Addyi (flibanserin)

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

Addyi (fllibanserin) is a serotonin 5-HT1A agonist and 5-HT2A antagonist with moderate antagonist activities at the 5-HT2B, 5-HT2C, and dopamine D4 receptors.

FDA-Approved Indications
Addyi (flibanserin) is indicated for the treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD) as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is not due to a co-existing medical or psychiatric condition, problems within the relationship, or the effects of a medication or other drug substance.

Limitations of Use
- Addyi is not indicated for the treatment of HSDD in postmenopausal women or in men
- Addyi is not indicated to enhance sexual performance

POLICY

Addyi (flibanserin) is considered **not covered** for all indications, including the treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD), due to the serious safety concerns and limited clinical benefits demonstrated in clinical trials.

CLINICAL RATIONALE

Hypoactive sexual desire disorder (HSDD) is a disease that represents a subset of symptoms associated with “desire” within the overarching diagnosis of sexual dysfunction. HSDD was a stand-alone diagnosis in the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV. In DSM V, HSDD is now incorporated into female sexual interest/ arousal disorder (FSIAD). FSIAD is defined as a lack of, or significantly reduced, sexual interest or arousal for 6 months or greater when a patient meets 3 of the 6 diagnostic criteria.

Addyi (flibanserin) was approved by the FDA on August 18, 2015 and is the first agent approved for the treatment of HSDD. Addyi (flibanserin) demonstrated limited efficacy in multiple clinical trials, and there are serious safety concerns regarding the risk of hypotension and syncope when patients consume alcohol or receive interacting medications.

The efficacy of Addyi (flibanserin) was assessed in three 24-week, multicenter, double-blind, randomized, controlled trials. All three trials included premenopausal women with HSDD in North America and measured

changes in the number of monthly satisfying sexual events (SSEs) as well as scores of sexual desire. In all three trials, Addyi (flibanserin) resulted in statistically significant improvement compared to placebo in the change from baseline in monthly SSEs at Week 24 (1.6 vs. 0.8, 1.8 vs. 1.1, and 2.5 vs.1.5). In Study 1 and 2, there were no statistically significant differences between Addyi (flibanserin) and placebo for the eDiary sexual desire endpoint (change in baseline to Week 24). In contrast, in Study 3 there was statistically significant improvement in the change from baseline to Week 24 in sexual desire (using the Female Sexual Function Index Desire Domain) with Addyi (flibanserin) compared to placebo (increases of 1 vs. 0.7). In summary, treatment with Addyi (flibanserin) resulted in small but statistically significant increases in the number of satisfying sexual events but conflicting results regarding increases in sexual desire.

The 52-week, open-label, flexible dose, uncontrolled extension SUNFLOWER trial was also conducted with Addyi (flibanserin) in 1,723 premenopausal women (mean age 37.5 years) who participated in one of five previous trials of Addyi (flibanserin). During the SUNFLOWER trial, women received Addyi (flibanserin) 50 mg every night at bedtime for four weeks followed by an optimized dose based on efficacy and tolerability. The doses allowed included 50 mg once nightly, 100 mg once nightly, 25 mg twice daily, and 50 mg twice daily. Safety was the primary endpoint of this trial. Overall, 74.4% of women experienced any adverse event, and 10.7% of women discontinued treatment due to an adverse event. Commonly reported adverse events included somnolence (15.8%), fatigue (7.6%), dizziness (6.9%), and nausea (6.3%). At the end of treatment, 55.1% of 1,491 women stated that they experienced a meaningful benefit from treatment with Addyi (flibanserin). However, it should be noted that 761 women discontinued the trial prior to the end of treatment, including 207 women (12%) who discontinued due to lack of efficacy.

The 24-week, multicenter, double-blind, randomized, controlled SNOWDROP trial was performed to assess the effect of Addyi (flibanserin) in 949 postmenopausal women with HSDD (mean age: 55.5 years). Women were randomized to receive Addyi (flibanserin) 100 mg or placebo every night at bedtime. Compared to a mean baseline of two satisfying sexual events per 28 days, the number of satisfying sexual events per 28 days increased by 1.0 with Addyi (flibanserin) compared with 0.6 with placebo ($p = 0.004$). Compared with baseline, the Female Sexual Function Index (FSFI) desire domain score increased by 0.7 with Addyi (flibanserin) and 0.4 with placebo ($p < 0.001$). The FSFI desire domain includes two questions scored from 1 to 5 assessing frequency and intensity of sexual desire over past four weeks. The total domain score ranges from 1.2 to 6, and the mean baseline score was 1.8 among patients in the trial. Although Addyi (flibanserin) had a statistically significant improvement in satisfying sexual events in postmenopausal women with HSDD, the magnitude of the placebo-correct effect was approximately half as large as that found in trials of premenopausal women. In addition, the placebo-corrected proportion of women in the SNOWDROP trial that stated they experienced a meaningful benefit with Addyi (flibanserin) was 9.6%. Overall, Addyi (flibanserin) appears to have very limited efficacy in postmenopausal women with HSDD.

Addyi (flibanserin) is available through a REMS program because of the increased risk of severe hypotension and syncope due to an interaction between flibanserin and alcohol. Prescribers and pharmacies must enroll in the REMS program prior to prescribing or dispensing Addyi (flibanserin), and patients must be educated about the risk of hypotension and syncope associated with the drug due to the interaction with alcohol. Patients must sign a Patient-Provider Agreement Form prior to receiving a prescription for Addyi (flibanserin). Cases of hypotension or syncope where an interaction of alcohol cannot be ruled out must be reported to the manufacturer.

In October of 2019, the FDA provided updates to Addyi's labeling. These updates were intended to clarify the risk of consuming alcohol close in time to taking Addyi and to highlight that it does not have to be avoided completely. Specifically, the boxed warning, contraindication, warnings and precautions, and adverse reactions sections of labeling were updated to reflect that women should discontinue drinking alcohol at least two hours before taking Addyi at bedtime or to skip the Addyi dose that evening. Women

should not consume alcohol at least until the morning after taking Addyi at bedtime. The boxed warning, REMS program, and contraindication about alcohol still remain in the product labeling.

The FDA's decision to order modifications to the warnings about Addyi and alcohol, instead of removing the boxed warning and contraindication completely, is based on two sets of postmarket research studies.

In the FDA-required postmarketing trial in women who took Addyi and drank alcohol at the same time, there were missing or delayed measurements for blood pressure from when the women were first laying down to when they stood up that are critical in determining the risk of hypotension and syncope when taking Addyi and alcohol together. The pattern of the missing or delayed measurements provides further evidence of an interaction between Addyi and alcohol that can increase the risk of hypotension and syncope. Given these results, the FDA determined that the boxed warning and contraindication continue to be warranted. Women at home will not have the safety measures that were included in this trial or necessarily have access to immediate assistance if they were to experience severe hypotension or syncope, which can lead to serious outcomes including falls, accidents and bodily harm.

In other postmarketing trials, results showed that the risk of severe hypotension and syncope was reduced when women who consumed up to two alcoholic drinks waited at least two hours before taking Addyi. The FDA has found these results sufficient to support a modification to the boxed warning and contraindication stating that Addyi and alcohol must not be taken close in time (i.e. not within two hours).

Although flibanserin has demonstrated improvement in treating HSDD, the overall results of the clinical trials were numerically small, and continued assessment of long-term benefits and risks associated with flibanserin is still warranted. Addyi (flibanserin) is associated with a risk of serious hypotension and syncope, particularly when administered concomitantly with alcohol or numerous interacting drugs. In summary, Addyi (flibanserin) is associated with safety concerns that do not justify the limited clinical benefit it provides.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

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POLICY HISTORY

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