What you need to know (and do) to prescribe the new drug flibanserin

11 questions and answers highlight indications, risks, adverse reactions, and requirements for prescribers

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It was a long road to approval by the US Food and Drug Administration (FDA), but flibanserin (Addyi) got the nod on August 18, 2015. Its New Drug Application (NDA) originally was filed October 27, 2009. The drug launched October 17, 2015.

Although there has been a lot of fanfare about approval of this drug, most of the coverage has focused on its status as the "first female Viagra"—a less than accurate depiction. For a more realistic and practical assessment of the drug, OBG MANAGEMENT turned to Michael Krychman, MD, executive director of the Southern California Center for Sexual Health and Survivorship Medicine in Newport Beach, to determine the types of information clinicians need to know to begin prescribing flibanserin. This article highlights 11 questions (and answers) to help you get started.

1. How did the FDA arrive at its approval?

In 2012, the agency determined that female sexual dysfunction was one of 20 disease areas that warranted focused attention. In October 2014, as part of its intensified look at female sexual dysfunction, the FDA convened a 2-day meeting "to advance our understanding," reports Andrea Fischer, FDA press officer.

"During the first day of the meeting, the FDA solicited patients' perspectives on their condition and its impact on daily life. While this meeting did not focus on flibanserin, it provided an opportunity for the FDA to hear directly from patients about the impact of their condition," Ms. Fischer says. During the second day of the meeting, the FDA "discussed scientific issues and challenges with experts in sexual medicine."

As a result, by the time of the FDA's June 4, 2015 Advisory Committee meeting on the flibanserin NDA, FDA physician-scientists were well versed in many nuances of female sexual function. That meeting included an open public hearing "that provided an opportunity for members of the public, including patients, to provide input specifically on the flibanserin application," Ms. Fischer notes.

Nuances of the deliberations

"The FDA's regulatory decision making on any drug product is a science-based process that carefully weighs each drug in terms of its risks and benefits to the patient population for which the drug would be indicated," says Ms. Fischer.

The challenge in the case of flibanserin was determining whether the drug provides "clinically meaningful" improvements in sexual activity and desire.

"For many conditions and diseases, what constitutes 'clinically meaningful' is well known and accepted," Ms. Fischer notes, "such as when something is cured or a severe symptom that is life-altering resolves completely. For others, this is not the case. For

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example, a condition that has a wide range of degree of severity can offer challenges in assessing what constitutes a clinically meaningful treatment effect. Ascertaining this requires a comprehensive knowledge of the disease, affected patient population, management strategies and the drug in question, as well as an ability to look at the clinical trial data taking this all into account."

"In clinical trials, an important method for assessing the impact of a treatment on a patient's symptoms, mental state, or functional status is through direct self-report using well developed and thoughtfully integrated patient-reported outcome (PRO) assessments," Ms. Fischer says. "PROs can provide valuable information on the patient perspective when determining whether benefits outweigh risks, and they also are used to support medical product labeling claims, which are a key source of information for both health care providers and patients. PROs have been and continue to be a high priority as part of FDA's commitment to advance patient-focused drug development, and we fully expect this to continue. The clinical trials in the flibanserin NDA all utilized PRO assessments."

Those assessments found that patients taking flibanserin had a significant increase in "sexually satisfying events." Three 24-week randomized controlled trials explored this endpoint for flibanserin (studies 1–3).

As for improvements in desire, the first 2 trials utilized an e-diary to assess this aspect of sexual function, while the 3rd trial utilized the Female Sexual Function Index (FSFI).

Although the e-diary reflected no statistically significant improvement in desire in the first 2 trials, the FSFI did find significant improvement in the 3rd trial. In addition, when the FSFI was considered across all 3 trials, results in the desire domain were consistent. (The FSFI was used as a secondary tool in the first 2 trials.)

In addition, sexual distress, as measured by the Female Sexual Distress Scale (FSDS), was decreased in the trials with use of flibanserin, notes Dr. Krychman. The Advisory Committee determined that these findings were sufficient to demonstrate clinically meaningful improvements with use of the drug.

Although the drug was approved by the FDA, the agency was sufficiently concerned about some of its potential risks (see questions 4 and 5) that it implemented rigorous mitigation strategies (see question 7). Additional investigations were requested by the agency, including drug-drug interaction, alcohol challenge, and driving studies.

FAST TRACK

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2. What are the indications?

Flibanserin is intended for use in premenopausal women who have acquired, generalized hypoactive sexual desire disorder (HSDD). That diagnosis no longer is included in the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* but is described in drug package labeling as "low sexual desire that causes marked distress or interpersonal difficulty and is not due to:

- a coexisting medical or psychiatric condition,
- problems within the relationship, or
- the effects of a medication or other drug substance."[1]

Although the drug has been tested in both premenopausal and postmenopausal women, it was approved for use only in premenopausal women. Also note inclusion of the term "acquired" before the diagnosis of HSDD, indicating that the drug is inappropriate for women who have never experienced a period of normal sexual desire.

3. How is HSDD diagnosed?

One of the best screening tools is the Decreased Sexual Desire Screener, says Dr. Krychman. It is available at http://www.obgynalliance.com/filesfsd/DSDS_Pocketcard.pdf. This tool is a validated instrument to help clinicians identify what HSDD is and is not.

4. Does the drug carry any warnings?

Yes, it carries a black box warning about the risks of hypotension and syncope:

- when alcohol is consumed by users of the

drug. (Alcohol use is contraindicated.)
- when the drug is taken in conjunction with moderate or strong CYP3A4 inhibitors or by patients with hepatic impairment. (The drug is contraindicated in both circumstances.) See question 9 for a list of drugs that are CYP3A4 inhibitors.

5. Are there any other risks worth noting?

The medication can increase the risks of hypotension and syncope even without concomitant use of alcohol. For example, in clinical trials, hypotension was reported in 0.2% of flibanserin-treated women versus less than 0.1% of placebo users. And syncope was reported in 0.4% of flibanserin users versus 0.2% of placebo-treated patients. Flibanserin is prescribed as a once-daily medication that is to be taken at bedtime; the risks of hypotension and syncope are increased if flibanserin is taken during waking hours.

The risk of adverse effects when flibanserin is taken with alcohol is highlighted by one case reported in package labeling: A 54-year-old postmenopausal woman died after taking flibanserin (100 mg daily at bedtime) for 14 days. This patient had a history of hypertension and hypercholesterolemia and consumed a baseline amount of 1 to 3 alcoholic beverages daily. She died of acute alcohol intoxication, with a blood alcohol concentration of 0.289 g/dL.[1] Whether this patient's death was related to flibanserin use is unknown.[1]

It is interesting to note that, in the studies of flibanserin leading up to the drug's approval, alcohol use was *not* an exclusion, says Dr. Krychman. "Approximately 58% of women were self-described as mild to moderate drinkers. The clinical program was extremely large—more than 11,000 women were studied."

Flibanserin is currently not approved for use in postmenopausal women, and concomitant alcohol consumption is contraindicated.

6. What is the dose?

The recommended dose is one tablet of 100 mg daily. The drug is to be taken at bedtime to reduce the risks of hypotension, syncope, accidental injury, and central nervous system (CNS) depression, which can occur even in the absence of alcohol.

7. Are there any requirements for clinicians who want to prescribe the drug?

Yes. Because of the risks of hypotension, syncope, and CNS depression, the drug is subject to Risk Evaluation and Mitigation Strategies (REMS), as determined by the FDA. To prescribe the drug, providers must:
- review its prescribing information
- review the Provider and Pharmacy Training Program
- complete and submit the Knowledge Assessment Form
- enroll in REMS by completing and submitting the Prescriber Enrollment Form.

Before giving a patient her initial prescription, the provider must counsel her about the risks of hypotension and syncope and the interaction with alcohol using the Patient-Provider Agreement Form. The provider must then complete that form, provide a designated portion of it to the patient, and retain the remainder for the patient's file.

For more information and to download the relevant forms, visit https://www.addyirems.com.

8. What are the most common adverse reactions to the drug?

According to package labeling, the most common adverse reactions, with an incidence greater than 2%, are dizziness, somnolence, nausea, fatigue, insomnia, and dry mouth.

Less common reactions include anxiety, constipation, abdominal pain, rash, sedation, and vertigo.

In studies of the drug, appendicitis was reported among 0.2% of flibanserin-treated patients, compared with no reports of appendicitis among placebo-treated patients. The FDA has requested additional investigation of the association, if any, between flibanserin and appendicitis.

FAST TRACK

Alcohol use is contraindicated with flibanserin

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9. What drug interactions are notable?

As stated earlier, the concomitant use of flibanserin with alcohol or a moderate or strong CYP3A4 inhibitor can result in severe hypotension and syncope. Flibanserin also should not be prescribed for patients who use other CNS depressants such as diphenhydramine, opioids, benzodiazepines, and hypnotic agents.

Some examples of strong CYP3A4 inhibitors are ketoconazole, itraconazole, posaconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, boceprevir, telaprevir, telithromycin, and conivaptan.

Moderate CYP3A4 inhibitors include amprenavir, atazanavir, ciprofloxacin, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil, and grapefruit juice.

In addition, the concomitant use of flibanserin with multiple weak CYP3A4 inhibitors—which include herbal supplements such as ginkgo and resveratrol and nonprescription drugs such as cimetidine—also may increase the risks of hypotension and syncope.

The concomitant use of flibanserin with digoxin increases the digoxin concentration and may lead to toxicity.

10. Is the drug safe in pregnancy and lactation?

There are currently no data on the use of flibanserin in human pregnancy. In animals, fetal toxicity occurred only in the presence of significant maternal toxicity. Adverse effects included decreased fetal weight, structural anomalies, and increases in fetal loss when exposure exceeded 15 times the recommended human dosage.

As for the advisability of using flibanserin during lactation, it is unknown whether the drug is excreted in human milk, whether it might have adverse effects in the breastfed infant, or whether it affects milk production. Package labeling states: "Because of the potential for serious adverse reactions, including sedation in a breastfed infant, breastfeeding is not recommended during treatment with [flibanserin]."[1]

11. When should the drug be discontinued?

If there is no improvement in sexual desire after an 8-week trial of flibanserin, the drug should be discontinued.

Reference

1. Addyi [package insert]. Raleigh, NC: Sprout Pharmaceuticals; 2015.