Hypoactive Sexual Desire Disorder (HSDD) Prior Authorization with Quantity Limit Program Summary

This program applies to FlexRx Closed, FlexRx Open, FocusRx, GenRx Closed, GenRx Open, and KeyRx formularies.

This is a FlexRx Standard and GenRx Standard prior authorization program.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
03-01-2024	02-01-2016

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Addyi® (flibanserin) Tablet	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 • The effects of a medication or other drug substance. Limitations of Use: • Not indicated for the treatment of HSDD in postmenopausal women or in men. • Not indicated to enhance sexual performance		1
Vyleesi® (bremelanotide) Subcutaneous injection	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 • The effects of a medication or other drug substance 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: • Not indicated for the treatment of HSDD in postmenopausal women or in men • Not indicated to enhance sexual performance		2

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Hypoactive Sexual Desire Disorder	Hypoactive sexual desire disorder (HSDD) is the most common sexual dysfunction in women. It is associated with medical conditions, including depression, and negative emotional and psychological states. HSDD is defined as persistent and recurrent lack of motivation for sexual activity in women who report a loss of desire to initiate or participate in sexual activity with clinically significant personal distress for a minimum of 6 months. The International Society for the Study of Women's Sexual Health recommends the use of the Decreased Sexual Desire Screener and/or a sexual history to accurately diagnosis and determine type of HSDD. Modifiable contributing factors (e.g., relationship dissatisfaction, stress, fatigue, problems related to arousal, pain, and orgasm) should also be evaluated.(3) Although the underlying biological causes of HSDD remain unknown, generalized HSDD likely involves either a predisposition toward inhibitory processes or neuroadaptations that result in decreased excitation, increased inhibition, or a mixture of the two.(3) Neurotransmitters such a dopamine, estrogen, norepinephrine, progesterone, and testosterone are generally considered to be intrinsic to the excitatory aspects of sexual desire and response. But opioids, prolactin, and serotonin are considered to be inhibitory. Many of the existing pharmacological treatments that are utilized for HSDD target some of the hormones and neurotransmitters involved in these pathways.(4) There are several other variables that contribute to HSDD including psychosocial factors (such as self-image and relationship satisfaction), menopause, medications and substances, and comorbid conditions.(3,4) Treatment for HSDD should be focused on the needs of the patient. First line therapy for HSDD is education (including modification of any potentially contributing factors). This may include cognitive behavior therapy, couples counseling, and office-based counseling. Presently there are two pharmacological options that are specifically indicated for HSDD among premenopausal women, bremelanotide and flibanserin. Flibanserin is considered a third line option for premenopausal women, according to the International Society for the Study of Women's Sexual Health treatment algorithm and is taken once daily at bedtime.(3) Bremelanotide is administered via autoinjector and is taken on an as needed basis prior to sexual encounters. Patients should not exceed more than one dose in a 24-hour period or eight doses within a 30-day period.(3,4)
Addyi Efficacy	The efficacy of flibanserin for the treatment of HSDD in premenopausal women was established in three 24-week, randomized, double-blind, placebo-controlled trials (studies 1, 2, and 3). The three trials included premenopausal women with acquired, generalized HSDD of at least 6 months duration. In the clinical trials, acquired HSDD was defined as HSDD that developed in patients who previously had no problems with sexual desire. Generalized HSDD was defined as HSDD that was not limited to certain types of stimulation, situations or partners. The patients were treated with Addyi 100 mg once daily at bedtime (n equal to 1187) or placebo (n equal to 1188). The completion rate across these three trials was 69% and 78% for the Addyi and placebo groups, respectively.(1) These trials each had two co-primary efficacy endpoints, one for satisfying sexual events (SSEs) and the other for sexual desire: • The change from baseline to Week 24 in the number of monthly SSEs (i.e., sexual intercourse, oral sex, masturbation, or genital stimulation by the partner). The SSEs were based on patient responses to the following questions: "Did you have a sexual event?" and "Was the sex satisfying for you?" • Studies 1 and 2 had a different sexual desire endpoint than study 3: ○ In studies 1 and 2, the sexual desire co-primary endpoint was the change from baseline to Week 24 in the calculated monthly sexual desire score and was based on patient responses to the question: "Indicate your most intense level of sexual desire." Every day, patients

	rated their sexual desire level from 0 (no desire) to 3 (strong desire) and recorded their response in an electronic Diary (eDiary). These responses were summed over a 28-day period to yield the calculated monthly sexual desire score, which ranged from 0 to 84. ○ In study 3, the desire domain of the Female Sexual Function Index (FSFI Desire) was the sexual desire co-primary endpoint. The desire domain of the FSFI has two questions. The first question asks patients "Over the past 4 weeks, how often did you feel sexual desire or interest?", with responses ranging from 1 (almost never or never) to 5 (almost always or always). The second question asks patients "Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?", with responses ranging from 1 (very low or none at all) to 5 (very high). The FSFI Desire score was calculated by adding the patient's responses to these two questions then multiplying that sum by 0.6. The FSFI Desire domain score ranged from 1.2 to 6.(1) The three trials had a secondary endpoint that measured bother (a component of distress) related to sexual desire using Question 13 of the Female Sexual Distress Scale-Revised (FSDS-R). This question asks, "How often did you feel: Bothered by low sexual desire?" Patients assessed their sexual distress over a 7-day recall period and responded on a scale of 0 (never) to 4 (always). The desire domain of the Female Sexual Function Index (FSFI Desire) was also used as a secondary endpoint in Studies 1 and 2. (1) In all three trials, Addyi resulted in statistically significant improvement compared to placebo in the change from baseline in monthly SSEs at Week 24. In study 1 and 2, there were no statistically significant differences between Addyi 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 FSFI Desire Domain) with Addyi compared to placebo. The FSFI Desire Domain findings were consistent across all three trials as were the findings for the secondary endpoint that assessed distress using Question 13 of the FSDS-R.(1) Additional analyses defined responders for each efficacy endpoint by anchoring change from baseline to end of treatment with the Patient's Global Impression of Improvement (PGI-I). The first analysis considered responders to be those who reported being "much improved" or "very much improved." In this analysis, the absolute difference in the percentage of responders with Addyi and the percentage of responders with placebo across the three trials was 8-9% for SSEs (29-39% for Addyi; 21-31% for placebo), 10-13% for FSFI desire domain (43-48% for Addyi; 31-38% for placebo), and 7-13% for FSDS-R Question 13 (21- 34% for Addyi; 14-25% for placebo). The second analysis considered responders to be those who reported being at least minimally improved. The absolute difference in the percentage of responders with Addyi and the percentage of responders with placebo across the three trials was 10-15% for SSEs (44-48% for Addyi; 33-36% for placebo), 12-13% for FSFI desire domain (43-51% for Addyi; 31-39% for placebo), and 9-12% for FSDS-R Question 13 (50-60% for Addyi; 41-48% for placebo).(1)
Vylessi Efficacy	The efficacy in premenopausal women was evaluated in two identical phase 3, randomized, double-blinded, placebo controlled trials. Both trials included premenopausal women with acquired, generalized HSDD of at least 6 months' duration. A majority of patients (74% in Study 1 and 67% in Study 2) reported HSDD with concomitant decreased arousal. The trials consisted of two phases: a Core Study Phase (24-week placebo-controlled, double-blind treatment period) and an uncontrolled, 52-week Open-label Extension Study Phase. Study participants were randomized to subcutaneous injections of Vyleesi 1.75 mg (n= 635) or placebo (n= 632), self-administered by an autoinjector on an as-needed basis. Patients were instructed to administer the drug approximately 45 minutes prior to anticipated sexual activity. Patients were not to administer more than one dose within a 24-hour period and no more than twelve doses per month. The mean duration of HSDD was approximately 4 years. Across the two trials, the median number of Vyleesi injections was 10 in the 24-week double-blind treatment period and 12 during the uncontrolled

	open-label extension. Most patients used Vyleesi two to three times per month and no more than once a week.(2) Study 1 and Study 2 had the following co-primary efficacy endpoints: • Change from baseline to end of study (EOS) in the Desire domain from the Female Sexual Function Index (FSFI) (Questions 1 and 2). Question 1 asks patients "Over the past 4 weeks, how often did you feel sexual desire or interest?", with responses ranging from 1 (almost never or never) to 5 (almost always or always). Question 2 asks patients "Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?", with responses ranging from 1 (very low or none at all) to 5 (very high). The FSFI Desire domain score was calculated by adding the patient's responses to these two questions then multiplying that sum by 0.6. The FSFI Desire Domain score ranged from 1.2 to 6. An increase in the FSFI Desire domain score over time denotes improvement in sexual desire. • Change from baseline to EOS in the score for feeling bothered by low sexual desire as measured by the Female Sexual Distress Scale – Desire/Arousal/Orgasm Question 13 (FSDS-DAO Q13). This question asks patients, "How often did you feel: Bothered by low sexual desire?" Patients assessed their sexual distress over a 30-day recall period and responded on a scale of 0 (never) to 4 (always). A decrease in the FSDSDAO Q13 score over time denotes improvement in the level of distress associated with low sexual desire. EOS is defined as the patient's last study visit during the double-blind treatment period.(2) For patients who completed the double-blind treatment period, the EOS visit occurred at Week 24. In both studies, Vyleesi showed a statistically significant increase in the FSFI Desire Domain score and a statistically significant decrease in the FSDS-DAO Q13 score from baseline to the EOS visit compared to placebo. The magnitude of the treatment differences was similar in both studies. There was no significant difference between treatment groups in the change from baseline to end of study visit in the number of satisfying sexual events (SSEs), a secondary endpoint.(2)
Safety	Addyi carries the following boxed warning: • The use of Addyi and alcohol together close in time increases the risk of severe hypotension and syncope. Counsel patients to wait at least two hours after consuming one or two standard alcoholic drinks before taking Addyi at bedtime or to skip their Addyi dose if they have consumed three or more standard alcoholic drinks that evening.(1) Addyi carries the following contraindications: • Addyi is contraindicated in patients taking a moderate or strong CYP3A4 inhibitor. Concomitant use with moderate or strong CYP3A4 inhibitors increases flibanserin concentrations, which can cause severe hypotension and syncope. • Addyi is contraindicated in patients with hepatic impairment. Use in patients with hepatic impairment increases flibanserin concentrations, which can cause severe hypotension and syncope.(1) Vyleesi is contraindicated in patients who have uncontrolled hypertension or known cardiovascular disease.(2)

REFERENCES

Number	Reference
1	Addyi prescribing information. Sprout Pharmaceuticals Inc. September 2021.

Number	Reference
2	Vyleesi prescribing information. AMAG Pharmaceuticals, Inc. October 2020.
3	Clayton, Anita H, et al. "The International Society for the Study of Women's Sexual Health Process of Care for Management of Hypoactive Sexual Desire Disorder in Women." Mayo Clinic Proceedings, vol. 93, no. 4, 12 Mar. 2018, pp. 467–487., doi: https://doi.org/10.1016/j.mayocp.2017.11.002.
4	Pachano Pesantez, G. S., & Clayton, A. H. (2021). Treatment of Hypoactive Sexual Desire Disorder Among Women: General Considerations and Pharmacological Options. *Focus (American Psychiatric Publishing)*, *19*(1), 39–45. https://doi.org/10.1176/appi.focus.20200039

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Vyleesi	bremelanotide acet subcutaneous soln auto-inj	1.75 MG/0.3ML	M ; N ; O ; Y	N		
Addyi	flibanserin tab	100 MG	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Addyi	Flibanserin Tab 100 MG	100 MG	30	Tablets	30	DAYS			
Vyleesi	Bremelanotide Acet Subcutaneous Soln Auto-Inj 1.75 MG/0.3ML	1.75 MG/0.3 ML	6	Pens	30	DAYS	Quantity limit for Vyleesi will allow for 6 doses per 30 days.		

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Addyi	flibanserin tab	100 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; KeyRx
Vyleesi	bremelanotide acet subcutaneous soln auto-inj	1.75 MG/0.3ML	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; KeyRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Addyi	Flibanserin Tab 100 MG	100 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; KeyRx
Vyleesi	Bremelanotide Acet Subcutaneous Soln Auto-Inj 1.75 MG/0.3ML	1.75 MG/0.3ML	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; KeyRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient's benefit plan covers the requested agent **AND** 2. The patient is premenopausal **AND** 3. The patient has had a diagnosis of acquired, generalized hypoactive sexual desire disorder (HSDD) and BOTH of the following: A. The patient's diagnosis is characterized by low sexual desire that causes marked distress or interpersonal difficulty **AND** B. The patient's symptoms of low sexual desire have been present for at least 6 months **AND** 4. The HSDD is NOT due to ANY of the following: A. A co-existing medical or psychiatric condition **OR** B. Problems within the relationship **OR** C. The effects of a medication or other drug substance **AND** 5. The patient has tried and had an inadequate response to other treatment modalities (e.g., education, couples counseling, office-based counseling, cognitive behavioral therapy) **AND** 6. The patient will NOT be using the requested agent in combination with another target agent in this program **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 8 weeks NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's prior authorization process **AND** 2. The patient's benefit plan covers the requested agent **AND** 3. The patient is premenopausal **AND** 4. The patient has had clinical benefit with the requested agent (e.g., HSDD symptoms have improved) **AND** 5. The patient will NOT be using the requested agent in combination with another target agent in this program **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Quantity limit for the Target Agent(s)** will be approved when the requested quantity (dose) does NOT exceed the program quantity limit **Length of Approval:** Initial: 8 weeks; Renewal: 12 months