CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

22526Orig1s008

Trade Name:	**ADDYI**
Generic or Proper Name:	flibanserin
Sponsor:	SPROUT PHARMACEUTICALS, INC
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. .

CENTER FOR DRUG EVALUATION AND RESEARCH

22526Orig1s008

CONTENTS

Reviews / Information Included in this NDA Review.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22526Orig1s008

APPROVAL LETTER

NDA 022526/S-008

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.

We also refer to our Safety Labeling Change Notification letter dated February 27, 2018, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling of ADDYI. This information pertains to the risk of the concomitant use of alcohol with ADDYI.

We further refer to our Safety Labeling Change Order Letter dated, April 11, 2019, and our Formal Dispute Resolution Denial letter dated August 18, 2019.

This supplemental new drug application provides for revisions to the labeling for ADDYI consistent with the August 18, 2019, Denial letter and the comments sent to you in our correspondences dated September 19, 20, 23, and 24, 2019.

Your approved Medication Guide will become part of the risk evaluation and mitigation strategy (REMS) in your pending supplemental application NDA 022526/S-009, when approved.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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.

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[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

REPORTING REQUIREMENTS

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

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

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

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHRISTINE P NGUYEN
10/09/2019 09:59:27 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

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22526Orig1s008

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 ≥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.

----------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 ≥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 ≥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 ≥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, 5.3and 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

Alcohol	
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 Warnings and Precautions (5.1) and Clinical Pharmacology (12.2)]*.
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 Boxed Warning Warnings and Precautions (5.1), and Adverse Reactions (6.1)]*.
Other CNS Depressants	
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.
Moderate or Strong CYP3A4 Inhibitors	
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 Warnings and Precautions (5.2), Adverse Reactions (6.1), and Clinical Pharmacology (12.3)]*.
Preventing or Managing DI	The concomitant use of ADDYI with moderate or strong CYP3A4 inhibitors is contraindicated.
Weak CYP3A4 Inhibitors	
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.
Strong CYP2C19 Inhibitors	
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.
CYP3A4 Inducers	
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.
Digoxin or Other P-glycoprotein Substrates	
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 Clinical Pharmacology (12.3)]*. 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 ≥ 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.

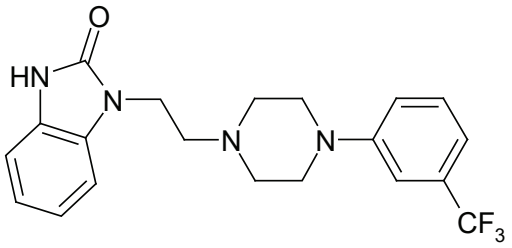
10 OVERDOSAGE

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 $C_{20}H_{21}F_3N_4O$ 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_{1A} and antagonist activity at 5-HT_{2A}. Flibanserin also has moderate antagonist activities at the 5-HT_{2B}, 5-HT_{2C}, and dopamine D_4 receptors.

Alcohol Interaction

See Clinical Trials Experience (6.1)

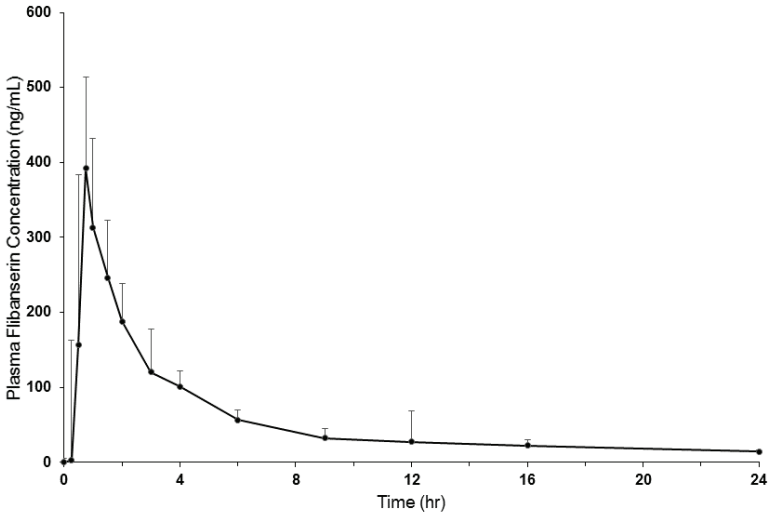
Cardiac Electrophysiology

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 Cmax 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 ($AUC_{0-\infty}$) 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) Cmax was 419 (206) ng/mL and mean (SD) $AUC_{0\text{-}inf}$ was 1543 (511) ng*hr/mL. Median (range) time to reach Cmax 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 $AUC_{0\text{-}inf}$ by 1.18-, 1.43-, and 1.56-fold; increased Cmax by 1.02-, 1.13-, and 1.15-fold; and prolonged median Tmax 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 ^{14}C-radiolabeled flibanserin, 44% of the total ^{14}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 ($AUC_{0\text{-}inf}$) 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 ($AUC_{0\text{-}inf}$) 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 ($AUC_{0\text{-}inf}$) 7-fold and Cmax 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 ($AUC_{0\text{-}inf}$) 4.5-fold and Cmax 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 ($AUC_{0\text{-}inf}$)

2.6-fold and Cmax 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 ($AUC_{0\text{-}inf}$) by 1.4-fold and Cmax 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 Cmax 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**	
			Cmax	**$AUC_{0\text{-}inf}$**
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 $AUC_{0\text{-}inf}$ by 2.0-fold and C_{max} 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 $AUC_{0\text{-}inf}$ of simvastatin, a substrate of CYP3A4, 1.3-fold and Cmax by 1.2-fold. Flibanserin co-administered with simvastatin increased simvastatin acid $AUC_{0\text{-}inf}$ by 1.5-fold and Cmax 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 $AUC_{0\text{-}inf}$ by 1.09-fold and the EE Cmax by 1.1-fold. Flibanserin decreased the LNG $AUC_{0\text{-}inf}$ by 1.06-fold and did not change the LNG Cmax. [*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 $AUC_{t,ss}$ (1.0-fold change) and C_{max} (1.0-fold change) but hydroxybupropion $AUC_{t,ss}$ decreased by 9% and C_{max} 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**	
			Cmax	**$AUC_{0\text{-}inf}$**
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, Cmax and $AUC_{0\text{-inf}}$ 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 Cmax 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, Cmax and $AUC_{0\text{-inf}}$ 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 bother (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 FSDS-R.

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

	Study 1		Study 2[1]		Study 3	
	ADDYI	**Placebo**	**ADDYI**	**Placebo**	**ADDYI**	**Placebo**
Full Analysis Set	n=280	n=290	n=365	n=372	n=532	n=536
Number of satisfying sexual events (per 28 days)						
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,		1.0 (0.4, 1.5)	
Change from baseline	1.0	0.0	1.2)	0.5	1.0	0.5
(Median)			1.0			
Median treatment difference	1.0				0.5	
p-value vs placebo	*p<0.01*		0.5		*p<0.0001*	
			p<0.01			
e-Diary Desire						
Baseline (Mean)	12.9	11.8	12.1	10.2	*Not Used*	*Not*
Change from baseline at	9.1	6.9	8.3	6.7		*Used*
Week 24 (Mean)						
Treatment diff. (95% CI)	2.3 (-0.1, 4.7)		1.7 (-0.5, 4.0)			
p-value vs placebo	NS		NS			
FSFI Desire						
Baseline (Mean)	1.9	1.9	1.8	1.8	1.9	1.9
Change from baseline at Week	0.9	0.5	0.9	0.5	1.0	0.7
24 (Mean)						
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	*N/A*[2]		*N/A*[2]		*p<0.0001*	
FSDS-R Question 13[3]						
Baseline (Mean)	3.2	3.2	3.2	3.2	3.4	3.4
Change from baseline at	-0.8	-0.5	-0.8	-0.5	-1.0	-0.7
Week 24 (Mean)						
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	*N/A*[2]		*N/A*[2]		*p=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.
[1]Excludes subjects from two study sites that had data integrity issues
[2]p-value not reported for secondary endpoints because the trial failed on the eDiary Desire co-primary efficacy endpoint
[3]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)]*.

Distributed by:
Sprout Pharmaceuticals, Inc.
Raleigh, NC 27609 USA

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Sprout Pharmaceuticals, Inc.

ADDYI tablets are covered by U.S. Patents Nos. 7,151,103; 7,420,057; 7,183,410; 8,227,471; 9,468,639; and 9,782,403.

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addyi®
(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
    - atazanavir (REYATAZ®)
    - fosamprenavir (LEXIVA)
    - ritonavir (NORVIR)
    - saquinavir (INVIRASE®)
    - nelfinavir (VIRACEPT®)
    - indinavir (CRIXIVAN®)
  - certain medicines that you take by mouth used to treat fungal infections, such as:
    - fluconazole (DIFLUCAN®)
    - ketoconazole
    - itraconazole (ONMEL, SPORANOX®)
    - posaconazole (NOXAFIL®)
  - certain antibiotics, including:
    - ciprofloxacin (CIPRO, CIPRO XR)
    - erythromycin (ERY-TAB®,ERYC®,PCE®)
    - telithromycin (KETEK®)
    - 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 depression

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

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 to25°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.

For more information go to www.ADDYI.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:

22526Orig1s008

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	9-24-19	9-24-19
			Request for Waiver of Labeling Requirement		

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_{1A} (serotonin) receptor agonist and 5-HT_{2A} 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) (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.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARCEA B WHITAKER
10/09/2019 09:52:22 PM

CHRISTINA Y CHANG
10/09/2019 09:54:44 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22526Orig1s008

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: September 18, 2019

To: Meredith Hillig
Safety Regulatory Project Manager
Division of Bone, Reproductive and Urologic Products (DBRUP)

From: Jina Kwak, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter
Team Leader, OPDP

Subject: **NDA 022526/S-008**
OPDP labeling comments for ADDYI (flibanserin) tablets, for oral use

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In response to DBRUP consult request dated September 18, 2019 for a focus review, OPDP has reviewed the proposed product labeling (PI) for ADDYI (flibanserin) tablets, for oral use. This supplement pertains to updated information on drug and alcohol interaction.

OPDP has no comments on the proposed labeling received by electronic mail from DBRUP (Meredith Hillig) on September 18, 2019.

Thank you for your consult. If you have any questions, please contact Jina Kwak: 301-796-4809; Jina.Kwak@fda.hhs.gov

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

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/s/

JINA KWAK
09/18/2019 01:53:00 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22526Orig1s008

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR VETERINARY MEDICINE

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 Octobers 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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/s/

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

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

From: Jaye Thompson, Ph.D.
To: Hillig, Meredith
Subject: RE: Addyi PI and MG 9.20.19 (to FDA)
Date: Tuesday, September 24, 2019 10:45:33 AM

Meredith,

Thank you. We will submit it today.

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
e: jaye@sproutpharma.com
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From: Hillig, Meredith <Meredith.Hillig@fda.hhs.gov>
Sent: Tuesday, September 24, 2019 9:43 AM
To: Jaye Thompson, Ph.D. <jaye@sproutpharma.com>
Subject: RE: Addyi PI and MG 9.20.19 (to FDA)

Hi Jaye,

We are fine with the changes. Please submit as an amendment to PAS NDA 22526/S-008. Just a reminder that the language is not approved until we approve the supplement.

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
Email: meredith.hillig@fda.hhs.gov

From: Jaye Thompson, Ph.D. <jaye@sproutpharma.com>
Sent: Tuesday, September 24, 2019 8:54 AM
To: Hillig, Meredith <Meredith.Hillig@fda.hhs.gov>
Subject: RE: Addyi PI and MG 9.20.19 (to FDA)

Meredith,

I have attached the package insert to identify the changes in the references. The submission is ready to send through the gateway so I would appreciate a notification from you as soon as possible. Please let me know if you have any questions.

Regards,
Jaye

Jaye Thompson, Ph.D.
VP of Regulatory Affairs
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From: Hillig, Meredith <Meredith.Hillig@fda.hhs.gov>
Sent: Tuesday, September 24, 2019 7:40 AM
To: Jaye Thompson, Ph.D. <jaye@sproutpharma.com>
Subject: RE: Addyi PI and MG 9.20.19 (to FDA)

Hi Jaye,

Would you please send over the corrected version and then if we agree, you can submit as final version as amendment to the PAS?

Thank you,
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
Email: meredith.hillig@fda.hhs.gov

From: Jaye Thompson, Ph.D. <jaye@sproutpharma.com>
Sent: Monday, September 23, 2019 7:53 PM
To: Hillig, Meredith <Meredith.Hillig@fda.hhs.gov>
Subject: RE: Addyi PI and MG 9.20.19 (to FDA)

Meredith,

In addition to the changes in wording you recommend, please note that if you approve, we will be correcting three references in the package insert that were incorrect. Two are in the highlights section and the third is in section 17. We will mark them in the red-line version.

Please let me know if you would like to manage these corrections in a different manner.

Regards,
Jaye

Jaye Thompson, Ph.D.
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From: Jaye Thompson, Ph.D. <Jaye@sproutpharma.com>
Sent: Monday, September 23, 2019 6:40 PM
To: 'Hillig, Meredith' <Meredith.Hillig@fda.hhs.gov>
Subject: RE: Addyi PI and MG 9.20.19 (to FDA)

Meredith,

We approve of the changes the division recommends and we are in the process of preparing the submission as you recommend. Can you clarify if you want this filed as draft or final labeling in the eCTD? Should this be filed as a PAS?

Regards,
Jaye

Jaye Thompson, Ph.D.

VP of Regulatory Affairs
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From: Hillig, Meredith <Meredith.Hillig@fda.hhs.gov>
Sent: Monday, September 23, 2019 11:56 AM
To: Jaye Thompson, Ph.D. <jaye@sproutpharma.com>
Cc: 'Josephine M. Torrente' <JTorrente@hpm.com>
Subject: RE: Addyi PI and MG 9.20.19 (to FDA)

Hi Jaye,

Please submit the agreed upon labeling to the PI, in both word and pdf (clean and marked up), as an amendment to S-008. Also, we should have the REMS materials to you within the next few days.

There are two areas in the MG we'd like to read a little differently is shown in bolded text in yellow highlight:

The changes to the first bullet in the MedGuide seem to have inadvertently omitted "to when"

- drink alcohol close in time to when you take your ADDYI dose.
  - FDA's requested change: **drink alcohol close to the time you take your ADDYI dose**.

The changes to the first bullet under "What should I avoid while taking ADDYI?" in the MedGuide seem to have inadvertently omitted the same two words

- Do not drink alcohol close in time to when you take your ADDYI dose because this increases your risk of severe low blood pressure and fainting (loss of consciousness).
  - FDA's requested change: **drink alcohol close to the time you take your ADDYI dose** because…

Please let me know if you agree to the above changes for the MG.

Thank you,
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
Email: meredith.hillig@fda.hhs.gov

From: Jaye Thompson, Ph.D. <jaye@sproutpharma.com>
Sent: Friday, September 20, 2019 9:41 AM
To: Hillig, Meredith <Meredith.Hillig@fda.hhs.gov>
Cc: 'Josephine M. Torrente' <JTorrente@hpm.com>
Subject: Addyi PI and MG 9.20.19 (to FDA)

Meredith,

We are in agreement with the edits you provided yesterday in both the Medication Guide and Package Insert. However, we did find a few minor changes as described below and noted in the redline versions attached.

The changes to the second bullet in Section 17 of the PI seem to have inadvertently omitted a "to", inserted here in red text

- 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).

The changes to the first bullet in the MedGuide seem to have inadvertently omitted "to when"

- drink alcohol close in time to when you take your ADDYI dose.

The changes to the first bullet under "What should I avoid while taking ADDYI?" in the MedGuide seem to have inadvertently omitted the same two words

- Do not drink alcohol close in time to when you take your ADDYI dose because this increases your risk of severe low blood pressure and fainting (loss of consciousness).

Unless you object, we plan to accept all changes and make these corrections prior to submitting to the NDA. Can you please confirm that these edits are acceptable?

Regards,
Jaye

Jaye Thompson, Ph.D.
VP of Regulatory Affairs
Sprout Pharmaceuticals, Inc.

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/s/

MEREDITH B HILLIG
09/25/2019 09:38:28 AM