

## Flibanserin is poised for FDA approval. But why this drug? And why now?

👉 Women with hypoactive sexual desire disorder have long sought a remedy for this common complaint. With an advisory committee recommending approval of flibanserin, their wait may be over.

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Women's sexual health took a step forward last month when an advisory panel to the US Food and Drug Administration (FDA) recommended approval of the drug flibanserin for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women. The approval came with

some reservations regarding safety (use with certain medications and alcohol). And it's worthwhile to note that the FDA had on hand its own Drug Safety and Risk Management Committee during deliberations. However, assuming the agency follows the recommendations of the Bone, Reproductive, and Urologic Drugs Advisory Committee, women will soon have available the first agent for sexual dysfunction—aside from a medication for intercourse-associated pain—developed specifically for them.

Had the panel voted down the approval, it would have set a dangerous precedent that likely would have led to a standstill in new drug development in all therapeutic classes of women's sexual health for the next decade.

Why do I say that—and state it so emphatically?

To answer that question, let's review the approval process for flibanserin, as well as for the 2 testosterone

products that preceded its appearance before the FDA.

### A tale of 2 products: The testosterone story

In 2004, Procter & Gamble filed a new drug application (NDA) for a testosterone patch (Intrinsa) developed for the treatment of female sexual dysfunction. Specifically, the patch was created for the treatment of HSDD in surgically menopausal women (those who had undergone bilateral oophorectomy) who were receiving concomitant estrogen therapy.

Both the FDA and the advisory committee considering the NDA agreed that the patch was effective. The question was whether its efficacy outweighed its risks. Recall that this discussion was taking place only 2 years after the initial publication of findings from the Women's Health Initiative (WHI) estrogen-progestin arm. That arm had been halted prematurely because the risk of breast

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cancer exceeded the prespecified stopping boundary. In addition, the global index summarizing the balance of risks and benefits showed that risks outweighed benefits in regard to breast cancer, coronary heart disease, stroke, and pulmonary embolism.<sup>1</sup> As a result, the safety of all forms of hormone therapy was being closely scrutinized.

The FDA was also on “high alert” for safety as rofecoxib (Vioxx) had just been removed from the market due to unforeseen risks, with much media fanfare and large numbers of lawsuits.

After consideration of the NDA for the testosterone patch, the FDA advised Procter & Gamble to undertake an adequately designed and powered safety study to confirm that it would not increase the risks of coronary heart disease or breast cancer among users, since testosterone can be converted to estradiol in women.

Procter & Gamble ultimately withdrew its NDA. Such a safety study would have taken an additional 5 years to complete and cost upwards of \$300 million. And because testosterone is not a patentable compound, a study that long and costly didn't seem like a smart business proposition. Shortly after the NDA was withdrawn, the European Medicines Agency—the European counterpart of the FDA—approved the Intrinsic testosterone patch for the same indication as proposed in the United States.

Next up, BioSante Pharmaceuticals filed its NDA for LibiGel, a testosterone gel formulated specifically for postmenopausal women with HSDD. In its efficacy study, LibiGel failed to demonstrate superiority above and beyond placebo. The manufacturer, which was concurrently conducting a large, long-term safety study to

satisfy the FDA's concerns, ran out of money shortly thereafter, and that was the end of that.

## Flibanserin's focus: premenopausal women

In contrast to the 2 testosterone products, flibanserin was developed for premenopausal women. Although preliminary data on flibanserin use among postmenopausal women are available,<sup>2</sup> the drug was studied primarily in premenopausal women with HSDD, the indication sought at this time.

In the premenopausal population, problems such as pain with intercourse or hypoestrogenism aren't typically present, simplifying the identification of HSDD. (See the sidebar on page 8, “What is HSDD and how is it diagnosed?”) In clinical trials of the drug, HSDD was secondary,

generalized, and acquired—that is, it followed a period of normal sexual function. And it didn't come and go but was present regardless of location and circumstance. Study participants had had a normal sex drive before their desire “turned off,” an occurrence they found distressing.<sup>3-6</sup>

Boehringer Ingelheim, a German concern, developed flibanserin and filed the initial NDA in 2009. In clinical trials, that company ran into problems because the electronic diary it was using to measure desire failed to demonstrate efficacy for flibanserin. It turns out that, if you ask women who are distressed about having low desire to report their level of desire every single day, they quickly get turned off by the question and eventually stop answering altogether. Such changes in behavior play havoc with the validity of the instrument to assess desire.



**H**ypoactive sexual desire disorder (HSDD) is the most common sexual dysfunction in women. Few interventions have proven to be effective for the treatment of HSDD. Education, counseling, and psychotherapy may be helpful in some women. Exogenous testosterone has been reported to be effective in the treatment of low sexual desire in postmenopausal women taking estrogen, but this treatment is not approved by the US Food and Drug Administration (FDA), and the long-term safety of exogenous testosterone in women is not established. Clinicians who treat women with sexual desire disorders are frustrated by their inability to prescribe an effective treatment for this common problem. An FDA advisory panel recently voted to support the approval of flibanserin for the treatment of HSDD in premenopausal women.

In this month's editorial, Dr. James Simon provides a history of the FDA review process for medications designed to treat HSDD, including the decision to not approve testosterone and the vote of the FDA advisory panel to support the approval of flibanserin. Readers of OBG MANAGEMENT should be aware that Dr. Simon, as is apparent in this piece and fully disclosed, has served as Medical Director and an advisor to Sprout Pharmaceuticals, the company with the rights to flibanserin. As editors we have concluded that Dr. Simon's unique perspective, knowledge, and insights about the history of the FDA review of treatments of HSDD, including testosterone, would be of great interest to our readers.

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After flibanserin failed the electronic diary desire domain—one of the study’s endpoints—the company substituted a different measure, the Female Sexual Function Index (FSFI) desire domain. Although the FSFI showed statistically significantly greater efficacy for flibanserin than placebo, the FDA argued that it was unreasonable for the company to change the rules to fit the outcome. For that and other reasons, it turned down the NDA.

In response, Boehringer Ingelheim went back to the drawing board and undertook a new study intended to achieve several goals:

- substitute the FSFI desire score for the electronic diary desire score
- reduce the number of restricted medications to see if the results could be more generalizable to the normal population of women with HSDD
- determine whether there were any safety signals for drug-drug interaction that weren’t apparent in the first 3 trials, in which a large number of medications had been excluded.

About the time this study was drawing to a conclusion, the company got cold feet and decided to shelve its plans for the drug.

## Sprout steps in

I was among the delegation of medical and pharmaceutical professionals who visited Boehringer Ingelheim in 2011 to explore the possibility of Sprout Pharmaceuticals acquiring flibanserin. Boehringer Ingelheim agreed to the deal, and Sprout took over drug development, resubmitting the NDA to the FDA in 2013 with the additional study and other data. The FDA again denied the application. In response, Sprout filed a request for a dispute resolution, a formal

## What is hypoactive sexual desire disorder and how is it diagnosed?

In the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), hypoactive sexual desire disorder (HSDD) is described as having the following characteristics:

- persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity
- marked distress or interpersonal difficulty in response to this deficiency
- lack of another explanation, such as another Axis I disorder or use of a substance known to affect sexual function.

In the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V), published in 2013, HSDD was folded with female sexual arousal disorder into a new diagnosis, female sexual interest and arousal disorder. This is somewhat confusing in that the physiologies of these 2 disorders are quite separate and distinct.

In clinical practice, HSDD is easily identified using the Decreased Sexual Desire Screener (DSDS), a simple screening test that asks 4 yes/no questions:

1. In the past, was your level of sexual desire or interest good and satisfying to you?
2. Has there been a decrease in your level of sexual desire or interest?
3. Are you bothered by your decreased level of sexual desire or interest?
4. Would you like your level of sexual desire or interest to increase?

A “yes” response to each of these questions is required. In addition, a fifth question asks whether a number of conditions, drugs, or circumstances might be responsible for the decreased desire or interest:

- an operation, depression, injuries, or other medical condition
- medications, drugs, or alcohol you are currently taking
- pregnancy, recent childbirth, or menopausal symptoms
- other sexual issues you may be having (pain, decreased arousal or orgasm)
- your partner’s sexual problems
- dissatisfaction with your relationship or partner
- stress or fatigue.

Only when all of these items are excluded as possibilities can a diagnosis of HSDD be made.

procedure convened when the sponsor of an NDA cannot reach agreement with the FDA. In the course of this procedure, the FDA asked for additional analyses, as well as some pharmacogenomics and a driving study.

Around this time, the FDA had determined that the sleep aid zolpidem (Ambien) is metabolized differently in women than in men and that, in some of these women, there is a significant cognitive deficit carried over to the next day when the drug is taken as prescribed at bedtime. Because flibanserin came on the heels of this determination and was known to cause drowsiness, the

FDA requested the driving study. It also requested a drug-drug interaction study to determine whether flibanserin is metabolized differently in some women with genetically different medication metabolism.

Sprout conducted those studies, both of which came back “clean.” Armed with this new data, the FDA scheduled a meeting of its advisory committee on June 4, 2015. And the rest, as they say, is history.

## Flibanserin vs placebo

During the advisory committee’s deliberations on June 4, discussion

## Flibanserin dosing and side effects

Flibanserin is indicated for the treatment of hypoactive sexual desire disorder in premenopausal women. It is taken daily in a 100-mg tablet. Bedtime dosing is preferred to mitigate potential side effects such as drowsiness, hypotension, and syncope. These effects can occur with flibanserin alone, in combination with certain drugs, or in combination with alcohol.

Significant drug-drug interactions have been documented for flibanserin in combination with moderate and strong CYP3A4 inhibitors such as fluconazole and ketoconazole. Package labeling for flibanserin will detail this risk.

Of greater concern to the US Food and Drug Administration is the drug's interaction with alcohol, as flibanserin must be taken chronically and because alcohol use is prevalent in the United States. It remains to be seen what restrictions the FDA will impose in this regard if and when it grants final approval to the drug.

focused, in part, on how flibanserin performed in comparison with placebo. It was noted that flibanserin increased the number of satisfying sexual events (SSEs) by only 1 per month, compared with placebo. But that conclusion doesn't accurately convey the findings of the efficacy studies.

First, even without flibanserin, women in the trials reported that they continued to have sex with their partners 2 to 3 times per month. That established a baseline number of SSEs of approximately 2.5. The consent form for the flibanserin trial contained a clause stating that the woman would agree to try and have sex at least 1 additional time per month. This requirement, independent of any treatment, was bound to increase the placebo effect because, regardless of the drug given (flibanserin or placebo), the participant was going to try to have sex at least 1 more time per month.

In the flibanserin trials, the placebo effect was 1.5 additional SSEs per month. Add that to the baseline number of SSEs and you have a total of 4 SSEs per month. Among flibanserin users, the number of SSEs per month was about 5. And even though that's only 1 more time per

month than the placebo group, those 5 events were more *desired* events. That means that the baseline of 2.5 SSEs, among flibanserin users, had a different *character* by the end of the study period.

There is also a ceiling effect in play. Consider that the participants in the flibanserin trials were women who had been married an average of 10 years, with an average age of approximately 36 years. How much more sex is likely even possible in this population?

This isn't to say that women are incapable of having more sex. It is merely a reflection of the data, which show that, among married women aged 30 to 39 years, only roughly 25% have sex more often than weekly, and only 5.1% have sex 4 or more times per week.<sup>7</sup> If women were shown to be having sex more than 5 times per month, a likely criticism would have been that the drug was making them hypersexual or even abnormal.

Also keep in mind that the drug doesn't work in every woman, just as antidepressants are not effective in every person. So when the responders and nonresponders were lumped together, the magnitude of the drug's response in the combined group was

smaller. In reality, approximately 25% of women in the flibanserin trials experienced an increase of 4 or more SSEs per month, compared with 15% among placebo users.

## Why now?

As I stated earlier, a failure to approve flibanserin would set a dangerous precedent. Why? Because the company did everything the FDA asked it to do, and the results came out statistically significantly better than placebo—which was the desired endpoint. If the FDA were to deny approval of the drug, it would be saying, in effect, that it can change its mind in the middle of the argument—something it faulted Boehringer Ingelheim for in earlier deliberations (switching the insensitive electronic diary for the statistically significant FSFI).

In reality, the FDA is likely to say yes to approval, but with restrictions, as that is what its advisory committee recommended. What those restrictions will be remains to be determined, but they are likely to resemble those of other drugs in the class, such as selective serotonin reuptake inhibitors (SSRIs), including a warning to be careful using flibanserin with alcohol until the drug's effects are clear.

## Opposition to flibanserin misses the mark

During the public hearing portion of the advisory committee meeting, most of the testimony came from women seeking approval of the drug. However, there were some naysayers. Their arguments against approval boiled down to 4 perspectives:

- **the view that development of flibanserin represents “medicalization” of a disorder that can be treated effectively with**

### psychotherapy and education.

This perspective is best embodied by an organization called the New View Campaign. Refuting this perspective, however, is research in animal models that clearly demonstrates that HSDD (or its equivalent in animals) is the result of an imbalance between dopamine and norepinephrine on the positive end and serotonin on the negative end. These findings are supported by functional magnetic resonance imaging (MRI) and positron emission tomography (PET) scans of the brains of women with HSDD who are shown erotic stimuli.<sup>8,9</sup> The scans demonstrate that their brains respond differently from those of normal women. So if it's all about education and counseling, why are the brains of women with HSDD functioning differently? I would argue that, if depression and HSDD are both abnormalities of the serotonergic system (flibanserin is essentially an SSRI), then how can depression be a biologically based disorder but HSDD can't? In my opinion, the New View Campaign isn't new at all.

- **the view, represented by an organization called PharmedOUT, that marketing by pharmaceutical companies overly influences prescribers,** ultimately medicalizing problems that don't require medication or overselling medications for problems that may require drug treatment for a short time only. This organization is headed by an academic physician who has not seen patients in many years and has never treated women for HSDD.
- **the view, represented by the Public Citizen Health Research Group, that the safety profile of flibanserin is lacking.** This organization argues not just against

flibanserin but against pretty much any drug. In its view, there are never enough safety data. I would argue that, when it comes to flibanserin, there are more safety and efficacy data than there are for almost any other women's health drug. Most drug companies test their medications in 1,500 to 2,000 people, as the FDA requires. Sprout Pharmaceuticals tested flibanserin in almost 8,000 women. The total number of individuals who have been studied, in fact, exceeds 11,000.

- **the view, represented by the National Women's Health Network, that the drug's risks outweigh its modest benefits.** As I have pointed out, however, the benefits of flibanserin have been downplayed in data analysis, and the body of safety data for the drug is substantial.

There is also the sociological view that HSDD is a normal variant of healthy sexual function. Its adherents argue that women with HSDD feel distress because their male partners are forcing them to feel inadequate. But I have yet to hear a single critical voice from a physician who actually treats women and who can prescribe drugs. The opposition to flibanserin, such as it is, flows from people who don't see patients and can't prescribe medications.

These naysayers are negative in a theoretical vacuum. It's very easy to fall into that trap when you don't have to look across the consultation desk to a patient who is asking you for a remedy—a woman who's been suffering for 25 years, say—and have to tell her you have nothing to offer. You might mention testosterone, explaining that it was approved for men but you'll try to prescribe an appropriate dose. But be sure to include discussion of its many side effects.

## A long and winding road

Flibanserin's journey from inception to probable approval has been long and eventful, and you can be sure that the pharmaceutical industry has been paying attention. Hundreds of millions of dollars in funding for drug development hang in the balance. That women deserve remedies developed specifically for their needs and metabolism is a given. The approval of flibanserin will send a hopeful signal to them as well as to industry—that the FDA takes them seriously and seeks to identify effective remedies. In this case, it seems likely, the agency will end up on the right side of history. 🚫

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