DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022526/S-006

LABELING ORDER

Sprout Pharmaceuticals, Inc.
Attention: Jaye Thompson, PhD
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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ADDYI (flibanserin) 100 mg tablet.

We acknowledge receipt of your amendments dated April 13, July 3, August 10, September 10, October 15, November 13, November 30, December 7, December 21, 2018, and January 24 and March 18, 2019. We also refer to our Advice Letter dated March 5, 2019, and to your response received on March 18, 2019.

On February 27, 2018, we sent you a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related labeling changes (SLC) to address the increased risk of severe hypotension and syncope with concomitant use of ADDYI and alcohol. The decision to require safety labeling changes was based on new safety information from a required postmarketing trial (PMR 2939-5, or PMR 5) about this risk identified since this product was approved. You were directed to submit, within 30 days of the date of that letter, a supplement proposing changes to the approved labeling, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

On March 29, 2018, you submitted a prior approval supplement (S-006) proposing changes to the approved labeling to reflect the new safety information. You proposed to (1) remove the boxed warning about the risk of hypotension and syncope from the interaction of ADDYI with alcohol, with moderate/strong CYP3A4 inhibitors, and in patients with hepatic impairment, (2) remove the contraindication related to alcohol and (3) provided alternative labeling information about the PMR 5 findings in Warnings and Precautions.

Section 505(o)(4) requires FDA to promptly review your submission and initiate discussions if the Agency disagrees with the proposed changes. The several rounds of labeling discussions and your submissions of an amended final study report for PMR 5 and final study reports for three additional alcohol-interaction trials during the SLC review cycle required discussion extensions outlined in letters dated April 16, May 15, June 18, July 19, August 10, December 20, 2018, and January 25, 2019, to allow us to complete our review and negotiate labeling.

A teleconference with FDA staff and Sprout representatives was held on April 10, 2018, to discuss your submission S-006. During this teleconference, we clarified that the findings of PMR 5 supported the safety concerns of the Addyi-alcohol interaction that prompted the boxed warning and contraindication and that the boxed warning and contraindication needed to remain in place. On April 13, 2018, you submitted a revised label that continued to exclude the boxed warning and contraindication, with updates to add the findings of PMR 5 to the Warnings and Precautions section of the label. On May 23, 2018, you submitted an amended final study report for PMR 5 where you stated that few subjects experienced adverse events of interest (e.g., dizziness, hypotension) and that no alcohol dose-response in adverse events was observed. In our Information Request letter dated June 18, 2018, we directed you to restore the boxed warning and the alcohol contraindication. In this letter, we explained the findings from PMR 5 supported the safety concerns of hypotension and syncope with the use of Addyi and alcohol together. In this study, women were not permitted to stand up for orthostatic measurements if they had hypotension or symptoms consistent with hypotension (e.g., dizziness) in the semi-recumbent position because of the study site's concerns that these women would not tolerate standing upright and/or experience syncope. A notably greater proportion of women had missing orthostatic measurements when they received Addyi and alcohol together, compared to when taking Addyi alone or alcohol alone. Also, the proportion of missing data increased with increasing alcohol dose. Furthermore, the peak time for the missing data occurred between one and four hours after taking Addyi and alcohol, which is the time when Addyi achieves maximum blood concentrations; this observation further supports the Addyi-alcohol interaction. The primary reasons for the missing data were that these women were hypotensive or had symptoms consistent with hypotension in the semi-recumbent position and were precluded from standing up to prevent a possible occurrence of orthostatic hypotension and syncope. No severe hypotension or syncope was observed in this study because safety precautions were in place to avoid the occurrence of such events in hypotensive or symptomatic women who were not allowed to stand up for orthostatic measurements. On July 3, 2018, you submitted your rationale supporting the removal of the boxed warning and alcohol contraindication, stating that hypotension and syncope do not meet the regulatory definition of a serious adverse reaction and that no events of severe hypotension and syncope occurred in PMR 5.

On June 6, July 10, and August 10, 2018, you submitted the final study reports for three additional alcohol-interaction studies where alcohol was ingested several hours before taking Addyi. One study showed discontinuing alcohol (equivalent to 2 drinks in a 70 kg person) at least two hours before taking Addyi decreased the risk of hypotension and syncope. In the other two smaller studies, women drank alcohol with dinner (approximately 2 to 4 hours before bedtime) and received Addyi at bedtime; women were instructed to lie down for bed within 5 minutes after taking Addyi. Vital signs after taking Addyi were not assessed until the following morning upon awakening. There were no cases of syncope or symptoms consistent with hypotension in these three studies.

We considered the findings from all alcohol interaction studies submitted to date and modified the labeling accordingly. We note that you have not submitted any new evidence regarding the use of Addyi with moderate/strong CYP3A4 inhibitors or in patients with hepatic impairment. We held a teleconference on January 22, 2019, to discuss the rationale for our labeling revisions. In your January 24, 2019, amendment to S-006, you continued to propose the removal of the

boxed warning for the interaction of Addyi with alcohol, with moderate/strong CYP3A4 inhibitors, and in patients with hepatic impairment and continued to state that you do not believe hypotension and syncope are serious adverse reactions that warrant a boxed warning.

We refer to the modified labeling language that we forwarded to you by email on February 19, 2019, and to our March 5, 2019, advice letter indicating that we determined that the labeling revisions contained in the February 19, 2019, email are needed.

We have completed the review of your submissions received through March 18, 2019, discussed your submissions with you, and you and the agency have not reached agreement. We find that your proposed labeling changes do not adequately address the new safety information described above.

The labeling revisions contained in the February 19, 2019, email communication and that we referred to in our March 5, 2019, advice letter reflect our assessments of the totality of the available evidence, as follows:

- Boxed Warning and Contraindication: Based on the totality of the evidence, we conclude that taking alcohol and Addyi at the same time increases the risk of severe hypotension and syncope. This serious risk of the drug-alcohol interaction was observed in the preapproval study SPR-12-03 and is supported by the findings from PMR 5 described above. We determine that severe hypotension and syncope are serious adverse drug reactions because they could jeopardize a patient by leading to accidents and serious injuries. FDA may require a Boxed Warning for certain contraindications or serious warnings. This includes situations where there is an adverse reaction so serious in proportion to the potential benefit of the drug that it is essential that it be considered in assessing the risks and benefits of the drug or where a serious adverse reaction can be prevented or reduced in frequency or severity by appropriate use of the drug.[1] We consider the risk of severe hypotension/syncope when (1) Addyi and alcohol are taken at the same time, (2) Addyi is taken with moderate to strong CYP3A4 inhibitors, or (3) Addyi is used in patients with hepatic impairment, to be so serious in proportion to the potential drug benefit that it is essential that it be considered in assessing the risks and benefits of using the drug. We also consider these adverse reactions to be ones that can be prevented or reduced in frequency or severity by appropriate use of the drug (not taking Addyi close in time with alcohol, not using Addyi with moderate or strong CYP3A4 inhibitors or in patients with hepatic impairment). For the aforementioned reasons, the retention of the boxed warning is warranted.

[1] See 21 CFR 201.57(c)(1); Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling for Human Prescription Drugs and Biological Products – Content and Format (Oct. 2011) ("Labeling Guidance") at § IV.

The Contraindications section of prescription drug labeling must describe situations in which the drug should not be used because the risk of use clearly outweighs any possible therapeutic benefit of that drug.[2] We consider a contraindication against taking Addyi within 2 hours of discontinuing alcohol to be warranted. Given the known interaction between alcohol and Addyi taken at the same time described above, with their immediate attendant risks (e.g., sudden falls with potentially serious injuries) that may jeopardize a patient, the risk of their use close in time clearly outweighs any potential benefit of Addyi. The other post-marketing studies show that discontinuing alcohol (up to 2 alcohol drinks for a 70 kg person) at least 2 hours prior to taking Addyi decreases this risk. We have determined that this additional information belongs in labeling, but this finding does not negate the need for a boxed warning and contraindication for taking Addyi and alcohol close together in time. The absence of serious injuries or death from severe syncope or hypotension in the subjects in these alcohol-interaction studies does not predict that such events would be unlikely to occur in real life. Subjects in these studies were carefully monitored in study units, were not allowed to stand when their blood pressures were low or they were symptomatic and/or were instructed to go to bed right after taking Addyi. In the real world, safety measures such as these are not in place to prevent or provide immediate assistance to women experiencing severe hypotension or syncope. It is also not realistic to assume that, in the real world, women would consistently go to bed immediately after taking Addyi and not ambulate during the night.

- Warnings and Precautions about the REMS: At this time, a REMS is required to ensure that the benefit of Addyi outweighs the risks of hypotension/syncope with Addyi-alcohol interaction. Therefore, retaining this Warnings/Precautions, and the information about the REMS in the Boxed Warning, is necessary.
- Adverse Reactions: We are requiring the inclusion of the details of the Addyi-alcohol interaction studies and relevant findings to assist prescribers in drawing informed conclusions about the study results and understanding the study limitations. We do not agree with your revisions because they do not support these objectives.

Under the authority of Section 505(o)(4)(E) of the FDCA, we are ordering you to make all of the changes in the labeling listed in the February 27, 2018, SLC Notification letter (attached), as modified in accordance with our email dated February 19, 2019 (attached).

Pursuant to Section 505(o)(4)(E), a changes being effected (CBE) supplement containing all of the changes to the labeling that are listed in the February 27, 2018, SLC Notification letter, as modified in accordance with our email dated February 19, 2019, must be received by FDA by April 26, 2019, for Addyi.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

[2] See 21 CFR 201.57(c)(5); Labeling Guidance at § III.

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED

We will consider your submission of the CBE supplement a request to withdraw your prior approval supplement submitted on March 29, 2018, under 21 CFR 314.65.

Alternatively, by April 16, 2019, you may appeal this Order using the Agency's established formal dispute resolution process as described in 21 CFR 10.75 and the Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level." http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM343101.pdf. The appeal should be submitted as a correspondence to your NDA referenced above. Identify the submission as "**Formal Dispute Resolution Request**" both on the cover letter and on the outside envelope. A copy of the submission should be sent to:

J. Paul Phillips, M.S.
CDER Formal Dispute Resolution Project Manager
Food and Drug Administration
Office of New Drugs
Building 22, Room 6300
10903 New Hampshire Avenue
Silver Spring, MD 20993

In addition, to expedite coordination of any such appeal, a copy of the submission should also be sent to:

Meredith Hillig, M.S.
Safety Regulatory Project Manager
Food and Drug Administration
Division of Bone, Reproductive and Urologic Products
Building 22, Room 5324
10903 New Hampshire Avenue
Silver Spring, MD 20993

Refer to the Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level" for further instruction regarding the content and format of your request. Questions regarding the formal dispute resolution process may be directed to J. Paul Phillips, M.S., CDER Formal Dispute Resolution Project Manager, at (301) 796-1270. Appeals received by the Agency later than April 16, 2019, will not be entertained.

Failure to respond to this Order within the specified timeframes is a violation of section 505(o)(4) of the FDCA and could subject you to civil monetary penalties under section 303(f)(4) of the FDCA, 21 U.S.C. § 333(f)(4), in the amount of up to $250,000 per violation, with additional penalties if the violation continues uncorrected. Further, such a violation would cause your product to be misbranded under section 502(z) of the Act, 21 U.S.C. § 352(z), which could subject you to additional enforcement actions, included but not limited to seizure of your product and injunction.

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

Sincerely,

{See appended electronic signature page}

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

ENCLOSURES:

Safety Labeling Change Notification Letter (February 27, 2018)
Redlined Prescribing Information (via email February 19, 2019, and referred to in the March 5, 2019, advice letter)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022526

SAFETY LABELING CHANGE NOTIFICATION

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 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Addyi® (flibanserin) Tablets.

Section 505(o)(4) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to make safety labeling changes based upon new safety information that FDA becomes aware of after approval of the drug or biological product.

We also refer to your submissions, dated December 21, 2016, containing the final clinical study report and dated October 16, 2017, containing an amendment to the final clinical study report, for Study SPR 15-001, conducted to address the following postmarketing requirement (PMR) listed in the August 18, 2015, approval letter:

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

We further refer to our January 2, 2018, fulfillment of postmarketing requirement letter for PMR 2939-5, informing you that safety labeling changes would be required based on the information identified in Study 15-001, which substantiated the safety concerns of concomitant administration of Addyi and alcohol in premenopausal women. In Study SPR 15-001, orthostatic hypotension was experienced by 60% of subjects co-administered Addyi and either 1.6 g/Kg or 0.4 g/Kg of alcohol, and orthostatic hypotension was experienced by 48% of subjects co-administered Addyi and 0.2 g/Kg of alcohol. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above and the teleconference held on June 22, 2017, we

believe that the new safety information should be included in the labeling for Addyi, as outlined below.

1. Under Section 5.1 Hypotension and Syncope due to an Interaction with Alcohol

   Revise existing language in the first paragraph (in regular font) to add the following text in *italics*:

   The use of ADDYI and alcohol increases the risk of severe hypotension and syncope. *In a dedicated alcohol interaction study conducted in 96 healthy premenopausal women, hypotension or orthostasis occurred in 60% of subjects co-administered high (0.6 g/kg) or mid dose alcohol (0.4 g/kg) and flibanserin 100 mg, and in 48% of subjects co-administered low dose alcohol (0.2 g/kg) and flibanserin 100 mg. High dose alcohol (0.6 g/kg) is the equivalent of three 12-ounce cans of beer containing 5% alcohol content, three 5-ounce glasses of wine containing 12% alcohol content, or three 1.5-ounce shots of 80-proof spirit in a 70 kg person. Mid dose alcohol (0.4 g/kg) is the equivalent of 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. Low dose alcohol (0.2 g/kg) is the equivalent of one 12-ounce cans of beer containing 5% alcohol content, one 5-ounce glasses of wine containing 12% alcohol content, or one-1.5 ounce shots of 80-proof spirit in a 70 kg person. Alcohol was consumed over 10 minutes in the morning while subjects were in the upright, seated position. The effect was most pronounced between 1 and 3 hours but persisted up to 10 hours post-dose.*

   In the same alcohol interaction study, flibanserin alone and in combination with alcohol caused somnolence in more than 80% of subjects. Approximately 50% of subjects reported dizziness. These effects were related to the dose of alcohol administered and correspond to known time to achieve peak plasma flibanserin concentrations (0.75 to 4.0 hours). Syncope was not observed because subjects were not permitted to stand for measurement of orthostatic vital signs if their initial blood pressures were <90/60 mmHg or if they already complained of dizziness after dosing. Subjects without a drinking history or mild drinkers appeared to be more susceptible to blood pressure changes. The study specifically excluded subjects with a history of syncope, orthostatic hypotension, hypotensive events, dizziness, or those with a resting systolic blood pressure less than 110 mmHg or diastolic blood pressure less than 60 mmHg. [See Clinical Pharmacology (12.2)]

   A prior study in 25 subjects (23 men and 2 premenopausal women), 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 ADDYI 100 mg and 0.4 g/kg alcohol (equivalent of 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, consumed over 10 minutes in the morning)

2. Under section 12.2, subsection Alcohol Interaction, add the following information from Study SPR 15-001 (in italic text) so that this information precedes existing information from Study SPR-12-03:

A randomized, placebo-controlled, single-dose, seven-way crossover study was conducted in 96 healthy premenopausal women (18-45 years of age) evaluating dizziness, syncope and hypotension following concomitant ingestion of different amounts of alcohol with and without flibanserin 100 mg. Subjects were equally stratified by drinking habit across treatment groups: 0-1, 2-4, 5-7, ≥8 drinks per week. Subjects received the following treatments randomized to 12 different sequences separated by a washout period.

- *0.6 g/kg (high dose alcohol) + flibanserin 100 mg*
- *0.6 g/kg (high dose alcohol) + placebo*
- *0.4 g/kg (mid dose alcohol) + flibanserin 100 mg*
- *0.4 g/kg (mid dose alcohol) + placebo*
- *0.2 g/kg (low dose alcohol) + flibanserin 100 mg*
- *0.2 g/kg (low dose alcohol) + placebo*
- *Flibanserin 100 mg*

Flibanserin alone and in combination with alcohol caused somnolence in more than 80% of subjects. In subjects receiving high or mid dose alcohol plus flibanserin, 60% met criteria for orthostatic hypotension. In subjects receiving low dose alcohol plus flibanserin, 48% met criteria for orthostatic hypotension. The effect of co-administration peaked between 1 and 3 hours and persisted up to 10 hours post-dose. Approximately 50% of subjects reported dizziness. These effects are related to the dose of alcohol administered and correspond to the timing of maximum observed plasma concentrations. Subjects without a drinking history or mild drinkers appear to be more susceptible to the blood pressure changes. Syncope was not observed in the study because the subjects were not permitted to stand for orthostatic vital signs if initial blood pressures were <90/60 mmHg or if the subject complained of dizziness after dosing. This study specifically excluded subjects with a history of syncope, orthostatic hypotension, hypotensive events, dizziness, or those with a resting systolic blood pressure less than 110 mmHg or diastolic blood pressure less than 60 mmHg.

3. Insert the following table showing the incidence of adverse events of special interest in Study SPR-15-001.

Adverse events of special interest: subjects (% subjects)

	0.6 g/kg + flibanserin	***0.6 g/kg + Placebo***	***0.4 g/kg + flibanserin***	***0.4 g/kg + Placebo***	***0.2 g/kg + flibanserin***	***0.2 g/kg + Placebo***	***flibanserin***
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Somnolence	*73 (88)*	*34 (41)*	*76 (89)*	*33 (39)*	*77 (81)*	*22 (25)*	*76 (84)*
Dizziness*	*46 (55)*	*18 (21)*	*41 (48)*	*16 (19)*	*29 (31)*	*6 (7)*	*30 (33)*
Any orthostasis†	*50 (60)*	*36 (43)*	*51 (60)*	*35 (41)*	*46 (48)*	*46 (52)*	*38 (42)*
Hypotension	*34 (41)*	*14 (17)*	*32 (38)*	*13 (15)*	*25 (26)*	*10 (11)*	*16 (18)*

AE*							

**WOCF, worst observation carried forward*
† greatest number of subjects meeting any criteria for orthostasis at any time point during treatment (Source, Applicant Table 14.3.5.3, 3/20/17 submission)
Subjects in "Any orthostasis" and "Hypotension AE" overlap and are not mutually exclusive

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a rebuttal statement detailing the reasons why such a change is not warranted. If you submit a supplement that includes only language identical to that specified above, the supplement may be submitted as a changes being effected (CBE-0) supplement. If the supplement includes proposed language that differs from that above, submit a prior approval supplement (PAS).

Requirements under section 505(o)(4) apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug approved under an NDA, including discontinued products, unless approval of an application has been withdrawn in the Federal Register. Therefore, the requirements described in this letter apply to you, unless approval of your application has been withdrawn in the Federal Register.

Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – REBUTTAL (CHANGE NOT WARRANTED)."

Prominently identify subsequent submissions related to the safety labeling changes supplement with the following wording in bold capital letters at the top of the first page of the submission:

SUPPLEMENT <<insert assigned #>>
SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT

In addition, we propose additional labeling changes that are not considered new safety information as defined in section 505-1(b)(3) of the FDCA. We ask that you submit revised labeling to address our comments #4 and #5 above in 30 days.

4. Incidence of anxiety in controlled trials:
   On further review of your Phase 3 clinical trial adverse event datasets used to support the approval of flibanserin 100mg taken daily at bedtime, the incidence rate of anxiety and anxiety-related conditions appears to exceed the 2% threshold. Therefore, the incidence should be reflected in current labeling. We ask that you:

   a. Reanalyze your data from Studies 511.71, 511.75, 511.77, 511.147 and include events of anxiety, generalized anxiety disorder, nervousness, panic attacks, panic disorders. Explore MedDRA version 13.1 to include all relevant terms.

   b. Propose a labeling update to reflect the data obtained. The update should include amendments to Tables 1 and 2 of labeling and the "Less Common Adverse Reactions" section of labeling.

5. For Phase 3 Studies 511.71, 511.75, and 511.147, provide cumulative distribution function (CDF) plots showing the percentage of patients who received flibanserin 100 mg and placebo for the following:
   a. The mean change from baseline for satisfying sexual events (SSEs) per 28 days
   b. The mean change from baseline for Female Sexual Function Index (FSFI) sexual desire domain score.
   c. The mean change from baseline for Female Sexual Distress Scale - revised (FSDS-R), Question 13 response.

   We also request a bar chart for the mean changes from baseline for FSDS-R Question 13 response.

If you have any questions, call Meredith Hillig, MS, Safety Regulatory 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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINE P NGUYEN
02/27/2018

- 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; therefore, taking ADDYI sooner than two hours after alcohol consumption is contraindicated. Counsel patients about the importance of separating alcohol and ADDYI by at least two hours. (4, 5.1)**
- **ADDYI is available only through a restricted program called the ADDYI REMS Program. (5.2)**
- **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, 5.3, 5.6)**

----------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----------
- Within two hours after alcohol consumption (4, 5 1)
- Moderate or strong cytochrome P450 3A4 (CYP3A4) inhibitors (4, 5 3)
- Hepatic impairment (4, 5 6)

----------WARNINGS AND PRECAUTIONS----------
- Hypotension and Syncope due to an Interaction with Alcohol: Counsel patients to wait at least two hours after consuming alcohol before taking ADDYI at bedtime Alternatively, counsel patients to skip the ADDYI dose at bedtime if the patient consumes alcohol in the evening After taking ADDYI at bedtime, advise patients to not use alcohol until the following day (5 1)
- ~~)~~
- ~~Hypotension and Syncope with CYP3A4 Inhibitors: The concomitant use of ADDYI with moderate or strong CYP3A4 inhibitors significantly increases flibanserin concentrations, which can lead to hypotension and syncope If the patient requires a moderate or strong CYP3A4 inhibitor discontinue ADDYI at least two days prior to starting the moderate or strong CYP3A4 inhibitor Discontinue the moderate or strong CYP3A4 inhibitor for two weeks before restarting ADDYI (5 2, 7)~~
- 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 5)
- 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 4)
- ~~Hypotension and Syncope 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 (5 5)~~
- ~~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 6 hours after each dose and until they know how ADDYI affects them (5 42)~~

----------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: X/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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FULL PRESCRIBING INFORMATION

WARNING: HYPOTENSION AND SYNCOPE IN CERTAIN SETTINGS

Contraindicated 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)]*. Therefore, taking ADDYI sooner than two hours after alcohol consumption is contraindicated *[see Contraindications (4)]*. Counsel patients about the importance of waiting at least two hours after consuming alcohol before taking ADDYI. Because of the increased risk of hypotension and syncope due to an interaction with alcohol, ADDYI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ADDYI REMS Program *[see Warnings and Precautions (5.2)]*.

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 (5.3)]*. 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 (5.6)]*. 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 (5.3)]*.

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:

- Within two hours after alcohol consumption [*see Boxed Warning* and *Warnings and Precautions (5.1, 5.2, 5.4)*].
- With concomitant use with moderate or strong CYP3A4 inhibitors *[see Boxed Warning and Warnings and Precautions (5.2, 5.4)]*.
- In patients with hepatic impairment *[see Boxed Warning and Warnings and Precautions (5.6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypotension and Syncope due to an Interaction with Alcohol

Taking ADDYI within two hours after consuming alcohol ~~may~~ increases the risk of severe hypotension and syncope, and is contraindicated *[see Contraindications (4)]*. To reduce this risk, counsel patients to wait at least two hours after consuming alcohol before taking ADDYI at bedtime. Alternatively, counsel patients to skip the ADDYI dose if the patient consumed alcohol ~~in the~~that evening. After taking ADDYI at bedtime, advise patients to not use alcohol until the following day.

ADDYI is available only through a restricted program under a REMS *[see Boxed Warning and Warnings and Precautions (5.2)]*.

5.2 ADDYI REMS Program

ADDYI is available only through a restricted program under a REMS called the ADDYI REMS Program, because of the increased risk of severe hypotension and syncope due to an interaction between ADDYI and alcohol *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Notable requirements of the ADDYI REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- Pharmacies must be certified with the program and must only dispense to patients pursuant to a prescription from a certified prescriber.

Further information, including a list of qualified pharmacies, is available at www.AddyiREMS.com or 844-746-5745.

5.3 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 to 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)]*.

5.4 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, 5.3), 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)]*.

5.5 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.

5.6 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)]*.

5.7 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, 5.3, 5.5, 5.6)]*
- CNS depression *[see Warnings and Precautions (5.4)]*

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 (5.4)]*. 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

Commented [A1]: To Sprout: We have revised this section describing details of the 4 alcohol interaction studies However, we are providing a clean version of this section, and not a tracked version, for ease of review

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, those with 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, Contraindications (4), Warnings and Precautions (5.1, 5.4 and 5.5)*].

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 severe 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 (5.4, 5.5)*].

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 or resting blood pressure less than 110/60 mmHg. 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 (5.3), 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 (5.3), 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 concomitant use 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	The concomitant use of ADDYI with alcohol is contraindicated.
Other CNS Depressants	
Examples	Diphenhydramine, opioids, hypnotics, benzodiazepines
Clinical Implications	The concomitant use~~co-administration~~ 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 (5.3), 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. Johns 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 (5.6), 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.

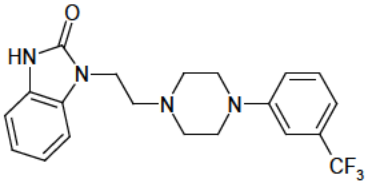
10 OVERDOSAGE

Overdosage of ADDYI may cause an increase in the incidence or severity of any of the reported adverse reactions *[see Warnings and Precautions (5.4, 5.5) 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)

~~. A randomized, double-blind, single-dose, cross-over, dedicated alcohol interaction study was conducted in 25 healthy subjects (23 men and 2 premenopausal women). In this study, 68%, 16%, 8% and 8% subjects reported a history of drinking 5-6, 7-10, 11-15 and 16-21 drinks per week, respectively. Subjects received~~

~~one of the following five treatments [ADDYI and alcohol were administered in the morning and the alcohol was consumed in 10 minutes. ADDYI is to be only administered at bedtime, *see Dosage and Administration (2.1)]*:~~

- ~~100 mg of ADDYI alone~~
- ~~0.4 g/kg 95% ethanol (equivalent to two 12-ounce cans of beer containing 5% alcohol content, two 5-ounce glasses of wine containing 12% alcohol, or two 1.5-ounce shots of 80-proof spirit in a 70-kg person)~~
- ~~0.8 g/kg 95% ethanol (equivalent to four 12-ounce cans of beer containing 5% alcohol content, four 5-ounce glasses of wine containing 12% alcohol, or four 1.5-ounce shots of 80-proof spirit in a 70-kg person)~~
- ~~100 mg of ADDYI in combination with 0.4 g/kg 95% ethanol~~
- ~~100 mg of ADDYI in combination with 0.8 g/kg 95% ethanol~~

~~Patients who received ADDYI with alcohol had a higher incidence of somnolence than patients who received ADDYI alone or alcohol alone *[see Warnings and Precautions (5.4)]*. There were no significant changes in the pharmacokinetics of flibanserin when administered with or without alcohol.~~

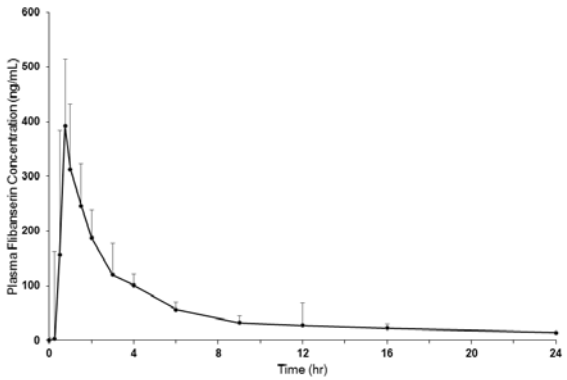
Cardiac Electrophysiology

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 (5.6)]*.

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-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 (5.3), Adverse Reactions (6.1) and Drug Interactions (7)]*.

Strong CYP3A4 Inhibitor (Ketoconazole)
In a study of 24 healthy female subjects, ketoconazole 400 mg administered once daily for 5 days following a light breakfast increased flibanserin 50 mg single-dose exposure (AUC_{0-inf}) 4.5-fold and Cmax 1.8-fold compared to flibanserin 50 mg alone *[see Warning and Precautions (5.3), Adverse Reactions (6.1) and Drug Interactions (7)]*.

Strong CYP3A4 Inhibitor (Itraconazole)
In a study of 12 healthy male and female subjects, itraconazole 200 mg administered once daily for 4 days following a loading dose of 400 mg increased flibanserin 50 mg single dose exposure (AUC_{0-inf}) 2.6-fold and 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-inf}) by 1.4-fold and Cmax 1.1-fold compared to flibanserin 100 mg alone *[see Warning and Precautions (5.3), 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	AUC0-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 Cmax 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 Cmax (1.0-fold change) but hydroxybupropion $AUC_{t,ss}$ decreased by 9% and Cmax 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	**AUC0-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, 1.2)		1.0 (0.4, 1.5)	
Change from baseline (Median)	1.0	0.0	1.0	0.5	1.0	0.5
Median treatment difference	1.0		0.5		0.5	
p-value vs placebo	*p<0.01*		*p<0.01*		*p<0.0001*	
e-Diary Desire						
Baseline (Mean)	12.9	11.8	12.1	10.2	*Not Used*	*Not Used*
Change from baseline at Week 24 (Mean)	9.1	6.9	8.3	6.7		
Treatment diff. (95% CI)	2.3 (-0 1, 4.7)		1.7 (-0.5, 4.0)			
p-value vs placebo	NS		NS			
FSFI Desire						
Baseline (Mean)	1.9	1.9	1.8	1.8	1.9	1.9
Change from baseline at Week 24 (Mean)	0.9	0.5	0.9	0.5	1.0	0.7
Treatment diff. (95% CI)	0.4 (0.2, 0.5)		0.3 (0.2, 0.5)		0.3 (0.2, 0.4)	
p-value vs placebo	*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 Week 24 (Mean)	-0.8	-0.5	-0.8	-0.5	-1.0	-0.7
Treatment diff. (95% CI)	-0.4 (-0 5, -0 2)		-0 3 (-0 4, -0 1)		-0 3 (-0 4, -0 1)	
p-value vs placebo	*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 (5.4)]*.

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 with alcohol or with moderate or strong CYP3A4 inhibitors. Inform patients that alcohol use and moderate or strong CYP3A4 inhibitors are contraindicated. Counsel patients about the importance of abstaining from alcohol and to ask about drug interactions before starting a new prescription or non-prescription medication or using other products that contain CYP3A4 inhibitors (e.g., grapefruit juice or 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, 5.3)]*.

Commented [A2]: To Sprout: please make the language in this section align with sections 4 and 5

ADDYI is available only through a restricted program called the ADDYI REMS Program. Patients can only obtain ADDYI from certified pharmacies participating in the program. Therefore, provide patients with the telephone number and website for information on how to obtain ADDYI.

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, benzodiazepenes, 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 (5.4)]*.

Nursing Mothers

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

Bedtime Dosing

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

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/s/

JULIE G BEITZ
04/11/2019 09:46:27 AM