Stephen Ostroff
Acting Commissioner
Food and Drug Administration

July 13, 2015

Dear Commissioner Ostroff,

The undersigned researchers and clinicians ask that you support FDA scientists and the integrity of the drug approval process by rejecting flibanserin. FDA scientists made a clear scientific case that the substantial harms of flibanserin outweigh its scant benefits at the June 4, 2015 advisory committee meeting that considered this drug.

Flibanserin is minimally effective: the absolute difference in percentage of subjects with hypoactive sexual desire disorder who experienced any improvement is only 9-15% higher in the flibanserin group, compared to placebo. There is no identifiable population for whom benefits outweigh harms.

Flibanserin can cause serious harms, including unpredictable hypotension and sudden unconsciousness, and its adverse effects are exacerbated by alcohol, oral contraceptives, antifungals, triptans and many other drugs. Specific safety concerns from the FDA's own presentation and briefing documents include:

Adverse CNS effects are common

One in five subjects (21%) in clinical trials experienced CNS depression (somnolence, sedation, fatigue). Accidental injuries associated with CNS depression occurred more than twice as often in flibanserin-treated patients as placebo-treated patients.

Flibanserin interacts dangerously with alcohol

In an alcohol interaction study performed at the request of the FDA, flibanserin alone was more sedating than the equivalent of four alcoholic drinks. Although the drug is meant only for use in women, the manufacturers performed the alcohol interaction study in 23 men and only two women. Four of the 25 subjects experienced symptomatic hypotension.

Flibanserin interacts dangerously with many drugs

The proposed dose of 100 mg daily is too close to the maximum tolerated dose of 250 mg. Many common drugs will increase flibanserin levels beyond tolerable doses. For example, oral contraceptives increase flibanserin levels 42%. Triptans, used to treat migraines, increase flibanserin 4.5-fold. Ketoconazole, a common antifungal, increases drug levels 7-fold. Fluconazole, another antifungal, increases levels 4.6-fold, with an attendant increase in adverse effects. A flibanserin-fluconazole interaction study was abandoned after all of the first 15 subjects experienced adverse effects. Three subjects in this study experienced syncope or dangerously low blood pressure, with diastolic readings in the 40s.

Other dangerous drug interactions are to be expected. Many other drugs besides ketoconazole and fluconazole inhibit drug-metabolizing enzyme CYP3A4, including antibiotics (clarithromycin, telithromycin), hepatitis drugs (telaprevir), anti-HIV drugs (ritonavir, saquinavir, nelfinavir, lopinavir), and grapefruit juice. Besides CYP3A4, flibanserin is also metabolized by CYP2C19 and possibly other CYP enzymes. People with low levels of CYP2C19 (up to 5% of Caucasians and up to 15% of Asians), may be exposed to doubled levels of flibanserin. Many commonly used antidepressants, anticonvulsants, and proton pump inhibitors inhibit CYP2C19 and can be expected to increase exposure to flibanserin.

Flibanserin also interacts dangerously with digoxin, a drug with a narrow therapeutic window. An interaction study found that flibanserin increased digoxin levels 81%; every one of the 24 subjects in this study experienced a drug-related adverse effect, including two severe adverse effects. Digoxin is metabolized by p-glycoprotein, not CYP enzymes, so interactions can be expected with loperamide, (a common OTC antidiarrheal), dabigatran (an anticoagulant, so increased levels will increase risks of hemorrhage), protease inhibitors, and many other drugs.

We believe that harms of flibanserin outweigh benefits

The FDA rejected flibanserin twice because benefits did not outweigh harms. This third submission provides no new evidence of benefit and additional evidence of harms. The incidence of syncope and hypotensive episodes requiring medical intervention in a healthy, highly selected clinical trial population is disturbingly high and will be far higher in the general population. The safety margin for flibanserin will be exceeded easily by concomitant use of alcohol or many common drugs. The interaction with alcohol is of especial concern. Flibanserin is a long-term treatment. Alcohol use is common – especially in conjunction with planned sexual encounters – and the expectation that those who enjoy alcohol will forswear its use forever is unreasonable.

An epidemic of serious adverse events can be expected once this drug is on the market and prescribed to women with cardiovascular problems, other comorbid conditions, those on multiple drugs, and social drinkers. Injuries, hospitalizations, and potential fatalities resulting from falls and accidents can be expected.

The harms and narrow margin of safety of flibanserin might be acceptable in a cancer drug, but are entirely unacceptable in a drug given to healthy women for a questionable condition. Low libido can be effectively treated by therapy.

FDA advisory committee members were clearly concerned about safety, with six voting against approval, 18 voting for approval with a Risk Evaluation and Mitigation Strategy, and not a single person voting to approve the drug outright.

We are concerned that the unprecedented and unwarranted manufacturer-funded public relations campaign that accused the FDA of sexism prior to and during the advisory

committee meeting may have confused advisory committee members and undermined the integrity of the drug approval process. It is not sexist to hold drugs for women to the same standard of safety as drugs for men.

Approving flibanserin will not only unleash an unsafe drug onto the U.S. market, but will send a message to industry that pressuring the FDA through public relations campaigns can get a drug approved. We ask that the FDA stand behind its own scientists and its own mission, and reject flibanserin.

Sincerely,

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