placebo in the afternoon. The study excluded subjects with a history or presence of orthostatic hypotension, history of

hypotension, syncope, or dizziness. Prior to receiving alcohol, the subjects in the ADDYI arm had taken ADDYI for three days to achieve steady state. Syncope occurred in one subject who received alcohol alone. The incidences of orthostatic hypotension and hypotension (blood pressure below 90/60 mmHg) at all time points were similar among subjects administered alcohol before ADDYI, subjects administered alcohol alone, and subjects administered ADDYI alone. Three subjects were unable to stand due to feeling dizzy or hypotension; two following alcohol and ADDYI separated by 2 and 6 hours, and one subject who received ADDYI alone.

In this study, somnolence was reported in 35-53% of subjects administered ADDYI and alcohol, compared to 5-8% of subjects taking alcohol alone and 50% of subjects taking ADDYI alone. Dizziness was reported in 5-13% of subjects administered ADDYI and alcohol, compared to 0-3% of subjects taking alcohol alone and 12% of subjects taking ADDYI alone.

#### Alcohol Use in the Evening Before Bedtime ADDYI Administration

In another alcohol interaction study, 24 premenopausal women consumed 0.4 g/kg alcohol (equivalent to 2 alcoholic drinks in a 70 kg person) during the evening meal two and a half to four hours prior to taking ADDYI 100 mg at bedtime. There were no cases of syncope. Upon rising the following morning, the incidence of hypotension was 23% among subjects administered ADDYI after alcohol, 23% among subjects administered alcohol alone and 36% with ADDYI alone. No cases of somnolence or dizziness were reported in this study. Conclusions are limited because blood pressure and orthostatic measurements were not taken after ADDYI administration until the following morning.

#### *Hypotension and Syncope with Fluconazole*

In a pharmacokinetic drug interaction study of 100 mg ADDYI and 200 mg fluconazole (a moderate CYP3A4 inhibitor, moderate CYP2C9 inhibitor, and a strong CYP2C19 inhibitor) in healthy subjects, hypotension or syncope requiring placement supine with legs elevated occurred in 3/15 (20%) subjects treated with concomitant ADDYI and fluconazole compared to no such adverse reactions in subjects treated with ADDYI alone or fluconazole alone. One of these 3 subjects became unresponsive with a blood pressure of 64/41 mm Hg and required transportation to the hospital emergency department where she required intravenous saline. Due to these adverse reactions, the study was stopped. In this study, the concomitant use of ADDYI and fluconazole increased flibanserin exposure 7-fold [see *Warnings and Precautions (5.2), Drug Interactions (7) and Clinical Pharmacology (12.3)*].

#### *Syncope with Ketoconazole*

In a pharmacokinetic drug interaction study of 50 mg flibanserin and 400 mg ketoconazole, a strong CYP3A4 inhibitor, syncope occurred in 1/24 (4%) healthy subjects treated with concomitant flibanserin and ketoconazole, 1/24 (4%) receiving flibanserin alone, and no subjects receiving ketoconazole alone. In this study, the concomitant use of flibanserin and ketoconazole increased flibanserin exposure 4.5-fold [see *Warnings and Precautions (5.2), Drug Interactions (7) and Clinical Pharmacology (12.3)*].

#### *Syncope in Poor CYP2C19 Metabolizers*

In a pharmacogenomic study of 100 mg ADDYI in subjects who were poor or extensive CYP2C19 metabolizers, syncope occurred in 1/9 (11%) subjects who were CYP2C19 poor metabolizers (this subject had a 3.2 fold higher flibanserin exposure compared to CYP2C19 extensive metabolizers) compared to no such adverse reactions in subjects who were CYP2C19 extensive metabolizers [see *Drug Interactions (7), Use in Specific Populations (8.7) and Clinical Pharmacology (12.5)*].

## 7 DRUG INTERACTIONS

Table 3 contains clinically significant drug interactions (DI) with ADDYI.

**Table 3: Clinically Significant Drug Interactions with ADDYI**

<b>Alcohol</b>	
Clinical Implications	The coadministration of ADDYI with alcohol increased the risk of hypotension, syncope, and CNS depression compared to the use of ADDYI alone or alcohol alone [see <i>Warnings and Precautions (5.1) and Clinical Pharmacology (12.2)</i> ].
Preventing or Managing DI	Counsel patients to wait at least two hours after consuming one or two standard alcoholic drinks before taking ADDYI at bedtime or to skip their ADDYI dose if they have consumed three or more alcoholic drinks that evening. [see <i>Boxed Warning Warnings and Precautions (5.1), and Adverse Reactions (6.1)</i> ].
<b>Other CNS Depressants</b>	
Examples	Diphenhydramine, opioids, hypnotics, benzodiazepines
Clinical Implications	The concomitant use of ADDYI with CNS depressants may increase the risk of CNS depression (e.g., somnolence) compared to the use of ADDYI alone.
Preventing or Managing DI	Discuss the concomitant use of other CNS depressants with the patient when prescribing ADDYI.
<b>Moderate or Strong CYP3A4 Inhibitors</b>	
Examples of strong CYP3A4 inhibitors	Ketoconazole, itraconazole, posaconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, boceprevir, telaprevir, telithromycin and conivaptan
Examples of moderate CYP3A4 inhibitors	Amprenavir, atazanavir, ciprofloxacin, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil, and grapefruit juice
Clinical Implications	The concomitant use of ADDYI with moderate or strong CYP3A4 inhibitors increases flibanserin exposure compared to the use of ADDYI alone. The risk of hypotension and syncope is increased with concomitant use of ADDYI and moderate or strong CYP3A4 inhibitors [see <i>Warnings and Precautions (5.2), Adverse Reactions (6.1), and Clinical Pharmacology (12.3)</i> ].
Preventing or Managing DI	The concomitant use of ADDYI with moderate or strong CYP3A4 inhibitors is contraindicated.
<b>Weak CYP3A4 Inhibitors</b>	
Examples	Oral contraceptives, cimetidine, fluoxetine, ginkgo, ranitidine
Clinical Implications	The concomitant use of ADDYI with multiple weak CYP3A4 inhibitors may increase the risk of adverse reactions.
Preventing or Managing DI	Discuss the use of multiple weak CYP3A4 inhibitors with the patient when prescribing ADDYI.
<b>Strong CYP2C19 Inhibitors</b>	
Examples	Proton pump inhibitors, selective serotonin reuptake inhibitors, benzodiazepines, antifungals
Clinical Implications	The concomitant use of ADDYI with strong CYP2C19 inhibitors may increase flibanserin exposure which may increase the risk of hypotension, syncope, and CNS depression.

Preventing or Managing DI	Discuss the use of a strong CYP2C19 inhibitor with the patient when prescribing ADDYI.
<b>CYP3A4 Inducers</b>	
Examples	Carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapetine, St. John's Wort
Clinical Implications	The concomitant use of ADDYI with CYP3A4 inducers substantially decreases flibanserin exposure compared to the use of ADDYI alone.
Preventing or Managing DI	The concomitant use of ADDYI with CYP3A4 inducers is not recommended.
<b>Digoxin or Other P-glycoprotein Substrates</b>	
Examples	Digoxin, sirolimus
Clinical Implications	The concomitant use of ADDYI with digoxin, a drug that is transported by P-glycoprotein (P-gp), increases the digoxin concentration [see <i>Clinical Pharmacology (12.3)</i> ]. This may lead to digoxin toxicity.
Preventing or Managing DI	Increase monitoring of concentrations of drugs transported by P-gp that have a narrow therapeutic index (e.g., digoxin).

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

There are no studies of ADDYI in pregnant women to inform whether there is a drug-associated risk in humans. In animals, fetal toxicity only occurred in the presence of significant maternal toxicity including reductions in weight gain and sedation. Adverse reproductive and developmental effects consisted of decreased fetal weight, structural anomalies and increases in fetal loss at exposures greater than 15 times exposures achieved with the recommended human dosage [see *Data*]. Animal studies cannot rule out the potential for fetal harm.

In the general population (not taking ADDYI), the estimated background risk of major birth defects is 2% to 4% of live births, and the estimated background risk of miscarriage of clinically recognized pregnancies is 15% to 20%.

#### Data

##### *Animal Data*

Pregnant rats were administered flibanserin at doses of 0, 20, 80 and 400 mg/kg/day (3, 15 and 41 times clinical exposures at the recommended human dose based on AUC) during organogenesis. The highest dose was associated with significant maternal toxicity as evidenced by severe clinical signs and marked reductions in weight gain during dosing. In the litters of high-dose dams, there were decreased fetal weights, decreased ossification of the forelimbs and increased number of lumbar ribs, and two fetuses with anophthalmia secondary to severe maternal toxicity. The no adverse effect level for embryofetal toxicity was 80 mg/kg/day (15 times clinical exposure based on AUC).

Pregnant rabbits were administered flibanserin at doses of 0, 20, 40 and 80 mg/kg/day (4, 8 and 16 times the clinical exposure at the recommended human dose) during organogenesis. Marked decreases in maternal body weight gain (>75%), abortion and complete litter resorption were observed at 40 and 80 mg/kg/day indicating significant maternal toxicity at these doses. Increases in resorptions and decreased fetal weights were observed at  $\geq 40$  mg/kg/day. No treatment-related teratogenic effects were observed in fetuses at any dose level. The no adverse effect level for maternal and embryofetal effects was 20 mg/kg/day (3-4 times clinical exposure based on AUC).

Pregnant rats were administered flibanserin at doses of 0, 20, 80 and 200 mg/kg/day (3, 15 and ~ 20 times clinical exposures at the recommended human dose) from day 6 of pregnancy until day 21 of lactation to assess for effects on peri- and postnatal development. The highest dose was associated with clinical signs of toxicity in pregnant and lactating rats. All doses resulted in sedation and decreases in body weight gain during pregnancy. Flibanserin prolonged gestation in some dams in all dose groups and decreased implantations, number of fetuses and fetal weights at 200 mg/kg/day. Dosing dams with 200 mg/kg also decreased pup weight gain and viability during the lactation period and delayed opening of the vagina and auditory canals. Flibanserin had no effects on learning, reflexes, fertility or reproductive capacity of the F1 generation. The no adverse effect level for maternal toxicity and peri/postnatal effects was 20 mg/kg/day [see *Nonclinical Toxicology (13.1)*].

## 8.2 Lactation

### Risk Summary

Flibanserin is excreted in rat milk. It is unknown whether flibanserin is present in human milk, whether ADDYI has effects on the breastfed infant, or whether ADDYI affects milk production. Because of the potential for serious adverse reactions including sedation in a breastfed infant, breastfeeding is not recommended during treatment with ADDYI.

## 8.4 Pediatric Use

ADDYI is not indicated for use in pediatric patients.

## 8.5 Geriatric Use

ADDYI is not indicated for use in geriatric patients. Safety and effectiveness have not been established in geriatric patients.

## 8.6 Hepatic Impairment

ADDYI is contraindicated for use in patients with any degree of hepatic impairment. Flibanserin exposure increased 4.5-fold in patients with hepatic impairment, compared to those with normal hepatic function, increasing the risk of hypotension, syncope, and CNS depression [see *Boxed Warning, Contraindications (4), Warnings and Precautions (5.5), and Clinical Pharmacology (12.3)*].

## 8.7 CYP2C19 Poor Metabolizers

CYP2C19 poor metabolizers had increased flibanserin exposures compared to CYP2C19 extensive metabolizers. Additionally, syncope occurred in a subject who was a CYP2C19 poor metabolizer [see *Adverse Reactions (6.1) and Clinical Pharmacology (12.5)*]. Therefore, increase monitoring for adverse reactions (e.g., hypotension) in patients who are CYP2C19 poor metabolizers. The frequencies of poor CYP2C19 metabolizers are approximately 2–5% among Caucasians and Africans and approximately 2–15% among Asians.

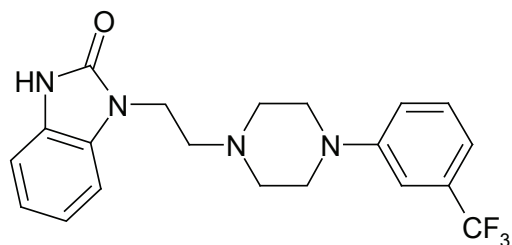
## 10 OVERDOSAGE

Overdosage of ADDYI may cause an increase in the incidence or severity of any of the reported adverse reactions [see *Warnings and Precautions (5.3, 5.4) and Adverse Reactions (6.1)*]. In the event of overdosage, treatment should address the symptoms and supportive measures, as needed. There is no known specific antidote for flibanserin.

## 11 DESCRIPTION

ADDYI (flibanserin) is a tablet for oral administration. The chemical name of flibanserin is 2H-Benzimidazol-2-one, 1,3-dihydro-1-[2-[4-[3-(trifluoromethyl)phenyl]-1-piperazinyl]ethyl]. Its empirical formula is C<sub>20</sub>H<sub>21</sub>F<sub>3</sub>N<sub>4</sub>O and its molecular weight is 390.41.

The structural formula is:



Flibanserin is a white to off-white powder, insoluble in water, sparingly soluble in methanol, ethanol, acetonitrile and toluene, soluble in acetone, freely soluble in chloroform, and very soluble in methylene chloride.

Each ADDYI tablet contains 100 mg of flibanserin. Inactive ingredients consist of lactose monohydrate, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate, talc, macrogol, and the coloring agents, titanium dioxide and iron oxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The mechanism of action of ADDYI in the treatment of premenopausal women with hypoactive sexual desire disorder is not known.

### 12.2 Pharmacodynamics

#### Receptor Binding:

In vitro, flibanserin demonstrated high affinity for the following serotonin (5-hydroxytryptamine or 5-HT) receptors: agonist activity at 5-HT<sub>1A</sub> and antagonist activity at 5-HT<sub>2A</sub>. Flibanserin also has moderate antagonist activities at the 5-HT<sub>2B</sub>, 5-HT<sub>2C</sub>, and dopamine D<sub>4</sub> receptors.

#### Alcohol Interaction

See Clinical Trials Experience (6.1)

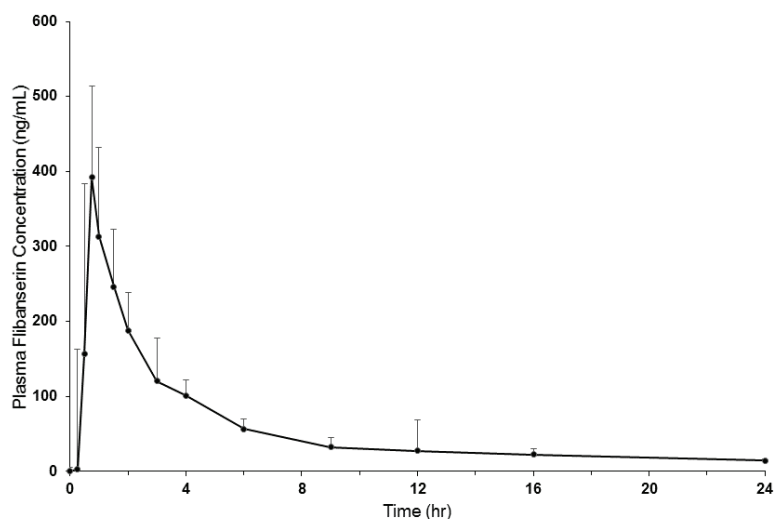
#### Cardiac Electrophysiology

The effect of ADDYI on the QT interval was evaluated in a randomized, double-blind, placebo- and active- (single dose moxifloxacin) controlled crossover study in 56 healthy men and women. Subjects in the ADDYI groups received either 50 mg twice a day (equivalent to the daily recommended dosage) or 100 mg three times a day (3 times the daily recommended dosage) administered for 5 days. The time frame for electrocardiogram (ECG) measurements covered maximum plasma concentrations of flibanserin and relevant metabolites. In this study, ADDYI did not prolong the QT interval to any clinically relevant extent. The mean increase in heart rate associated with the 100 mg three times a day dose of ADDYI compared to placebo ranged from 1.7 to 3.2 beats per minute.

### 12.3 Pharmacokinetics

Flibanserin showed dose-proportional pharmacokinetics for C<sub>max</sub> after single oral doses of 100 mg to 250 mg (the recommended and 2.5 times the recommended dosage, respectively) in healthy female subjects. Steady state was achieved after 3 days of dosing. The extent of exposure (AUC<sub>0-∞</sub>) with once-daily dosing of 100 mg of flibanserin was increased 1.4-fold as compared to a single dose.

**Figure 1 Mean + SD Plasma Flibanserin Concentration-Time Profiles in Healthy Female Subjects Following a Single Oral Dose of 100 mg of Flibanserin (Linear Scale)**



### Absorption

Following oral administration of a single 100 mg dose of flibanserin in healthy premenopausal women (N=8), mean (SD) C<sub>max</sub> was 419 (206) ng/mL and mean (SD) AUC<sub>0-inf</sub> was 1543 (511) ng\*hr/mL. Median (range) time to reach C<sub>max</sub> was 0.75 (0.75 to 4.0) hours. Absolute bioavailability of flibanserin following oral dosing is 33%.

### Effect of Food

Food increased the extent of absorption and slowed the rate of absorption of a 50 mg dose of flibanserin (one half the recommended dosage). Low-, moderate-, and high-fat meals increased flibanserin AUC<sub>0-inf</sub> by 1.18-, 1.43-, and 1.56-fold; increased C<sub>max</sub> by 1.02-, 1.13-, and 1.15-fold; and prolonged median T<sub>max</sub> to 1.5, 0.9, 1.8 hours from 0.8 hours under fasted conditions, respectively.

### Distribution

Approximately 98% of flibanserin is bound to human serum proteins, mainly to albumin.

### Elimination

#### *Metabolism*

Flibanserin is primarily metabolized by CYP3A4 and, to a lesser extent, by CYP2C19. Based on in vitro and/or in vivo data, CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP2D6 contribute minimally to the metabolism of flibanserin. After a single oral solution dose of 50 mg <sup>14</sup>C-radiolabeled flibanserin, 44% of the total <sup>14</sup>C-flibanserin related radioactivity was recovered in urine, and 51% was recovered in feces. Flibanserin is extensively metabolized to at least 35 metabolites, most of them occurring in low concentrations in plasma. Two metabolites could be characterized that showed plasma concentrations similar to that achieved with flibanserin: 6,21-dihydroxy-flibanserin-6,21-disulfate and 6-hydroxy-flibanserin-6-sulfate. These two metabolites are inactive.

#### *Excretion*

Flibanserin has a mean terminal half-life of approximately 11 hours.

### Specific Populations

#### *Hepatic Impairment*

Single 50 mg oral doses of flibanserin were administered to 10 patients with mild hepatic impairment (Child-Pugh score of 6 points), 4 patients with moderate hepatic impairment (Child-Pugh score of 8-9 points), and 14 healthy subjects matched by age, weight, and gender. Systemic flibanserin exposure ( $AUC_{0-inf}$ ) increased 4.5-fold in patients with mild hepatic impairment, compared to subjects with normal hepatic function, and  $t_{1/2}$  was longer (26 hours compared to 10 hours in matching healthy controls). Due to the small number of patients ( $n=4$ ) with moderate hepatic impairment enrolled in the study, it is not possible to make conclusions about the quantitative effect of moderate hepatic impairment on flibanserin exposure. ADDYI is contraindicated in patients with hepatic impairment [see *Warnings and Precautions (5.5)*].

#### *Renal Impairment*

Single 50 mg oral doses of flibanserin were administered to 7 patients with mild to moderate renal impairment (GFR 30 to 80 mL/min), 9 patients with severe renal impairment (GFR <30 mL/min, not on dialysis), and 16 healthy subjects matched by age, weight, and gender. Flibanserin exposure ( $AUC_{0-inf}$ ) increased 1.1-fold in patients with mild to moderate renal impairment and 1.2-fold in patients with severe renal impairment, compared to the healthy control subjects.

#### *Race/Ethnicity*

A cross-study comparison between healthy Japanese women and Caucasian women with HSDD showed that flibanserin exposure was approximately 1.4-fold higher in Japanese women. When the mean flibanserin exposure in Japanese women was adjusted for weight, the  $AUC_{tau,ss}$  in Japanese women was 2246 ng\*hr/mL, which is comparable to 2080 ng\*hr/mL in Caucasian women. The similarity in weight-adjusted  $AUC_{tau,ss}$  suggests that weight, not race, is the factor contributing to the observed difference in flibanserin exposure between Japanese and Caucasian women.

#### *Age*

No formal study has been conducted to study the effect of age on flibanserin exposures.

### Drug Interaction Studies

#### *Drugs that Increase Flibanserin Exposure*

The effects of other drugs on the pharmacokinetics of flibanserin are presented in Table 4 as change relative to flibanserin administered alone (test/reference).

#### *Moderate CYP3A4/Moderate CYP2C9/Strong CYP2C19 Inhibitor (Fluconazole)*

In a study of 15 healthy female subjects, a fluconazole 400 mg loading dose followed by 200 mg administered once daily for 5 days increased flibanserin 100 mg single dose exposure ( $AUC_{0-inf}$ ) 7-fold and  $C_{max}$  2.2-fold compared to flibanserin 100 mg alone. Three of 15 subjects (20%) experienced hypotension or syncope from concomitant use of fluconazole and flibanserin; therefore, the study was stopped early [see *Warning and Precautions (5.2)*, *Adverse Reactions (6.1)* and *Drug Interactions (7)*].

#### *Strong CYP3A4 Inhibitor (Ketoconazole)*

In a study of 24 healthy female subjects, ketoconazole 400 mg administered once daily for 5 days following a light breakfast increased flibanserin 50 mg single-dose exposure ( $AUC_{0-inf}$ ) 4.5-fold and  $C_{max}$  1.8-fold compared to flibanserin 50 mg alone [see *Warning and Precautions (5.2)*, *Adverse Reactions (6.1)* and *Drug Interactions (7)*].

#### *Strong CYP3A4 Inhibitor (Itraconazole)*

In a study of 12 healthy male and female subjects, itraconazole 200 mg administered once daily for 4 days following a loading dose of 400 mg increased flibanserin 50 mg single dose exposure ( $AUC_{0-inf}$ )

2.6-fold and C<sub>max</sub> 1.7-fold when flibanserin was given 2 hours after itraconazole on Day 5, compared to exposures with flibanserin 50 mg alone. The 200 mg itraconazole dose does not maximally inhibit the CYP3A4 enzyme [see *Drug Interactions (7)*].

*Moderate CYP3A4 Inhibitor (Grapefruit Juice)*

In a study of 26 healthy female subjects, grapefruit juice (240 mL) increased flibanserin 100 mg single dose exposure (AUC<sub>0-inf</sub>) by 1.4-fold and C<sub>max</sub> 1.1-fold compared to flibanserin 100 mg alone [see *Warning and Precautions (5.2)*, *Adverse Reactions (6.1)* and *Drug Interactions (7)*].

*Weak CYP3A4 Inhibitor (Oral Contraceptives)*

In a meta-analysis of 17 oral contraceptive users and 91 non-users in Phase 1 studies, the oral contraceptive users had a 1.4-fold higher flibanserin AUC and 1.3-fold higher C<sub>max</sub> compared to the non-users [see *Adverse Reactions (6.1)* and *Drug Interactions (7)*].

*Strong CYP2D6 Inhibitor (Paroxetine)*

Paroxetine is a strong CYP2D6 inhibitor. In a study of 19 healthy male and female subjects, flibanserin exposure decreased by approximately 4% when flibanserin 50 mg twice daily was given with paroxetine compared to flibanserin alone. Paroxetine was dosed at 20 mg once daily for 3 days followed by 40 mg once daily for 7 days.

**Drugs that Decrease Flibanserin Exposure**

*Strong CYP3A4 Inducer (Rifampin)*

In a study of 24 healthy female subjects, rifampin 600 mg given once daily for 7 days prior to administration of 100 mg flibanserin significantly decreased flibanserin exposure by 95% [see *Drug Interactions (7)*].

*Moderate CYP3A4 Inducer (Etravirine)*

Steady state etravirine, a moderate CYP3A4 inducer, decreased flibanserin exposures by approximately 21% [see *Drug Interactions (7)*].

**Table 4 Drugs That Increase Flibanserin Exposure**

Coadministered Drug(s) and Dose(s)	Dose of ADDYI	n	Geometric Mean Ratio (90% Confidence Interval) of Pharmacokinetic Parameters of Flibanserin with/without Coadministered Drug No Effect =1.00	
			C <sub>max</sub>	AUC <sub>0-inf</sub>
Fluconazole 200 mg	100 mg	15	2.2 (1.8 – 2.8)	7.0 (6.0 – 8.2)
Ketoconazole 400 mg	50 mg	24	1.8 (1.7 – 2.1)	4.5 (4.0 – 5.1)
Itraconazole 200 mg*	50 mg	12	1.7 (1.4 – 2.0)	2.6 (2.1 – 3.0)
Oral Contraceptives	50 mg	39	1.3 (1.1 – 1.6)	1.4 (1.2 – 1.7)
Paroxetine 40 mg	50 mg twice daily	19	1.0 (0.9 – 1.2)	1.0 (0.9 – 1.0)

\* itraconazole dose was not optimal for maximal inhibition of CYP3A4 enzyme.

### Effects of Flibanserin on Other Drugs

The effects of flibanserin on the pharmacokinetics of other drugs are presented in Table 5 as change relative to the other drug administered alone (test/reference).

#### *Digoxin and P-glycoprotein Substrates*

A single center, open-label, randomized, two-way crossover study in 24 healthy men and women evaluated the effect of flibanserin on the pharmacokinetics of digoxin. Flibanserin 100 mg was administered once daily over 5 days followed by a single dose of 0.5 mg digoxin, a P-gp substrate. Flibanserin increased digoxin AUC<sub>0-inf</sub> by 2.0-fold and C<sub>max</sub> by 1.5-fold, compared to digoxin alone [see *Drug Interactions (7)*].

#### *Drugs Metabolized by CYP3A4 (Simvastatin)*

An open-label, randomized, crossover study in 12 healthy men and women evaluated the effect of flibanserin 50 mg twice daily for 4 days on the pharmacokinetics of simvastatin 40 mg once daily. Flibanserin increased the AUC<sub>0-inf</sub> of simvastatin, a substrate of CYP3A4, 1.3-fold and C<sub>max</sub> by 1.2-fold. Flibanserin co-administered with simvastatin increased simvastatin acid AUC<sub>0-inf</sub> by 1.5-fold and C<sub>max</sub> by 1.4-fold.

#### *Oral Contraceptives*

A study in 24 healthy women evaluated the effect of 100 mg flibanserin once daily for 2 weeks on the pharmacokinetics of a single-dose of ethinyl estradiol (EE) 30 mcg/levonorgestrel (LNG) 150 mcg. Flibanserin increased the EE AUC<sub>0-inf</sub> by 1.09-fold and the EE C<sub>max</sub> by 1.1-fold. Flibanserin decreased the LNG AUC<sub>0-inf</sub> by 1.06-fold and did not change the LNG C<sub>max</sub>. [see *Adverse Events (6.1)*, *Drug Interactions (7)*].

#### *Drugs Metabolized by CYP2B6 (Bupropion)*

An open-label, randomized, two-period crossover study in 28 healthy women evaluated the effect of flibanserin on the pharmacokinetics of bupropion. Flibanserin 50 mg twice daily was administered for 2 days followed by 100 mg once daily for 13 days. Bupropion 150 mg twice daily was given for 8 days beginning on Day 6 of flibanserin treatment. Flibanserin did not change bupropion AUC<sub>t,ss</sub> (1.0-fold change) and C<sub>max</sub> (1.0-fold change) but hydroxybupropion AUC<sub>t,ss</sub> decreased by 9% and C<sub>max</sub> by 11%.

**Table 5 Effects of Flibanserin on Exposure of Other Drugs**

Coadministered Drug(s) and Dose(s)	Dose of ADDYI	n	Geometric Mean Ratio (90% Confidence Interval) of Pharmacokinetic Parameters of Coadministered Drug with/without Flibanserin No Effect =1.00	
			C <sub>max</sub>	AUC <sub>0-inf</sub>
Simvastatin 40 mg	50 mg twice daily	12	1.7 (1.4 – 2.0)	2.6 (2.1 – 3.1)
Digoxin 0.5 mg	100 mg	24	1.5 (1.3 – 1.6)	2.0 (1.5 – 2.5)
Ethinyl estradiol 30 mcg/ Levonorgestrel 150 mcg	100 mg	24	1.1 (1.0 – 1.1) 1.0 (0.9 – 1.0)	1.1 (1.0 – 1.2) 1.0 (0.9 – 1.1)
Bupropion 150 mg	100 mg	28	1.0 (0.9 – 1.1)	1.0 (1.0 – 1.1)

### **12.5 Pharmacogenomics**

Patients who are poor metabolizers of CYP2D6, CYP2C9 or CYP2C19 are deficient in CYP2D6, CYP2C9 or CYP2C19 enzyme activity, respectively. Extensive metabolizers have normal functioning CYP enzymes.

### CYP2C19 Poor Metabolizers

A study comparing flibanserin exposure in CYP2C19 poor metabolizers to CYP2C19 extensive metabolizers was conducted in lieu of a drug interaction study with ADDYI and a strong CYP2C19 inhibitor. In 9 women who were poor metabolizers of CYP2C19, C<sub>max</sub> and AUC<sub>0-inf</sub> of flibanserin 100 mg once daily increased 1.5-fold (1.1-2.1) and 1.3-fold (0.9-2.1), compared to exposures among 8 extensive metabolizers of CYP2C19. Flibanserin half-life was increased from 11.1 hours in the extensive metabolizers of CYP2C19 to 13.5 hours in the poor metabolizers of CYP2C19 [see *Adverse Reactions (6.1) and Use in Specific Populations (8.7)*].

The frequencies of poor metabolizers of CYP2C19 are approximately 2–5% among Caucasians and Africans and approximately 2–15% among Asians.

### CYP2D6 Poor Metabolizers

A study comparing flibanserin exposure in CYP2D6 poor metabolizers to CYP2D6 extensive metabolizers was conducted in addition to a drug interaction study with paroxetine, a strong CYP2D6 inhibitor. In 12 poor metabolizers of CYP2D6, steady state C<sub>max</sub> and AUC of flibanserin 50 mg twice daily was decreased by 4% and increased by 18%, respectively, compared to exposures among 19 extensive metabolizers, intermediate metabolizers and ultra rapid metabolizers of CYP2D6.

### CYP2C9 Poor Metabolizers

A study comparing flibanserin exposure in CYP2C9 poor metabolizers to CYP2C9 extensive metabolizers was conducted in lieu of a drug interaction study with ADDYI and a strong CYP2C9 inhibitor. In 8 women who were poor metabolizers of CYP2C9, C<sub>max</sub> and AUC<sub>0-inf</sub> of flibanserin 100 mg once daily decreased 23% and 18%, compared to exposures among 8 extensive metabolizers of CYP2C9.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### Carcinogenesis

A two-year carcinogenicity study was conducted in CD-1 mice with dietary administration of 0, 10, 80, 200 and 1000/1200 mg/kg/day of flibanserin. Statistically significant increases in combined mammary tumors (adenocanthomas and adenocarcinomas) were observed in female mice administered flibanserin at doses of 200 and 1200 mg/kg/day (exposures, based on AUC, were 3 and 10 times the clinical exposures at the recommended clinical dose). No increases in mammary tumors were observed in male mice. Statistically significant increases were also seen for combined hepatocellular adenomas/carcinomas in female mice treated with flibanserin 1200 mg/kg/day and for hepatocellular carcinomas in male mice treated with flibanserin 1000 mg/kg/day (exposures, based on AUC, were 8 times the clinical exposure at the recommended clinical dose).

There were no significant increases in tumor incidence in a two year carcinogenicity study conducted in Wistar rats with dietary administration of 0, 10, 30 and 100 mg/kg/day flibanserin (up to 5-8 times human exposure at the recommended clinical dose).

#### Mutagenesis

Flibanserin was negative for mutagenesis *in vitro* in *Salmonella typhimurium* (Ames test) and in Chinese hamster ovary cells. Flibanserin was positive for chromosomal aberrations in cultured human lymphocytes but negative for chromosomal aberrations *in vivo* in the rat bone marrow micronucleus assay and negative for DNA damage in rat liver in the Comet assay.

## Impairment of Fertility

Female and male rats were administered flibanserin 14 and 28 days before mating, respectively, to assess for potential effects on fertility and early reproductive performance. Flibanserin slightly increased the duration of the estrus cycle but had no adverse effects on fertility or early embryonic development at doses up to 200 mg/kg/day (~20 times human exposure at the recommended clinical dose).

## **14 CLINICAL STUDIES**

### **14.1 Trials in Premenopausal HSDD Patients**

The efficacy of ADDYI for the treatment of HSDD in premenopausal women was established in three 24-week, randomized, double-blind, placebo-controlled trials (Studies 1, 2, and 3). The three trials included premenopausal women with acquired, generalized HSDD of at least 6 months duration. In the clinical trials, acquired HSDD was defined as HSDD that developed in patients who previously had no problems with sexual desire. Generalized HSDD was defined as HSDD that was not limited to certain types of stimulation, situations or partners. The patients were treated with ADDYI 100 mg once daily at bedtime (n = 1187) or placebo (n = 1188). Most of the trial participants were Caucasian (88.6%); the remainder were Black (9.6%) and Asian (1.5%). The mean age of study participants was 36 years old (range 19 to 55 years old); the mean duration in the monogamous, heterosexual relationship was 11 years, and the mean duration of HSDD was approximately 5 years. The completion rate across these three trials was 69% and 78% for the ADDYI and placebo groups, respectively.

These trials each had two co-primary efficacy endpoints, one for satisfying sexual events (SSEs) and the other for sexual desire:

- The change from baseline to Week 24 in the number of monthly SSEs (i.e., sexual intercourse, oral sex, masturbation, or genital stimulation by the partner). The SSEs were based on patient responses to the following questions: “Did you have a sexual event?” and “Was the sex satisfying for you?”
- Studies 1 and 2 had a different sexual desire endpoint than Study 3:
  - In Studies 1 and 2, the sexual desire co-primary endpoint was the change from baseline to Week 24 in the calculated monthly sexual desire score and was based on patient responses to the question: “Indicate your most intense level of sexual desire.” Every day, patients rated their sexual desire level from 0 (no desire) to 3 (strong desire) and recorded their response in an electronic Diary (eDiary). These responses were summed over a 28-day period to yield the calculated monthly sexual desire score, which ranged from 0 to 84.
  - In Study 3, the desire domain of the Female Sexual Function Index (FSFI Desire) was the sexual desire co-primary endpoint. The desire domain of the FSFI has two questions. The first question asks patients “Over the past 4 weeks, how often did you feel sexual desire or interest?”, with responses ranging from 1 (almost never or never) to 5 (almost always or always). The second question asks patients “Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?”, with responses ranging from 1 (very low or none at all) to 5 (very high). The FSFI Desire score was calculated by adding the patient’s responses to these two questions then multiplying that sum by 0.6. The FSFI Desire domain score ranged from 1.2 to 6.

The desire domain of the Female Sexual Function Index (FSFI Desire) was also used as a secondary endpoint in Studies 1 and 2.

The three trials had a secondary endpoint that measured both (a component of distress) related to sexual desire using Question 13 of the Female Sexual Distress Scale-Revised (FSDS-R). This question asks “How often did you feel: Bothered by low sexual desire?” Patients assessed their sexual distress over a 7-day recall period and responded on a scale of 0 (never) to 4 (always).

The efficacy results from Studies 1, 2, and 3 are summarized in Table 6. In all three trials, ADDYI resulted in statistically significant improvement compared to placebo in the change from baseline in monthly SSEs at Week 24. In Study 1 and 2, there were no statistically significant differences between ADDYI and placebo for the eDiary sexual desire endpoint (change in baseline to Week 24). In contrast, in Study 3 there was statistically significant improvement in the change from baseline to Week 24 in sexual desire (using the FSFI Desire Domain) with ADDYI compared to placebo. The FSFI Desire Domain findings were consistent across all three trials as were the findings for the secondary endpoint that assessed distress using Question 13 of the FSDDS-R.

Table 6 Efficacy Results in Premenopausal HSDD Patients in Studies 1, 2, and 3

	Study 1		Study 2 <sup>1</sup>		Study 3	
	ADDYI n=280	Placebo n=290	ADDYI n=365	Placebo n=372	ADDYI n=532	Placebo n=536
<b>Full Analysis Set</b>						
<b>Number of satisfying sexual events (per 28 days)</b>						
Baseline (Mean)	3.0	2.7	2.6	2.7	2.5	2.7
Change from baseline (Mean)	1.6	0.8	1.8	1.1	2.5	1.5
Treatment diff. (95% CI)	0.9 (0.3, 1.4)		0.6 (-0.03, 1.2)		1.0 (0.4, 1.5)	
Change from baseline (Median)	1.0	0.0	1.0	0.5	1.0	0.5
Median treatment difference	1.0				0.5	
p-value vs placebo	<i>p</i> <0.01		<i>p</i> <0.01		<i>p</i> <0.0001	
<b>e-Diary Desire</b>						
Baseline (Mean)	12.9	11.8	12.1	10.2	<i>Not Used</i>	<i>Not Used</i>
Change from baseline at Week 24 (Mean)	9.1	6.9	8.3	6.7		
Treatment diff. (95% CI)	2.3 (-0.1, 4.7)		1.7 (-0.5, 4.0)			
p-value vs placebo	NS		NS			
<b>FSFI Desire</b>						
Baseline (Mean)	1.9	1.9	1.8	1.8	1.9	1.9
Change from baseline at Week 24 (Mean)	0.9	0.5	0.9	0.5	1.0	0.7
Treatment diff. (95% CI)	0.4 (0.2, 0.5)		0.3 (0.2, 0.5)		0.3 (0.2, 0.4)	
p-value vs placebo	<i>N/A</i> <sup>2</sup>		<i>N/A</i> <sup>2</sup>		<i>p</i> <0.0001	
<b>FSDS-R Question 13<sup>3</sup></b>						
Baseline (Mean)	3.2	3.2	3.2	3.2	3.4	3.4
Change from baseline at Week 24 (Mean)	-0.8	-0.5	-0.8	-0.5	-1.0	-0.7
Treatment diff. (95% CI)	-0.4 (-0.5, -0.2)		-0.3 (-0.4, -0.1)		-0.3 (-0.4, -0.1)	
p-value vs placebo	<i>N/A</i> <sup>2</sup>		<i>N/A</i> <sup>2</sup>		<i>p</i> =0.0001	

CI = Confidence Interval; NS= not statistically significant; *N/A*=not applicable

Shaded cells show the results for the co-primary efficacy endpoints for each trial.

e-Diary desire was evaluated as a co-primary endpoint in Studies 1 and 2; FSFI desire was evaluated as a co-primary endpoint in Study 3.

The efficacy results are based on the full analysis set comprised of all randomized patients who took at least one dose of study medication and had at least one on-treatment efficacy assessment. Missing values were imputed using last-observation-carried-forward.

The unadjusted means are presented for the baseline values.

For satisfying sexual events, p-values are based on the Wilcoxon rank sum test stratified by pooled center. Median change from baseline is shown because the data are not normally distributed.

For FSFI-desire, e-Diary desire, and FSDS-R Question 13, reported p-values are based on an ANCOVA model using baseline as a covariate with treatment and pooled center as main effect terms. For the change from baseline, the adjusted least squares mean (standard error) are presented.

<sup>1</sup>Excludes subjects from two study sites that had data integrity issues

<sup>2</sup>p-value not reported for secondary endpoints because the trial failed on the eDiary Desire co-primary efficacy endpoint

<sup>3</sup>A decrease in score represents improvement

Exploratory analyses were conducted to assess whether the treatment effects varied depending on baseline number of SSEs, FSFI desire score, and FSDS-R Question 13 distress score. No notable differences were identified among these subgroups.

Supportive analyses were conducted to help interpret the clinical meaningfulness of the observed treatment effects. These analyses defined responders for each efficacy endpoint by anchoring change from baseline to

end of treatment with the Patient's Global Impression of Improvement (PGI-I). The first analysis considered responders to be those who reported being “much improved” or “very much improved.” In this analysis, the absolute difference in the percentage of responders with ADDYI and the percentage of responders with placebo across the three trials was 8-9% for SSEs (29-39% for ADDYI; 21-31% for placebo), 10-13% for FSFI desire domain (43-48% for ADDYI; 31-38% for placebo), and 7-13% for FSDS-R Question 13 (21-34% for ADDYI; 14-25% for placebo). The second analysis considered responders to be those who reported being at least minimally improved. The absolute difference in the percentage of responders with ADDYI and the percentage of responders with placebo across the three trials was 10-15% for SSEs (44-48% for ADDYI; 33-36% for placebo), 12-13% for FSFI desire domain (43-51% for ADDYI; 31-39% for placebo), and 9-12% for FSDS-R Question 13 (50-60% for ADDYI; 41-48% for placebo).

## 14.2 Effects on Driving

In a randomized, placebo-controlled, 4-way crossover study in 83 healthy premenopausal female subjects, no adverse effect was detected on measures of driving performance itself or psychomotor performance thought to be important for driving performance when assessed 9 hours following single and multiple doses of ADDYI 100 mg once daily at bedtime or single doses of ADDYI 200 mg at bedtime (two times the maximum recommended dosage) [see *Warnings and Precautions* (5.3)].

## 16 HOW SUPPLIED/STORAGE AND HANDLING

ADDYI is available as a 100 mg oval, pink, film-coated tablet debossed on one side with “f100” and blank on the other side. Available in bottles of 30 tablets. (NDC 58604-214-30)

### Storage

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP controlled room temperature].

## 17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Medication Guide).

### Hypotension and Syncope

Inform patients that ADDYI can cause severe hypotension and syncope, particularly when taken close in time with alcoholic drinks or with moderate or strong CYP3A4 inhibitors.

- Counsel patients to wait at least two hours after consuming one or two standard alcoholic drinks before taking ADDYI at bedtime or to skip their ADDYI dose if they have consumed 3 or more standard alcoholic drinks that evening.

After taking ADDYI at bedtime, advise patients to not use alcohol until the following day.

- Advise patients that moderate or strong CYP3A4 inhibitors are contraindicated with ADDYI and ask patients to report the use of a new prescription or non-prescription medication or other products that contain CYP3A4 inhibitors (e.g., grapefruit juice, St. John's Wort).
- Advise patients who experience pre-syncope or lightheadedness to lie down and to call for help if symptoms persist [see *Contraindications* (4), *Warnings and Precautions* (5.1, 5.2)].

### CNS Depression

Advise patients that ADDYI can cause CNS depression, such as somnolence and sedation, and that the risk is increased with other CNS depressants and with certain drug interactions (e.g., hypnotics, benzodiazepines, opioids). The risk is also increased if ADDYI is taken during waking hours. Advise patients to avoid engaging in activities requiring full alertness (e.g., operating machinery or driving) until at least 6 hours after the ADDYI dose and until they know how ADDYI affects them [see *Warnings and Precautions* (5.3)].

### Nursing Mothers

Advise patients not to breastfeed if they are taking ADDYI [*see Use in Specific Populations (8.2)*].

Bedtime Dosing

Advise patients to take only one tablet at bedtime and not to take ADDYI at any other time of day [*see Dosage and Administration (2)*].

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addyi<sup>®</sup>  
(flibanserin)  
100mg tablets

## MEDICATION GUIDE

### ADDYI® (add-ee) (flibanserin) Tablets

Read this Medication Guide before you start taking ADDYI® and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor.

#### What is the most important information I should know about ADDYI?

Your risk of severe low blood pressure and fainting (loss of consciousness) is increased if you take ADDYI and:

- **drink alcohol close to the time you take your ADDYI dose.**
  - Wait at least 2 hours after drinking 1 or 2 standard alcoholic drinks before taking ADDYI at bedtime.  
**Examples of 1 standard alcoholic drink include:**
    - one 12-ounce regular beer
    - 5 ounces of wine
    - 1.5 ounces of distilled spirits or shot
  - If you drink 3 or more standard alcoholic drinks in the evening, skip your ADDYI dose at bedtime.
  - After you have taken your ADDYI at bedtime **do not** drink alcohol until the following day.
- **take certain prescription medicines, over-the-counter medicines, or herbal supplements. Do not take or start taking any prescription medicines, over-the-counter medicines, or herbal supplements** while taking ADDYI until you have talked with your doctor. Your doctor will tell you if it is safe to take other medicines or herbal supplements while you are taking ADDYI.
- **have liver problems.** Do not take ADDYI if you have liver problems.

**If you take ADDYI and you feel lightheaded or dizzy**, lie down right away. Get emergency medical help or ask someone to get emergency medical help for you if the symptoms do not go away or if you feel like you could faint (lose consciousness). If you faint (lose consciousness), tell your doctor as soon as you can.

#### What is ADDYI?

ADDYI is a prescription medicine used to treat hypoactive (low) sexual desire disorder (HSDD) in women who have not gone through menopause, who have not had problems with low sexual desire in the past, and who have low sexual desire no matter the type of sexual activity, the situation, or the sexual partner. Women with HSDD have low sexual desire that is troubling to them. Their low sexual desire is **not** due to:

- a medical or mental health problem
- problems in the relationship
- medicine or other drug use

ADDYI is not for use for the treatment of HSDD in women who have gone through menopause or in men.

ADDYI is not for use to improve sexual performance.

ADDYI is not for use in children.

#### Who should not take ADDYI?

##### Do not take ADDYI if you:

- take certain other medicines. Taking ADDYI with certain other medicines can increase the amount of ADDYI in your blood and cause severe low blood pressure, fainting (loss of consciousness), and sleepiness.  
Do not take ADDYI if you are taking any of the following medicines:
    - certain medicines used to treat HIV-1 infection, such as:
      - amprenavir
      - ritonavir (NORVIR)
      - indinavir (CRIXIVAN®)
      - atazanavir (REYATAZ®)
      - saquinavir (INVIRASE®)
      - fosamprenavir (LEXIVA)
      - nelfinavir (VIRACEPT®)
    - certain medicines that you take by mouth used to treat fungal infections, such as:
      - fluconazole (DIFLUCAN®)
      - itraconazole (ONMEL, SPORANOX®)
      - ketoconazole
      - posaconazole (NOXAFIL®)
    - certain antibiotics, including:
      - ciprofloxacin (CIPRO, CIPRO XR)
      - telithromycin (KETEK®)
      - erythromycin (ERY-TAB®, ERYC®, PCE®)
      - clarithromycin (BIAXIN®)
    - certain medicines used to treat Hepatitis C infection, such as:
      - boceprevir (VICTRELIS®)
      - telaprevir
    - certain medicines used to treat high blood pressure, chest pain (angina), or other heart problems, such as:
      - diltiazem (CARDIZEM®, CARDIZEM CD®, CARDIZEM LA®, CARTIA XT, DILT CD, DILTZAC, TAZTIA XT, Tiazac®)
      - verapamil (CALAN®, CALAN® SR, COVERA-HS®, Verelan®, Verelan PM)
      - conivaptan (Vaprisol®)
    - nefazodone: a medicine used to treat depressionAsk your doctor or pharmacist if you are not sure if you take any of the medicines listed above. These are examples of the medicines that you should not take if you are taking ADDYI. Tell your doctor about all of the medicines you take before you start taking ADDYI.
- have liver problems

**What should I tell my doctor before taking ADDYI?**

**Before you take ADDYI, tell your doctor about all of your medical conditions, including if you:**

- drink alcohol, use drugs or have a history of alcohol or drug abuse
- have ever had depression or other mental health problems
- have low blood pressure or a medical condition that can cause low blood pressure
- are pregnant or plan to become pregnant. It is not known if ADDYI will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ADDYI passes into your breast milk. You and your doctor should decide if you will take ADDYI or breastfeed. You should not do both.

**Tell your doctor about all of the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ADDYI can affect the way other medicines work, and other medicines can affect the way ADDYI works, and can cause serious side effects.

Know the medicines and herbal supplements you take. Keep a list of them to show your doctor or pharmacist each time you get a new medicine.

**How should I take ADDYI?**

- Take ADDYI exactly as your doctor tells you to take it.
- Take 1 ADDYI tablet one time a day at bedtime.
- Take ADDYI only at bedtime. Taking ADDYI at a time other than bedtime can increase your risk of low blood pressure, fainting (loss of consciousness), accidental injury, and sleepiness.
- **If you drink alcohol, see “What is the most important information I should know about ADDYI?”**
- **If you skip a dose of ADDYI, take your next dose at bedtime the next day.**
- If you miss a dose of ADDYI, skip your missed dose. Take your next dose at bedtime the next day. **Do not** take ADDYI the next morning or double your next dose. If you take too much ADDYI, call your doctor.
- Tell your doctor if your symptoms of HSDD have not improved after you have taken ADDYI for 8 weeks.

**What should I avoid while taking ADDYI?**

- **Do not drink alcohol close to the time you take your ADDYI dose because this increases your risk of severe low blood pressure and fainting (loss of consciousness).**
- Do not drive, operate machinery, or do things that require clear thinking until at least 6 hours after you take ADDYI and until you know how ADDYI affects you.
- Do not drink grapefruit juice if you take ADDYI. Drinking grapefruit juice during your treatment with ADDYI increases your risk of severe low blood pressure and fainting (loss of consciousness).
- You should not take the herbal supplements St. John’s Wort, ginkgo, or resveratrol or certain over-the-counter medicines such as cimetidine until you talk to your doctor. Taking ADDYI with these herbal supplements and over-the-counter medicine may increase your risk of low blood pressure, fainting (loss of consciousness), and sleepiness.

**What are the possible side effects of ADDYI?**

**ADDYI can cause serious side effects, including:**

- See “**What is the most important information I should know about ADDYI?**”
- **Sleepiness** is a common side effect of ADDYI and can be serious. Taking ADDYI can increase your risk of sleepiness if taken during waking hours, if you drink alcohol, or take certain medicines or herbal supplements.
- **Low blood pressure and fainting (loss of consciousness)** can happen when you take ADDYI even if you do not drink alcohol or take other medicines or herbal supplements. Your risk of low blood pressure and fainting (loss of consciousness) is increased if ADDYI is taken during waking hours, if you drink alcohol within 2 hours of taking ADDYI, or if you take certain medicines or herbal supplements.

**The most common side effects of ADDYI include:**

- dizziness
- nausea
- tiredness
- difficulty falling asleep or staying asleep
- dry mouth

These are not all of the possible side effects of ADDYI.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store ADDYI?**

- Store ADDYI at room temperature between 68°F to 77°F (20°C to 25°C).

**Keep ADDYI and all medicines out of the reach of children.**

**General information about the safe and effective use of ADDYI**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ADDYI for a condition for which it was not prescribed. Do not give ADDYI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your doctor or pharmacist for information about ADDYI that is written for health professionals.

**What are the ingredients in ADDYI?**

**Active ingredient:** flibanserin

**Inactive ingredients:** lactose monohydrate, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate, talc, macrogol, and the coloring agents, titanium dioxide and iron oxide.

Sprout Pharmaceuticals, Inc. Raleigh, NC 27609 USA  
Copyright © 2019 Sprout Pharmaceuticals, Inc.  
For more information go to [www.ADDY1.com](http://www.ADDY1.com) or call 1-844-PINK-PILL (1-844-746-5745).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: 10/2019

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**22526Orig1s009**

**REMS**

**Initial REMS Approval: 08/2015**

**Most Recent Modification: 10/2019**

**NDA 22526 Addyi® (flibanserin)**

Serotonin 1A receptor agonist and a Serotonin 2A receptor antagonist

Sprout Pharmaceuticals, Inc.  
4350 Lassiter at North Hills Avenue, #260  
Raleigh, NC 27609  
Phone: 844-746-5745

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

**I. GOAL:**

To inform patients about the increased risk of hypotension and syncope associated with Addyi due to an interaction with alcohol.

**II. ELEMENTS:**

**A. Medication Guide**

A Medication Guide will be dispensed with each Addyi prescription in accordance with 21 C.F.R. 208.24.

The Medication Guide is part of the REMS.

**B. Timetable for Submission of Assessments**

Sprout Pharmaceuticals must submit REMS assessments 6 months from 10/9/2019, 18 months, 3 years and 7 years thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Sprout must submit each assessment so that it will be received by the FDA on or before the due date.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22526Orig1s009**

**CLINICAL REVIEW(S)**

**Clinical Review**

NDA#	DARRTS SDN	EDR#	Document Type	Letter Date	Received Date
22526	417	0267	S-008 Labeling Supplement (b) (4)	8-29-19	8-29-19
	418	0268	S-009 Proposed REMS Modification	8-29-19	8-29-19
	425	0275	Safety Labeling Change Request for Waiver of Labeling Requirement	9-24-19	9-24-19

**Date:** October 9, 2019

**Re:** Addyi® (Flibaserin)

**Applicant:** Sprout, Inc. (Sprout)

**Introduction:** This review is a DBRUP clinical review to document revisions to labeling for Addyi. Addyi is a 5-HT<sub>1A</sub> (serotonin) receptor agonist and 5-HT<sub>2A</sub> receptor antagonist. Addyi is available as 100 mg oral tablets to be taken nightly prior to bedtime. The subject of this review is a labeling supplement (S-008), which provides for revisions in the Prescribing Information (PI) and Medication Guide (MG) in accordance with the Appeal Denied Letter issued by the Office of New Drugs (OND) on August 18, 2019.

Addyi was approved in 2015 to treat general, acquired hypoactive sexual desire disorder (HSDD) in premenopausal women. Major safety concerns with Addyi include hypotension and syncope with Addyi use alone and when Addyi is taken concomitantly with alcohol or moderate/strong CYP3A4 inhibitors, or in patients with hepatic impairment. Approved Addyi labeling includes a boxed warning (BW) and contraindication to address these safety concerns. A risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) was also implemented to mitigate the risks of hypotension and syncope arising from alcohol interaction. As a condition of the initial approval, the Division requested alcohol interaction studies to be conducted postapproval to assess the risks of hypotension and syncope when alcohol and Addyi are taken concomitantly. The premarket alcohol interaction data were derived predominantly from men.

**Background:** After reviewing data from the first alcohol interaction study conducted solely in women (SPR-15-001, as a postmarketing requirement, PMR5), the Division concluded that the

study confirmed the risks of syncope and hypotension related to concomitant administration of Addyi and alcohol in women, and that the BW and contraindication continued to be warranted. The Office of Drug Evaluation III issued a Safety Labeling Change Notification on February 27, 2018, requesting inclusion of PMR5 results into labeling. Subsequently, there have been extensive, ongoing discussions between FDA and Sprout regarding labeling revisions.

Sprout (b) (4) referencing data from three additional Phase 1 alcohol interaction studies in women assessing the effect of alcohol dose and timing with Addyi administration, and proposed removal of the BW and the ETASU REMS. Results from these later alcohol interaction studies showed that a separation of two hours between up to two standard alcohol drinks and Addyi dosing may mitigate the risks hypotension and syncope.

Because negotiation between the FDA and Sprout failed to achieve mutually acceptable language in labeling, a Labeling Order was issued on April 11, 2019, pursuant to FDA's authority under Section 505(o)(4)(E) of the Food, Drug and Cosmetic Act. On the same day of the Order, the Applicant submitted a formal dispute resolution request (FDRR), appealing to the OND Director, Dr. Peter Stein. (b) (4) On June 24, 2019, Dr. Stein issued the first Appeal Denied letter, denying Sprout's appeal to remove the BW but allowing the removal of the contraindication for use with alcohol. On June 27, Sprout submitted a correspondence, stating that an ETASU REMS is not required to mitigate any potential Addyi-alcohol interaction. In an updated Appeal Denied letter issued on August 18, 2019, that superseded the June 2019 Appeal Denied letter, Dr. Stein subsequently determined that an ETASU REMS is no longer necessary and may be replaced by a MG-only REMS. A comprehension study of the MG were to be conducted under the MG-only REMS.

On August 29, 2019, Sprout submitted an updated PI and MG that deleted both the REMS and the alcohol contraindication as a CBE-0 supplement. At that time FDA noted that Sprout had also published this version of the PI on their website, along with issuing press releases and complimentary promotional materials stating that the FDA had removed those elements. (b) (4)

(b) (4) The labeling supplement was subsequently recoded as a Prior Approval Supplement.

### **Current submission:**

Submission S-008 includes the proposed PI and a (b) (4) Submission S-009 includes a request for REMS modification, which is reviewed by the Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology. After the approval of the labeling supplement, DBRUP (b) (4)

Review of Proposed PI and MG submitted on August 29, 2019:

The following changes were made:

- Removal of the Contraindication for taking Addyi “within two hours after alcohol” from Boxed Warning, Highlights, Contraindications (4), Warnings and Precautions (5.1).
- Removal of REMS (Boxed Warning, Warnings and Precautions, 5.2)
- Changes to Section 7 Drug Interactions: Replacement of alcohol interaction with mitigating measure of counseling patients on importance of separating alcohol and Addyi by 2 hours.
- Changes to Patient Counseling information (Section 17) consistent with changes outlined above.
- The remainder of the label was consistent with the version sent to the Sponsor February 2019 and were agreed upon by Sprout.
- Minor typographical changes were also made.

DBRUP edits were sent to the Sponsor on September 12, 2019, and the company responded to DBRUPs suggested edits on September 13, 2019, in which edits to the BW were further streamlined and these edits were found to be acceptable by DBRUP.

The updated draft MG was reviewed and Division of Medical Policy Programs (DMPP) provided the following edits:

- Simplified wording and clarified concepts where possible
- Ensured that the MG is consistent with the Prescribing Information (PI)
- Removed unnecessary or redundant information
- Ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- Ensured that the MG meets the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006)
- Added examples of standard alcohol drinks

On September 24, 2019, the Applicant submitted the agreed-upon PI and MG, incorporating the Division’s edits.

Per the DRISK review dated October 9, 2019, the Applicant has submitted all necessary REMS documents to support the proposed REMS modifications. DRISK deems the materials adequate to approve the proposed REMS modification.

**Conclusion and Recommendations:**

- The final PI and MG may be approved. Approval of this labeling supplement should occur concurrently with the approval of the proposed REMS modification.
- DBRUP/DRISK has informed Sprout that the protocol for the MG comprehension study should be submitted within one month of the approval of the REMS modification.

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22526Orig1s009**

**OTHER REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: September 17, 2019

To: Hylton Joffe, MD  
Director  
**Division of Bone, Reproductive and Urologic Products (DBRUP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Marcia Williams, PhD  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Nyedra W. Booker, PharmD, MPH  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): ADDYI (flibanserin)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 022526

Supplement Number: S-009

Applicant: Sprout Pharmaceuticals

## 1 INTRODUCTION

On August 29, 2019 Sprout Pharmaceuticals submitted for the Agency's review a Prior Approval Supplement (PAS)- Proposed Risk Evaluation and Mitigation Strategy (REMS) Modifications Due to Safety Labeling Changes (SLCs) (b) (4)

(b) (4) On April 11, 2019, the Agency issued a SLC order requiring the Applicant to revise safety labeling information about the risk of hypotension and syncope associated with ADDYI due to an interaction with alcohol. Based on the results of three postmarketing studies, the Agency determined that the labeling should be revised to clarify that there is still a concern about consuming alcohol close in time to taking ADDYI, but alcohol does not need to be avoided completely.

The Applicant appealed the SLC order to seek removal of the contraindication, Boxed Warning and REMS with Elements to Assure Safe Use (ETASU). On August 18, 2019 in an Appeal Denied Letter, the Agency agreed to the removal of the alcohol contraindication and to a modification to the current REMS.

The submission of this PAS is to comply with the ordered SLC and directives outlined in the Appeal Denied Letter dated August 18, 2019.

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Bone, Reproductive and Urologic Products (DBRUP) on September 13, 2019 for DMPP to provide a focused review of the Applicant's proposed Medication Guide (MG) for ADDYI (flibanserin) tablets, for oral use.

## 2 MATERIAL REVIEWED

- Draft ADDYI (flibanserin) tablets, for oral use MG received on August 29, 2019, revised by the Review Division throughout the review cycle, and received by DMPP on September 13, 2019.
- Draft ADDYI (flibanserin) tablets, for oral use Prescribing Information (PI) received on August 29, 2019, revised by the Review Division throughout the review cycle, and received by DMPP on September 13, 2019.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

APPEARS THIS WAY ON ORIGINAL



6 Page(s) of Draft Medication Guide has been Withheld in Full as b4 (CCI/TS) immediately following this page

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22526Orig1s009**

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

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

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<b>Application Type</b>	NDA
<b>Application Number</b>	22526, S-009
<b>OSE RCM #</b>	2019-1928
<b>Reviewer Names</b>	Theresa Ng, PharmD, BCPS, CDE; Carolyn Tieu, PharmD, MPH
<b>Team Leaders</b>	Laura Zendel, PharmD, BCPS; Shelly Harris, ScD, MPH
<b>Deputy Division Director</b>	Jamie Wilkins, PharmD
<b>Review Completion Date</b>	October 9, 2019
<b>Subject</b>	Evaluation of REMS Modification
<b>Established Name</b>	flibanserin
<b>Trade Name</b>	Addyi
<b>Name of Applicant</b>	Sprout Pharmaceuticals, Inc. (Sprout)
<b>Therapeutic Class</b>	Serotonin 1A receptor agonist and a Serotonin 2A receptor antagonist
<b>Formulation(s)</b>	Oral film-coated tablets
<b>Dosing Regimen</b>	100 mg daily before bedtime

## Table of Contents

1	Introduction .....	3
2	Background .....	3
2.1	Product Information .....	3
2.2	Regulatory History.....	3
3	Results of Review of the Proposed REMS Modification.....	5
3.1	REMS Document.....	5
3.1.1	REMS Goal.....	5
3.1.2	Timetable for Submission of Assessments.....	5
3.2	REMS Materials.....	6
3.2.1	Medication Guide.....	6
3.2.2	REMS Website.....	6
4	REMS Supporting Document.....	6
4.1	Assessment Plan.....	6
5	Conclusion and Recommendation .....	8
6	Appendix.....	8
7	References.....	8

# 1 Introduction

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This review by the Division of Risk Management (DRISK) evaluates the proposed major modification to the risk evaluation and mitigation strategy (REMS) for Addyi (flibanserin), NDA 22526, Supplement 9 (S-009), submitted by Sprout Pharmaceuticals, Inc. (Sprout) on August 29, 2019 and amended on September 26, 2019, and October 4 and 7, 2019.

The modification proposes removal of the Elements to Assure Safe Use (ETASU) and Implementation System and inclusion of the Medication Guide (MG) as an element of the REMS to conform with the directives in the Appeal Denied Letter issued by the Office of New Drugs (OND) on August 18, 2019.<sup>1</sup> Sprout also submitted Supplement-8 (S-008) to modify the Prescribing Information (PI) and MG in accordance with the Appeal Denied Letter issued on August 18, 2019 and the Safety Label Change (SLC) order issued on April 11, 2019.<sup>2</sup> S-008 will be evaluated separately by the Division of Medical Policy Program (DMPP) Patient Labeling Team (PLT) and the Division of Bone, Reproductive, and Urologic Products (DBRUP).

## 2 Background

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### 2.1 PRODUCT INFORMATION

Addyi is a serotonin 1A receptor agonist and serotonin 2A receptor antagonist indicated to treat hypoactive sexual desire disorder (HSDD) in premenopausal women. Addyi is available as 100 mg oral tablets to be taken daily prior to bedtime.

Addyi was approved with a REMS on August 18, 2015 to address the risk of hypotension and syncope due to an interaction with alcohol and Addyi. The REMS was last modified on April 2, 2019.

The goal of the REMS is to mitigate the increased risk of hypotension and syncope associated with Addyi due to an interaction with alcohol by:

- Ensuring prescribers and pharmacists are educated about the increased risk of hypotension and syncope associated with Addyi due to an interaction with alcohol and the need to counsel patients about the risk.
- Informing patients of the increased risk of hypotension and syncope associated with Addyi due to an interaction with alcohol

The REMS consists of Elements to Assure Safe Use (ETASU), an implementation system, and a timetable for submission of assessments.

### 2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 22526 relevant to this review:



(b) (4)

OND Office of Drug Evaluation III (ODE III) issued a Safety Labeling Change Order<sup>4</sup> requiring the Sponsor to make the changes to the label to retain the Boxed warning with amended language regarding separation of Addyi and alcohol by at least 2 hours and retaining the Contraindication for Addyi use within 2 hours after alcohol consumption.

The Sponsor submitted a formal dispute resolution request (FDRR) (b) (4) (b) (4) to discuss issues raised in the request for FDRR.

- (b) (4)
- 6/24/2019: OND issued a letter<sup>5</sup> denying the Sponsor's appeal of the updated label to remove the Boxed Warning but allows for the Contraindication for use with alcohol to be removed.
- 6/27/2019: The Sponsor submitted rationale that the REMS was at issue in the April 11, 2019 FDRR, specifically whether a REMS with ETASU is required to mitigate any potential flibanserin-alcohol interaction.
- 8/18/2019: OND issued a modified letter<sup>6</sup>, superseding the previous response from 6/24/2019, denying the Sponsor's appeal of the updated label to remove the Boxed Warning, however the letter did state that after a re-evaluation of the risk - benefit profile of the drug, removal of the contraindication for use of Addyi with alcohol and removal of the ETASU and Implementation System, and addition of the MG as an element of the REMS should occur.
- 8/29/2019: Sprout submitted a REMS modification, Supplement 9 (S-009), proposing to remove the ETASU and Implementation System, and add a MG as part of the REMS in response to the Appeal Denied Letter issued by OND on August 18, 2019.
- 9/23/2019: The Agency issued comments<sup>7</sup> via email on the proposed REMS modification to change the REMS goal, remove the REMS website, and update the supporting document and assessment plan.
- 9/25/2019: Sprout responded to the Agency's comments via email and included a clean and redlined REMS document, supporting document, and assessment metrics.
- 9/26/2019: Sprout submitted a REMS amendment containing the same materials as included in the email response from 9/25/2019.
- 9/27/2019: The Agency met with Sprout via teleconference to discuss the proposed changes to the Assessment Plan.<sup>8</sup>
- 9/30/2019: The Agency issued comments on the assessment plan via email reflecting the teleconference discussion from 9/27/2019.
- 10/1/2019: Sprout emailed the Agency (b) (4) (b) (4)

- 10/2/2019: The Agency emailed Sprout clarifying that (b) (4) (b) (4) within the assessment plan.
- 10/3/2019: Sprout emailed a response including a REMS document and supporting document. The Sponsor agreed with the agency's comments (b) (4) for the Medication Guide comprehension study.
- 10/4/2019: Sprout submitted a REMS amendment containing the same materials as included in the email response from 10/3/2019.
- 10/7/2019: The Agency emailed comments<sup>9</sup> to the Sponsor providing (b) (4) (b) (4) related to the timing of consumption of alcohol and flibanserin administration/dose and requesting that it should remain in the assessment plan.

Sprout submitted a REMS amendment consisting of a REMS document and REMS supporting document.

### 3 Results of Review of the Proposed REMS Modification

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Sprout proposes to modify the Addyi REMS by removing the ETASU and Implementation System and adding the MG as an element of the REMS.

#### 3.1 REMS DOCUMENT

Sprout proposes to remove the ETASU and Implementation System from the REMS document, including reference to all appended REMS materials. After the comments from the Agency dated September 23 and 30 2019 and October 2 and 7 2019, the Sponsor incorporated all of the Agency's recommendations, including updating the REMS goal and timetable for submission of assessments.

##### 3.1.1 REMS Goal

Sprout incorporated the Agency's comments and revised the REMS goal as follows:

The goal of the Addyi REMS is to inform patients about (b) (4) the increased risk of hypotension and syncope associated with Addyi due to an interaction with alcohol (b) (4)

**Reviewer Comment:** *The proposed changes to the REMS goal are acceptable.*

##### 3.1.2 Timetable for Submission of Assessments

Sprout incorporated the Agency's comments and revised the Timetable for Submission of Assessments as follows:

Sprout Pharmaceuticals must submit REMS Assessments 6 months from 10/9/2019, and 18 months, 3 years and 7 years thereafter (b) (4) To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Sprout must submit each assessment so that it will be received by the FDA on or before the due date.

**Reviewer Comment:** *The proposed changes to the REMS document are acceptable.*

### **3.2 REMS MATERIALS**

The Sponsor proposes to remove all REMS materials including the Prescriber Enrollment Form, Prescriber and Pharmacy Training, Program Knowledge Assessment, Patient-Provider Agreement Form, Multiple Location Pharmacy Enrollment Form, Individual Location Pharmacy Enrollment form, Inpatient Pharmacy enrollment Form, and Distributor Enrollment Form. The Sponsor proposes to add the MG as an element of the REMS.

#### **3.2.1 Medication Guide**

Sprout submitted a revised MG in the labeling supplement, S-008, incorporating the updated risk messaging on the Addyi-alcohol interaction.

**Reviewer Comment:** *DRISK defers the evaluation of the proposed changes to the Addyi MG to the DMPP Patient Labeling Team and DBRUP.*

#### **3.2.2 REMS Website**

Sprout's 8/29/2019 submission included a revised REMS website that incorporated the revised Addyi REMS goal, the revised Box Warning, an indication statement, information on limitations of use, and the Sponsor's contact information, as well as links to the MG and PI. Sprout incorporated the Agency's comments to remove the REMS website as part of the REMS in the September 26, 2019 and October 4 and 7, 2019 REMS amendments.

**Reviewer Comment:** *The proposed changes are acceptable. The REMS website is no longer necessary to include as part of the REMS as the MG is available on the commercial Addyi website, and metrics regarding how frequently it is accessed will be provided in the REMS assessment.*

## **4 REMS SUPPORTING DOCUMENT**

Sprout removed all content related to the ETASU and Implementation system and revised the supporting document to align with changes to the REMS.

### **4.1 ASSESSMENT PLAN**

Sprout proposes an Assessment Plan which assesses the following objectives:

1. REMS Operational Metrics (beginning with the 18-month assessment and cumulatively)
  - Number of visits and unique visits to the Medication Guide from [Addyi.com](http://Addyi.com).
  - Time spent viewing the Medication Guide from [Addyi.com](http://Addyi.com).
2. REMS Compliance (beginning with the 18-month assessment and cumulatively)
  - Assessment of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
    - 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)
  - 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)
  - 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)
  - 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)
  - 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.

**Reviewer Comment:** *DRISK finds the proposed changes to the REMS supporting document acceptable.*

*The assessment plan is modified to incorporate metrics specific to the change in the structure of the REMS to eliminate the ETASU and Implementation System and add a MG as an element of the REMS.*

*The MG comprehension study to be submitted with the 6-month assessment report is required to ensure adequate comprehension of the MG among a representative sample of the target population. Having an easily understood MG ensures that patients who receive and read the MG will be able to understand the risk message. As the ETASU will be eliminated, there will no longer be required counseling by prescribers and pharmacists. In the absence of required counseling under the REMS, we cannot assume that counseling will occur, nor can we assume that patients will be adequately counseled about the timing of consumption of alcohol and Addyi. Therefore, the target level of comprehension related to the timing of consumption of alcohol and flibanserin administration/dose should have a higher target level of 90% to ensure a clear risk message, while the target level of comprehension related to the increased risk of hypotension and syncope associated with Addyi due to an interaction with alcohol should be a minimum of 80%. As discussed with DBRUP and DRISK, if the results of the MG are acceptable, the requirement for the patient knowledge survey may be removed in future assessments.*

*Since the key focus of this REMS is to inform patients about the risk message, achievement of this goal would be assessed through compliance data, which ensure that the MG is being dispensed as required under the REMS. Compliance metrics include a survey of pharmacists to determine if the MG is dispensed accordingly and a survey of patients to assess patient's receipt of the MG. The compliance*

*metrics will provide data to determine if the MG is being provided to patients therefore allowing us to determine if the REMS is effective and meeting its goals.*

*Other data to support the REMS include use of the MG (operational metrics), adverse events of special interest pertaining to this REMS (safety surveillance), and patient’s understanding of the risk message (knowledge evaluation).*

## 5 Conclusion and Recommendation

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DRISK finds the proposed REMS document and REMS supporting document as amended on October 7, 2019 acceptable provided that the DMPP PLT and DBRUP find the MG is adequate prior to the approval of the application.

## 6 Appendix

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REMS document

## 7 References

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<sup>1</sup> Stein P. Dispute Appeal Denied Letter. Office of New Drugs. Dated August 18, 2019.

<sup>2</sup> Beitz, J. Labeling Change Order for Addyi (b) (4)  
(b) (4)

(b) (4)

<sup>4</sup> Beitz, J. Labeling Change Order for Addyi (b) (4)  
(b) (4)

<sup>5</sup> Stein, P. Office of New Drugs. Dispute Appeal Denied Letter. Dated June 24, 2019.

<sup>6</sup> Stein, P. Office of New Drugs. Dispute Appeal Denied Letter. Dated August 18, 2019.

<sup>7</sup> Hillig, M. Information Request: “Addyi S-009 REMS Comments.” Issued September 23, 2019. Dated October 8, 2019.

<sup>8</sup> Hillig, M. Memorandum of Meeting Minutes. Teleconference Addyi NDA 022526. Meeting date September 27, 2019. Dated October 8, 2019.

<sup>9</sup> Hillig, M. Information Request: “REMS Revision S-009.” Issued October 7, 2019. Dated October 8, 2019.

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/s/  
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LAURA A ZENDEL  
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JAMIE C WILKINS PARKER  
10/09/2019 03:03:30 PM

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22526Orig1s009**

**ADMINISTRATIVE AND CORRESPONDENCE  
DOCUMENTS**

## Memorandum to File

**Date:** October 9, 2019

**To:** File – NDA 22526/S008 and S009

**From:** Meredith Hillig, MS  
Safety Regulatory Project Manager

Christine P. Nguyen, MD  
Deputy Director for Safety

DBRUP

**Subject:** Labeling Supplement (S008) and REMS Modification (S009)  
after Dispute Resolution Appeal Denied

This memo recommends the approval of Supplement 008, which proposes to remove information related to the Addyi REMS and revises the information about alcohol interaction with Addyi, and also Supplement 009 (REMS modification). These labeling revisions, and REMS-related discussions, follow an extensive regulatory history; refer to the following key documents for details:

- FDAAA SLC notification dated February 28, 2018
- FDAAA SLC Order letter dated April 11, 2019
- Sponsor's dispute resolution dated April 11, 2019
- Dispute Appeal Denied letter dated June 24, 2019, which was superseded by the August 18, 2009 Appeal Denied Letter

In his Dispute Appeal Denied Letter dated August 18, 2019, Dr. Peter Stein, OND Director, rendered the following decisions:

- Alcohol interaction with Addyi in drug labeling:
  - Remove the alcohol contraindication.
  - The Boxed Warning and Warnings/Precautions should advise that alcohol consumption of 2 or fewer standard alcoholic drinks should be completed at least 2 hours prior to taking Addyi at bedtime. Consumption of more alcoholic drinks will require longer separation of time to ensure adequate metabolism of alcohol to mitigate the risk of alcohol interacting with Addyi to product hypotension/syncope.
  - Adverse Reactions section should describe the alcohol-Addyi interaction studies consistent with that outlined in the April 2019 SLC Order letter, although revisions to more succinctly convey the information may be considered.
- CYP3A4 and hepatic impairment interaction with Addyi increasing the risk of hypotension/syncope remains in the Boxed Warning.
- The REMS to be modified to eliminate the ETASUs and add the Medication Guide. The Medication Guide is to undergo consumer comprehension and revised as needed to optimize

patient understanding of the alcohol-Addyi interaction and ways to mitigate such interaction. It should be noted that the REMS document and REMS supporting document were finalized and the REMS modification supplement (S-009) was approved the same day as the approval of this labeling supplement. Therefore, the information regarding the ETASU REMS was removed with the approval of this labeling supplement. The REMS modification memo will be finalized after the approval of supplement 009 because this is an administrative action rather than decisional. The rationale supporting the REMS modification is provided in the August 18, 2019, Appeal Denied Letter. Dr. Stein has made the decision to eliminate the ETASUS and add the Medication Guide to the REMS.

The sponsor submitted Supplement 008 on August 28, 2019. The Medication Guide revisions were reviewed by the Patient Labeling Team, and the revisions to the Prescribing Information was reviewed by OPDP and found acceptable. The clinical team concurred with the revisions in both labeling documents. The sponsor submitted Supplement 009 on August 29, 2019 to revise the REMS, removing the ETASUs and add the Medication Guide. DRISK reviewed the REMS modifications and agreements were reached. For further details, refer to DRISK's review of the REMS modifications and memo capturing the evaluation of rationale for REMS Modification, both dated October 9, 2019. DBRUP agreed in full of both DRISK's memos and had no additional clarification. The agreed upon REMS modification and labeling changes were submitted on September 24, and October 8, 2019.

Supplements 008 and 009 were reviewed and reflected the agreed-upon changes. These supplements should be approved.

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**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.**  
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/s/  
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MEREDITH B HILLIG  
10/09/2019 03:38:17 PM

CHRISTINE P NGUYEN  
10/09/2019 07:58:24 PM

**From:** [Josephine M. Torrente](#)  
**To:** [Hillig, Meredith](#)  
**Cc:** [Jaye Thompson, Ph.D.](#)  
**Subject:** RE: Addyi S-009 REMS comments  
**Date:** Wednesday, September 25, 2019 12:09:32 PM  
**Attachments:** [SPROUT 9-25 Draft REMS Document \(00586921\).docx](#)  
[Sprout Redline REMS Document 9-25 \(00586963\).docx](#)  
[SPROUT 9-25 Draft REMS Supporting Document \(00586920\).docx](#)  
[SPROUT Redline Assessment Metrics 9-25 \(00586998\).docx](#)

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Dear Meredith

Jaye is at a conference today and asked that I send you this response.

Sprout has reviewed FDA's comments on the REMS Modification and has revised the files as outlined below. Courtesy copies of the following documents (in Word) are attached, and these documents will also be submitted through the Electronic Submissions Gateway. Please note that since FDA did not provide its edits within the REMS Supporting Document, we are only submitting a clean version of that document as we have nothing to redline against. For ease of your review, we are also including the excerpted Summary of the REMS Assessment Plan, redlined against FDA's 9-23-19 version.

- Sprout Proposed REMS Document – Clean
- Sprout Proposed REMS Document – Redlined against FDA's 9-23-19 version
- Sprout Proposed REMS Supporting Document – Clean
- Sprout Proposed Assessment Plan (excerpted from Supporting Document) - Redlined against FDA's 9-23-19 version

#### *REMS Document*

Sprout modified the REMS Document to follow the currently approved format. Sprout has also made the following changes to the REMS Document as FDA requested:

1. Revised REMS Goal: "To inform patients about the increased risk of hypotension and syncope associated with Addyi due to an interaction with alcohol."
2. Removed the Addyi REMS website from the REMS Elements.
3. Revised the Timetable for Submission of Assessments.

The only remaining difference from FDA's version is typographical.

#### *Supporting Document*

Sprout is mindful of the Appeal Denied Letter's objective that the Medication Guide be part of a REMS to ensure that it is "readily understandable" by patients who are prescribed Addyi and has focused the Assessment Plan on analyzing whether this objective is being met. Sprout has updated the Supporting Document to be consistent with the changes to the REMS Document (i.e., updated REMS Goal, removal of REMS website, revised timetable). Sprout has also incorporated those elements of FDA's suggested Assessment Plan that will help evaluate whether the Addyi REMS program is meeting its goal of informing patients about the increased risk of hypotension and syncope associated with Addyi due to an interaction with alcohol. We believe that certain elements of the Assessment Plan as outlined by FDA (e.g., Utilization Data) would be burdensome to obtain and have no obvious role in assessing whether patients are informed about the increased risk of hypotension and syncope associated with Addyi due to an interaction with alcohol - the stated REMS Goal. As such, we have not incorporated these. If FDA believes that they must be included for some other purpose we would be happy to immediately have a short phone call to understand that reasoning and then quickly amend the documents as needed. The REMS Operational Metrics and Safety Surveillance also do not appear tailored to the assessment of the REMS Goal, but have nonetheless been included in the Assessment Plan.

#### *Protocol for the Medication Guide Comprehension Study*

Sprout appreciates FDA's advance comments on the protocol for the Medication Guide Comprehension Study. Sprout will take FDA's comments into consideration as we develop a protocol for a study and looks forward to discussing the design with FDA. Sprout will submit a protocol to FDA for the Medication Guide Comprehension Study within 30 days of the date of approval letter.

We look forward to quick resolution of any remaining items and finalization of the REMS and labeling.

Thanks very much  
Josephine

Josephine M. Torrente, JD  
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---

**From:** Jaye Thompson, Ph.D. <[jaye@sproutpharma.com](mailto:jaye@sproutpharma.com)>  
**Subject:** FW: Addyi S-009 REMS comments

**Jaye Thompson, Ph.D.**  
VP of Regulatory Affairs  
Sprout Pharmaceuticals, Inc.  
**p:** 844-PINK-PILL / 844-746-5745 **x:** 6000  
**c:** 713 410-2257  
**e:** [jaye@sproutpharma.com](mailto:jaye@sproutpharma.com)  
**w:** [www.sproutpharma.com](http://www.sproutpharma.com)



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**From:** Hillig, Meredith <[Meredith.Hillig@fda.hhs.gov](mailto:Meredith.Hillig@fda.hhs.gov)>  
**Sent:** Monday, September 23, 2019 3:48 PM  
**To:** Jaye Thompson, Ph.D. <[jaye@sproutpharma.com](mailto:jaye@sproutpharma.com)>  
**Subject:** Addyi S-009 REMS comments  
**Importance:** High

Dear Jaye:

The following comments and attached documents are based on the Agency's review of the proposed REMS modification for Addyi (NDA 22526/S9) submitted on August 29, 2019. To facilitate further review, we ask that you respond to these comments and submit a REMS amendment within 2 business days. Your submission should include Clean MS Word and Tracked MS Word versions of the REMS document and Supporting Document. The Assessment Plan is also being provided as an attachment for ease of

work for incorporating this into your Supporting Document. The REMS Document is also attached.

**1. REMS Document:**

Revert the REMS document to the currently approved format. Please see attached material.

a. REMS Goal:

The REMS goal should be revised to reflect removal of the ETASU as follows (i.e. removes the objectives associated with the ETASU and only reflect the MG):

To inform patients about the increased risk of hypotension and syncope associated with Addyi due to an interaction with alcohol.

b. Timetable for Submission of Assessments:

The Timetable for Submission of Assessments should be changed to 6 months from the date of approval of the REMS modification and 18 months, 3 years, and 7 years thereafter. Please see additional added text in the document, and what will be expected to be submitted with each assessment within the provided Assessment Plan.

**2. REMS Website:**

Remove the Addyi REMS website from the REMS. A REMS Website is not necessary to include as part of the REMS as the Medication Guide is available on the commercial Addyi website.

**3. Supporting Document:**

Update the supporting document to be consistent with changes to the REMS document, including the updated REMS Goal, removal of the REMS website, and revised Assessment Plan. We agree with all other changes to the content of the supporting document unless otherwise indicated.

a. Assessment Plan:

Submit the protocol for the Medication Guide comprehension study within 30 days of the approval letter. At the 6-month assessment, submit the results of the Medication Guide comprehension study only. At the 18-month, 3-year, and 7-year assessments, submit a full assessment report for our review.

The Assessment Plan must be modified as follows:

The 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](http://Addyi.com). Include time spent viewing the Medication Guide. Include average, standard deviation, median, interquartile range, minimum, and maximum.
  - b. Number of downloads of the Medication Guide
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
  - b. Assessment of patient's receipt of the Medication Guide (e.g. follow-up survey of patients who have received a prescription for Addyi)
  - c. Assessment of pharmacy's policies and procedures for distribution and dispensing of the Medication Guide

- d. Assessment of pharmacy's adherence to the distribution and dispensing of the Medication Guide
    - e. For any report received regarding failure to adhere to distribution and dispensing, determine the root cause of noncompliance and include corrective and preventative actions taken.
3. Assessment of the comprehension of the Medication Guide (6-month assessment)
  - a. If comprehension is below the prespecified threshold, outline steps to address it to ensure adequate comprehension (i.e. enhancing the Medication Guide).
4. Addyi Utilization Data (beginning with the 18-month assessment and cumulatively)
  - a. Number of Addyi prescriptions (new and refills) dispensed stratified by:
    - i. healthcare provider type (i.e. medical doctor, nurse practitioner), medical specialty and geographic region
    - ii. patient age and geographic region
    - iii. pharmacy type (i.e. retail, specialty pharmacy).
  - b. Number of Addyi prescriptions that are dispensed from mail order or specialty pharmacy.
  - c. Number of prescriptions that originate from telemedicine services.
5. 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. Include an overall summary and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication. Sources of the report are to include but not limited to:
    - i. 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
    - ii. Literature searches
    - iii. Social Media
  - b. Include a line listing of all cases that includes: source of the report, manufacturer control number, narrative, alcohol use around the time of the event, timing of dosing, concomitant medications, and assessment of causality.
    - 1.
6. 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.

7. 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.

#### 4. Protocol for the Medication Guide Comprehension Study

- a. Include a representative sample of the target population (i.e., women with demographics and other important characteristics similar to those likely to be prescribed this medication).

Demographics and characteristics to consider:

- Equal proportion of females who have taken Addyi in the last three months and females who have never taken Addyi
- Age distribution of the females who are taking Addyi
- Race/ethnicity
- Level of education. Females with a high school degree or less should be over sampled.
- Females who speak English as a second language
- Geographic region

Exclude the following females:

- Healthcare professionals
- Females with advanced educational degrees (i.e. Masters, doctorate-level degrees)
- Females who are currently participating in clinical studies involving Addyi
- Females who have taken a previous Addyi REMS patient knowledge survey
- Females who are currently working for Sprout, third party contractors, or the FDA

Example shell table:

Characteristics	Target # of Interviews
<b>Females</b>	
Females who have taken Addyi in the last 3 months	
Females who have never taken Addyi	
<b>Age</b>	
18 – 24	
25 – 34	
35 – 44	
45 – 49	
>50	
<b>English as a second language</b>	
Yes	
No	
<b>Race/ethnicity</b>	
Non-Hispanic White	

Non-Hispanic African American	
Hispanic	
Other minorities (American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander)	
Two or more races	
<b>Region</b>	
Northeast	
South	
Midwest	
West	
<b>Education</b>	
High School Diploma/GED or Less	
Some college or associate's degree	
Bachelor's degree	

- b. Ensure that the readability of the Medication Guide is written in a 6<sup>th</sup> grade level
- c. Include the interview questionnaire
- d. 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.

Regards,

Meredith B. Hillig, M.S.  
 Safety Regulatory Project Manager  
 Center for Drug Evaluation and Research  
 Office of New Drugs  
 Division of Bone, Reproductive and Urologic Products  
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/s/  
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MEREDITH B HILLIG  
10/08/2019 10:44:20 AM

**From:** [Jaye Thompson, Ph.D.](#)  
**To:** [Hillig, Meredith](#)  
**Cc:** ["Josephine M. Torrente"](#)  
**Subject:** RE: REMS Revision S-009  
**Date:** Monday, October 07, 2019 12:04:21 PM

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Meredith,

We received your email and agree to the changes the team has recommended. We will submit a REMS revision as soon as possible through the gateway.

Regards,  
Jaye

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**Jaye Thompson, Ph.D.**  
VP of Regulatory Affairs  
Sprout Pharmaceuticals, Inc.  
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**c:** 713 410-2257  
**e:** [jaye@sproutpharma.com](mailto:jaye@sproutpharma.com)  
**w:** [www.sproutpharma.com](http://www.sproutpharma.com)



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**From:** Hillig, Meredith <Meredith.Hillig@fda.hhs.gov>  
**Sent:** Monday, October 7, 2019 7:08 AM  
**To:** Jaye Thompson, Ph.D. <jaye@sproutpharma.com>  
**Cc:** 'Josephine M. Torrente' <JTorrente@hpm.com>  
**Subject:** RE: REMS Revision S-009

Dear Jaye:

We received your email communication dated October 3, 2019 containing a redlined supporting document and assessment plan. We agree with the proposed changes to the supporting document and assessment plan except for the (b) (4)

(b) (4) We also understand that physician communication with a patient and the Medication Guide may both contribute to patients' understanding of the risk. However, the ETASU will be eliminated so there will no longer be required counseling by prescribers. In the absence of required counseling under a REMS, we cannot assume that counseling will occur, nor can we assume that patients will be adequately counseled about the timing of consumption of alcohol and Addyi. Our comments stated that 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%.

In order to more fully understand why you believe (b) (4)

(b) (4)

we would need to see your full study protocol.

We would like to also point out that the target threshold determination of 90% is the level we consider the MG to be an acceptable tool for conveying the key message to the patient. Below that, we would likely expect revisions to address the comprehension gap.

Further, the additional details added to the assessment plan are more suitable to remain in the supporting document. Therefore, the assessment plan to be appended to the approval letter will be as follows:

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](http://Addyi.com).
  - b. Time spent viewing the Medication Guide from [Addyi.com](http://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.**

If you have any questions, contact me. Please reply to confirm receipt.

Regards,  
Meredith

Meredith B. Hillig, M.S.  
Safety Regulatory Project Manager  
Center for Drug Evaluation and Research  
Office of New Drugs  
Division of Bone, Reproductive and Urologic Products  
Phone: 301-796-1218, Fax: 301-796-9897  
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---

**From:** Jaye Thompson, Ph.D. <[jaye@sproutpharma.com](mailto:jaye@sproutpharma.com)>  
**Sent:** Thursday, October 03, 2019 3:51 PM  
**To:** Hillig, Meredith <[Meredith.Hillig@fda.hhs.gov](mailto:Meredith.Hillig@fda.hhs.gov)>  
**Cc:** Wilkins, Jamie <[Jamie.Wilkins@fda.hhs.gov](mailto:Jamie.Wilkins@fda.hhs.gov)>; 'Josephine M. Torrente' <[JTorrente@hpm.com](mailto:JTorrente@hpm.com)>  
**Subject:** REMS Revision S-009

Meredith,

Thank you and your team for meeting with us last week and providing your written comments on Monday. Sprout has reviewed your comments on the REMS modification and we have revised the supporting document with your suggestions. I have attached two documents to facilitate your review:

- Sprout Proposed REMS Supporting Document with redline changes noted from Sprout's September 26<sup>th</sup> S-009 submission
- A redline of the FDA's written comments from Monday, September 30<sup>th</sup>. Please note comment responses are included.

The complete REMS revision will be submitted through the gateway as soon as possible. We look forward to a quick resolution of any remaining issues and finalization of both the labeling and REMS.

Regards,  
Jaye

---

**Jaye Thompson, Ph.D.**  
VP of Regulatory Affairs  
Sprout Pharmaceuticals, Inc.  
**p:** 844-PINK-PILL / 844-746-5745 **x:** 6000  
**c:** 713 410-2257  
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16 Page(s) of Draft REMS Supporting Document has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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MEREDITH B HILLIG  
10/08/2019 10:48:22 AM

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** September 27, 2019  
**TIME:** 3:00-3:23 PM ET  
**LOCATION:** Teleconference  
**APPLICATION:** NDA 022526  
**DRUG NAME:** ADDYI  
**TYPE OF MEETING:** Teleconference

**MEETING CHAIRS:** Jamie Wilkins

**MEETING RECORDER:** Meredith Hillig

### **FDA ATTENDEES:**

Christine Nguyen, MD, Deputy Director for Safety, DBRUP  
Christina Chang, MD, MPH, Clinical Team Leader, DBRUP  
Marcea Whitaker, MD, Clinical Reviewer, DBRUP  
Meredith Hillig, MS, Safety Regulatory Project Manager, DBRUP  
Jamie Wilkins PharmD, Deputy Director, Division of Risk Management (DRISK)  
Laura Zendel PharmD, Team Leader, DRISK  
Carolyn Tieu, Pharm.D. Analyst, DRISK  
Claudia Manzo, Director, Office of Medication Error Prevention and Risk Management  
Elaine Lippman, Senior Regulatory Counsel, Office of Regulatory Policy (ORP)  
Eleanor Mayer, Attorney, Office of Chief Counsel (OCC)

### **EXTERNAL CONSTITUENT ATTENDEES:**

Cynthia Eckart, CEO, Sprout  
Louise Brown, Advisor, Sprout  
Jaye Thompson, PhD, Vice President, Regulatory, Sprout  
Josephine Torrente, Outside Regulatory Counsel

### **SUMMARY OF DISCUSSION:**

The Agency scheduled a teleconference with Sprout to negotiate the REMS assessment plan for in-house REMS supplement S-009, which includes a request to eliminate the current ETASU REMS and replace it with a Medication Guide-only REMS. DRISK led the meeting by walking the applicant through each section of the Agency's recommended REMS assessment plan, clarifying which additions and which strikethroughs they agreed or disagreed with, and also providing their rationale as needed. The teleconference concluded with Sprout's concurrence, and plan to submit an amendment to the in-house supplement with the agreed upon changes as soon as possible.

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/s/  
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MEREDITH B HILLIG  
10/08/2019 10:51:39 AM