Addyi™ Prior Authorization and Quantity Limit Criteria Program Summary

This prior authorization applies Commercial, NetResults A series, and NetResults F series formularies.

OBJECTIVE

The intent of the Addyi Prior Authorization and Quantity Limit is to encourage appropriate selection of patients for treatment according to product labeling, and/or clinical studies, and/or guidelines. The program will approve the use of Addyi for patients in plans which cover it under the benefit plan. Addyi will be approved for patients who are premenopausal and who have had a diagnosis of hypoactive sexual desire disorder (HSDD), as characterized by low sexual desire that causes marked distress or interpersonal difficulty for at least 6 months. The HSDD must not be due to a co-existing medical or psychiatric condition, problems within the relationship, or effects of a medication or other drug substance. The program will not allow approval for patients who have an FDA labeled contraindication to the requested agent. The program will approve for doses within the set limit. Requests will be reviewed when patient specific documentation is provided.

TARGET DRUG

Addyi™ (flibanserin)

Brand (generic)	GPI	Multisource Code	Quantity Limit Per Day
Addyi (flibanserin)			
100 mg tablets	62175030000320	M, N, O, Y	1 tablet

PRIOR AUTHORIZATION AND QUANTITY LIMIT CRITERIA FOR APPROVAL

Initial Evaluation

Addyi 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 hypoactive sexual desire disorder (HSDD), as characterized by low sexual desire that causes marked distress or interpersonal difficulty, 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 does NOT have any FDA labeled contraindication(s) to the requested agent
   AND
6. The requested quantity (dose) is NOT greater than the program quantity limit

Length of Initial Approval: 3 months

Renewal Evaluation

Addyi will be approved when ALL of the following are met:

1. The patient has been previously approved through the Prime Therapeutics prior authorization process for the requested agent
   AND
2. Patient's HSDD symptoms have improved after 8 weeks of therapy with the requested agent
   AND
3. The patient does NOT have any FDA labeled contraindication(s) to the requested agent
   AND
4. The requested quantity (dose) is NOT greater than the program quantity limit

Length of Renewal Approval: 12 months

FDA APPROVED INDICATIONS AND DOSAGE[1]

Agent	Indication	Dosage & Administration
Addyi™ (flibanserin)	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

CLINICAL RATIONALE

Efficacy[1,2]

The efficacy of flibanserin for the treatment of hypoactive sexual desire disorder (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 (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.

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.

Efficacy Results in Premenopausal HSDD Patients in Studies 1, 2, and 3

Full Analysis Set	**Study 1**		**Study 2[1]**		**Study 3**	
	flibanserin	placebo	flibanserin	placebo	flibanserin	placebo
	n=280	n=290	n=365	n=372	n=532	n=536
Number of satisfying sexual events (per 28 days)						
Baseline (Mean)	3.0	2.7	2.6	2.7	2.5	2.7
Change from baseline (Mean)	1.6	0.8	1.8	1.1	2.5	1.5
Treatment diff. (95% CI)	0.9 (0.3, 1.4)		0.6 (-0.03, 1.2)		1.0 (0.4, 1.5)	
Change from baseline (Median)	1.0	0.0	1.0	0.5	1.0	0.5
Median treatment difference	1.0		0.5		0.5	
p-value vs. placebo	$p<0.01$		$p<0.01$		$p<0.0001$	
e-Diary Desire						
Baseline (Mean)	12.9	11.8	12.1	10.2	Not Used	
Change from baseline at Week 24 (Mean)	9.1	6.9	8.3	6.7		
Treatment diff. (95% CI)	2.3 (-0.1, 4.7)		1.7 (-0.5, 4.0)			
p-value vs. placebo	NS		NS			
FSFI Desire						
Baseline (Mean)	1.9	1.9	1.8	1.8	1.9	1.9
Change from baseline at Week 24 (Mean)	0.9	0.5	0.9	0.5	1.0	0.7
Treatment diff. (95% CI)	0.4 (0.2, 0.5)		0.3 (0.2, 0.5)		0.3 (0.2, 0.4)	
p-value vs. placebo	N/A[2]		N/A[2]		$p<0.0001$	
FSDS-R Question 13[3]						
Baseline (Mean)	3.2	3.2	3.2	3.2	3.4	3.4
Change from baseline at Week 24 (Mean)	-0.8	-0.5	-0.8	-0.5	-1.0	-0.7
Treatment diff. (95% CI)	-0.4 (-0.5, -0.2)		-0.3 (-0.4, -0.1)		-0.3 (-0.4, -0.1)	
p-value vs. placebo	N/A[2]		N/A[2]		$p<0.0001$	

CI = Confidence Interval; NS= not statistically significant; N/A=not applicable

Shaded cells show the results for the co-primary efficacy endpoints for each trial.
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 FSDS-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.
[1] Excludes subjects from two study sites that had data integrity issues
[2] p-value not reported for secondary endpoints because the trial failed on the eDiary Desire co-primary efficacy endpoint
[3] A decrease in score represents improvement

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).

Safety[1,2]

The use of flibanserin is contraindicated for use with alcohol, for use with strong to moderate CYP3A4 inhibitors, and for use in patients with hepatic impairment. Concomitant use with alcohol increases the risk of severe hypotension and syncope. Before prescribing flibanserin, the healthcare provider must assess the likelihood of the patient abstaining from alcohol use, taking into account the patient's current and past drinking behavior, and other pertinent social and medical history. Healthcare providers should counsel patients who are prescribed flibanserin about the importance of abstaining from alcohol use. Use with strong and moderate CYP3A4 inhibitors or in those with hepatic impairment increases the concentration of flibanserin and increases the risk of sever hypotension and syncope. Due to the risk of severe hypotension and syncope, flibanserin is available only through a Risk Evaluation and Mitigation Strategy (REMS) program where both the prescriber and pharmacy must be registered with the REMS program. The benefits of flibanserin should be weighed against the risks of hypotension and syncope in patients with pre-existing conditions that predispose patients to hypotension.

The discontinuation rate of flibanserin due to adverse effects was 13% among patients treated with 100 mg flibanserin at bedtime and 6% among patients treated with placebo. The leading adverse reactions to cause discontinuation that were higher for flibanserin compared to placebo are:

	Placebo (N=1556)	**Flibanserin (N=1543)**
Dizziness (%)	0.1	1.7
Nausea (%)	0.1	1.2
Insomnia (%)	0.2	1.1
Somnolence (%)	0.3	1.1

Anxiety (%)	0.3	1.0

The most common adverse reactions that were higher for flibanserin than placebo are:

	Placebo (N=1556)	**Flibanserin (N=1543)**
Dizziness (%)	2.2	11.4
Somnolence (%)	2.9	11.2
Nausea (%)	3.9	10.4
Fatigue (%)	5.5	9.2
Insomnia (%)	2.8	4.9
Dry Mouth (%)	1.0	2.4

REFERENCES

1. Addyi prescribing information. Sprout Pharmaceuticals Inc. August 2015.
2. Pharmaceuticals, S. (2015, June 5). Flibanserin Advisory Committee Briefing Document. In *FDA Advisory Committees*. Retrieved June 30, 2015, from http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM449090.pdf.