

ADDYI®
(flibanserin) tablets 100 mg

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 increases the risk of severe hypotension and syncope; therefore, alcohol use is contraindicated. Before prescribing ADDYI, assess the likelihood of the patient abstaining from alcohol. Counsel patients prescribed ADDYI about the importance of abstaining from alcohol. (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

- Alcohol (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 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 6 hours after each dose and until they know how ADDYI affects them. (5.4)

ADVERSE REACTIONS

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

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

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: 05/2018

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FULL PRESCRIBING INFORMATION

WARNING: HYPOTENSION AND SYNCOPE IN CERTAIN SETTINGS

Contraindicated with Alcohol

The use of ADDYI® (flibanserin) tablets and alcohol increases the risk of severe hypotension and syncope [see *Warnings and Precautions (5.1)*]. Therefore, alcohol use is contraindicated in patients taking ADDYI [see *Contraindications (4)*]. Before prescribing ADDYI, assess the likelihood of the patient abstaining from alcohol, taking into account the patient's current and past drinking behavior, and other pertinent social and medical history. Counsel patients who are prescribed ADDYI about the importance of abstaining from alcohol use. 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® (flibanserin) tablets are 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:

- With use of alcohol [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

Alcohol use is contraindicated in patients taking ADDYI. Before prescribing ADDYI, the healthcare provider must assess the likelihood of the patient abstaining from

alcohol use, taking into account the patient's current and past drinking behavior, and other pertinent social and medical history. Counsel patients who are prescribed ADDYI about the importance of abstaining from alcohol use [see *Drug Interactions (7)*].

The use of ADDYI and alcohol increases the risk of severe hypotension and syncope. In a dedicated alcohol interaction study conducted in 25 subjects (23 men and 2 premenopausal women), hypotension or syncope requiring therapeutic intervention (ammonia salts and/or placement in supine or Trendelenburg 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) [see *Clinical Pharmacology (12.2)*]. In these four subjects, all of whom were men, the magnitude of the systolic blood pressure reductions ranged from about 28 to 54 mmHg and the magnitude of the diastolic blood pressure reductions ranged from about 24 to 46 mmHg. In addition, 6 (25%) of the 24 subjects co-administered ADDYI 100 mg and 0.8 g/kg alcohol experienced orthostatic hypotension when standing from a sitting position. The magnitude of the systolic blood pressure reductions 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.

ADDYI is available only through a restricted program under a REMS [see *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 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 $\geq 1\%$ of patients receiving 100 mg ADDYI at bedtime and at a higher incidence than placebo-treated patients.

Most Common Adverse Reactions

Table 2 summarizes the most common adverse reactions reported in four trials of premenopausal women with HSDD. This table shows adverse reactions reported in at least 2% of patients treated with ADDYI and at a higher incidence than with placebo [see Warnings and Precautions (5.4)]. 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 $\geq 2\%$ of patients receiving 100 mg ADDYI at bedtime and at a higher incidence than placebo-treated patients.

Less Common Adverse Reactions

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

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

Appendicitis

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

Accidental Injury

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

Adverse Reactions in Patients Who Reported Hormonal Contraceptive Use

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

Data from Other Trials

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

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

Hypotension, Syncope, and CNS Depression with Alcohol

In a cross-over alcohol interaction study of 100 mg ADDYI and alcohol in 25 healthy subjects dosed in the morning [see Clinical Pharmacology (12.2)], somnolence was reported in 67%, 74%, and 92% of subjects who received ADDYI alone, ADDYI in combination with 0.4 g/kg ethanol, and ADDYI in combination with 0.8 g/kg ethanol, respectively. In the group receiving ADDYI in combination with 0.4 g/kg ethanol, 4/23 (17%) subjects had substantial reductions in blood pressure, resulting in hypotension and/or syncope requiring medical intervention. In the group receiving ADDYI in combination with 0.8 g/kg ethanol, 6/24 (25%) subjects experienced orthostatic hypotension [see Boxed Warning, Contraindications (4), Warnings and Precautions (5.1, 5.3)].

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 <i>Warnings and Precautions (5.1) and Clinical Pharmacology (12.2)</i>].
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 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 <i>Warnings and Precautions (5.3), Adverse Reactions (6.1), and Clinical Pharmacology (12.3)</i>].
Preventing or Managing DI	The concomitant use of ADDYI with moderate or strong CYP3A4 inhibitors is contraindicated.
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, rifapentine, St. John's Wort
Clinical Implications	The concomitant use of ADDYI with CYP3A4 inducers substantially decreases flibanserin exposure compared to the use of ADDYI alone.
Preventing or Managing DI	The concomitant use of ADDYI with CYP3A4 inducers is not recommended.
Digoxin or Other P-glycoprotein Substrates	
Examples	Digoxin, sirolimus
Clinical Implications	The concomitant use of ADDYI with digoxin, a drug that is transported by P-glycoprotein (P-gp), increases the digoxin concentration [see <i>Clinical Pharmacology (12.3)</i>]. This may lead to digoxin toxicity.
Preventing or Managing DI	Increase monitoring of concentrations of drugs transported by P-gp that have a narrow therapeutic index (e.g., digoxin).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

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

Pregnant rabbits were administered flibanserin at doses of 0, 20, 40 and 80 mg/kg/day (4, 8 and 16 times the clinical exposure at the recommended human dose) during organogenesis. Marked decreases in maternal body weight gain (>75%), abortion and complete litter resorption were observed at 40 and 80 mg/kg/day indicating significant maternal toxicity at these doses. Increases in resorptions and decreased fetal weights were observed at ≥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.

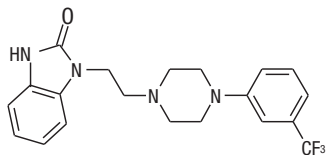
10 OVERDOSAGE

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 D₄ receptors.

Alcohol Interaction

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.

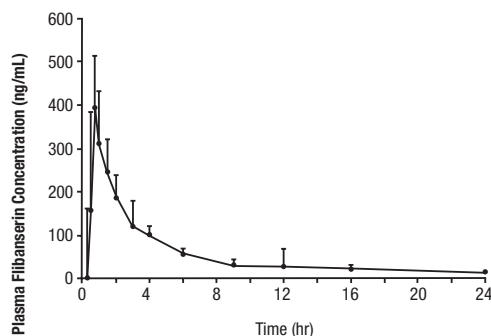
Cardiac Electrophysiology

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 C_{max} 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-∞}) with once-daily dosing of 100 mg of flibanserin was increased 1.4-fold as compared to a single dose.

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



Absorption

Following oral administration of a single 100 mg dose of flibanserin in healthy premenopausal women (N=8), mean (SD) C_{max} was 419 (206) ng/mL and mean (SD) AUC_{0-inf} was 1543 (511) ng*hr/mL. Median (range) time to reach C_{max} 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-inf} by 1.18-, 1.43-, and 1.56-fold; increased C_{max} by 1.02-, 1.13-, and 1.15-fold; and prolonged median T_{max} 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 ¹⁴C-radiolabeled flibanserin, 44% of the total ¹⁴C-flibanserin related radioactivity was recovered in urine, and 51% was recovered in feces. Flibanserin is extensively metabolized to at least 35 metabolites, most of them occurring in low concentrations in plasma. Two metabolites could be characterized that showed plasma concentrations similar to that achieved with flibanserin: 6,21-dihydroxy-flibanserin-6,21-disulfate and 6-hydroxy-flibanserin-6-sulfate. These two metabolites are inactive.

Excretion

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

Specific Populations

Hepatic Impairment

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

possible to make conclusions about the quantitative effect of moderate hepatic impairment on flibanserin exposure. ADDYI is contraindicated in patients with hepatic impairment [see Warnings and Precautions (5.6)].

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-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_{0-inf} 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_{0-inf} 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 Warnings 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 Warnings 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 Warnings 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	AUC _{0-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-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-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-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-inf} by 1.09-fold and the EE Cmax by 1.1-fold. Flibanserin decreased the LNG AUC_{0-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_{0-inf} (1.0-fold change) and Cmax (1.0-fold change) but hydroxybupropion AUC_{0-inf} decreased by 9% and Cmax by 11%.

Table 5 Effects of Flibanserin on Exposure of Other Drug

Coadministered Drug(s) and Dose(s)	Dose of ADDYI	n	Geometric Mean Ratio (90% Confidence Interval) of Pharmacokinetic Parameters of Coadministered Drug with/without Flibanserin No Effect =1.00	
			Cmax	AUC _{0-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, C_{max} and AUC_{0-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 C_{max} and AUC of flibanserin 50 mg twice daily was decreased by 4% and increased by 18%, respectively, compared to exposures among 19 extensive metabolizers, intermediate metabolizers and ultra rapid metabolizers of CYP2D6.

CYP2C9 Poor Metabolizers

A study comparing flibanserin exposure in CYP2C9 poor metabolizers to CYP2C9 extensive metabolizers was conducted in lieu of a drug interaction study with ADDYI and a strong CYP2C9 inhibitor. In 8 women who were poor metabolizers of CYP2C9, C_{max} and AUC_{0-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 (adenoacanthoma and adenocarcinomas) were observed in female mice administered flibanserin at doses of 200 and 1200 mg/kg/day (exposures, based on AUC, were 3 and 10 times the clinical exposures at the recommended clinical dose). No increases in mammary tumors were observed in male mice. Statistically significant increases were also seen for combined hepatocellular adenomas/carcinomas in female mice treated with flibanserin 1200 mg/kg/day and for hepatocellular carcinomas in male mice treated with flibanserin 1000 mg/kg/day (exposures, based on AUC, were 8 times the clinical exposure at the recommended clinical dose).

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

Mutagenesis

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

Impairment of Fertility

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

14 CLINICAL STUDIES

14.1 Trials in Premenopausal HSDD Patients

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

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

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

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

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

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

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

Full Analysis Set	Study 1		Study 2 ¹		Study 3	
	ADDYI	Placebo	ADDYI	Placebo	ADDYI	Placebo
	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	<i>Not Used</i>	<i>Not Used</i>
Change from baseline at Week 24 (Mean)	9.1	6.9	8.3	6.7		
Treatment diff. (95% CI)	2.3 (-0.1, 4.7)		1.7 (-0.5, 4.0)			
p-value vs placebo	NS		NS			

Full Analysis Set	Study 1		Study 2 ¹		Study 3	
	ADDYI	Placebo	ADDYI	Placebo	ADDYI	Placebo
	n=280	n=290	n=365	n=372	n=532	n=536
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 13³						
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.

¹Excludes subjects from two study sites that had data integrity issues

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

³A 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° to 30°C (59° to 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)].

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, benzodiazepines, opioids). The risk is also increased if ADDYI is taken during waking hours. Advise patients to avoid engaging in activities requiring full alertness (e.g., operating machinery or driving) until at least 6 hours after the ADDYI dose and until they know how ADDYI affects them [see Warnings and Precautions (5.4)].

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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ADDYI tablets are covered by U.S. Patents Nos. 7,151,103; 7,420,057;

7,183,410; 8,227,471; 9,468,639; and 9,782,403

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MEDICATION GUIDE
ADDYI® (add-ee)
(flibanserin)Tablets

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

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

Your risk of SEVERE LOW BLOOD PRESSURE AND FAINTING (LOSS OF CONSCIOUSNESS) is increased if you take ADDYI and:

- **drink alcohol. Do not drink alcohol if you take ADDYI.**
- **take certain prescription medicines, over-the-counter medicines, or herbal supplements. Do not take or start taking any prescription medicines, over-the-counter medicines, or herbal supplements while taking ADDYI until you have talked with your doctor.** Your doctor will tell you if it is safe to take other medicines or herbal supplements while you are taking ADDYI.
- **have liver problems.** Do not take ADDYI if you have liver problems.

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

ADDYI is only available through the ADDYI risk evaluation and mitigation strategy (REMS) Program because of the increased risk of severe low blood pressure and fainting (loss of consciousness) with alcohol use. You can only get ADDYI from pharmacies that are enrolled in the ADDYI REMS Program. For more information about the Program and a list of pharmacies that are enrolled in the ADDYI REMS Program, go to www.AddyiREMS.com or call 1-844-PINK-PILL (1-844-746-5745).

What is ADDYI?

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

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

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

ADDYI is not for use to improve sexual performance.

ADDYI is not for use in children.

Who should not take ADDYI?

Do not take ADDYI if you:

- drink alcohol
- take certain other medicines. Taking ADDYI with certain other medicines can increase the amount of ADDYI in your blood and cause severe low blood pressure, fainting (loss of consciousness), and sleepiness.

Do not take ADDYI if you are taking any of the following medicines:

- certain medicines used to treat HIV-1 infection, such as:
 - amprenavir
 - ritonavir (NORVIR)
 - indinavir (CRIXIVAN)
 - atazanavir (REYATAZ)
 - saquinavir (INVIRASE)
 - fosamprenavir (LEXIVA)
 - nelfinavir (VIRACEPT)
- certain medicines that you take by mouth used to treat fungal infections, such as:
 - fluconazole (DIFLUCAN)
 - itraconazole (ONMEL, SPORANOX)
 - ketoconazole
 - posaconazole (NOXAFIL)
- certain antibiotics, including:
 - ciprofloxacin (CIPRO, CIPRO XR)
 - telithromycin (KETEK)
 - erythromycin (ERY-TAB, ERYC, PCE)
 - clarithromycin (BIAVIN)
- certain medicines used to treat Hepatitis C infection, such as:
 - boceprevir (VICTRELIS)
 - telaprevir
- certain medicines used to treat high blood pressure, chest pain (angina), or other heart problems, such as:
 - diltiazem (CARDIZEM®, CARDIZEM CD, CARDIZEM LA, CARTIA XT, DILT CD, DILTZAC, TAZTIA XT, Tiazac)
 - verapamil (CALAN, CALAN SR, COVERA-HS, Verelan, Verelan PM)
 - conivaptan (Vaprisol)
- nefazodone: a medicine used to treat depression

Ask your doctor or pharmacist if you are not sure if you take any of the medicines listed above.

These are examples of the medicines that you should not take if you are taking ADDYI. Tell your doctor about all of the medicines you take before you start taking ADDYI.

- have liver problems

What should I tell my doctor before taking ADDYI?

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

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

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

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

How should I take ADDYI?

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

What should I avoid while taking ADDYI?

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

What are the possible side effects of ADDYI?

ADDYI can cause serious side effects, including:

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

The most common side effects of ADDYI include:

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

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

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

How should I store ADDYI?

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

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

General information about the safe and effective use of ADDYI

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

What are the ingredients in ADDYI?

Active ingredient: flibanserin

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



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For more information go to www.ADDYI.com or call 1-844-PINK-PILL (1-844-746-5745).

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

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