FDA Panel Backs New Emergency Contraceptive

BY ELIZABETH MECHCATIE
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GAITHERSBURG, MD. — A Food and Drug Administration advisory panel unanimously agreed that the selective progesterone receptor modulator ulipristal acetate is an effective emergency contraceptive with an acceptable safety profile, when used within 5 days of unprotected intercourse or a known or suspected contraceptive failure.

The FDA's Reproductive Health Drugs Advisory Committee voted 11 to 0 that the manufacturer, HRA Pharma, had provided enough information to conclude that the proposed 30-mg dose of micronized ulipristal "reduces the likelihood of pregnancy" when taken as soon as possible within 120 hours after unprotected intercourse or a known or suspected contraceptive failure. The primary mechanism of action of ulipristal, which has a potent affinity for the progesterone receptor, is presumed to be the inhibition or the delay of ovulation, according to the company.

If approved by the FDA, the company plans to market it as a prescription-only product under the trade name "ella." Ulipristal was approved as an emergency contraceptive in Europe in May 2009 and has been marketed there since October, under the trade name "ellaOne."

The FDA usually follows the recommendations of its advisory panels.

Currently, the levonorgestrel-based emergency contraceptive marketed as Plan B or Next Choice, is the only available emergency contraceptive in the United States.

Plan B is recommended for use for up to 72 hours within unprotected intercourse or contraceptive failure; it is available by prescription and—for women aged 18 years and older—over the counter, in a 1.5-mg single-dose (Plan B One-Step) and two 0.75-mg doses to be taken 12 hours apart (Plan B or Next Choice).

Ulipristal was evaluated in two phase III prospective, multicenter studies of women aged 18 years and older (in the United States) or aged 16 years and older (in Europe), who received 30 mg of micronized ulipristal within 48-120 hours of unprotected intercourse.

The first trial was an open-label study conducted in the United States of 1,241 women, who were give a dose of ulipristal within 48-120 hours after unprotected intercourse. The pregnancy rate was 2.10%, which was significantly lower than the expected pregnancy rate of 5.53%.

The second study was a randomized, controlled, inferiority study in which ulipristal was compared with levonorgestrel in women in the United States and Europe. Among the 1,694 women who took either medication within 72 hours of unprotected intercourse, the pregnancy rate was 1.78% among those who took ulipristal, which was significantly lower than the expected pregnancy rate of 5.54%. The pregnancy rate among those who received the levonorgestrel emergency contraceptive was 2.59%.

The pregnancy rate was higher among women with a higher body mass index (BMI), in a pooled analysis of the two studies: The pregnancy rate was 3.13% among those with a BMI above 30 kg/m^2. The panel agreed that it should not be restricted in women with higher BMIs, but split on whether to recommend that the label include information about the lower efficacy in that population.

In a randomized study, the pregnancy rates were 1.78% in women who took ulipristal and 2.59% in those who took levonorgestrel within 72 hours of unprotected intercourse.

Among more than 4,700 women in ulipristal studies who received single doses up to 200 mg, including 2,700 women who received the 30-mg proposed dose, the most common side effects reported were headache, nausea, dysmenorrhea, and abdominal pain, according to the company. The one serious adverse event associated with ulipristal was in an 18 year old, who experienced severe dizziness after taking the drug. No ectopic pregnancies were reported; two ruptured ovarian cysts were reported in women who received the 30-mg dose in phase II/III and phase III studies.

The limited data on pregnancies exposed to ulipristal suggest that the miscarriage rate is not increased with exposure, according to the company. Only 21 exposed pregnancies have been reported to date; of those, 14 are ongoing normal pregnancies, 2 were elective terminations, 1 was a miscarriage and 4 were lost to follow-up. The company is planning a postmarketing study in Europe, which will follow up with 1,000 health care practitioners to collect detailed clinical data on the course of pregnancies and outcomes among patients who get pregnant despite treatment with ulipristal. The FDA has proposed that if ulipristal is approved, this program should be expanded to include health care providers in the United States. ■

Disclosures: *Members of FDA advisory panels have been cleared of potential conflicts of interest by the FDA prior to the meeting, but occasionally, the FDA grants a waiver to a panelist with a conflict of interest.*

Panel: Hypoactive Sexual Desire Disorder Drug Ineffective

BY ELIZABETH MECHCATIE

FROM A MEETING OF THE FDA'S REPRODUCTIVE HEALTH DRUGS ADVISORY COMMITTEE

GAITHERSBURG, MD. — A Food and Drug Administration advisory panel unanimously agreed that concerns about the risks of flibanserin outweighed any evidence that the drug was effective as a treatment for premenopausal women with hypoactive sexual desire disorder.

Moreover, the evidence provided by Boehringer Ingelheim Pharmaceuticals that flibanserin (Girosa) is effective treatment for hypoactive sexual desire disorder (HSDD) did not sway the FDA's Reproductive Health Drugs Advisory Committee, reflected by their 10 to 1 no vote on that question.

The panel was not asked to vote on a separate safety question, but members expressed concerns about adverse effects associated with the drug in clinical trials, including high rates of somnolence and fatigue, a slightly higher rate of depression, the potential for drug and alcohol interactions, the lack of safety data on long-term use and during nursing and pregnancy—as well as the high withdrawal rate for adverse events in clinical trials.

However, panelists encouraged the company to continue studying the drug, noting the importance of finding treatments for HSDD, defined as a persistent or recurrent deficiency or absence of desire for sexual activity.

Boehringer Ingelheim has proposed that 100 mg of flibanserin, a centrally acting drug, taken orally every night at bedtime be approved for the treatment of HSDD in premenopausal women. The drug, first studied for depression, is a postsynaptic 5-HT1A agonist and 5-HT2A antagonist, and results in increases in dopamine and norepinephrine and decreases serotonin. No drug on the market has this neurotransmitter activity, according to the FDA.

In two pivotal, randomized, double-blind trials in the United States and Canada, the 100-mg dose was compared with placebo in healthy, premenopausal adult women (almost 700 patients were in each group with an average age of 35-36 years). Participants were in stable, heterosexual, monogamous relationships and were diagnosed with HSDD based on DSM–IV-TR criteria; most were white and 78% were married and had been with their partner for at least 10 years; exclusions included having a psychiatric disorder or taking a medication that could affect sexual functioning.

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DR. RICE

The primary end points were the changes from baseline in the number of Satisfying Sexual Events (SSEs), and the sexual desire score (the "eDiary Sexual Desire score), based on answers to questions answered on an online diary every day, regarding the respondent's level of sexual desire, whether she had sex, and whether it was satisfying.

The study failed to meet these two coprimary end points: After 24 weeks, the increase in SSEs was slightly less than one satisfactory event per month more than those in placebo group, in the two studies. (The increase in the mean number of SSEs over placebo was 0.8 per month in both studies.) Changes over 24 weeks in the eDiary Sexual Desire Score increased among those on flibanserin but were not significantly different from those on placebo in the two studies.

A secondary end point, the change in the total distress score on a scale measuring female sexual distress, showed a statistically significant effect of treatment over placebo.

The most common side effects of treatment were dizziness, nausea, fatigue, somnolence, insomnia, dry mouth, and anxiety. Safety concerns raised by the FDA were a higher rate of accidental injuries, syncope, and depression among those treated with the 100-mg dose, compared with lower doses in other studies and placebo, as well as the effects of hepatic impairment and coadministration with drugs that are strong CYP3A4 inhibitors on the concentration of flibanserin.

"I'm concerned about the safety signals that we saw. I'm especially concerned about the risk and the generalizability in a very heterogeneous population that would take this drug if we were to approve it," committee member Valerie Montgomery Rice, professor of obstetrics and gynecology at Meharry Medical College, Nashville, said. She also cited doubts about generalizability of the efficacy findings to a more heterogeneous population than was studied in the pivotal trials.

The FDA usually follows the recommendations of its advisory panels. Currently, no drug is approved for HSDD, but testosterone and bupropion are used off-label for this indication. ■

Disclosures: *Members of FDA advisory panels have been cleared of conflicts related to the topic under discussion.*

Sue Sutter of Elsevier's "The Pink Sheet" contributed to this report.