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

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

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

**FDA APPROVED INDICATIONS AND DOSAGE**¹,²

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Dosage &amp; Administration</th>
</tr>
</thead>
</table>
| 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 | Recommended dosage is 100 mg taken once daily at bedtime  
Flibanserin is dosed at bedtime because administration during waking hours increases risks of hypotension, syncope, accidental injury, and central nervous system (CNS) depression  
Discontinue treatment after 8 weeks if no improvement |
<table>
<thead>
<tr>
<th><strong>Agent</strong></th>
<th><strong>Indication</strong></th>
<th><strong>Dosage &amp; Administration</strong></th>
</tr>
</thead>
</table>
| 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  

|  |  |  |
| 1.75 mg SC in the abdomen or thigh, as needed at least 45 minutes before anticipated sexual activity. Duration of efficacy after each dose is unknown and the optimal window for administration has not been fully characterized.  

Patients should not administer more than one dose within 24 hours. Administering more than 8 doses per month is not recommended. More frequent dosing increases the risk for focal hyperpigmentation and the length of time per month when blood pressure is increased.  

Discontinue treatment after 8 weeks if no improvement  

**CLINICAL RATIONALE**

Hyposexual 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

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. Flibanserin is considered a second line option, according to the International Society for the Study of Women’s Sexual Health treatment algorithm.³

**Addyi**  
**Efficacy**³

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 = 1187) or
placebo (n = 1188). The completion rate across these three trials was 69% and 78% for the ADDYI and placebo groups, respectively.

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 (eDia). 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.

The desire domain of the Female Sexual Function Index (FSFI Desire) was also used as a secondary endpoint in Studies 1 and 2.

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 efficacy results from Studies 1, 2, and 3 are summarized in the table below. 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.

<table>
<thead>
<tr>
<th>Efficacy Results in Premenopausal HSDD Patients in Studies 1, 2, and 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Full Analysis Set</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>n=280</td>
</tr>
<tr>
<td><strong>Number of satisfying sexual events (per 28 days)</strong></td>
</tr>
</tbody>
</table>
## Safety

Addyi carries the following boxed warning:

### Additional Analyses of Efficacy

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 SSEx (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 FSFS-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 SSEx (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 FSFS-R Question 13 (50-60% for ADDYI; 41-48% for placebo).

<table>
<thead>
<tr>
<th>Full Analysis Set</th>
<th>Study 1</th>
<th>Study 2(^1)</th>
<th>Study 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>fibanserin</td>
<td>placebo</td>
<td>fibanserin</td>
</tr>
<tr>
<td><strong>Change from baseline (Mean)</strong></td>
<td>1.6</td>
<td>0.8</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>Treatment diff. (95% CI)</strong></td>
<td>0.9 (0.3, 1.4)</td>
<td>0.6 (-0.03, 1.2)</td>
<td>1.0 (0.4, 1.5)</td>
</tr>
<tr>
<td><strong>Change from baseline (Median)</strong></td>
<td>1.0</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Median treatment difference</strong></td>
<td>p-value vs. placebo</td>
<td>p&lt;0.01</td>
<td>0.5</td>
</tr>
</tbody>
</table>

### e-Diary Desire

<table>
<thead>
<tr>
<th></th>
<th>Baseline (Mean)</th>
<th>Change from baseline at Week 24 (Mean)</th>
<th>Treatment diff. (95% CI)</th>
<th>p-value vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline (Mean)</strong></td>
<td>12.9</td>
<td>11.8</td>
<td>12.1</td>
<td>10.2</td>
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<tr>
<td><strong>Change from baseline at Week 24 (Mean)</strong></td>
<td>9.1</td>
<td>6.9</td>
<td>8.3</td>
<td>6.7</td>
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<tr>
<td><strong>Treatment diff. (95% CI)</strong></td>
<td>2.3 (-0.1, 4.7)</td>
<td>1.7 (-0.5, 4.0)</td>
<td></td>
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<tr>
<td><strong>p-value vs. placebo</strong></td>
<td>N/S</td>
<td>N/S</td>
<td></td>
<td></td>
</tr>
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</table>

### FSFI Desire

<table>
<thead>
<tr>
<th></th>
<th>Baseline (Mean)</th>
<th>Change from baseline at Week 24 (Mean)</th>
<th>Treatment diff. (95% CI)</th>
<th>p-value vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline (Mean)</strong></td>
<td>1.9</td>
<td>1.9</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>Change from baseline at Week 24 (Mean)</strong></td>
<td>0.9</td>
<td>0.5</td>
<td>0.9</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Treatment diff. (95% CI)</strong></td>
<td>0.4 (0.2, 0.5)</td>
<td>0.3 (0.2, 0.5)</td>
<td>0.3 (0.2, 0.4)</td>
<td></td>
</tr>
<tr>
<td><strong>p-value vs. placebo</strong></td>
<td>N/A(^2)</td>
<td>N/A(^2)</td>
<td></td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

### FSFS-R Question 13\(^3\)

<table>
<thead>
<tr>
<th></th>
<th>Baseline (Mean)</th>
<th>Change from baseline at Week 24 (Mean)</th>
<th>Treatment diff. (95% CI)</th>
<th>p-value vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline (Mean)</strong></td>
<td>3.2</td>
<td>3.2</td>
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<td>3.2</td>
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<tr>
<td><strong>Change from baseline at Week 24 (Mean)</strong></td>
<td>-0.8</td>
<td>-0.5</td>
<td>-0.8</td>
<td>-0.5</td>
</tr>
<tr>
<td><strong>Treatment diff. (95% CI)</strong></td>
<td>-0.4 (-0.5, -0.2)</td>
<td>-0.3 (-0.4, -0.1)</td>
<td>-0.3 (-0.4, -0.1)</td>
<td></td>
</tr>
<tr>
<td><strong>p-value vs. placebo</strong></td>
<td>N/A(^2)</td>
<td>N/A(^2)</td>
<td></td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

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\(\text{CI} = \text{Confidence Interval}; \text{N/S} = \text{not statistically significant}; \text{N/A} = \text{not applicable}\)

Shaded cells show the results for the co-primary efficacy endpoints for each trial.

\(^1\) e-Diary desire was evaluated as a co-primary endpoint in Studies 1 and 2; FSFI desire was evaluated as a co-primary endpoint in Study 3.

The efficacy results are based on the full analysis set comprised of all randomized patients who took at least one dose of study medication and had at least one on-treatment efficacy assessment. Missing values were imputed using last-observation-carried-forward.

The unadjusted means are presented for the baseline values.

For satisfying sexual events, **p-values** are based on the Wilcoxon rank sum test stratified by pooled center. Median change from baseline is shown because the data are not normally distributed.

For FSFI-desire, e-Diary desire, and FSFS-R Question 13, reported **p-values** are based on an ANCOVA model using baseline as a covariate with treatment and pooled center as main effect terms. For the change from baseline, the adjusted least squares mean (standard error) are presented.

\(^2\) Excludes subjects from two study sites that had data integrity issues

\(^3\) A decrease in score represents improvement
• 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.

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.

**Vyleesi 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.

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 FSDS-DAO 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.

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.

**Safety**

Vyleesi is contraindicated in patients who have uncontrolled hypertension or known cardiovascular disease. Vyleesi transiently increases blood pressure and reduces heart rate after each dose. In clinical studies, Vyleesi induced maximal increases of 6 mmHg in systolic blood pressure (SBP) and 3 mmHg in diastolic blood pressure (DBP) that peaked between 2 to 4 hours post dose. There was a corresponding reduction in heart rate up to 5 beats per minute. Blood pressure and heart rate returned to baseline usually within 12 hours post dose. No additive effects were seen for blood pressure or heart rate following repeat daily dosing 24-hours apart for up to 16 days.

**REFERENCES**

HSDD Prior Authorization with Quantity Limit

TARGET AGENT(S)
Addyi™ (flibanserin)
Vyleesi™ (bremelanotide)

QUANTITY LIMIT TARGET AGENTS - RECOMMENDED LIMITS*

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Multisource Code</th>
<th>Quantity Limit Per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addyi (flibanserin)</td>
<td>62175030000320 M, N, O, or Y</td>
<td>1 tablet</td>
<td></td>
</tr>
<tr>
<td>Vyleesi (bremelanotide)</td>
<td>6217351510D520 M, N, O, or Y</td>
<td>1.8 mL (6 pens)/30 days</td>
<td></td>
</tr>
</tbody>
</table>

* Quantity limit for Vyleesi will allow for 6 doses per 30 days.

PRIOR AUTHORIZATION WITH QUANTITY LIMIT 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. ONE of the following:
   a. The patient is NOT currently being treated with another target agent in this program
   OR
   b. The patient is currently being treated with another target agent in this program AND will discontinue prior to starting the requested agent
   AND
7. The patient does NOT have any FDA labeled contraindications to the requested agent
   AND
8. The requested quantity (dose) does NOT exceed the program quantity limit

Length of Approval: 8 weeks
Renewal Evaluation
Target Agent(s) will be approved when ALL of the following are met:
1. The patient has been previously approved through the plan’s prior authorization process for the requested agent
   AND
2. The patient’s benefit plan covers the requested agent
   AND
3. The patient is premenopausal
   AND
4. Patient’s HSDD symptoms have improved with the requested agent
   AND
5. ONE of the following:
   a. The patient is NOT currently being treated with another target agent in this program
   OR
   b. The patient is currently being treated with another agent in this program AND will discontinue prior to continuing the requested agent
   AND
6. The patient does NOT have any FDA labeled contraindication to the requested agent
   AND
7. The requested quantity (dose) does NOT exceed the program quantity limit

Length of Approval: 12 months