Brand Name: Addyi

Generic Name: Flibanserin

Manufacturer: Sprout Pharmaceuticals

Drug Class: Central Nervous System Agent, Serotonin Agonist, Dopamine antagonist

Uses:

Labeled Uses: 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.
Unlabeled Uses: none.

Mechanism of Action:
The mechanism of action for flibanserin in the treatment of hypoactive sexual desire disorder is unknown. Flibanserin has high affinity for serotonin (5-hydroxytryptamine or 5-HT) 1A receptors, as an agonist, and 5-HT2A receptors, as an antagonist, and moderate affinity for 5-HT2B, 5-HT2C, and dopamine D4 receptors as an antagonist

Pharmacokinetics:

Absorption:

T_{max}	0.75 hours
V_d	50L
$t_{½}$	11 hours
Clearance	Not reported
Protein binding	98% (albumin)
Bioavailability	33%

Metabolism: Flibanserin is extensively metabolized primarily by CYP3A4 and, to a lesser extent, CYP2C19 to at least 35 metabolites, with most of the metabolites occurring in low concentrations in plasma.

Elimination: Flibanserin is primarily excreted through the kidneys in to urine (44%) and feces (51%). Two metabolites could be characterized that showed plasma concentration similar to that achieved with flibanserin: 6,21-dihydroxy-flibanserin-6,21-disulfate and 6-hydroxy-flibanserin-6-sulfate. These two metabolites are inactive.

Efficacy:

Katz M, DeRogatis LR, Ackerman R, et al. Efficacy of flibanserin in women with hypoactive sexual desire disorder: results from the BEGONIA trial. J Sex Med. 2013;10(7):1807-15.

Study Design: Multicenter, randomized, double-blind, placebo-controlled trial.

Description of Study: *Methods*: In the study 543 women were assigned to flibanserin 100mg every night. 547 women received placebo using an interactive voice response system. This included a 4-week baseline period followed by a 42 week treatment period, and a 1-week post-treatment period. Women included in the trial must have been diagnosed with generalized acquired HSDD. These women were diagnosed by a clinician who was experienced and trained in the diagnosis of female sexual disorders and were ruled out for depression. The women included in the study also must be willing to engage in sexual activity at least once monthly. Any women with any other sexual dysfunction were excluded from the study. Investigators also excluded women taking any of the following drugs that could impact sexual function: antiepileptics, CYP3A4 inducers, dopamine agonists and other antiparkinson drugs, metoclopramide, androgens and antiandrogens, antiestrogens, fluoxetine or any long-acting hormonal implant, gonadotrophin-releasing hormone analogues and other hormones and inhibitors, benzodiazepines, sleep aids, sedatives and hypnotics, antidepressants, antipsychotics, mood stabilizers, St. John's Wort, narcotics, and vaginal lubricants/moisturizers containing enhancing agents. The two coprimary end pints were change from baseline(week 0) to week 24 in FSFI desire domain score and in number of SSE standardized to a 28-day period. The FSFI desire domain score includes two questions. The SSE was measure using an eDiary where women would record on a daily basis the number of sexual events that she had experienced. A sexual even was defined for the participants as sexual intercourse, oral sex, masturbation, or genital stimulation by a partner. Secondary end points included change from baseline to week 24 in the Female Sexual Distress Scale-Revised(FSDS-R) Item 13 and total scores and FSFI total score; and Patient's Global Impression of Improvement (PGI-I) score and Patient Benefit Evaluation (PBE) at week 24. Safety assessments included evaluation of adverse events (AEs), clinical laboratory param-meters (testosterone, prolactin, hematology, bio-chemistry, and urinalysis), vital signs (blood pressure and pulse rate), suicide ideation(C-SSRS), and physical examinations. *Outcome Results*: Compared with placebo, flibanserin led to increases in mean (standard deviation) SSE of 2.5 (4.6) vs. 1.5 (4.5), mean (standard error [SE]) FSFI desire domain score of 1.0 (0.1) vs. 0.7 (0.1), and mean (SE) FSFI total score of 5.3 (0.3) vs. 3.5 (0.3); and decreases in mean (SE) FSDS-R Item 13 score of -1.0 (0.1) vs. -0.7 (0.1) and mean (SE) FSDS-R total score of -9.4 (0.6) vs. -6.1 (0.6); all $P \leq 0.0001$. The most frequently reported adverse events in the flibanserin group were somnolence, dizziness, and nausea, with adverse events leading to discontinuation in 9.6% of women receiving flibanserin vs. 3.7% on placebo.

Limitations: The biggest limitation to this study was the exclusion criteria. Many women are prescribed the medication listed in the exclusion criteria which would make this study not applicable to a large sum of the women population. Other limitations included conflicts of interest. Authors Lynna Lesko, Miguel Garcia, and Michael Sand were employees of Boehringer Inglelheim, which is the company that funded the study.

Conclusion: The study showed that flibanserin has the potential to improve sexual desire and sexual function in premenopausal women compared to placebo. There were no notable safety concerns associated with flibanserin during the trial.

Thorp J, Simon J, Dattani D, et al. Treatment of hypoactive sexual desire disorder in premenopausal women: efficacy of flibanserin in the DAISY study. J Sex Med. 2012; 9(3):793-804.

Study Design: Randomized, double-blind, placebo-controlled

Description of Study: *Methods*: This study included a 4-week baseline period followed by a 24 week treatment period during which 396 women received flibanserin 25mg twice daily, 393 women received 50mg twice daily, 396 women received 100mg once daily at bedtime, and 399 women received placebo. Women included in the study were at least 18 years old, premenopausal, and had to have a diagnosis of generalized, acquired HSDD. Other inclusion criteria included a Female Sexual Distress Scale-Revised(FSDS-R) of at least 15 and a rating on the receptivity item of the Sexual Interest and Desire Inventory-Female of 0 or 1. Women had to be in a stable, communicative, monogamous, hererosexual relationship of greater than or equal to 1 year. Women were excluded if they have clinically relevant conditions such as major depressive disorder, substance abuse, or clinical disorder that might interfere with their participation. Investigators also excluded women taking any of the following drugs that could impact sexual function: antiepileptics, CYP3A4 inducers, dopamine agonists and other antiparkinson drugs, metoclopramide, androgens and antiandrogens, antiestrogens, fluoxetine or any long-acting hormonal implant, gonadotrophin-releasing hormone analogues and other hormones and inhibitors, benzodiazepines, sleep aids, sedatives and hypnotics, antidepressants, antipsychotics, mood stabilizers, St. John's Wort, narcotics, and vaginal lubricants/moisturizers containing enhancing agents. There were two co-primary endpoints: the change from baseline to study end in the number of satisfying sexual events and increase in sexual desire score (SSE). And eDiary was used to answer questions on sexual activity. Secondary efficacy endpoints included change from baseline to study end in sexual desire and in sexual function assessed using the Female Sexual Function Index(FSFI) and in distress associated with sexual dysfunction using the FSDS-R. Safety and tolerability assessments were also made in this study including an evaluation of adverse events and laboratory parameters. Outcome Results: A total of 1,584 women were randomized in to the treatment groups. Flibanserin 100 mg once daily was associated with an increase in SSE ($P<0.01$ vs. placebo) but the 25 mg and 50 mg twice daily doses were not. No group showed a significant increase in eDiary desire score vs. placebo. All flibanserin regimens improved FSDS-R total, FSDS-R Item 13, FSFI total, and FSFI desire domain scores vs. placebo ($P<0.05$, for all). More women receiving

flibanserin 50 mg twice daily and 100 mg once daily considered their HSDD to have improved than women receiving placebo (44.1% and 47.0% vs. 30.3%, respectively) (P<0.0001 vs. placebo). The most frequently reported adverse events in women receiving flibanserin were somnolence (11.8%), dizziness (10.5%), and fatigue (10.3%).

Limitations: Sexual activity can be affected by many factors other than a woman's sexual desire, and a women may experience sexual desire in the absence of sexual activity for reasons unrelated to desire. There are many factors that may affect whether sexual activity is satisfying to a woman. This includes placebo effect. Another limitation is that this study only includes women that are heterosexual in a stable relationship for greater than or equal to one year. This excludes a large population of women that could benefit from flibanserin. The study also excluded women with any sort of psychiatric disorder, as were women taking a range of medications that may impact sexual function. This ruled out another large portion of women that could have been included in the study.

Conclusion: The results of the study showed that flibanserin 100mg once daily at bedtime is the most effective dose for this study population. Overall, flibanserin was well tolerated at all doses. Although women receiving flibanserin 25mg twice daily and 50mg twice daily did not have statistically significant results, they reported that they considered their HSDD to have improved.

Aldenkamp AP, Alpherts WCJ. The effect of the new antiepileptic drug rufinamide on cognitive functions. Epilepsia. 46(7);2006:1153-59.

Study Design: Multicenter, multinational, double blind, randomized, placebo-controlled parallel study

Description of Study: *Methods*: In the study, 213 patients were randomized to receive either placebo or four different doses of rufinamide (200 mg/day, 400 mg/day, 800 mg/day and 1,600 mg/day) as adjunct therapy for 3 months. Cognitive assessments were completed at baseline and the end of the trial period. Cognitive tests included auditory reaction time and visual reaction time for attentional function, Binary Choice Reaction Test and Computerized Visual Searching Task for mental information-processing speed, dominant and nondominant hand Finger Tapping Task for psychomotor speed and motor fluency and recognition of words and figures for working memory. Results of baseline and post-treatment assessments were compared to determine how rufinamide affects cognitive function. *Outcome Results*: No significant changes in cognitive function were observed when comparing placebo and treatment groups or changes at the end of the study from baseline within the treatment group. Patients in the treatment group showed improvement when compared to baseline in all cognitive tests though none reached statistical significance.

Limitations: The average age of the patients studied was 37.5 years making it difficult to assess how this drug affects cognitive function in children. Cognitive function effects over extended durations of therapy are not addressed in this study. Neither of the authors address possible conflicts of interest making it impossible to assess how conflicts could

have influence the results of the study. Cognitive effects were only assessed at the end of the study. Patients may have exhibited cognitive effects upon initiation of the study drug but may have adapted to the effects by the time the tests were completed.

Conclusion: Despite its finding that rufinamide does not exhibit significantly serious cognitive effects; it cannot be guaranteed that these effects will not be seen in patients. This is especially true for patients being initiated on rufinamide therapy in addition to their other antiepileptic drugs. The study only evaluated the effects on patients 3 months after initiation. At this time, patients may have adapted to the side effects of the drug. Additionally, long-term effects of rufinamide on function were not assessed. More studies need to be completed on short-term and long-term effects of rufinamide on cognitive function.

Contraindications:

Concomitant alcohol use: The use of flibanserin and alcohol increases the risk of severe hypotension and syncope.

Concomitant use of moderate or strong CYP3A4 inhibitors: The concomitant use of flibanserin and moder or strong CYP3A4 inhibitors increases flibanserin concentrations, which can cause severe hypotension and syncope.

Hepatic Impairment: The use of flibanserin in patient with hepatic impairment increases flibanserin concentrations, which can cause severe hypotension and syncope.

Precautions:

Black Box Warning: Concomitant alcohol use is contraindicated and flibanserin is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ADDYI REMS Program due to increased risk of severe hypotension and syncope; assess likelihood of patient abstaining from alcohol and counsel patients on the importance of abstaining

Black Box Warning: Concomitant use of moderate or strong CYP3A4 inhibitors is contraindicated due to increased risk of severe hypotension and syncope; if a moderate or strong CYP3A4 inhibitor is required, discontinue flibanserin at least 2 days before starting the inhibitor or monitor patient if benefits of starting the inhibitor prior to 2 days outweigh the risk; discontinue the inhibitor for 2 weeks before restarting flibanserin.

Black Box Warning: Contraindicated in hepatic impairment due to increased risk of sever hypotension and syncope.

Cardiovascular: Hypotension and syncope have been reported, with an increased risk with use during waking hours, higher than recommended doses, or in patients with preexisting conditions that predispose to hypotension.

Neurologic: CNS depression (eg, somnolence, sedation) has been reported, with an increased risk with use during waking hours or with CNS depressants or CYP3A4 inhibitors; counsel patient to avoid activities requiring full alertness, including driving, until at least 6 hours after use.

Special Populations: Syncope has been reported in CYP2C19 poor metabolizers due to increased exposure; monitoring recommended.

Adverse Effects:

Occurring in >10% of patients

Gastrointestinal

Nausea (10.4%)

Neurologic

Central nervous system depression (21%)
Dizziness (11.4%)
Somnolence (11.2%)

Occurring in >1% to <10% of patients

Central Nervous System

Anxiety (1%)
Fatigue (9.2%)
Insomnia (4.9%)
Sedation (1.3%)
Vertigo (1%)

Dermatologic

Gastrointestinal

Dry mouth (2.4%)
Constipation (1.6%)
Abdominal pain (1.5%)

Hematologic

Metrorrhagia (1.4%)

Uncommon (<1%) but serious

Cardiovascular

Hypotension (0.2%)
Syncope (0.4%)

Gastrointestinal

Appendicitis (0.2%)

Drug Interactions:

Alcohol

The concomitant use of flibanserin with alcohol increases the risk of hypotension and syncope.

CNS Depressants: Diphenhydramine, opioids, hypnotics, benzodiazepines

- The concomitant use of flibanserin with CNS depressants may increase the risk of CNS depression.

Moderate or strong CYP3A4 Inhibitors: Ketoconazole, itraconazole, posaconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, boceprevir, telaprevir, telithromycin,conivaptan, amprenavir, atazanavir, ciprofloxacin, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil, and grapefruit juice.

- Concomitant use of flibanserin with these drugs increases flibanserin exposure compared to the use of flibanserin alone. The risk of hypotension and syncope is increased.

Weak CYP3A4 Inhibitors: Oral contraceptive, cimetidine, fluoxetine, ginkgo, and ranitidine.

- Concomitant use of flibanserin with these agents may increase the risk of adverse reactions.

Strong CYP2C19 Inhibitors: Proton pump inhibitors, SSRIs, benzodiazepines, antifungals

- This may increase flibanserin exposure which may increase the risk of hypotension, syncope, and CNS depression.

CYP3A4 Inducers: Carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapetine, St. Johns Wort.

- Concomitant use of flibanserin with these agents substantially decrease flibanserin exposure.

Digoxin or other P-glycoprotein Substrates: Digoxin, sirolimus

- The concomitant use of flibanserin with digoxin, a drug that is transported by P-glycoprotein, increases the digoxin concentration and may lead to digoxin toxicity.

Dosing/Administration[1,2,3,4,5]:

Adult Dosing

A. Recommended dosage: 100 mg orally once daily at bedtime. Discontinue treatment after 8 weeks if no improvement.
B. If initiating flibanserin after discontinuation of a moderate or strong CYP3A4 inhibitor, start flibanserin 2 weeks after the last dose of the CYP3A4 inhibitor.
C. If initiating a moderate or strong CYP3A4 inhibitor after flibanserin discontinuation, start the moderate or strong CYP3A4 inhibitor 2 days after the last dose of flibanserin.

Elderly

Safety and efficacy have not been established in geriatric patients.

Renal impairment

Recommendations are not available. Pharmacokinetic study reported flibanserin exposure 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.

Hepatic impairment

Contraindicated in patients with any degree of hepatic impairment.

Use in special circumstances:

Pregnancy: There are no studies of flibanserin 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.

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

Pediatric Use: Flibanserin is not indicated for use in pediatric patients.

Geriatric Use: Flibanserin is not indicated for use in geriatric patients. Safety and effectiveness have not been established in geriatric patients.

Hepatic Impairment: Flibanserin is contraindicated for the use in patients with any degree of hepatic impairment.

Overdosage: Overdosage may cause an increase in the incidence or severity of any of the reported adverse reactions. There is no known specific antidote for flibanserin.

Pertinent Information: Flibanserin is only available through the REMS Program. This is because of the increased risk of severe hypotension and syncope due to an interaction between flibanserin and alcohol. Notable requirements of the REMS Program include:

- 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.

Conclusion:

Flibanserin is an effective therapy for the treatment of generalized hypoactive sexual desire disorder (HSDD). It is only approved for the use in premenopausal women characterized by low sexual desire that causes marked distress and is not due to a co-existing medical or psychiatric condition, problems within the relationship, or the effects of medication or other drug substance. Flibanserin is not indicated to enhance sexual performance or for postmenopausal women or in men. One of the major disadvantages to flibanserin is the extensive drug interaction list. Because it is metabolized by CYP3A4, there are many common medications that interact with it. Another disadvantage to flibanserin is the central nervous system depression adverse effect that occurs in about 21% according the package insert. Not only does this cause drug interactions, but also can impair function and limit its use to only being used at night time. The last disadvantage is the the REMS program that the patient must be enlisted in, which can cause inconvenience. The biggest advantage of flibanserin is that it is the first and only FDA-approved medication for acquired, generalized HSDD in premenopausal women. This is a breakthrough for many women who often acquire this disorder as they age.

Recommended References:

1. Flibanserin. Clinical Pharmacology [Internet Database]. Gold Standard, Inc., 2015. Available at: http://www.clinicalpharmacology.com Accessed: November 18, 2015.
2. Addyi [package insert].Raleigh, NC: Sprout Pharmaceuticals;2015.
3. Flibanserin. In: DRUGDEX® System [Internet Database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed: November 18, 2015.
4. Katz M, DeRogatis LR, Ackerman R, et al. Efficacy of flibanserin in women with hypoactive sexual desire disorder: results from the BEGONIA trial. J Sex Med. 2013;10(7):1807-15.
5. Thorp J, Simon J, Dattani D, et al. Treatment of hypoactive sexual desire disorder in premenopausal women: efficacy of flibanserin in the DAISY study. J Sex Med. 2012; 9(3):793-804.

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