Flibanserin- A Novel drug for Hypoactive Sexual Desire Disorder

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ABSTRACT

Low sexual desire is a very common symptom in women of any age with potential negative consequences on quality of life and well-being according to The American Psychiatric Association’s Diagnostic, Statistical Manual of Mental Disorders (DSM-IV TR) and the World Health Organization’s International Classifications of Disease. They also established that the definition of hypoactive sexual desire disorder (HSDD) should include not only the lack or absence of sexual fantasies or desire for any form of sexual activity, but also the presence of personal distress and/or interpersonal difficulties. Flibanserin, a novel, non-hormonal, multifunctional serotonin agonist antagonist (MSAA) was used in most of the pre-menopausal women diagnosed with Hypoactive Sexual Desire Disorder (HSDD) but its approval also faced a little scepticism.

Keywords: Flibanserin, Sexual disorders, Hypoactive sexual desire disorder.

INTRODUCTION

Hypoactive sexual desire disorder (HSDD) affects nearly 1 in 10 women.[1] Hypoactive Sexual Desire Disorder (HSDD) was recognized as a distinct sexual function disorder for more than 30 years, but was removed from the Diagnostic and Statistical Manual of Mental Disorders in 2013, and replaced with a new diagnosis called female sexual interest/arousal disorder(FSIAD).[2]

Approval of Flibanserin by the US FDA on 18th August 2015 as a novel, non-hormonal, multifunctional serotonin agonist antagonist (MSAA) was welcomed by most of the pre-menopausal women hormonal, multifunctional serotonin agonist antagonist (MSAA) was welcomed by most of the pre-menopausal women diagnosed with Hypoactive Sexual Desire Disorder (HSDD) but its approval also faced a little scepticism. Some people believe that HSDD is a completely made up condition that does not exist and that the actual number of women who apparently suffer
from this condition has largely been inflated by big pharmaceutical companies in order to push medication for purpose of financial profits alone.\textsuperscript{[3,6]}

Previous advisory committees had unanimously rejected Flibanserin as offering little benefit and potential risks to those who took it. Sprout Pharmaceuticals, which acquired the compound from Boehringer-Ingelheim, conducted additional work demanded by the FDA and submitted it again for consideration.\textsuperscript{[5]} The company (sprout pharmaceuticals) also instigated a “grassroots” marketing campaign for the drug that, among other things, practically accused the FDA of sexism for approving drugs for male but not for female sexual dysfunction.\textsuperscript{[6]}

**HSDD IN WOMEN**

Low sexual desire is a very common symptom in women of any age with potential negative consequences on quality of life and well-being.\textsuperscript{[11-13]} The American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (DSM-IV TR)\textsuperscript{[14]} and the World Health Organization’s International Classifications of Disease-10 (ICD-10)\textsuperscript{[15]} established that the definition of hypoactive sexual desire disorder (HSDD) should include not only the lack or absence of sexual fantasies or desire for any form of sexual activity, but also the presence of personal distress and/or interpersonal difficulties.

Generalized acquired HSDD is the most common diagnosis when the condition is not dependent on a specific situation or relationship and has developed after a period in which sexual desire and sexual functioning were considered normal. A diagnosis of HSDD may be comorbid with another sexual dysfunction, but it cannot be exclusively attributed to another medical condition or to the physiological effects of a medication.\textsuperscript{[16,17]}

The prevalence of HSDD ranged from 6%–13% in Europe and 12%–19% in the US, and the proportion of women with low desire associated with distress was significantly higher in younger women in comparison with older women.\textsuperscript{[18,19]} A recent conceptualization of HSDD implies that such sexual dysfunction may be the result of the inability of the neuroendocrine circuitries to integrate the complex nature of sexual response encompassing physiological, psychological, emotional, and/or relationship components.\textsuperscript{[20-22]}

**Background**

Boehringer Ingelheim studied Flibanserin in men and women for the treatment of major depression. In phase 2a trials for depression, Flibanserin failed to demonstrate efficacy; however, the subjects reported little sexual dysfunction. For this reason, in four phase 2b studies in the depression program, the Arizona Sexual Experiences Scale (ASEX) was used to compare the effect of Flibanserin both to an approved antidepressant and to placebo on sexual function. Although the phase 2b trials failed to demonstrate consistent efficacy for depression, Flibanserin was found to be superior to both placebo and active comparator with respect to the “How strong is your sex drive?” item on the ASEX scale. This finding was the basis for the Applicant’s decision to pursue the indication of HSDD.\textsuperscript{[8]} However, development of Flibanserin by Boehringer Ingelheim was halted in October 2010 following a negative evaluation by the USFDA.\textsuperscript{[7]} The rights to the drug were then transferred to Sprout Pharmaceuticals, which achieved approval of Flibanserin after undergoing third review cycle for Flibanserin NDA. It was then approved as ADDYI (Flibanserin) 100 mg tablets by the US FDA on August 18, 2015. Flibanserin has been dubbed the “Female Viagra” and “the little pink pill”; however compared to Viagra, Flibanserin has a distinctly different mechanism.

**Pharmacology**

Flibanserin 3-[4-[4-(Trifluoromethyl)phenyl]piperazin-1-yl]ethyl]-1H-benzimidazol-2-one molecular formula C20H25F3N3O.\textsuperscript{[4]}

**Pharmacokinetic Characteristics**

In adults, it is rapidly absorbed after oral administration. Following single 100 mg oral dose of Flibanserin in healthy premenopausal women:

- Mean Cmax was 419 (standard deviation 206) ng/mL
- Mean AUC0-inf was 1543 (standard deviation 511) ng*hr/mL
- Median Tmax was 0.75 (range 0.75 – 4.0) hours
- Mean t1/2 was 11.7 (standard deviation 1.9) hours

In vivo clinical data has shown that CYP3A4 is the primary enzyme for Flibanserin metabolism. Additional in vivo data have shown CYP2C19 as a contributing enzyme.\textsuperscript{[8]}

**Receptor Profile and Mechanism of Action**

Preclinical and functional evidence has revealed that Flibanserin shows functional preference for 5HT1A and 5HT2A receptors in the cortex, over other brain regions. It is a post-synaptic 5-hydroxytryptamine (5-HT) 1A receptor agonist and 5-HT 2A antagonist that leads to decreased serotonin levels in the prefrontal cortex, nucleus accumbens and hypothalamus. In addition to its activity at 5-HT 1A and 5-HT 2A serotonin receptors, Flibanserin binds with moderate affinity to 5-HT 2B, 5-HT 2C, and dopamine D4 receptors. Flibanserin’s mechanism of action in the treatment of HSDD is unknown.\textsuperscript{[8,9]}

Sexual desire is regulated not only by the sex hormones testosterone and estrogen, but also by the neurotransmitters dopamine and norepinephrine, which enhance sexual interest and desire, and serotonin, which inhibits sexual interest and desire. Brain circuits that connect the prefrontal cortex (PFC) with limbic pleasure centers theoretically mediate motivation, interest, and desire. These circuits are hypothesized to be the sites of inefficient information processing associated with sexual disorders that are characterised by reduced interest and desire. The
multifunctional serotonergic agent Flibanserin theoretically improves sexual functioning by enhancing downstream release of dopamine and norepinephrine while reducing serotonin release.[9,10,23]

Clinical Evidence for efficacy

The three pivotal trials conducted in North America with Flibanserin 100 mg (at bedtime) showed a statistically significant difference between Flibanserin and placebo on the endpoints of SSEs (satisfying sexual events), FSFI-(female sexual function index) desire score (but not daily desire measured by an eDiary) and FSDS-R(female sexual distress scale) Q13 distress score. These findings and the magnitude of the treatment effects were consistent across the three trials. [24-27]

Side effects and drug interactions with Flibanserin should be well understood by both provider and patient. Flibanserin is contraindicated for use with alcohol, in patients with liver impairment, and in patients taking moderate-to-strong CYP3A4 inhibitors. Flibanserin is being approved with a risk evaluation and mitigation strategy (REMS), which includes elements to assure safe use (ETASU), as well as a Black Box Warning.[8]

Adverse effect data

Clinical studies with Flibanserin found that the most common side effects were dizziness, nausea and sleepiness.[28,29] The risk of fainting, particularly when combined with alcohol, is a major concern. Due to this interaction Flibanserin will only be available from certified health care professionals and certified pharmacies. Health care professionals must assess the likelihood of the patient reliably abstaining from alcohol before prescribing Flibanserin and pharmacists must counsel patients on this interaction. The risk of fainting is also increased due to drug interactions with moderate or strong CYP3A4 inhibitors that interfere with the breakdown of flibanserin in the body. FDA is requiring the manufacturer to conduct additional post-marketing studies to better define the interaction between flibanserin and alcohol.[8]

Flibanserin has been recommended to be taken once daily, at bedtime, to help decrease the risk of fainting, sleepiness and sedation. Patients should discontinue treatment after eight weeks if they do not report an improvement in sexual desire and associated distress.

At present its been approved only for HSDD in premenopausal women but few studies have shown improvement in post-menopausal women also.[31] Flibanserin is slated to be commercially available in the United States from October, 2015.[30]

The market for Flibanserin that enhances female sexual desire has been estimated by some analysts to be worth up to $2bn (£1.3bn; €1.5bn) in the United States alone.[32]

CONCLUSION

Apart from Flibanserin there are no medications that are FDA approved for the treatment of HSDD or FSIAD. The FDA has recognized for a long time that there are women who have reduced sexual desire that causes distress, and who would benefit from safe and effective treatment. This condition is clearly an area of unmet medical need. However, for any product intended to treat an unmet medical need, the FDA is still required to base its regulatory decisions on an assessment of whether the benefits outweigh its risks. This has been the FDA’s approach with Flibanserin, which has a challenging benefit/risk assessment. Nevertheless, it is hard to escape comparison with Viagra (Sildenafil) which has already topped billions of dollars and similar to Viagra, Flibanserin may also have a very large potential market.

What this study adds:

1. What is known about this subject?
Flibanserin as offering little benefit and potential risks to those who took it. Sprout Pharmaceuticals, which acquired the compound from Boehringer-Ingelheim, conducted additional work demanded by the FDA and submitted it again for consideration

2. What new information is offered in this study?
Flibanserin can be very effective in women who have reduced sexual desire that causes distress, and would benefit from safe and effective treatment.

REFERENCES

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