ADDYI FACTS

SUMMARY

Flibanserin was approved by the FDA in August, 2015 as a treatment for "Hypoactive Sexual Desire Disorder" in premenopausal women. A mixed serotonin agonist/antagonist that appears to decrease serotonin levels and increase norepinephrine and dopamine levels, flibanserin failed efficacy trials as an antidepressant and was rejected twice for its current indication before being approved.

Flibanserin can cause serious harms, including CNS depressant effects, unpredictable hypotension, and sudden prolonged unconsciousness. Its adverse effects are exacerbated by alcohol, oral contraceptives, antifungals, triptans and many other drugs.[2] Prescribers and pharmacies must be certified to prescribe or dispense flibanserin (addyirems.com).

HSDD NO LONGER EXISTS

Hypoactive sexual desire disorder was recently dropped from the latest edition of the DSM-5. Disorders of desire and arousal have now been combined in the term 'female sexual interest/arousal disorder' (FSI/AD),[3] which takes into account the fact that for many women, desire follows rather than precedes arousal.

IS ADDYI EFFECTIVE?

Women who took flibanserin had less than one (0.7) more satisfying sexual events (SSE) per month than women who took placebo.[2] A satisfying sexual event did not necessarily involve an orgasm or a partner. Addyi has no effect on orgasm or painful intercourse.

CNS DEPRESSION

One in five patients (21%) in clinical trials experienced fatigue, somnolence, or sedation – events consistent with CNS depression.[2, 4] Accidental injuries associated with CNS depression occurred more than twice as often (24% vs. 9%) in flibanserin-treated patients, compared to placebo-treated patients.[2, 4]

SYNCOPE AND HYPOTENSION

Flibanserin can cause sudden unconsciousness, with drops in diastolic blood pressure into the 40s. Tolerance to syncope does not appear to develop.[4]

SEDATION

Flibanserin alone is more sedating than four alcoholic drinks.[2] Although one study found no effect of flibanserin on simulated driving or reflexes 9 hours after dosing, no information is available on driving soon after dosing.[1]

ADVERSE EFFECTS IN ASIANS

More Asians (15%) than Caucasians (5%) have low levels of CYP2C19, which can double exposure to flibanserin.[2] Flibanserin exposure was approximately 1.4-fold higher in Japanese women, compared to Caucasian women.[1]

HEPATIC IMPAIRMENT

Mild hepatic impairment increases flibanserin levels 4.5-fold and the half-life increases from 10 hours to 26 hours.[1]

INTERACTIONS WITH DRUGS

Flibanserin is primarily metabolized by CYP3A4 and, to a lesser extent, by CYP2C19.[1]

Many common drugs will increase flibanserin levels.[4] Oral contraceptives increase flibanserin levels 42%. Triptans increase flibanserin 4.5-fold. Fluconazole and ketoconazole increase drug levels 7-fold and 4.5-fold, respectively.[1] A fluconazole-flibanserin interaction study was abandoned after all of the first 15 subjects experienced adverse effects, including syncope and hypotension, with diastolic readings in the 40s.[4] Interactions can be expected with other CYP3A4 inhibitors. Many commonly used antidepressants, anticonvulsants, and proton pump inhibitors inhibit CYP2C19 and can be expected to increase exposure to flibanserin. (see page 3)

Flibanserin increases blood levels of digoxin. An interaction study found flibanserin increased digoxin levels 81%; all 24 subjects in this study experienced adverse effects. Digoxin is metabolized by p-glycoprotein, not CYP enzymes, so interactions can be expected with other drugs metabolized by p-glycoprotein. Opioids, benzodiazepines, sedative-hypnotics, diphenhydramine and other CNS depressants may increase the risk of CNS depression.

Drugs that can increase flibanserin levels:

Fluconazole, ketoconazole, itraconazole, posaconazole
Triptans
Oral contraceptives
Clarithromycin, telithromycin, erythromycin
Nefazodone
Diltiazem
Verapamil
Telaprevir, ritonavir, saquinavir, nelfinavir, indinavir, boceprevir, and lopinavir, amprenavir, atazanavir, fosamprenavir
Ciprofloxacin
Conivaptin
Grapefruit juice
Proton pump inhibitors, SSIs, benzodiazepines, antifungals
Many other drugs

Flibanserin can increase levels of these drugs:

Digoxin
Simvastatin
Protease inhibitors
Sirolimus
Loperamide
Dabigatran
Many other drugs

Drugs unaffected by flibanserin:

Bupropion
Levonogestrel

For a complete list of CYP inhibitors, visit http://medicine.iupui.edu/clinpharm/ddis/

INTERACTION WITH ALCOHOL

Alcohol increases adverse effects with flibanserin. In an alcohol interaction study that included only two women, 4 of 23 subjects (17%) who received flibanserin with the equivalent of two drinks experienced syncope or symptomatic hypotension. Six of 24 subjects (25%) who received flibanserin with the equivalent of four drinks developed orthostatic hypotension.[1]

PHARMEDOUT

This factsheet was created by PharmedOut, a Georgetown University Medical Center project that educates prescribers on the effects of pharmaceutical marketing on prescribing. To find out more, visit pharmedout.org

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