Kansas City

An Independent Licensee of the Blue Cross and Blue Shield Association

Addyi (flibanserin)

Policy Number: 5.01.605
Origination: 10/2015
Last Review: 10/2018
Next Review: 10/2019

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Addyi when it is determined to be medically necessary because the following criteria are met.

When Policy Topic is covered

Coverage of Addyi is recommended in those who meet the following criteria:

Food and Drug Administration (FDA)-Approved Indications

1. Premenopausal female, AND
2. Diagnosed with acquired, generalized hypoactive sexual desire disorder (HSDD) that 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, AND
3. Prescribers and pharmacist must be certified with the REMS program

If criteria are met, initial authorization will be for 8 weeks. Continuing therapy will require physician documentation of improved symptoms.

When Policy Topic is not covered

Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria, including, but not limited to, enhancing sexual performance. Criteria will be updated as new published data are available.

Coverage is not medically necessary for males, or postmenopausal women.

Considerations

Addyi requires prior authorization through the pharmacy services department.

This Blue Cross and Blue Shield of Kansas City policy Statement was developed using available resources such as, but not limited to: Food and Drug Administration (FDA) approvals, Facts and Comparisons, National specialty guidelines, Local medical policies of other health plans, Medicare (CMS), Local providers.

Description of Procedure or Service

Addyi 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.[1] Acquired HSDD refers to HSDD that develops in a patient who previously had no problems with sexual desire. Generalized HSDD refers to HSDD that occurs regardless of the type of stimulation, situation, or partner.

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.

Mechanism of Action
Addyi is a centrally-acting, post-synaptic serotonin 1A receptor agonist and a serotonin 2A receptor antagonist that has been shown to regulate levels of dopamine and norepinephrine and induce transient decreases in serotonin in specific regions of the brain.[1,7] The exact mechanism of action of Addyi in the treatment of premenopausal women with HSDD is not known.[1]

Dosing/Administration
The recommended dose is 100 mg by mouth daily at bedtime (QHS). Addyi is dosed at bedtime because administration during waking hours increases the risk of hypotension, syncope, accidental injury, and central nervous system (CNS) depression (such as somnolence and sedation). If a dose is missed, the next dose is taken at bedtime on the next day. Addyi should be discontinued after 8 weeks if the patient does not report an improvement in her symptoms.

Rationale

The efficacy of Addyi was established in three published, Phase III, 24-week, randomized, double-blind, placebo-controlled, multicenter, North American (US and Canada) pivotal studies.[1,4-7] The three pivotal studies are: DAISY (Dose Ascending Study over half a Year), VIOLET (The Evaluation of the Impact on Sexuality with Evening Treatment study), and BEGONIA.

Pivotal Data
All of the studies had a similar study design with a 4 week baseline period followed by a 24-week treatment period, similar inclusion/exclusion criteria, and assessment of efficacy endpoints.[1,4-

Endpoints
The co-primary efficacy endpoints were the change from baseline to study end (Weeks 24) in the number of satisfying sexual events (SSEs) and in the sexual desire score, both measured using a daily eDiary for the DAISY and VIOLET studies.[4-6] In the BEGONIA trial, sexual desire was assessed using the Female Sexual Function Index (FSFI) sexual desire domain questions, instead of the eDiary[1,4,7]. A sexual event in all pivotal trials was defined as sexual intercourse, oral sex, masturbation, or genital stimulation by one's partner.[1,4-7] The eDiary was a handheld electronic diary that prompted women to answer questions on a daily basis regarding their sexual activity. For the SSE endpoint the eDiary questions were: "Did you have a sexual event?" and "was the sex satisfying for you?" (yes or no for every sexual event).[1,4-5] An SSE was recorded when a woman reported that a recorded sexual event was satisfying for her.[6] The sexual desire question in the eDiary was, "Indicate your most intense level of sexual desire in the last 24 hours," scored on a four-point scale of 0 (no desire), 1 (low desire), 2 (moderate desire), or 3 (strong desire).[4-6] The results were standardized to a 28-day period. A woman's monthly SSE was calculated as 28 x (sum of SSE/number of entries) and the monthly eDiary desire standardized score was calculated as 28 x (sum of daily desire scores/number of entries).[5-6]

Secondary endpoints in the DAISY and VIOLET studies included the change from baseline to study end in sexual desire and in sexual function assessed using the FSFI questionnaire.[4-6] The FSFI sexual desire domain included one question on the frequency of sexual desire ("over the past 4 weeks, how often did you feel sexual desire or interest?") and one question on the level of sexual desire ("over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?").[4] Both questions were rated on a scale from 1 to 5, and the weighted (correction factor 0.6) score can range from 1.2 to 6, with higher scores indicating greater sexual desire.[4-6] Distress associated with sexual dysfunction and with low sexual desire was assessed using the FSDS-R. FSDS-R is a 13-item self-administered questionnaire that assessed sexual distress or bother. All 13 items were rated on a five point scale, for a total score ranging from 0 to 52 with lower scores indicating less distress. Item 13 on the FSDS-R specifically assessed distress due to low sexual desire with the following question: "How often did you feel bothered by low sexual desire?" The FSFI used a 4-week recall period and the FSDS-R used a 7-

day recall period. Women also evaluated the overall improvement in HSDD from the beginning of the trial using the Patient's Global Impression of Improvement (PGI-I) question at Weeks 4, 8, 16, and 24: "How's your condition – meaning decreased sexual desire and feeling bothered by it – today compared with when you started the study medication?"[4-7] The PGI-I question was rated on a seven-point scale (1 = very much improved, 4 = no change, and 7 = very much worse). On treatment discontinuation women were also asked the following Patient Benefit Evaluation (PBE) question: "Overall, do you believe that you have experienced meaningful benefit from the study medication?" with a "yes" or "no" response options.

Pivotal Trial Discussion

All three pivotal studies are published and had a similar study design. Each of the studies included a reasonable number of women, though the study design had restrictive inclusion/exclusion criteria which may not be representative of the women who may be prescribed Addyi in clinical practice. The pivotal studies were all conducted for 24 weeks, which is a relatively short timeframe especially considering that Addyi is likely to be prescribed on a chronic basis. For the DAISY and VIOLET studies, the co-primary efficacy endpoints of SSE and sexual desire score are subjective and relied upon daily entries into an eDiary. The patient-reported subjective endpoints are one of the limitations of the studies; however, since there are no objective measurements for HSDD, the patient reported outcomes are generally used in sexual dysfunction studies and are accepted by the Food and Drug Administration (FDA). In DAISY and VIOLET studies, the co-primary efficacy endpoint of eDiary sexual desire score did not achieve statistical significance in any of the Addyi treatment groups. Due to this, in the BEGONIA trial the eDiary sexual desire score was abandoned as a primary endpoint and instead the FSFI desire score was used as a co-primary endpoint. It is important to note that the FSFI score was based on a 4-week recall period, whereas the eDiary sexual desire score was recorded every day. It is unlikely that a 4-week recall of events is more robust than daily recall. It is also possible that women may be biased to rate the FSFI desire score higher retrospectively over the 4 weeks if they have experienced one or more SSE during that time compared with rating it on the same day in the eDiary without the benefit of considering the cumulative positive SSE events. In the FDA review document[4], it is noted that the manufacturer cited "diary fatigue" due to decreased compliance with daily diary entry over time as the reason for the lack of statistical significance with the eDiary co-primary endpoint in the DAISY and VIOLET pivotal studies. Overall, of the three pivotal studies only the BEGONIA study met the statistical significance for both the co-primary endpoints; however, the median treatment difference in the SSE and FSFI score was very minimal, so the clinical significance is unclear. For the secondary endpoints, FSDS-R Item 13, assessed distress due to low sexual desire using a 7-day recall period, the PGI-I endpoint assessed for overall improvements in the patient's HSDD condition, and the PBE question assessed if the patient experienced meaningful treatment benefit from the study medication. Again, these are all subjective endpoints; however, in the absence of objective measures the patient reported outcomes are necessary to assess treatment benefit.

Place in Therapy

HSDD is defined in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), as persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity that causes marked distress or interpersonal difficulty.[4-5] The judgement of deficiency or absence is made by the clinician taking into account factors that affect sexual functioning, such as age and the context of the person's life.[4] The sexual dysfunction should not be better accounted for by another Axis I disorder (except another Sexual Dysfunction) and is not exclusively due to the direct physiological effects of a substance (e.g., a drug of abuse, medication) or a general medical condition. HSDD is no longer a stand-alone diagnosis; the current DSM-5 describes a new condition, female sexual interest/arousal disorder, which combines features of both HSDD and another condition from DSM-IV known as female sexual arousal disorder. Addyi is the first approved drug therapy for HSDD.

References

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Billing Coding/Physician Documentation Information

NA Addyi is an oral tablet, pharmacy benefit

Additional Policy Key Words

5.01.605

Policy Implementation/Update Information

10/2015	New policy titled, Addyi (flibanserin)
10/2016	Annual review- no changes to policy statement
10/2017	Annual review- no changes to policy statement
10/2018	No changes made, just formatting