PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**ADDYI**™

Flibanserin Tablets

100 mg, Oral

Central Nervous System Agent

AHFS code 28:92

ATC code G02CX02

Sprout Pharmaceuticals, Inc.
4350 Lassiter at North Hills Ave, #260
Raleigh, North Carolina
27609, US

Date of Initial Authorization:
FEB 27, 2018

Date of Revision:
NOV 25, 2025

Imported/Distributed By
Searchlight Pharma Inc.
1600 Notre-Dame Street W. Suite 312
Montreal, QC
H3J 1M1

Submission Control Number: 300236

RECENT MAJOR LABEL CHANGES

N/A	
N/A	

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS AND CLINICAL USE

ADDYI (flibanserin tablets) is indicated for the treatment of premenopausal and naturally postmenopausal women ≤ 60 years of age with acquired, generalized hypoactive sexual desire disorder (HSDD), as characterized by low sexual desire for a minimum of 6 months, which occurs 75-100% of the time, 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.

Special Diagnostic Considerations

- "Acquired" refers to HSDD that develops in a patient who previously had no problems with sexual desire.
- "Generalized" refers to HSDD that occurs regardless of the type of stimulation, situation or partner.
- There is no normative age- or gender-related data on frequency or degree of sexual desire. Therefore, the diagnosis must rely on clinical judgement based on the individual's characteristics, interpersonal determinants, life context and cultural settings.
- The clinician may need to assess both partners when discrepancies in sexual desire prompt the call for professional attention.
- It is recommended to use the ADDYI Prescriber Checklist when making the diagnosis. The Checklist can be obtained from addyi.ca.

Limitations of Use

- ADDYI is not indicated for use in men.
- ADDYI is not indicated to enhance sexual performance.

1.1 Pediatrics

Safety and efficacy of ADDYI has not been established in patients under 18 years of age.

1.2 Geriatrics

Safety and efficacy of ADDYI has not been established in patients > 60 years of age.

2 CONTRAINDICATIONS

ADDYI is contraindicated in:

- Patients with known hypersensitivity to flibanserin or any component of the ADDYI tablet formulation. For a complete listing, see the DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the product monograph.

- Patients taking a moderate or strong CYP3A4 inhibitor due to the risk of significantly increased flibanserin plasma concentrations which may result in severe hypotension and syncope.
- Patients with hepatic impairment, due to the risk of significantly increased flibanserin plasma concentrations which may result in severe hypotension and syncope.
- Patients who are pregnant or breastfeeding.
- Patients whose resting systolic blood pressure is less than 110 mmHg or diastolic blood pressure less than 60 mmHg and who are using alcohol as this was not studied.
- Patients who are taking P-glycoprotein (P-gp) substrates (digoxin) as risk of digoxin toxicity is increased in these patients; Flibanserin increased exposure to digoxin by 2.0-fold and C_{max} by 1.5-fold, compared to digoxin alone (see Drug-Drug Interactions).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

RISK OF HYPOTENSION AND SYNCOPE IN CERTAIN SETTINGS

- The use of ADDYI can cause severe hypotension and syncope. Counsel patients to use ADDYI before bedtime and immediately lie supine if they feel they are about to pass out. Counsel patients that the use of ADDYI and alcohol together close in time increases the risk of severe hypotension and syncope [see WARNINGS AND PRECAUTIONS/Neurologic/Use with Alcohol].

- ADDYI can cause CNS depression (e.g., somnolence, sedation). Counsel patients not to drive or engage in other activities requiring full alertness after taking ADDYI until they know how ADDYI affects them. 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.

- The concomitant use of ADDYI with moderate or strong inhibitors of CYP3A4 or in patients with hepatic impairment causes a significant increase of flibanserin concentration. This increase in exposure to flibanserin may be associated with severe hypotension and syncope. The concomitant use of ADDYI with moderate or strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, fluconazole, ritonavir, or clarithromycin) is contraindicated (see CONTRAINDICATIONS; DRUG INTERACTIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- It is recommended to use the ADDYI Prescriber Checklist and ADDYI Pharmacist's Checklist before prescribing and dispensing ADDYI. The Checklists can be obtained from addyi.ca.
- Before prescribing ADDYI collect medical history and concomitant medications use from all patients.
- ADDYI is contraindicated for use in patients with any degree of hepatic impairment. See CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and DRUG INTERACTIONS sections.

- CYP2C19 poor metabolizers had increased flibanserin exposures compared to CYP2C19 extensive metabolizers (see DRUG INTERACTIONS and CLINICAL PHARMACOLOGY). Therefore, increase monitoring for adverse reactions (e.g., hypotension and syncope) in patients who are CYP2C19 poor metabolizers (see WARNINGS AND PRECAUTIONS/Endocrine and Metabolism/Genetic Polymorphism).
- Moderate or strong inhibitors of CYP3A4 cause a significant increase in exposure to flibanserin when co-administered with ADDYI and are therefore contraindicated (see CONTRAINDICATIONS, and DRUG INTERACTIONS).
- Counsel patients on the safe use of ADDYI (see WARNINGS AND PRECAUTIONS).

4.2 Recommended Dose and Dosage Adjustment

- The recommended dosage of ADDYI is 100 mg, taken orally once daily at bedtime. Discontinue treatment after 8 weeks if the patient does not report an improvement in sexual desire and/or a reduction in associated distress.
- Counsel patients to not exceed the recommended dose.

4.3 Administration

- ADDYI is dosed at bedtime because administration during waking hours increases the risks of hypotension, syncope, and CNS depression (such as somnolence and sedation).

Use of ADDYI Before or After 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.
- 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 severe hypotension and syncope, carefully monitor the patient for signs of hypotension and syncope.

4.5 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.

5 OVERDOSAGE

Limited information is available with regard to overdose in humans.

Overdosage may cause an increase in incidence or severity of any of the reported adverse reactions. Acute overdosage has also been associated with seizure-like activity, hypertension, unresponsiveness to pain, mydriasis, slurred speech and fever.

Treatment should address the symptoms and supportive measures as needed.

There is no known antidote specific for flibanserin.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 100 mg	croscarmellose sodium, hypromellose, iron oxide red, lactose monohydrate, macrogol, magnesium stearate, microcrystalline cellulose, talc, and titanium dioxide.

Each ADDYI tablet contains 100 mg of the active ingredient, flibanserin.

ADDYI is a pink, oval, film-coated tablet debossed on one side with “f100” and blank on the other side.

Available in bottles of 30 tablets.

7 WARNINGS AND PRECAUTIONS

Please see SERIOUS WARNINGS AND PRECAUTIONS BOX.

Carcinogenesis and Mutagenesis

Statistically significant increases in combined mammary tumours (adenoacanthomas and adenocarcinomas) were observed in female mice administered flibanserin at doses of 200 and 1200 mg/kg/day (approximately 3 and 10 times the clinical exposures) (see NON-CLINICAL TOXICOLOGY/Carcinogenesis).

The clinical significance of these findings is unknown.

Cardiovascular

Hypotension and Syncope: The use of ADDYI can cause hypotension and syncope. In eight, randomized, placebo-controlled, double-blind trials in women with HSDD, hypotension was reported in 0.1% of ADDYI-treated patients and <0.1% of placebo treated patients; syncope was reported in 0.2% of ADDYI-treated patients and <0.1% of placebo-treated patients. The risk of hypotension and syncope is increased if ADDYI is taken during waking hours or if higher than the recommended dose is taken. ADDYI should be used with caution 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.

Heart Rate: A double-blind study in 56 men and women conducted to assess the changes to the electrocardiogram in healthy individuals found mildly increased heart rates and an increased incidence in palpitations (3 vs. 0) after a supra-therapeutic dose of 100 mg tid flibanserin vs. placebo (see CLINICAL PHARMACOLOGY).

In Phase 3 trials, tachycardia and palpitations were reported more frequently in patients taking ADDYI than placebo.

Effects on heart rate were also noted in a study evaluating the interaction of ADDYI with alcohol, where alcohol intake corresponded to a dose-dependent increase in heart rate (see WARNINGS AND PRECAUTIONS/ Neurologic/Use with alcohol). The maximum alcohol intake tested corresponded to doses ≥0.6 g/kg of 95% ethanol, estimated to be about three 1.5 oz spirits-type drinks for a 70 kg person.

ADDYI should be used with caution in patients with pre-existing cardiac conditions.

Driving and Operating Machinery

ADDYI can cause CNS depression (e.g., somnolence, sedation). Patients should not drive or engage in other activities requiring full alertness after taking ADDYI until they know how ADDYI affects them.

Endocrine and Metabolism

Genetic polymorphism: CYP2C19 poor metabolizers had increased flibanserin exposures compared to CYP2C19 extensive metabolizers. In a study with 9 subjects who were poor CYP2C19 metabolizers, syncope occurred in one subject (see DRUG INTERACTIONS; CLINICAL PHARMACOLOGY). Therefore, increase monitoring for adverse reactions (e.g., hypotension, dizziness, syncope, etc.) 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.

Moderate and strong CYP3A4 inhibitors: The concomitant use of ADDYI with moderate or strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, fluconazole, ritonavir, or clarithromycin) is contraindicated (see CONTRAINDICATIONS). See DOSAGE AND ADMINISTRATION section for dosing considerations in cases where a patient needs to use a moderate or strong CYP3A4 inhibitor and is using, or is planning to use, ADDYI.

Weak CYP3A4 inhibitors: Concomitant use of multiple weak CYP3A4 inhibitors (including certain herbal supplements and non-prescription drugs) could also lead to clinically relevant increases in flibanserin concentrations which may increase the risk of hypotension and syncope (see DRUG INTERACTIONS).

Hepatic/Biliary/Pancreatic

Flibanserin exposure increased 4.5-fold in patients with mild hepatic impairment and t½ was longer (26 hours compared to 10 hours in matching healthy controls), compared to those with normal hepatic function (see CLINICAL PHARMACOLOGY). The use of ADDYI in patients with any degree of hepatic impairment significantly increases flibanserin concentrations, which can lead to severe hypotension and syncope. Therefore, the use of ADDYI is contraindicated in patients with hepatic impairment (see CONTRAINDICATIONS).

Immune

Anaphylactic/ Hypersensitivity reactions: Rare anaphylactic reactions have been reported. Symptoms included difficulty breathing or rash. Supportive treatment should address the symptoms**.**

Neurologic

Central Nervous System (CNS) Depression: ADDYI can cause CNS depression (e.g., somnolence, sedation). In eight randomized, placebo-controlled, double-blind trials of women with HSDD, the incidence of somnolence, sedation or fatigue was 18% in patients treated with 100 mg ADDYI once daily at bedtime and 8% in placebo. The risk of CNS depression may be 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.

Counsel patients to use ADDYI before bedtime and immediately lie supine if they feel they are about to pass out.

Counsel patients not to drive or engage in other activities requiring full alertness after taking ADDYI until they know how ADDYI affects them. 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. (See DRIVING AND OPERATING MACHINERY.)

Use with Alcohol: Taking ADDYI within two hours after consuming alcohol increases the risk of severe hypotension and syncope. To reduce this risk, counsel patients to wait at least two hours after drinking one or two standard alcoholic drinks before taking ADDYI at bedtime. Patients who drink three or more standard alcoholic drinks should skip their ADDYI dose that evening. One standard alcoholic drink contains 14 grams of pure alcohol and is equivalent to one 12-ounce regular beer (5% alcohol), 5-ounces wine (12% alcohol), or 1.5 ounces of distilled spirits/shot (40% alcohol). After taking ADDYI at bedtime, advise patients to not use alcohol until the following day.

Concomitant administration of ADDYI and alcohol was not studied in postmenopausal women. Postmenopausal women should be advised of the risk of CNS depression, hypotension and syncope with concomitant alcohol administration.

Four studies have been completed to establish the interaction with concomitant of ADDYI and alcohol in premenopausal women.

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

In this study, somnolence was reported in 67%, 74%, and 92% of subjects who received ADDYI alone, ADDYI in combination with 0.4 g/kg alcohol, and ADDYI in combination with 0.8 g/kg alcohol, respectively.

In the second alcohol interaction study, 96 healthy premenopausal women received a single dose of 100 mg ADDYI concurrently with 0.2 g/kg, 0.4 g/kg, or 0.6 g/kg alcohol (equivalent to one, two or three alcoholic drinks in a 70 kg person, respectively) in the morning. The study excluded subjects with a

history of syncope, orthostatic hypotension, hypotensive events, and dizziness, and those with a resting systolic blood pressure less than 110 mmHg or diastolic blood pressure less than 60 mmHg.

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

In this study, somnolence was reported in 81-89% of subjects administered ADDYI with alcohol, compared to 25-41% of subjects administered alcohol alone and 84% of subjects taking ADDYI alone. Dizziness was reported in 27-40% of subjects administered ADDYI with alcohol, compared to 6-20% of subjects administered alcohol alone and 31% of subjects taking ADDYI alone.

In a third alcohol interaction study to assess alcohol use at various time intervals before administration of ADDYI, 64 healthy premenopausal women consumed 0.4 g/kg alcohol (equivalent to 2 alcoholic drinks in a 70 kg person) two, four or six hours prior to receiving ADDYI 100 mg or placebo in the afternoon. The study excluded subjects with a history or presence of orthostatic hypotension, history of hypotension, syncope, or dizziness. Prior to receiving alcohol, the subjects in the ADDYI arm had taken ADDYI for three days to achieve steady state. Syncope occurred in one subject who received alcohol alone.

The incidences of orthostatic hypotension and hypotension (blood pressure below 90/60 mmHg) at all time points were similar among subjects administered alcohol before ADDYI, subjects administered alcohol alone, and subjects administered ADDYI alone. Three subjects were unable to stand due to feeling dizzy or hypotension; two following alcohol and ADDYI separated by 2 and 6 hours, and one subject who received ADDYI alone.

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

In another alcohol interaction study to assess alcohol use before bedtime administration of ADDYI, 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.

Women who take ADDYI and who have a resting systolic blood pressure of less than 110 mmHg or diastolic blood pressure less than 60 mmHg should be advised that the use of alcohol is contraindicated (see CONTRAINDICATIONS).

Use in Patients Taking Antidepressants: Antidepressants such as Selective Serotonin Reuptake Inhibitors (SSRI) are known to have a negative effect on the libido. ADDYI should not be prescribed for the treatment of low sexual desire that is attributed to antidepressant use.

Reproductive Health: Female and Male Potential

There are no studies of ADDYI in pregnant women to inform whether there is a drug-associated risk in humans. See WARNINGS AND PRECAUTIONS/Special Populations and NON-CLINICAL TOXICOLOGY for a summary of studies performed in mice, rats, and rabbits.

ADDYI is contraindicated in women who are pregnant or breastfeeding (see CONTRAINDICATIONS).

- **Fertility**

In rat studies, Flibanserin 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). See NON-CLINICAL TOXICOLOGY/Reproduction and Impairment of Fertility.

- **Function**

Studies are available in humans. See INDICATIONS AND CLINICAL USE, and CLINICAL TRIALS.

- **Teratogenic Risk**

In studies of pregnant rats, the no adverse effect level for embryofetal toxicity and teratogenicity was 20 mg/kg/day (3 times clinical exposure based on AUC). Flibanserin at doses of 80 and 400 mg/kg/day (15 and 41 times clinical exposures at the recommended human dose based on AUC) were associated with significant maternal toxicity as evidenced by severe clinical signs and marked reductions in weight gain during dosing. (See NON-CLINICAL TOXICOLOGY.)

7.1 Special Populations

7.1.1 Pregnant Women

There are no studies of ADDYI in pregnant women to inform whether there is a drug-associated risk in humans.

In animals, fetal toxicity occurred in the presence of significant maternal toxicity. Adverse reproductive and developmental effects consisted of increased fetal loss, decreased fetal weight, and structural anomalies at exposures greater than 3 times exposures achieved with the recommended human dosage (see NON-CLINICAL TOXICOLOGY).

The use of ADDYI in women who are pregnant is contraindicated (see CONTRAINDICATIONS).

7.1.2 Breast-feeding

It is unknown whether flibanserin is excreted in human breast milk.

In animals, flibanserin was excreted in milk after oral administration in rats. Females receiving flibanserin during lactation showed maternal toxicity, reduced fetal body weight gain, and reduced fetal viability at exposures greater than 3 times exposures achieved with the recommended human dosage (see NON-CLINICAL TOXICOLOGY).

Because of the potential for serious adverse reactions including sedation in a breastfed infant, ADDYI is contraindicated in women who are breastfeeding (see CONTRAINDICATIONS).

7.1.3 Pediatrics (< 18 years of age)

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

7.1.4 Geriatrics (> 60 years of age)

Safety and efficacy of ADDYI has not been established in patients > 60 years of age (see CLINICAL TRIALS).

7.1.5 Race/ethnicity

Safety and efficacy of ADDYI have not been established in postmenopausal Black or Asian women. Refer to section 10.3 (Pharmacokinetics/Elimination/Race) for additional information.

7.1.6 BMI

Safety and efficacy of ADDYI has not been established in underweight postmenopausal women with BMI< 18.5 kg/m^2. The occurrence of certain adverse reactions such as CNS depression and hypotension/syncope may be increased in women less than 50 kg of weight due to potential increased exposure to flibanserin (see CLINICAL PHARMACOLOGY).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In clinical trials of women with HSDD, patients were treated with ADDYI 100 mg as a single dose before bedtime. In premenopausal women, the most common adverse reactions were dizziness (flibanserin 11.4%; placebo 2.2%), somnolence (flibanserin 11.2%; placebo 3.1%), nausea (flibanserin 10.4%; placebo 3.7%) and fatigue (flibanserin 9.2%; placebo 5.0%). The majority of these adverse reactions were of mild to moderate intensity and emerged during the first 14 days of treatment. In postmenopausal patients, the most common adverse reactions were dizziness (flibanserin 8.4%; placebo 3.3%), somnolence (flibanserin 7.9%; placebo 1.8%), nausea (flibanserin 6.5%; placebo 3.8%), insomnia (flibanserin 6.4%; placebo 3.3%), and headache (flibanserin 5.7%; placebo 5.5%). The majority of these adverse reactions were of mild to moderate intensity and emerged during the first 4 weeks of treatment.

In five 24-week double-blind, placebo-controlled randomized studies in premenopausal women with HSDD (including the 3 studies presented in CLINICAL TRIALS), the discontinuation rate due to adverse events in patients treated with ADDYI (n=1543) was 12.8% compared to 5.9% in placebo-treated patients (n=1905). The adverse events most commonly causing discontinuation of ADDYI were dizziness (1.7%), nausea (1.2%), insomnia (1.1%), somnolence (1.1%), anxiety (1.0%), and fatigue (0.9%). Serious adverse reactions were reported in 0.8% of ADDYI-treated patients and 0.5% of placebo-treated patients.

In postmenopausal patients with HSDD, two double-blind, placebo-controlled, randomized studies reported the discontinuation rate due to adverse events in patients treated with ADDYI (n=843) was 9.1% compared to 5.2% in placebo-treated patients (n=849). The adverse events most commonly causing discontinuation of ADDYI were insomnia (1.5%), and anxiety (1.2%).

Serious adverse events were reported in 1.4% of ADDYI-treated patients and 0.8% of placebo-treated patients. Reports of serious adverse events in postmenopausal women, regardless of causality, are listed below. Causality was established for (liver function test abnormal, 0.1%).

- Cardiac disorders: myocardial infarction
- Gastrointestinal disorders: pancreatitis, duodenitis, haematemesis, upper gastrointestinal haemorrhage
- Infections and infestations: dengue fever, gastroenteritis viral
- Injury, poisoning and procedural complications: alcohol poisoning, meniscus lesion, road traffic accident, tibia fracture
- Investigations: hepatic enzyme increased, liver test abnormal
- Neoplasms benign, malignant and unspecified (incl cysts and polyps): breast cancer in situ, chronic lymphocytic leukaemia
- Nervous system disorders: intraventricular haemorrhage

Adverse reactions of syncope and hypotension are more common in patients who have elevated exposure to flibanserin due to concomitant use of moderate or strong CYP3A4 inhibitors (see DRUG INTERACTIONS; CONTRAINDICATIONS).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The 100 mg ADDYI dosage at bedtime was administered to 3,641 women with acquired, generalized HSDD in clinical trials. Of the 2,798 premenopausal patients, 2,141 received treatment for at least 6 months, 1,327 received treatment for at least 12 months, and 603 received treatment for at least 18 months. Of the 843 postmenopausal patients, 506 received treatment for at least 6 months.

Adverse reactions that occurred in at least 1% of women treated with ADDYI 100mg qhs in double-blind, placebo-controlled pivotal clinical trials are presented in Table 2.

Table 2 Treatment-Emergent Adverse Reactions* in Double-blind, Placebo-controlled Trials in Women

	Premenopausal Pivotal Study		Premenopausal Supporting Studies		Postmenopausal Pivotal Study	
	Placebo N = 545 (%)	**Flibanserin 100 mg qhs N = 542 (%)**	**Placebo N = 693** (%)	**Flibanserin 100 mg qhs N = 685** (%)	**Placebo N = 480** (%)	**Flibanserin 100 mg qhs N = 467** (%)
Cardiac disorders						
Palpitations	0.2	0.6	0.8	1.7	0.2	1.5
Ear and labyrinth disorders						
Vertigo	0.4	1.1	1.0	1.5	0.4	1.5
Gastrointestinal disorders						
Nausea	2.2	7.6	8.1	23.3	3.5	7.5
Diarrhoea	1.8	3.1	4.4	2.2	1.9	1.5
Dry mouth	1.5	2.6	1.8	5.1	0.6	1.9
Vomiting	0.4	1.7	3.0	3.9	1.0	1.5
Constipation	0.9	1.5	0.3	3.8	2.3	1.9
General disorders and administration site conditions						
Fatigue	3.3	5.7	9.5	15.8	3.5	3.0
Irritability	0.6	2.4	3.7	5.2	0.4	1.1
Oedema peripheral	0.4	0.9	0.3	1.3	0.4	1.5
Infections and infestations						
Upper respiratory tract infection	2.4	5.2	10.1	10.8	4.2	2.4
Urinary tract infection	3.1	3.0	5.0	4.9	3.5	4.3
Sinusitis	4.0	1.8	5.9	9.7	3.1	3.6
Bronchitis	1.5	0.7	2.5	3.5	0.8	1.3
Nervous system disorders						
Somnolence	3.5	14.4	6.6	22.9	1.5	8.8
Dizziness	1.1	10.3	3.7	21.2	3.1	9.9
Headache	3.1	4.6	18.5	19.0	4.8	6.0

	Premenopausal Pivotal Study		Premenopausal Supporting Studies		Postmenopausal Pivotal Study	
	Placebo N = 545 (%)	**Flibanserin 100 mg qhs N = 542 (%)**	**Placebo N = 693** (%)	**Flibanserin 100 mg qhs N = 685** (%)	**Placebo N = 480** (%)	**Flibanserin 100 mg qhs N = 467** (%)
Psychiatric disorders						
Insomnia	2.6	4.6	7.7	12.0	3.1	4.7
Abnormal Dreams	0.7	1.7	2.7	2.7	0.8	1.1
Anxiety	1.5	1.5	1.6	4.4	1.5	1.7
Sleep Disorder	0.4	0.4	0.0	1.4	0.2	1.7
Skin and subcutaneous tissue disorders						
Rash	0.7	1.8	2.2	2.7	1.5	1.3

* Events Reported in ≥1% of Patients treated with 100 mg flibanserin qhs and at a higher incidence than Placebo

qhs = once daily at bedtime; NR = not reported

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Not applicable

8.3 Less Common Clinical Trial Adverse Reactions

The following Adverse Reactions occurred in <1% of Patients treated with 100 mg flibanserin qhs, and at twice the incidence of Placebo.

- Blood and lymphatic system disorders: lymphadenopathy
- Cardiovascular disorders: tachycardia, syncope, hypotension, varicose vein, blood pressure increased
- Ear and labyrinth disorders: ear pain, motion sickness, balance disorder
- Endocrine disorders: hyperprolactinaemia
- Eye disorders: visual impairment
- Gastrointestinal disorders: abdominal pain, abdominal discomfort, abdominal tenderness, gastric ulcer, gingivitis, abdominal distension, dyspepsia
- General disorders: chest discomfort, feeling abnormal, feeling drunk, pyrexia
- Immune system disorders: drug hypersensitivity
- Metabolism and nutrition disorders: anorexia
- Musculoskeletal disorders: muscular weakness, sensation of heaviness, muscle spasms
- Nervous system disorders: sedation, paraesthesia, poor quality sleep, cognitive disorder, memory impairment, feeling jittery, tremor, dysgeusia, disturbance in attention, lethargy, tension headache

- Psychiatric disorders: Nightmare, depressed mood, mood swings, agitation, anger, nervousness, early morning awakening, panic attack, hallucination, dissociation, euphoric mood, tachyphrenia; anorgasmia
- Renal and urinary disorders: pollakiuria
- Skin and subcutaneous tissue disorders: acne, pruritus, urticaria, dry skin; night sweats, swelling face

Accidental Injury

Accidental injuries that occurred concomitantly (began within 3 days) with the sedation-related adverse events of dizziness, fatigue, and somnolence for all double-blind, placebo-controlled trials in women with HSDD, 7 of 2792 (0.25%) placebo patients and 12 of 2459 (0.49%) patients taking flibanserin 100 mg qhs.

Alcohol Poisoning

One death occurred in a 54 year-old postmenopausal woman treated with 100 mg ADDYI. 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.

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

Not applicable

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Investigations were reported for weight decreased and aspartate aminotransferase increased in <1% of patients treated with 100 mg flibanserin qhs, and at twice the incidence of placebo.

8.5 Post-Market Adverse Reactions

The following events have been spontaneously reported during post-marketing surveillance: Asthenia; Malaise; Swelling; Gait disturbance; Pain; Heart rate increased; Weight decreased; Migraine; Head discomfort; Presyncope; Hypoaesthesia; Dyspnoea; Mania, Suicidal ideation; Anaphylactic reaction; Impaired driving ability; Colitis; Diverticulum; Throat tightness, Head injury; Skin laceration; and Vaginal haemorrhage. The information in the reports has not been sufficient to establish a causality nor have most cases been medically confirmed.

Accidental exposure by a child has also been reported in literature.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

The concomitant use of ADDYI with moderate or strong inhibitors of CYP3A4 causes a significant increase in flibanserin concentration. This increase in exposure to flibanserin may be associated with severe hypotension and syncope. The concomitant use of ADDYI with moderate or strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, fluconazole, ritonavir, or clarithromycin) is contraindicated (see CONTRAINDICATIONS; Drug-Drug Interactions).

9.2 Drug Interactions Overview

Flibanserin is primarily metabolized by CYP3A4 and, to a lesser extent, by CYP2C19. Based on i*n vitro* and/or *in vivo* data, CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP2D6 contribute minimally to the metabolism of flibanserin. The concomitant use of ADDYI with moderate or strong CYP3A4 inhibitors or with strong CYP2C19 inhibitors increases flibanserin exposure which may increase the risk of severe hypotension, syncope, and CNS depression (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS/Endocrine and Metabolism, and DRUG INTERACTIONS).

Use of ADDYI and alcohol may increase the risk of severe hypotension and syncope (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

9.3 Drug-Behavioural Interactions

Alcohol: Co-administration of ADDYI with alcohol may increase the risk of CNS depression, hypotension and syncope. Patients should be counseled to use caution when consuming alcohol and to limit their alcohol consumption. Alcohol use is contraindicated in patients taking ADDYI, whose resting systolic blood pressure is less than 110 mmHg or diastolic blood pressure less than 60 mmHg as this was not studied (see CONTRAINDICATIONS).

Concomitant administration of ADDYI and alcohol was not studied in postmenopausal women. See WARNINGS AND PRECAUTIONS/Neurologic/Use in Alcohol).

Effects on Driving: Road traffic accidents have been reported in phase 3 studies in patients taking ADDYI (0.2%) vs. placebo (<0.1%). 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.

Patients should not drive or engage in other activities requiring full alertness after taking ADDYI until they know how ADDYI affects them due to the risk of adverse events such as hypotension, syncope and CNS depression.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on drug interaction studies and potential interactions based on the metabolism of flibanserin and genetic polymorphisms.

Table 3 Established or Potential Drug-Drug Interactions

Flibanserin	Source of Evidence	Effect	Clinical Comment
Effect of Other Drugs on Flibanserin			
Strong CYP3A4 Inhibitors (e.g., ketoconazole, itraconazole, posaconazole, clarithromycin, nefazodone*, ritonavir, saquinavir, nelfinavir, indinavir*, boceprevir*, telaprevir*, telithromycin*) Moderate CYP3A4 Inhibitors (e.g., amprenavir, atazanavir, ciprofloxacin, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil and grapefruit juice) *not available in Canada	CT	In a study of 24 healthy female subjects, ketoconazole 400 mg administered once daily for 5 days increased flibanserin 50 mg single-dose exposure 4.5-fold and C_{max} 1.8-fold relative to the values for flibanserin 50 mg alone. In a study of 12 healthy subjects, itraconazole 200 mg administered once daily for 4 days following a loading dose of 400 mg increased flibanserin 50 mg single dose exposure 2.6-fold and C_{max} 1.7-fold when given 2 hours later relative to values for flibanserin 50 mg alone. The 200 mg itraconazole dose does not maximally inhibit the CYP3A4 enzyme. 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 7-fold and C_{max} 2.2-fold relative to the values for flibanserin 100 mg alone. Three of 15 subjects (20%) experienced severe hypotension or syncope from concomitant use of fluconazole and flibanserin; therefore, the study was stopped early.	The concomitant use of ADDYI with moderate or strong CYP3A4 inhibitors increases flibanserin exposure compared to the use of ADDYI alone. The risk of severe hypotension, syncope and other adverse events is significantly increased with concomitant use of ADDYI and moderate or strong CYP3A4 inhibitors. The concomitant use of ADDYI with moderate or strong CYP3A4 inhibitors is contraindicated. If a patient needs to use a moderate or strong CYP3A4 inhibitor and is using ADDYI, please refer to dosing considerations in the DOSAGE AND ADMINISTRATION section.

Flibanserin	Source of Evidence	Effect	Clinical Comment
Weak CYP3A4 inhibitors (e.g. oral contraceptives, cimetidine, fluoxetine, ginkgo, resveratrol, ranitidine)	T	In a meta-analysis of 17 oral contraceptive users and 91 non-users in Phase 1 studies, the oral contraceptive users had a 1.4-fold higher flibanserin AUC and 1.3 fold higher C_{max} compared to the non-users.	The concomitant use of ADDYI with multiple weak CYP3A4 inhibitors may increase the risk of adverse reactions. Discuss the use of multiple weak CYP3A4 inhibitors with the patient when prescribing ADDYI.
CYP3A4 Inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifabutin*, rifampin, St. John's wort, etravirine) *not available in Canada	CT	Concomitant use of flibanserin with 600 mg rifampin given once daily for 8 days was shown to significantly decrease flibanserin exposure by 95%. Steady state etravirine, a moderate inducer of CYP3A4, decreased exposure to flibanserin by approximately 21%.	The concomitant use of ADDYI with CYP3A4 inducers substantially decreases flibanserin exposure compared to the use of ADDYI alone. The concomitant use of ADDYI with CYP3A4 inducers is not recommended.
Strong CYP2C19 Inhibitors (e.g. proton pump inhibitors, selective serotonin reuptake inhibitors, benzodiazepines, antifungals)	CT	In a 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.	The concomitant use of ADDYI with strong CYP2C19 inhibitors may increase flibanserin exposure which increases the risk of hypotension, syncope, and CNS depression (see WARNINGS AND PRECAUTIONS/Endocrine and Metabolism; CLINICAL PHARMACOLOGY). Discuss the use of a strong CYP2C19 inhibitor with the patient when prescribing ADDYI.
CYP2D6 Inhibitors (e.g. paroxetine)	CT	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.	No action needed

Flibanserin	Source of Evidence	Effect	Clinical Comment
CNS Depressants (e.g. diphenhydramine, opioids, hypnotics, benzodiazepines)	CT	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.	Discuss the concomitant use of other CNS depressants with the patient when prescribing ADDYI.
Effect of Flibanserin on Other Drugs			
P-glycoprotein (P-gp) substrates (e.g. digoxin, sirolimus)	CT	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 exposure to digoxin by 2.0-fold and C_{max} by 1.5-fold, compared to digoxin alone. Increased digoxin concentration may lead to digoxin toxicity.	Increase monitoring of concentrations of drugs transported by P-gp that have a narrow therapeutic index (e.g., digoxin).
Oral Contraceptives (OCs)	CT	A study done with ethinyl estradiol (EE) 30 mcg/levonorgestrel (LNG) 150 mcg and concomitant use of flibanserin did not show any influence on the expected metabolism of EE/LNG.	No action needed
Non-steroidal anti-inflammatory drugs (NSAIDS) (e.g., acetylsalicylic acid (ASA))	CT	Phase 3 studies found a slight increase in flibanserin-associated adverse events in NSAID users, as compared with non-users, as well as an increase potential in gastrointestinal bleeding.	Warning regarding increased potential for gastrointestinal bleeding with concomitant use of NSAIDS and flibanserin

Flibanserin	Source of Evidence	Effect	Clinical Comment
Drugs metabolized by CYP3A4 (e.g. simvastatin)	CT	The use of flibanserin 50 mg twice daily for 4 days and simvastatin 40 mg once daily resulted in an increased exposure to simvastatin by 1.3 fold and a 1.2-fold increase in C_{max}. Also noted was a 1.5 fold increase in exposure to simvastatin acid along with a 1.4-fold increase in C_{max}.	No action needed
Drugs metabolized by CYP2B6 (e.g. bupropion)	CT	Concomitant use of flibanserin and bupropion did not appear to have an effect on exposure to bupropion, nor on its C_{max}. However, exposure to hydroxybupropion and the corresponding C_{max} decreased by 9% and 11% respectively.	No action needed

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

In a study of 26 healthy female subjects, grapefruit juice (240 mL) increased flibanserin 100 mg single dose exposure by 1.4-fold and C_{max} 1.1-fold compared to flibanserin 100 mg alone.

The concomitant use of ADDYI with CYP3A4 inhibitors may increase the risk of adverse events such as hypotension and syncope. Discuss the use of multiple weak CYP3A4 inhibitors with the patient when prescribing ADDYI.

9.6 Drug-Herb Interactions

Patients should be advised to avoid non-prescription CYP3A4 inhibitors such as gingko or resveratrol. Administration of multiple such products may cause significant CNS depression.

The concomitant use of ADDYI with CYP3A4 inducers such as St. John's wort is not recommended.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The mechanism of action of flibanserin in the treatment of premenopausal women with hypoactive sexual desire disorder is not known. *In vitro*, flibanserin demonstrated high affinity for the following serotonin (5-hydroxytryptamine or 5-HT) receptors: agonist activity at 5-HT1A and antagonist activity at

5-HT2A. Flibanserin also has moderate antagonist activities at the 5-HT2B, 5-HT2C, and dopamine D4 receptors.

10.2 Pharmacodynamics

Effects on Sedation

Flibanserin administration was associated with sedation around 1 to 2.5 hours post-dose, as evidenced by declines in alertness and attention, which mostly subsided by 6 hours post-dose. Tolerance to the sedative effects generally developed within 2 months of flibanserin treatment, although in some women sedative effects persisted for the duration of treatment.

Serotonergic Effects

Objective and subjective signs of serotonin syndrome, such as changes in mood or occurrence of tremor, were assessed in 29 male and female healthy volunteers treated with flibanserin (50 mg twice daily) for 5 to 7 days, alone or in combination with paroxetine (40 mg once daily). No signs of a serotonin syndrome were observed when flibanserin was administered either alone or in combination with paroxetine.

However, Phase 3 double-blind trials reported a greater rate of serotonin related adverse events, such as tachycardia (0.3% vs. <0.1%), pyrexia (0.6% vs. 0.1%) and agitation (4.9% vs. 2.8%) in patients taking ADDYI vs. placebo, respectively.

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 (tid, 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. There was an increase in heart rate associated with the 100 mg tid of ADDYI compared to placebo, which ranged from 1.7 to 3.2 beats per minute. Also, there was a greater incidence in palpitations in patients taking 100 mg ADDYI tid compared to placebo (3 vs. 0, respectively).

10.3 Pharmacokinetics

The pharmacokinetics of flibanserin have been studied in healthy volunteers, and in women with HSDD. The pharmacokinetics of flibanserin are the same in healthy female subjects and in female HSDD patients across the age range studied.

Flibanserin shows dose-proportional pharmacokinetics after single oral doses of 100 mg to 250 mg (the recommended and 2.5 times the recommended dosage, respectively). Steady state is achieved after 3 days and the extent of exposure ($AUC_{0-\infty}$) is increased 1.4-fold as compared to single dose.

Table 4 Summary of Pharmacokinetic Parameters of Flibanserin 100 mg in Premenopausal Women with Hypoactive Sexual Desire Disorder

	C_{max}	T_{max} (h) (Median)	$t_{½}$ (h)	$AUC_{0-\infty}$	CL	Vd
Single Dose 100 mg	336 ng/mL	1.00	9.3	1630 ng*hr/ mL	1020 mL/min	827 L
	$C_{max, ss}$	T_{max} (h) (median)	$t_{½}$ (h)	$AUC_{\tau ss}$	CL	Vd
Steady State 100 mg	469 ng/mL	1.00	11.4	2080 ng*hr/mL	803 mL/min	795 L

Absorption

Following oral administration of a single 100 mg dose of flibanserin in premenopausal women with HSDD (N=28), mean (CV) C_{max} was 336 (51) ng/mL and mean (CV) $AUC_{0-\infty}$ was 1420 (55) ng*hr/mL. Median (range) time to reach C_{max} was 1.00 (0.5 to 3.00) hours. Absolute bioavailability of flibanserin following oral dosing is 33%.

Food increased the extent of absorption of a 50 mg dose of flibanserin (one half the recommended dosage). Low-, moderate-, and high-fat meals increased flibanserin $AUC_{0-\infty}$ by 1.02-, 1.43-, and 1.56-fold; respectively. There was no significant effect of food on C_{max} and T_{max}.

Grapefruit juice given with a single dose of ADDYI 100 mg increases exposure (AUC) approximately 38% and C_{max} by 10%.

Distribution:

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

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. 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.

Elimination

The mean terminal half-life of flibanserin after oral administration is approximately 10 hours. After a single oral solution dose of 50 mg ^{14}C-radiolabelled flibanserin, 44% of the total ^{14}C-flibanserin related radioactivity was recovered in urine, and 51% was recovered in feces.

Special Populations and Conditions

- **Genetic Polymorphism:** Patients who are CYP2D6, CYP2C9 or CYP2C19 poor metabolizers are deficient in CYP2D6, CYP2C9 or CYP2C19 enzyme activity, respectively. Extensive metabolizers have normal functioning CYP enzymes.

  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 CYP2D6 poor metabolizers, 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 CYP2D6 extensive metabolizers, intermediate metabolizers and ultra-rapid metabolizers.

  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 CYP2C9 poor metabolizers, C_{max} and $AUC_{0-\infty}$ of flibanserin 100 mg once daily decreased 23% and 18%, compared to exposures among 8 CYP2C9 extensive metabolizers.

  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 CYP2C19 poor metabolizers, C_{max} and $AUC_{0-\infty}$ 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 CYP2C19 extensive metabolizers. Flibanserin half-life was increased from 11.1 hours in the CYP2C19 extensive metabolizers to 13.5 hours in the CYP2C19 poor metabolizers. The frequencies of CYP2C19 poor metabolizers are approximately 2–5% among Caucasians and Africans and approximately 2–15% among Asians (see WARNINGS AND PRECAUTIONS/Endocrine and Metabolism).

- **Race:** 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. However, results adjusted for weight differences suggest that weight, not race, is the factor contributing to the observed difference in flibanserin exposure between Japanese and Caucasian women.

  A meta-analysis including 155 healthy females subjects with a mean weight of 65.4 kg (range 49.0 – 91.0 kg) compared the individual pharmacokinetic parameters versus weight. The analysis indicates there is no obvious dependence of C_{max} or AUC on body weight for individuals with weights between 50 kg and 85 kg. Lower body weight than 50 kg may be associated with higher than average exposures while a body weight greater than 85 kg may be associated with lower than average exposures.

- **Hepatic Insufficiency**: Systemic flibanserin exposure ($AUC_{0-\infty}$) increased 4.5-fold in patients with mild hepatic impairment, compared to subjects with normal hepatic function, and t1/2 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 CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS).

- **Renal Insufficiency:** Single oral doses of flibanserin 50 mg were administered to 7 subjects with mild to moderate renal impairment (GFR 30 to 80 mL/min), 9 subjects with severe renal impairment (GFR <30 mL/min, not on dialysis), and 16 healthy subjects matched by age, weight, and gender. Flibanserin exposure ($AUC_{0-\infty}$) 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.
- **Menopausal/Postmenopausal Women**: Single-dose and steady state pharmacokinetics of flibanserin and metabolites (6-hydroxyflibanserin, 6-hydroxy-flibanserin-sulfate, and trifluoromethyl-phenylpiperazine) were examined in an open-label study in naturally postmenopausal women with HSDD (Table 5).
- The impact of age was examined as 16 subjects were < 65 years old and 8 subjects were ≥ 65 years. The study showed the pharmacokinetics of flibanserin and metabolites in postmenopausal women are similar to pharmacokinetic results reported in premenopausal HSDD patients and healthy volunteers. The plasma exposure to flibanserin and its metabolites was largely comparable by age group.

Table 5 Summary of Pharmacokinetic Parameters of Flibanserin 100 mg in Postmenopausal Women with Hypoactive Sexual Desire Disorder

	C_{max}	T_{max} (h) (Median)	$t_{½}$ (h)	AUC_{0-24}	CL	Vd
Single Dose, 100 mg						
All ages	298	1.43	11.2	1980	649	627
< 65 years, Single Dose 100 mg	314	1.51	11.5	2250	554	551
≥ 65 years, Single Dose 100 mg	272	1.32	10.6	1580	856	784
	$C_{max, ss}$	T_{max} (h) (Median)	$t_{½}$ (h)	$AUC_{\tau ss}$	CL	Vd
Steady State 100 mg						
All ages	406	1.31	14.5	3000	555	699
< 65 years, Single Dose 100 mg	437	1.38	15.0	3480	479	624
≥ 65 years, Single Dose 100 mg	350	1.18	13.6	2230	747	879

11 STORAGE, STABILITY AND DISPOSAL

Store at 15°-30°C.

No special requirements for disposal.

Any unused product or waste material should be disposed of in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

Keep out of reach and sight of children.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

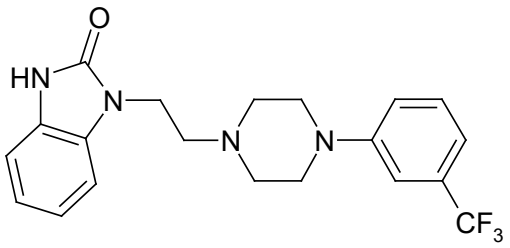
Drug Substance

Proper name: Flibanserin

Chemical name: 2H-Benzimidazol-2-one,1,3-dihydro-1-[2-[4-[3-(trifluoromethyl)phenyl]-1-piperazinyl]ethyl]

Molecular formula and molecular mass: $C_{20}H_{21}F_3N_4O$ 390.41

Structural formula:



Physicochemical properties: 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.

Product Characteristics:

Solubility profile: Solubility is strongly pH dependent with increased solubility at acidic pH (phosphate buffer at pH 8.0, 0.002 mg/mL; 0.01 N HCl, 3.3 mg/mL and water, 0.008 mg/mL).

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Premenopausal Women

Table 6 Summary of patient demographics for clinical trials in HSDD (Premenopausal Women)

Study #	Study design	Dosage, route of administration and duration	Study subjects (N)	Mean age (Range)	Sex
Pivotal Study	Randomized, double-blind, placebo-controlled	100 mg flibanserin oral tablets qhs Placebo qhs x 24 weeks	542 545	36.5 years (19-55)	Female (premenopausal)

Study #	Study design	Dosage, route of administration and duration	Study subjects (N)	Mean age (Range)	Sex
Supporting Study 1	Randomized, double-blind, placebo-controlled	100 mg flibanserin oral tablets qhs Placebo qhs x 24 weeks	290 295	35.8 years (19-54)	Female (premenopausal)
Supporting Study 2	Randomized, double-blind, placebo-controlled	50 mg flibanserin oral tablets qhs up-titrated to 100 mg qhs after 14 days Placebo qhs and bid x 24 weeks	395 398	35.5 years (19–52)	Female (premenopausal)

qhs = once daily at bedtime

The efficacy of ADDYI for the treatment of HSDD in premenopausal women was established in one pivotal and two supporting 24-week, randomized, double-blind, placebo-controlled trials.

The three trials included premenopausal women with acquired, generalized HSDD of at least 6 months duration.

- These trials each had two co-primary efficacy endpoints, one for satisfying sexual events (SSEs) and the other for sexual desire. The supporting studies had a different desire endpoint (the electronic diary (eDiary)) than the pivotal study (the desire domain of the Female Sexual Function Index (FSFI Desire)). Each co-primary endpoint was evaluated for change from baseline to Week 24.
- SSE measurement was based on patient responses to the following questions: “Did you have a sexual event?” and “Was the sex satisfying for you?” ("Satisfying" means gratifying, fulfilling, satisfactory, and/or successful for the patient.)
- The eDiary measured the 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.
- The FSFI-D domain contains 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-D score was calculated by adding the patient’s responses to these two questions and 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 the supporting studies.

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 1 pivotal and 2 supporting studies in premenopausal women were all 6-month, randomized, double-blind, placebo controlled, parallel-group North American studies. They included a total of 3548 premenopausal HSDD patients (White 88.6%, Black 9.6%, and Asian 1.5%) with a mean age of 36 years (range 19 to 55 years). The mean duration of HSDD in patients participating in these clinical studies was approximately 4 years. The mean duration in the monogamous, heterosexual relationship was 11 years. The completion rate across these three trials was 70% and 78% for the ADDYI and placebo groups, respectively. A total of 1227 patients received ADDYI (100 mg flibanserin) once daily at bedtime and 1238 received placebo.

Postmenopausal Women

Table 7 Summary of patient demographics for clinical trials in HSDD (Postmenopausal Women)

Study #	Study design	Dosage, route of administration and duration	Study subjects (N)	Mean age (Range)	Sex
Pivotal Study	Randomized, double-blind, placebo-controlled	100 mg flibanserin oral tablets qhs Placebo qhs x 24 weeks	467 480	55.5 (39 – 80)	Female (postmenopausal)

qhs = once daily at bedtime

The efficacy of ADDYI for the treatment of HSDD in postmenopausal women was established in one pivotal 24-week, randomized, double-blind, placebo-controlled trial.

The trial included postmenopausal women with acquired, generalized HSDD of at least 6 months duration.

- The trial had two co-primary efficacy endpoints, one for satisfying sexual events (SSEs) and the other for sexual desire.
- SSE measurement was based on patient responses to the following questions: “Did you have a sexual event?” and “Was the sex satisfying for you?” ("Satisfying" means gratifying, fulfilling, satisfactory, and/or successful for the patient.)
- The FSFI-D domain contains 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-D score was calculated by adding the patient’s responses to these two questions and multiplying that sum by 0.6. The FSFI Desire domain score ranged from 1.2 to 6.

The trial 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 6-month pivotal study in postmenopausal women was a randomized, double-blind, placebo controlled, parallel-group North American study. It included 947 postmenopausal HSDD patients (White 91.8%, Black 6.5%, and Asian 0.8%). The mean patient age was 56 years (range 39 to 80 years), with 83% of patients ≤ 60 years of age and 17% patients > 60 years of age. The average BMI of patients was 27.7 kg/m^2 with 35.9% of patients at the normal weight, 63.2% overweight, and 1.0% underweight[1]. The mean duration of HSDD in patients participating in the clinical study was approximately 5 years. The mean duration in the monogamous, heterosexual relationship was 21 years. The completion rate for the trial was 78% and 83% for the ADDYI and placebo groups, respectively. 467 patients received ADDYI (100 mg flibanserin) once daily at bedtime and 480 received placebo.

14.2 Study Results

Premenopausal Women

Efficacy results for studies in premenopausal women are summarized below in Table 8.

Table 8 Results of ADDYI in Premenopausal HSDD Patients (Mean Baseline and Change from Baseline)

	Pivotal Study		Supporting Study 1		Supporting Study 2	
	ADDYI 100 mg qhs	**Placebo**	**ADDYI 100 mg qhs**	**Placebo**	**ADDYI 100 mg qhs**	**Placebo**
Total Treated	N=542	N=545	N=290	N=295	N=395	N=398
Number of SSEs (standardized to 28 days)						
Baseline	2.5	2.7	3.0	2.7	2.6	2.7
Week 24	5.0	4.1	4.6	3.5	4.4	3.7
Change from baseline	2.5	1.5	1.6	0.8	1.9	1.1
p-value vs placebo	*p<0.0001*		*p=0.002*		*p=0.008*	
FSFI-D						
Baseline	2.5	2.7	3.0	2.7	2.6	2.7
Week 24	5.0	4.1	4.6	3.5	4.4	3.7
Change from baseline[1]	2.5	1.5	1.6	0.8	1.9	1.1
p-value vs placebo	*p<0.0001*		*p=0.002*		*p=0.008*	

[1] Underweight: < 18.5 kg/m^2; Normal Weight: 18.5 – 24.9 kg/m^2; Overweight: ≥ 25.0 kg/m^2

	Pivotal Study		Supporting Study 1		Supporting Study 2	
	ADDYI 100 mg qhs	**Placebo**	**ADDYI 100 mg qhs**	**Placebo**	**ADDYI 100 mg qhs**	**Placebo**
e-Diary						
Baseline	*N/A*	*N/A*	12.9	11.8	12.0	10.2
Week 24			21.2	18.1	20.1	16.9
Change from baseline[1]			9.1	6.9	8.5	6.8
p-value vs placebo			*NS*		*NS*	
FSDS-R Question 13						
Baseline	3.4	3.4	3.2	3.2	3.3	3.2
Week 24	2.4	2.7	2.4	2.7	2.5	2.7
Change from baseline[1]	-1.0	-0.7	-0.8	-0.5	-0.7	-0.5
p-value vs placebo	*p=0.0001*		*p=0.0001*		*p=0.0006*	

Shaded cells show the results for the co-primary efficacy endpoints for each trial.
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.
N/A = not applicable, *NS* = not significant; qhs = once daily at bedtime

NOTE: [1] The unadjusted means (standard deviation) are presented for the baseline and week-24 values. For SSE, p-values are based on the Wilcoxon rank sum test stratified by pooled center, and the change from baseline mean (standard deviation) are presented for the change from baseline.
For all other endpoints, p-values are based on an ANCOVA model using baseline as a covariate with main effect terms treatment and pooled center. For the change from baseline, the adjusted least squares mean (standard error) are presented.

In the pivotal study, premenopausal women with HSDD treated with ADDYI 100 mg qhs showed statistically significant differences from placebo for satisfying sexual events per 28 days, sexual desire (FSFI desire items), and distress (FSDS-R Question 13). Significant differences between placebo and treatment values were seen after 8 weeks of treatment and were sustained over the 24-week treatment period.

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.

The clinically meaningful effect of ADDYI qhs was established using the Patient's Global Impression of Improvement (PGI-I) scores, using PGI-I anchoring. Patients reporting "no change" (PGI-I scores of 4) were defined as non-responders, and patients reporting "minimal improvement" (PGI-I scores of 3) were defined as responders. For each of the key efficacy endpoints, the difference between patients answering "no change" and "minimally improved" was used as the responder criterion. Patients with values greater than the responder criterion were considered to be responders for that endpoint (see Table 9).

Table 9 Absolute difference in percentage of responders among patients treated with ADDYI and the percentage of responders among patients treated with placebo (%)

PGI-I anchored responder endpoints	Difference		
	Pivotal Study	Supporting Study 1	Supporting Study 2
SSE (standardized)	12.4*	14.6*	10.1*
FSFI-D	11.6*	12.2*	12.9*
e-Diary	N/A	2.9	6.0
FSDS-R Q13	11.7*	11.7*	9.4*

NOTE: p-value based on comparison vs placebo using the Cochran-Mantel-Haenszel test stratified by pooled center.
*p<0.01
N/A=not applicable

Responder analysis results demonstrate clinically meaningful and statistically significant superiority for ADDYI taken once daily at bedtime over placebo on SSEs, FSFI desire items, and total score as well as FSDS-R Question 13 and total score.

Postmenopausal Women

Efficacy results for studies in postmenopausal women are summarized below in Table 10.

Table 10 Results of ADDYI in Postmenopausal HSDD Patients (Mean Baseline and Change from Baseline)

	Pivotal Study	
	ADDYI 100 mg qhs	Placebo
Total Treated	N=467	N=480
Number of SSEs (standardized to 28 days)		
Baseline	2.1	2.0
Week 24	3.2	2.8
Change from baseline	1.1	0.8
p-value vs placebo	*p=0.0194*	
FSFI-D		
Baseline	1.8	1.8
Week 24	2.5	2.2
Change from baseline[1]	0.7	0.4
p-value vs placebo	*p<0.0001*	

	Pivotal Study	
	ADDYI 100 mg qhs	**Placebo**
Total Treated	N=467	N=480
FSDS-R Question 13		
Baseline	3.3	3.3
Week 24	2.5	2.7
Change from baseline[1]	-0.8	-0.6
p-value vs placebo	*p=0.0083*	

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.

qhs = once daily at bedtime

NOTE: [1] The unadjusted means (standard deviation) are presented for the baseline and week-24 values. For SSE, p-values are based on the Wilcoxon rank sum test stratified by pooled center, and the change from baseline mean (standard deviation) are presented for the change from baseline.

For all other endpoints, p-values are based on an ANCOVA model using baseline as a covariate with main effect terms treatment and pooled center. For the change from baseline, the adjusted least squares mean (standard error) are presented.

In pivotal study, postmenopausal women with HSDD treated with ADDYI 100 mg qhs showed statistically significant differences from placebo for satisfying sexual events (SSEs) standardized per 28 days, and sexual desire (FSFI-D), and distress (FSDS-R13). Significant differences between placebo and treatment values were seen after 4 or 8 weeks of treatment and were generally sustained over the 24-week treatment period.

The clinically meaningful effect of ADDYI qhs was established with responder analyses. The patient score change from baseline for FSFI-D and FSDS-R Q13 were evaluated, and PGI-I anchoring of the key efficacy endpoints was performed. For the FSFI-D patient score, a responder achieved an improvement of ≥ 1.2 points in their patient score during treatment (relative to baseline). For the FSDS-R Q13 patient score, a responder achieved a decrease of ≥ 1 point in their patient score during treatment (relative to baseline). For PGI-I anchoring, patients reporting “no change” (PGI-I scores of 4) were defined as non-responders, patients reporting “minimal improvement” (PGI-I scores of 3) and ‘much improvement’ (PGI-I scores of 2) were defined as responders. Patients with values greater than the responder criterion were considered to be responders for that endpoint.

The responder analyses are summarized in Table 11, Table 12, and Table 13.

Table 11 Absolute difference in percentage of responders among patients treated with ADDYI and the percentage of responders among patients treated with placebo. Responder defined as 'At Least One Point Improvement' in FSFI-D or FSDS-R Q13. Results by Age (%)

Responder Endpoint	Difference (%)		
	All Ages	Patient Age ≤ 60 years	Patient Age > 60 years
FSFI-D patient score improvement of ≥ 1.2 points (change from baseline)	12.6	14.6	1.4
FSDS-R Q13 patient score decrease of ≥ 1 point (change from baseline)	6.1	6.8	2.1

Table 12 Absolute difference in percentage of responders among patients treated with ADDYI and the percentage of responders among patients treated with placebo. Responder defined as 'Minimally Improved' in PGI-I Anchoring. Results by Age (%)

Responder Endpoint	Difference (%)		
	All Ages	Patient Age ≤ 60 years	Patient Age > 60 years
SSEs (standardized)	7.0*	6.2	10.6
FSFI-D	12.6 ***	14.6 ***	1.4
FSDS-R Q13	5.8	6.6	1.3

* $p < 0.05$; *** $p \leq 0.0001$

Table 13 Absolute difference in percentage of responders among patients treated with ADDYI and the percentage of responders among patients treated with placebo. Responder defined as 'Much Improved' in PGI-I Anchoring. Results by Age (%)

Responder Endpoint	Difference (%)		
	All Ages	Patient Age ≤ 60 years	Patient Age > 60 years
SSEs (standardized)	7.0*	5.8	12.6
FSFI-D	12.6 ***	14.6 ***	1.4
FSDS-R Q13	5.8	6.6	1.3

* $p < 0.05$; *** $p \leq 0.0001$

In postmenopausal patients aged ≤ 60 years, the FSFI-D score improved more than 1 point for 14.6% more flibanserin patients compared to placebo patients; and 6.8% more flibanserin patients reported an improvement of 1 point for FSDS-R Q13. Responders analyses where PGI-I anchoring defined a responder as 'minimally improved' or 'much improved', were analogous. In postmenopausal patients aged ≤ 60 years,~6% more flibanserin patients were responders based on an increase in SSEs, 14.6%

more flibanserin-treated patients were responders with an improvement in FSFI-D, and 6.6% more flibanserin-treated patients were responders with a decrease in FSDSR-Q13.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Carcinogenicity: 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 tumours (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 tumours 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 10 and 8 times, respectively, the clinical exposure at the recommended clinical dose).

A two-year carcinogenicity study was conducted in Wistar rats with dietary administration of 0, 10, 30 and 100 mg/kg/day flibanserin. A significant increase in hepatocellular carcinoma was observed in males at the 100 mg/kg/day dose (exposure based on AUC is 5-fold the clinical exposure in humans at the recommended clinical dose). No increases in hepatocellular tumors were observed in female rats at doses up to 100 mg/kg (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 lung 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 the Comet assay in rat liver.

Reproductive and Developmental Toxicology: 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 induced maternal toxicity and increased the duration of the estrous cycle at 80 mg/kg 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).

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 intermediate and highest doses were associated with significant maternal toxicity as evidenced by severe clinical signs and marked reductions in weight gain during dosing. Flibanserin and its metabolites crossed the placental barrier after oral dosing, and the embryo's exposure was similar to the dam's blood exposure. Elimination from the embryo was slower than in the dams. In the litters of intermediate and high-dose dams, there were decreased fetal weights, appearance of runts, decreased ossification of the forelimbs and increased number of lumbar ribs. Malformations were observed at the 400 mg/kg/day dose (one fetus with hydrocephalus, two fetuses with anophthalmia, and one fetus with cleft and fused vertebrae), and 80 mg/kg/day dose (two fetuses with cleft vertebrae). The no adverse effect level for embryofetal toxicity and teratogenicity was 20 mg/kg/day (3 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 26 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 80 and 200 mg/kg also decreased pup weight gain and viability during the lactation period. Flibanserin administered at 200 mg/kg delayed opening of the vagina and auditory canals, but 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.

Flibanserin and its metabolites are excreted in milk after oral administration in rats. Transfer to milk is rapid and flibanserin appears predominantly in the unchanged form.

17 SUPPORTING PRODUCT MONOGRAPHS

Not applicable

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrADDYI™

Flibanserin Tablets

Read this carefully before you start taking ADDYI and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about ADDYI.

Serious Warnings and Precautions

- **ADDYI can cause severe low blood pressure and fainting.**
- Take ADDYI at bedtime. If you take ADDYI and feel lightheaded or dizzy, lie down right away. Drinking alcohol close to the time you take ADDYI increases your risk of severe low blood pressure and fainting.
- ADDYI can cause sedation or make you feel very drowsy. After taking ADDYI, do not drive or perform other activities that require full attention until you know how it affects you. Using ADDYI with depressant drugs may increase the risk of sedation or drowsiness.
- You should not take ADDYI if you have liver problems.
- ADDYI should not be taken if you are taking certain other medicines. Before taking ADDYI, tell your healthcare professional about all the medicines you take. They will tell you if it is safe to take ADDYI.

What is ADDYI used for?

ADDYI is used to treat a condition called hypoactive sexual desire disorder (HSDD) in women. This means that you have had low sexual desire for a minimum of 6 months that happens 75 - 100% of the time and this causes you distress or difficulty in your relationships.

It is used in pre and naturally postmenopausal women, aged 60 years or younger, who:

- have not had problems with low sexual desire in the past
- have low sexual desire no matter the type of sexual activity, the situation or the sexual partner

Your healthcare professional may use a checklist to decide if ADDYI is right for you. They may prescribe ADDYI to you only if your low sexual desire is NOT due to:

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

ADDYI does not improve sexual performance.

How does ADDYI work?

ADDYI is a medicine that adjusts chemicals in your brain. These chemicals, called dopamine and serotonin, are involved in sexual interest and desire. The exact way that ADDYI works is not known.

What are the ingredients in ADDYI?

Medicinal ingredients: flibanserin

Non-medicinal ingredients: croscarmellose sodium, hypromellose, iron oxide red, lactose monohydrate, macrogol, magnesium stearate, microcrystalline cellulose, talc, titanium dioxide.

ADDYI comes in the following dosage forms:

100 mg tablets

Do not use ADDYI if:

- You are allergic to flibanserin or any of the other ingredients in ADDYI.
- You have liver problems.
- You are pregnant.
- You are breastfeeding.
- You have low blood pressure and you drink alcohol.
- You are a man.
- You are under 18 years old.
- You are over 60 years old.
- You take a drug called digoxin or a similar type of drug.
- Taking ADDYI with certain other medicines can increase the amount of ADDYI in your blood and this can cause severe low blood pressure, fainting (loss of consciousness) and sleepiness. Before taking ADDYI, tell your healthcare professional about all the medicines you take. They will tell you if it is safe to take ADDYI.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ADDYI. Talk about any health conditions or problems you may have, including if you:

- have low blood pressure.
- have a medical condition that can cause low blood pressure.
- have heart problems.
- are pregnant or trying to get pregnant.
- are breastfeeding or planning to breastfeed.
- drink alcohol.
- have been told that you have a variation in a liver enzyme called CYP2C19 which makes you process certain medicines poorly.
- have experienced allergic reactions or sensitivity to any medicines.

Other warnings you should know about:

Race/Ethnicity and Body Mass Index (BMI) in Postmenopausal Women:

- The effects of ADDYI were not studied in Black or Asian women who are postmenopausal, or postmenopausal women who are underweight.
- If you weigh less than 50 kg, there might be a higher risk of certain side effects. These side effects include central nervous system depression (sedation or feeling very sleepy), low blood pressure and fainting. Tell your healthcare professional right away if you feel these effects.

Alcohol:

- Drinking alcohol close to the time you take ADDYI increases your risk of severe low blood pressure, fainting and central nervous system depression like sleepiness. Wait at least 2 hours after drinking 1 or 2 standard alcoholic drinks before taking ADDYI at bedtime. Examples of 1 standard alcoholic drink include:
  - one 12-ounce regular beer (5% alcohol).
  - 5 ounces of wine (12% alcohol).
  - 1.5 ounces of distilled spirits or shot (40% alcohol).
- If you drink 3 or more standard alcoholic drinks in the evening, skip your ADDYI dose at bedtime. After you have taken your ADDYI at bedtime do not drink alcohol until the following day.

Driving and using machines:

- ADDYI can cause low blood pressure, fainting (loss of consciousness) and sleepiness. Using ADDYI with drugs (like diphenhydramine, opioids, hypnotics and benzodiazepines) that slow down your central nervous system can increase this risk. This can affect your ability to drive or use machines. You should not drive or perform other activities that need full attention after taking ADDYI until you know how it affects you. You should be extra careful when driving the morning after taking ADDYI until you know how it affects you.

Low blood pressure and fainting:

- The risk of low blood pressure and fainting is increased if ADDYI is taken during waking hours or if more than the recommended amount is taken. This is why you must take ADDYI at bedtime only and exactly as your doctor tells you to. If you take ADDYI and feel lightheaded or dizzy, lie down right away. Get immediate medical help or ask someone to get immediate medical help for you if the symptoms do not go away or if you faint (lose consciousness). If you faint, tell your healthcare professional as soon as you can.

Severe Allergic Reactions:

- Anaphylactic reactions (severe allergic reactions) may happen while taking ADDYI. Tell your healthcare professional right away if you have a hard time breathing or a serious rash.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ADDYI:

- digoxin, a medicine used to treat heart problems
- medicines called proton pump inhibitors used to treat acid reflux such as esomeprazole or omeprazole
- ranitidine, which is a medicine used to treat stomach ulcers, indigestion and heartburn
- selective serotonin reuptake inhibitors such as fluoxetine
- benzodiazepines such as diazepam or lorazepam
- medicines used to treat seizures such as carbamazepine, phenobarbital and phenytoin
- rifampin and rifabutin, which are medicines used to treat tuberculosis
- etravirine, which is a medicine used to treat HIV-1 infection
- non-steroidal anti-inflammatory drugs (NSAIDS) such as acetylsalicylic acid (ASA) and ibuprofen
- birth control pills
- alcohol
- certain herbal supplements such as St. John's Wort, ginkgo and resveratrol
- certain non-prescription medicines such as cimetidine
- sleeping pills such as zopiclone and zolpidem
- certain antihistamines (anti-allergy medicines) such as diphenhydramine
- narcotic pain relievers such as codeine, fentanyl and hydrocodone

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

- certain medicines used to treat HIV-1 infection such as:
  - amprenavir
  - atazanavir
  - fosamprenavir
  - ritonavir
  - saquinavir
  - nelfinavir
  - indinavir
- certain medicines that you take by mouth used to treat fungal infections such as:
  - fluconazole
  - ketoconazole
  - itraconazole
  - posaconazole
- certain antibiotics, including:
  - ciprofloxacin
  - erythromycin
  - telithromycin
  - clarithromycin
- certain medicines used to treat Hepatitis C infection such as:
  - boceprevir
  - telaprevir
- certain medicines used to treat high blood pressure, chest pain (angina), or other heart problems such as:
  - diltiazem
  - verapamil
- certain medicines used to treat depression, such as nefazodone

Do NOT drink grapefruit juice when taking ADDYI.

How to take ADDYI:

- Take ADDYI exactly as your doctor tells you to. They will tell you how to safely take this drug.
- Do not take more than the dose prescribed by the healthcare professional.
- Take ADDYI at bedtime only.
- Never take ADDYI at another time of the day. If you take ADDYI at a time other than bedtime you might get low blood pressure, faint (lose consciousness), get very sleepy and possibly injure yourself by accident.
- Talk to your healthcare professional if your symptoms of HSDD have not gotten better after taking ADDYI for 8 weeks.

Usual dose:

Take 1 tablet, once a day at bedtime.

Overdose:

If you think you, or a person you are caring for, have taken too much ADDYI, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- 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.
- Do not double your next dose.

What are possible side effects from using ADDYI?

These are not all the possible side effects you may have when taking ADDYI. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- dizziness
- vertigo
- nausea, vomiting
- muscle spasms
- swelling of hands and legs
- sleepiness, tiredness
- night sweats
- difficulty falling asleep or staying asleep

- dry mouth
- anxiety
- diarrhea
- constipation
- indigestion
- abdominal pain
- headache
- abnormal dreams
- rash
- acne

Your healthcare professional may decide to do some liver tests. They will tell you if your test results are abnormal and if you need treatment.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Sinusitis (inflammation or swelling of sinus tissue):	✓		
Urinary tract infection (infection in urinary system including kidneys, ureters, bladder and urethra): Pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine		✓	
UNCOMMON			
Fainting (loss of consciousness)			✓
Hypersensitivity (severe allergic reaction): fever, skin rash, hives, itching, swelling, shortness of breath, wheezing, runny nose, itchy, watery eyes			✓
Low blood pressure: blurred vision, dizziness or lightheadedness, feeling tired, nausea.		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Mental health changes: dissociation from reality, hallucination, intensely excited mood, racing thoughts.			✓
Tachycardia (abnormally fast heartbeat): chest pain, fast pulse, lightheadedness, racing or irregular heartbeat, shortness of breath.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store ADDYI at 15°C-30°C.

Keep out of reach and sight of children.

Ask your healthcare professional or pharmacist on how to safely throw away ADDYI tablets.

If you want more information about ADDYI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html, the manufacturer's website www.addyi.ca, or by calling 1 (844) 348-3406 .

This leaflet was prepared by Sprout Pharmaceuticals, Inc.

Last Revised NOV 25, 2025