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Flibanserin (Addyi) for Hypoactive Sexual Desire Disorder ........................................p 133

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The FDA has approved flibanserin (Addyi – Sprout) for treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD) not caused by another medical or psychiatric condition, the effects of another drug, or relationship difficulties. Flibanserin is the first drug to be approved for treatment of HSDD. It is not approved for use in men or postmenopausal women. Previous FDA reviews of flibanserin in 2010 and 2013 did not result in approval.

#### THE DISORDER

HSDD is defined as a deficiency or lack of sexual thoughts or desire that causes personal distress or interpersonal difficulty. It is characterized as lifelong or acquired, and as situational (related to a specific partner, situation, or type of stimulation) or generalized. Estimates of the prevalence of HSDD in women vary widely; one study found that 14% of premenopausal women 20-49 years old have HSDD.1

#### STANDARD TREATMENT

No drug has clearly been shown to be effective in treating pre- or postmenopausal women with HSDD, and none has previously been approved for such use by the FDA. Psychotherapy and cognitive behavioral therapy may be helpful.2,3

#### MECHANISM OF ACTION

The mechanism of action of flibanserin in treating HSDD is unknown. It is an agonist at serotonin 5-HT1A receptors and an antagonist at 5-HT2A receptors. In animal models, the drug decreases serotonin and increases norepinephrine and dopamine levels in the prefrontal cortex.4

#### CLINICAL STUDIES

Three randomized, double-blind, 24-week trials compared flibanserin 100 mg/day at bedtime to placebo in premenopausal women with acquired, generalized HSDD of at least 6 months’ duration. The coprimary endpoints were changes from baseline at week 24 in the number of satisfying sexual events and the frequency and intensity of experiencing sexual desire over the previous 4 weeks. Results are summarized in Table 2.

An FDA-conducted responder analysis asked women in the 3 trials to assess their changes in sexual desire and frequency of satisfying sexual events after 24 weeks. Those who found their condition was “very much improved” or “much improved” were considered responders. The placebo-adjusted response rate with flibanserin ranged from 10% to 13% for the desire endpoint (NNT 7.7-10.0) and from 8% to 9% for the satisfying sexual events endpoint (NNT 11.1-12.5).5
In another double-blind trial, 333 premenopausal women with HSDD who had responded to 24 weeks of treatment with flibanserin were randomized to continue taking the active drug or to switch to placebo for an additional 24 weeks. The frequency of satisfying sexual events declined significantly less in women taking flibanserin than in those switched to placebo (-1.4 vs -2.3 events/4 weeks). The authors speculate that the decline in sexually satisfying events in the flibanserin-continued group could have been due to a negative placebo effect.6

ADVERSE EFFECTS — In clinical trials, 21% of premenopausal women with HSDD taking flibanserin and 8% of those taking placebo experienced symptoms of CNS depression such as somnolence, sedation, and fatigue. Other adverse effects occurring in ≥2% of patients taking the drug and more frequently than with placebo included dizziness, nausea, insomnia, and dry mouth. Adverse effects led to discontinuation in 13% of women taking the active drug and in 6% of those taking placebo.

Severe hypotension and syncope have been reported in patients taking flibanserin. Use of alcohol increases this risk and is contraindicated; the labeling recommends that healthcare providers assess the likelihood of abstinence from alcohol before prescribing the drug. In an unpublished study (summarized in the package insert), among 23 mostly male subjects given 0.4 mg/kg of alcohol (the equivalent of two 5-ounce glasses of wine in a 70-kg person) with 100 mg of flibanserin, 4 (all males) experienced hypotension (-28 to -54 mmHg systolic; -24 to -46 diastolic) and/or syncope requiring therapeutic intervention.

Hepatic impairment increases exposure to flibanserin, increasing the risk of hypotension, syncope, and CNS depression. The drug is contraindicated in women with any degree of hepatic impairment.

In clinical trials, 6 of 3973 patients taking flibanserin developed appendicitis, compared to none taking placebo; a cause-and-effect relationship has not been established.

In a 2-year study in rodents, a small dose-related increase in malignant mammary tumors was observed in female mice receiving 3-10 times the recommended dose of flibanserin. Cancer rates were not increased in male mice or in rats.

PREGNANCY — In animal studies of flibanserin, fetal toxicity was observed only in the presence of significant maternal toxicity. The drug has not been studied in pregnant women.

DRUG INTERACTIONS — Use of flibanserin with other CNS depressants, such as opioids or hypnotics, could increase the risk of CNS depression.

Concurrent use of strong or moderate CYP3A4 inhibitors, such as clarithromycin or fluconazole, significantly increases exposure to flibanserin and is contraindicated. The drug should not be taken within 2 days before treatment with a strong or moderate CYP3A4 inhibitor (if possible), or within 2 weeks after treatment with one. Women taking a strong CYP2C19 inhibitor, such as fluvoxamine, or multiple weak CYP3A4 inhibitors, such as oral contraceptives or cimetidine, concurrently with flibanserin should be counseled about the possibility of an increased risk of hypotension, syncope, and CNS depression. Concurrent use of CYP3A4 inducers, such as rifampin, significantly reduces flibanserin exposure and is not recommended.7 Flibanserin increases exposure to the P-glycoprotein substrate digoxin and the CYP3A4 substrate simvastatin.

DOSAGE, ADMINISTRATION, AND COST — The recommended dosage of flibanserin is 100 mg taken once daily at bedtime. Taking the drug during waking hours increases the risk of injury related to hypotension, syncope, and CNS depression. If a dose is missed, it should be skipped. The drug should be discontinued after 8 weeks if symptoms of HSDD do not improve. According to the manufacturer, the wholesale acquisition cost of a 30-tablet bottle of flibanserin is $800.

As part of a Risk Evaluation and Mitigation Strategy (REMS) program, the FDA requires healthcare providers to receive training and certification before prescribing or dispensing flibanserin. Prescriber counseling about the risk of alcohol consumption must be documented.

CONCLUSION — Flibanserin (Addyi) is the first drug approved by the FDA for treatment of hypoactive sexual desire disorder in women. About 10% more premenopausal women who took flibanserin reported "much" or "very much" improvement in their condition, compared to those who took placebo. The drug must be taken every day, and it can cause hypotension, syncope, and CNS depression. Consumption of alcohol during treatment with flibanserin increases the risk of these effects and is contraindicated. Flibanserin is likely to interact with many other drugs, and its long-term safety is unknown.


5. FDA Summary Review for Regulatory Action. Available at: www.accessdata.fda.gov/drugsatfda_docs/nda/2015/022526Orig1s000SumR.pdf.
