Flibanserin (ADDYI)
National Drug Monograph
August 2016
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information[1]

Description/Mechanism of Action	The mechanism of flibanserin in the treatment of hypoactive sexual desire disorder (HSDD) is unknown. Flibanserin is a high affinity 5-hydroxytryptamine $(HT)_{1A}$ agonist/5-HT_{2A} antagonist and a moderate antagonist of 5-HT_{2B}, 5-HT_{2C}, and dopamine D_4. Flibanserin was originally developed as an antidepressant, but preliminary studies failed to show efficacy. Flibanserin was found to have a favorable effect on female sex drive in post hoc analysis, leading to additional study and eventual approval for this indication.
Indication(s) Under Review in this document (may include off label)	Flibanserin is indicated for the treatment of premenopausal women with acquired, generalized 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
Dosage Form(s) Under Review	100 mg oral tablets
REMS	☒ REMS ☐ No REMS ☐ Postmarketing Requirements *See Other Considerations for additional REMS information*
Pregnancy Rating	There are no studies of flibanserin in pregnant women. Animal studies cannot rule out the potential for fetal harm.

Executive Summary

Efficacy

- FDA approval of flibanserin for the treatment of premenopausal women with acquired, generalized, HSDD was based on three pivotal phase 3 trials (DAISY, VIOLET, BEGONIA) that were 24 weeks in duration. Additional studies provided supportive information.
- The FDA approved dose of flibanserin 100 mg daily at bedtime increased the number of sexually satisfying events (SSEs) from baseline by about one event per month compared to placebo.
- Improvements from baseline with flibanserin vs. placebo in sexual desire scores, distress due to low sexual desire, and global assessment of benefit were variable across the trials. Even though measures tended to favor flibanserin with varying levels of significance, two of the three trials (DAISY and VIOLET) failed to meet their co-primary endpoints, making the results of all other secondary endpoints nominal given their hierarchical study design.
- A sizable placebo effect was consistently observed across the three pivotal studies for the primary and secondary endpoints.
- Results from a systematic review and meta-analysis that included nearly 6,000 women from eight clinical trials showed that flibanserin increased the number of SSEs from baseline by about 0.5 episodes per month compared to placebo, at the expense of a significant 2-fold to 4-fold increased risk of adverse effects (dizziness, somnolence, and nausea). Of the eight trials included, three were unpublished and two evaluated postmenopausal women. Of note, the authors

	graded the overall quality of the evidence as very low.

Safety	• Contraindications: Flibanserin is contraindicated with alcohol, strong or moderate CYP3A4 inhibitors, and hepatic impairment of any degree.
	• Boxed warning: Hypotension and syncope in certain settings
	  ○ Use of flibanserin and alcohol increases the risk of severe hypotension and syncope; therefore, the combination is contraindicated.
	  ○ Use of flibanserin in combination with moderate or strong CYP3A4 inhibitors or patients with hepatic impairment increases the risk of severe hypotension and syncope; therefore, use in these settings is contraindicated.
	  ○ Flibanserin is only available through the ADDYI REMS program due to the risk of severe hypotension and syncope when flibanserin is combined with alcohol.
	• Hypotension and syncope: Flibanserin alone may cause clinically significant hypotension and syncope in some patients. In clinical trials with premenopausal women, hypotension was reported in 0.2% of flibanserin-treated patients (vs. <0.1% with placebo), and syncope was reported in 0.4% of flibanserin-treated patients (vs. 0.2% with placebo). Situations where flibanserin exposure is increased (e.g., due to drug interactions or impaired metabolism) or is combined with alcohol enhances the risk of hypotension and syncope.
	• Central Nervous System (CNS) Depression: Flibanserin alone causes CNS depression. In clinical trials with premenopausal women, 21% of flibanserin treated patients (vs. 8% with placebo) experienced somnolence, sedation, or fatigue. The risk of CNS depression is enhanced when flibanserin is taken during waking hours, combined with alcohol or other CNS depressants, or when flibanserin exposure is increased.
	• In clinical trials, commonly reported adverse reactions associated with flibanserin included dizziness, somnolence, nausea, and fatigue.
	• Overall, discontinuations due to adverse events occurred more frequently with flibanserin 100 mg dosed at bedtime compared to placebo (13% vs. 6%).
	• Safety data for flibanserin is based mostly on 24 week trials, with some open-label extension data where patients were exposed to drug for a median of one year and maximum of two years.

Other Considerations	• Of note, strict inclusion and exclusion criteria defined a specific population of premenopausal women who were in stable, heterosexual relationships, diagnosed with generalized, acquired HSDD made by an experienced, trained clinician, and without medical conditions or use of medications that could affect sexual function. As a result, information on the use of flibanserin is limited to the narrowly defined patients included in clinical trials. It is unknown whether the balance of benefits and risks differs for women outside of the studied populations. • Overall, there were more dropouts due to adverse events with flibanserin compared to placebo (13% vs. 6%). • Flibanserin is not indicated for postmenopausal women. See off-label section for additional information in these women.
Projected Place in Therapy	• Flibanserin is the first and only FDA approved medication for the treatment of HSDD in women. Flibanserin was studied in a very narrowly defined population, which limits the generalizability of the results. The clinical trials included premenopausal women with a required diagnosis of generalized, acquired HSDD made by a trained provider. Women with co-existing psychiatric or medical conditions, concurrent medications (e.g., antidepressants, sedatives and hypnotics, antiepileptics, mood stabilizers, and antipsychotics), or the presence of significant life stressors that could impact sexual dysfunction were excluded. • In the studied population, flibanserin was associated with small improvements in SSEs and variable improvements in desire and distress scores and global assessment of improvement that have to be balanced with the significantly

	increased risk for adverse events. Sizeable placebo effects were noted consistently in the clinical trials. • There are several safety precautions when considering the use of flibanserin including the risk of severe hypotension, syncope and CNS depression. There are multiple drugs that are contraindicated for use in combination with flibanserin (e.g., alcohol, strong or moderate CYP3A4 inhibitors) due to important safety concerns. Additional postmarketing data requirements defined by FDA will provide more information on the safety of flibanserin. • For approval, FDA required a REMS program to address the **contraindication with alcohol and the need for patients to abstain from alcohol for the entire duration of treatment because of the increased risk of severe hypotension and syncope.** • As a result, based on the evidence currently available, flibanserin is expected to have limited use given its modest effect in a very narrowly defined population of premenopausal women and significant safety concerns. Use should be considered only in premenopausal women with an established diagnosis of acquired, generalized HSDD associated with marked distress or interpersonal difficulty and not due to secondary causes and who closely match the studied population. For example, underlying, contributing medical conditions such as depression, post-traumatic stress disorder, and alcohol abuse, which may be more prevalent in the women Veteran population, should be ruled out prior to use. **The diagnosis of HSDD should be made by a trained provider, and the appropriateness of use should be assessed in coordination with Behavioral Health.** In addition, drug interactions, hepatic impairment, and predisposition to hypotension and syncope need to be evaluated before use. Patients should understand the benefits and risks and be willing to abstain from alcohol completely during treatment. If there is no improvement in eight weeks, flibanserin should be discontinued. • Flibanserin is **not indicated in post-menopausal women.**
Potential Impact	• Size of Drug Candidate Population: According to ICD-9 coding, there were less than 1,000 premenopausal women Veterans with documented diagnoses related to low libido, and very few patients with the specific diagnosis of HSDD. Documentation and diagnosis may be underreported. Although not specifically estimated, the VA population may likely have a higher prevalence of co-existing medical conditions that could contribute to HSDD (e.g., depression, PTSD, alcohol abuse) where use of flibanserin would not be appropriate. • Potential Impact to Patients: Flibanserin was shown to have a small effect on HSDD, significant safety concerns, and more discontinuations due to adverse effects. Patients need to completely abstain from alcohol during treatment with flibanserin to minimize risks of severe hypotension and syncope and avoid certain concomitant medications. About 10% more women who received flibanserin reported overall meaningful improvement after 24 weeks of treatment compared to placebo. • Potential Impact to Services: There may be a potentially small increase in Behavioral Health consultations to coordinate diagnosis of HSDD and rule out underlying, contributing causes. • Potential Impact to Costs: FSS cost for flibanserin is nearly $600 per month; however, low utilization of the drug is anticipated at this time.

Background

Purpose for review	Recent FDA approval **Issues to be determined:** ✔ Evidence of need ✔ Does flibanserin offer advantages to currently available alternatives? ✔ Does flibanserin offer advantages over current VANF agents?

✔ What safety issues need to be considered?
✔ Does flibanserin have specific characteristics best managed by the non-formulary process, prior authorization, criteria for use?

Other therapeutic options

There are no other FDA approved treatments for the management of HSDD in women. For completeness, other medications are listed that have been studied off label, though data are limited.

Formulary Alternatives	Other Considerations	CFU, Restrictions or Other Guidance
Testosterone	▪ Off-label ▪ Limited data, especially in premenopausal women where efficacy results are few and inconclusive ▪ In women of reproductive age, must consider teratogenic risk ▪ Difficulty in administration of studied dose (lower than available dosage forms approved for males) ▪ Unclear safety (potential for androgenic adverse effects, unfavorable lipid changes, increased estrogen exposure)	▪ CFU for males (n/a)
Bupropion	▪ Off-label ▪ 2 RCTs showed efficacy in premenopausal women with HSDD and without underlying depression	▪ none
Sildenafil	▪ Off-label ▪ Inconsistent results in women without psychotherapy-induced sexual dysfunction or an underlying medical condition	▪ CFU for males (n/a)
Non-formulary Alternative (if applicable)	**Other Considerations**	
none	n/a	n/a

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to July 2016) using the search terms <flibanserin> and <ADDYI>. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles were searched for relevant clinical trials. All relevant randomized controlled trials published in peer-reviewed journals were included as well as unpublished studies where needed.

Review of Efficacy

- The efficacy of flibanserin for FDA approval was based primarily on three randomized, double-blind, placebo-controlled, phase 3 trials, DAISY, VIOLET, and BEGONIA, in premenopausal women with a required diagnosis of generalized, acquired HSDD as defined by DSM-4 (Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition).[2] The studies evaluated the efficacy and safety of 24 weeks of flibanserin treatment following a 4-week baseline evaluation period. Co-primary endpoints included changes from baseline in the number of satisfying sexual events (SSE) and sexual desire. Strict inclusion and exclusion criteria defined a specific population of women who were in stable, heterosexual relationships. Women with co-existing psychiatric or medical conditions, concurrent medications, or the presence of significant life stressors that could impact sexual dysfunction were excluded. Women were also excluded if they had received recent psychotherapy (e.g., marital counseling) or had a partner with inadequately treated sexual dysfunction. Additional supportive clinical studies are also summarized.
    - The DAISY and VIOLET studies were similar in design and evaluated the same co-primary endpoints (SSE and Sexual Desire score). The BEGONIA trial was conducted after the DAISY

and VIOLET results were available. The BEGONIA trial design was generally similar to the 2 preceding studies but differed in the co-primary endpoints evaluated (SSE and FSFI Desire Domain Score) and in some of the inclusion and exclusion criteria in attempt to improve generalizability of the results.

- Women in the 3 studies were in their mid-30's and in their present relationship for about 10-11 years. The majority of women were white and married and carried the diagnosis of HSDD for about 5 years in the DAISY and VIOLET studies and for about 4 years in the BEGONIA study.
- Overall, the 3 studies showed modest but favorable effects with the FDA approved dose of flibanserin 100 mg:
    - Flibanserin improved the number of SSEs from baseline by about 1 more event per 28-day period than placebo.
    - Flibanserin-associated improvements from baseline in sexual desire as measured by the eDiary score were not statistically different from placebo (DAISY and VIOLET studies). When evaluated by the FSFI desire domain score, flibanserin was associated with small but statistically significant improvements from baseline compared to placebo in all 3 studies (increase of 0.3-0.4; score range of 1.2-6.0). However, since the co-primary endpoints were not met in DAISY and VIOLET, results of the secondary endpoints including the FSFI desire domain score were considered nominal based on the hierarchical design of the trials.
    - Other secondary endpoints including change from baseline in distress related to low sexual desire (measured by the FSDS-R Item 13 score) favored flibanserin over placebo across the studies. Significantly more patients treated with flibanserin reported global, meaningful benefit of treatment at the end of the studies compared to placebo.
    - A sizeable placebo effect was consistently observed across the 3 studies for the primary and secondary endpoints.
    - Flibanserin was associated with more drop outs than placebo.
- A supportive analysis was conducted by FDA to estimate the clinically meaningful benefit of flibanserin. FDA looked at the patient's global impression-improvement (PGI-I) scale that asks how their condition (decreased sexual desire and feeling bothered by it) is today compared to when study medication was started (24 wks ago). A response of "very much improved" or "much improved" was considered a positive responder. In the three pivotal trials, the overall rate of flibanserin responders ranged from 21 – 48%. Keeping in mind the sizeable placebo effect in the trials, the placebo-adjusted advantage of flibanserin ranged from 8 – 9% for SSEs, 10 – 13% for FSFI sexual desire, and 7 – 13% for distress.[2]

Key endpoints used in phase 3 clinical trials:

Outcome measure	Definition
Satisfying Sexual Events (SSE)	SSEs were defined as sexual intercourse, oral sex, masturbation, or genital stimulation by the partner. SSEs were based on responses to the question: "was the sex satisfying for you?" yes/no. Scores were recorded daily in an eDiary and standardized to 28-day periods.
Sexual Desire Score	The score was based on the answer to one question: "Indicate your most intense level of sexual desire in the last 24 hours" using a 4 point scale (0-no desire to 3-strong desire). Scores were recorded daily in an e-Diary and standardized to 28-day periods.
Female Sexual Function Index (FSFI) Desire Domain Score	The FSFI desire domain is one of six domains in the FSFI and includes two questions related to frequency and level of sexual desire or interest using a scale from 1 to 5 (higher scores indicating greater sexual desire).
FSFI Total Score	The 19-item self-administered FSFI questionnaire was used as a measure of overall sexual function in women in 6 domains. Scores were measured at baseline and at clinic visits using a 4-week recall period.
Female Sexual Distress Scale-Revised (FSDS-R) Item 13 score	Item 13 is one question from the FSDS-R questionnaire and was used to assess distress specifically due to low sexual desire.
FSDS-R Total Score	The 13-item self-administered FSDS-R questionnaire was used to assess sexual distress or bother using a scale from 0 (never) to 4 (always), with higher scores indicating more distress. Scores were measured at baseline and at clinic visits using a 7-day recall period.

DAISY[3]

- In the DAISY trial, 1,584 women were randomized to one of four treatment groups evaluating different doses and regimens of flibanserin (25 mg twice daily, 50 mg twice daily, 100 mg at bedtime) and placebo. The co-primary endpoints evaluated were the changes from baseline (weeks -4 to 0) to study end (weeks 21 to 24) in the number of SSE and the sexual desire score as measured by the eDiary.
- Roughly two-thirds of the women completed the trial, with similar dropout rates across the treatment arms. Patient baseline characteristics were similar across treatment groups except for statistically significant differences in baseline monthly eDiary desire scores.
- For the co-primary endpoint of SSE, flibanserin 100 mg once daily was associated with statistically greater improvements in the number of SSE compared to placebo as evaluated from baseline to the end of treatment (increase of 1.9 SSE with flibanserin 100 mg vs. 1.1 SSE with placebo; $p < 0.01$). The increases from baseline in the other flibanserin arms were not statistically different from placebo. No improvements with flibanserin over placebo were found for the other co-primary endpoint of change in monthly eDiary sexual desire score. Improvements in the secondary endpoints of the FSFI desire and total scores, FSDS Item 13 and total scores, and overall assessment of benefit were observed in all flibanserin arms compared to placebo; however, since only one of the co-primary endpoints reached statistical significance, the investigators stated that the secondary endpoint results are considered nominal.

VIOLET[4]

- In the VIOLET trial, 880 women were randomized to flibanserin 50 mg, 100 mg, or placebo, given once daily at bedtime. The co-primary endpoints evaluated were the changes from baseline (weeks -4 to 0) to study end (weeks 21 to 24) in the number of SSE and the sexual desire score as measured by the eDiary.
- About 75% of the women completed the study, with more women stopping treatment early in the flibanserin 100 mg group. Patient baseline characteristics were similar across treatment groups.
- Both flibanserin doses were associated with statistically significant increases in the co-primary endpoint of SSE vs. placebo as evaluated from baseline to the end of treatment (increase of 1.6 SSE with flibanserin 100 mg; 1.4 with flibanserin 50 mg; and 0.8 with placebo). No significant improvements with flibanserin compared to placebo were found in the co-primary endpoint of change in monthly eDiary sexual desire score. Improvements were noted in secondary endpoints including the FSFI desire and total scores for both flibanserin doses over placebo and in the FSDS-R Item 13, FSDS-R total scores, and overall assessment of benefit for the 100 mg flibanserin group over placebo. However, since only one co-primary endpoint was statistically significant, the statistical results of the secondary endpoints are considered nominal per the investigators.

BEGONIA[5]

- The BEGONIA study was conducted after the DAISY and VIOLET studies and used a different co-primary endpoint and slightly less restrictive inclusion criteria. The co-primary endpoints evaluated were the changes from baseline (weeks -4 to 0) to study end (weeks 21 to 24) in the number of SSE and in the FSFI desire domain score. A total of 1,090 women were randomized to receive flibanserin 100 mg daily at bedtime or placebo.
- About 78% of the women completed the study, with more women in the flibanserin group discontinuing prematurely. Baseline characteristics were similar between treatment groups.
- Flibanserin was associated with statistically significant improvements from baseline in both co-primary endpoints compared to placebo. The number of SSE improved in both groups, but the flibanserin group reported about 1 more SSE per 28-day period compared to placebo (2.5 events vs. 1.5 events). Similarly, both groups reported higher FSFI desire domain scores than baseline, but the improvements were statistically better with flibanserin compared to placebo (increases of 1 vs. 0.7). Flibanserin was associated with statistically significant improvements in secondary endpoints including the FSFI total score, FSDS-R item 13 and total scores, and in assessments of overall improvement from baseline.[6]

ADDITIONAL STUDIES (Premenopausal Population)

- **DAHLIA:** The DAHLIA study is an unpublished, phase 3, prospective, randomized, double-blind, North American clinical trial with similar eligibility criteria and design as the other pivotal phase 3 studies. A total of 1,392 women were randomized to treatment with flibanserin (25 mg twice daily, 50 mg twice daily, or 50 mg once daily at bedtime) or placebo. Flibanserin was not associated with

statistically significant improvements from baseline compared to placebo for the co-primary endpoints of SSE and eDiary desire score after 24 weeks of treatment. Of the secondary endpoints evaluated, only the FSFI-Desire domain showed some evidence of a treatment effect with flibanserin.[6]

- **ORCHID:** The ORCHID study is an unpublished, phase 3, prospective, randomized, double-blind, placebo controlled, European clinical trial with similar eligibility criteria and design as the other pivotal phase 3 studies. A total of 945 patients were randomized to flibanserin 50 mg, 100 mg, or placebo daily at bedtime. For the primary endpoint, flibanserin failed to show improvements in the number of SSEs from baseline compared to placebo after 24 weeks of treatment. The 100 mg dose of flibanserin was associated with improvements in some but not all of the secondary endpoints compared to placebo. There was a higher than expected number of dropouts (ranged from 24% to 36% in each arm) which lessened the power of the study to detect differences between treatments.[6]

- **ROSE:** The ROSE study was a two-part trial that evaluated the continued efficacy of flexible dose flibanserin vs. placebo as well as withdrawal effects in North American women who showed a prior, pre-defined response to 24 weeks of open-label treatment. In the open label portion of the trial, 63% of the women (n=333) met the pre-defined criteria for a positive response and were randomized to continue flibanserin or to placebo. At the end of the 24-week double-blind portion of the study where the women received a stable dose of flibanserin 50 mg or 100 mg once daily at bedtime, 50 mg twice daily, or placebo, the co-primary endpoints of SSE and sexual desire measured by the daily eDiary score deteriorated in both treatment groups. The magnitude of worsening with flibanserin was smaller than with placebo, and the outcomes favored flibanserin. Similar findings were found with secondary endpoints, and no apparent withdrawal effects were observed.[7]

- **SUNFLOWER:** A 52-week, open-label, flexible dose, uncontrolled extension study was conducted to evaluate the safety and tolerability of long-term flibanserin. Effectiveness was assessed as a secondary endpoint. North American women from one of the previous clinical trials (DAISY, VIOLET, DAHLIA, ROSE, or a pharmacokinetic study) were invited to be screened for the study, and 962 women (55.8%) completed the treatment period. Women were exposed to flibanserin for a median of 1 year and a maximum of 2 years. Numeric improvements from baseline in FSDS-R and FSFI scores were observed at week 52 (p values not provided). Most patients who previously responded to flibanserin maintained their response.[8]

Selected Efficacy Endpoints of Pivotal Flibanserin Trials

Study	Design	Treatment	Base SSE	Δ in SSE vs. Base	Base eDiary Desire	Δ in eDiary Desire vs. Base	Base FSFI Desire	Δ in FSFI Desire vs. Base	Base FSDS-R Desire	Δ in FSDS-R Desire† vs. Base
Thorp 2012[3] **DAISY** N = 1,584 MC, DB, PC, North America Funded by Boehringer Ingelheim	4 wks of baseline eval, then 24 wks of treatment Co-1° Endpts: Δ from baseline to 24 wks using daily eDiary: 1) SSE 2) Sexual desire score Note: baseline sexual desire scores different between groups (p <0.05)	FLI 100 HS	2.6	**1.9***	12.0	8.5	1.8	**0.9***	3.3	**-0.7***
		FLI 50 BID	2.9	1.4	11.8	8.8	1.8	**0.8***	3.3	**-0.7***
		FLI 25 BID	3.0	1.4	11.4	7.9	1.8	**0.8***	3.2	**-0.6***
		PBO	2.7	1.1	10.2	6.8	1.8	0.6	3.2	-0.5
DeRogatis 2012[4] **VIOLET**	4 wks of baseline eval, then 24 wks of treatment	FLI 100 HS	3.0	**1.6***	12.9	9.1	1.9	**0.9***	3.2	**-0.8***
		FLI 50 HS	2.7	**1.4***	11.0	8.2	1.8	**0.8***	3.2	-0.6
		PBO	2.7	0.8	11.8	6.9	1.9	0.5	3.2	-0.5

MC, DB, PC, North America Funded by Boehringer Ingelheim	Co-1° Endpts: Δ from baseline to 24 wks using daily eDiary: 1) SSE 2) Sexual desire score									
Katz 2013[5] **BEGONIA** MC, DB, PC, US Funded by Boehringer Ingelheim	4 wks of baseline eval, then 24 wks of treatment Co-1° Endpts: Δ from baseline to 24 wks using daily eDiary: 1) SSE 2) Sexual desire	FLI 100 HS PBO	2.5 2.7	**2.5*** 1.5	- -	- -	1.9 1.9	**1.0*** 0.7	3.4 3.4	**-1.0*** -0.7

†Negative values indicate improvement, less distress
*p <0.05 for difference vs. placebo
DB=double-blind; FLIB=flibanserin; MC=multicenter; PBO=placebo; PC=placebo controlled; SSE=sexually satisfying events;

META-ANALYSIS
A systematic review and meta-analysis was conducted that included a total of 5,914 women from eight randomized clinical trials evaluating the efficacy and safety of flibanserin in women with HSDD. The majority of the population was North American (7 of 8 studies) and premenopausal (6 of 8 studies). Five of the eight studies have been published. Overall, flibanserin 100 mg increased the number of SSEs from baseline by about 0.5 episodes per month compared to placebo at the expense of a significant 2-fold to 4-fold increased risk in adverse effects (dizziness, somnolence, and nausea). Other efficacy endpoints showed small but statistically significant improvements with flibanserin, though there was minimal to no improvement in the women's global assessment of improvement. About twice as many patients stopped flibanserin due to an adverse event compared to placebo. Serious adverse event rates were low. Even though the trials were randomized, the authors graded the overall quality of the evidence as very low due to significant risk of bias based on limitations in the study design, unclear generalizability of the results, and publication of the studies with more favorable results.[9]

Overall, there is a moderate quality of evidence to support the use of flibanserin for the treatment of acquired, generalized HSDD in premenopausal women (see Appendix A).

Potential Off-Label Use

- **HSDD in postmenopausal women** –Two phase 3 studies evaluated the use of flibanserin in naturally postmenopausal women. Both studies were randomized, placebo-controlled, multicenter studies with an overall similar design as the pivotal studies conducted in premenopausal women including similar diagnostic criteria, 28-day baseline evaluation, planned 24 weeks of treatment, and evaluated endpoints.
    - The published SNOWDROP trial was conducted in U.S. women with a diagnosis of generalized, acquired HSDD.[10] A total of 949 women were randomized to receive flibanserin 100 mg daily at bedtime or placebo, and about 20% of women did not complete the trial. The mean age of the population was 55 years, with about 5% of women 65 years or older. Flibanserin was associated with modest but statistically significant improvements from baseline compared to placebo in the co-primary endpoints of SSE and FSFI-desire domain scores. Starting from a baseline of 2 SSE per 28 days, flibanserin increased the number of SSEs by 1 vs. 0.6 with placebo (p=0.004) at 24 weeks. The mean FSFI desire score improved by 0.7 with flibanserin vs. 0.4 with placebo (p <0.001), from a baseline of 1.8. Commonly reported adverse events of dizziness, somnolence, nausea and headache were similar to reports in premenopausal women. More women on flibanserin compared to placebo discontinued drug due to adverse events (8.1% vs. 3.5%). Serious adverse events were more frequently reported with flibanserin (12 vs. 5 events), including one fatal event (alcohol poisoning), though none were

considered related to treatment according to the investigator. Women with induced menopause were not included in the trial.

- The PLUMERIA trial was conducted in North American women with a diagnosis of generalized, acquired HSDD. A total of 748 patients were randomized to flibanserin 100 mg daily at bedtime or placebo. The study was terminated early because the manufacturer discontinued development of the product, and the results are unpublished but available in the product dossier.[6] Patients received a mean of about 16 weeks of the planned 24 weeks of treatment. For the co-primary endpoints after 16 weeks of treatment, flibanserin did not significantly increase the number of SSEs from baseline compared to placebo but did improve sexual desire as measured by the FSFI Desire domain score. Improvements in sexual distress related to low desire as measured by the FSDS-R Item 13 score favored flibanserin (p=0.0597). Significant improvements were also noted in the FSDS-R total score (p=0.0002), the FSFI total score (p=0.0226), and the assessment of overall benefit (p=0.0182).

Safety

(for more detailed information refer to the product package insert)

	Comments
Contraindications and Boxed Warning[1]	**Flibanserin is contraindicated with:** • Alcohol • Strong or moderate CYP3A4 inhibitors • Hepatic impairment of any degree
Warnings/Precautions[1]	• **Hypotension and syncope:** Flibanserin alone is associated with hypotension and syncope in some patients. Consider benefits and risks in patients predisposed to hypotension from co-existing medical conditions. This risk is enhanced in settings where flibanserin exposure is increased or when flibanserin is taken during waking hours or combined with alcohol. o **Alcohol:** The use of alcohol with flibanserin increases the risk of severe hypotension and syncope and is therefore contraindicated. Because of this risk, flibanserin is only available through a restricted REMS program. Before flibanserin is prescribed, the patient's current and past drinking behavior and other pertinent history should be used to assess the likelihood of the patient abstaining from alcohol. Patients must be counseled about the importance of abstaining from alcohol. o **CYP3A4 Inhibitors:** Concomitant use of flibanserin and strong or moderate CYP3A4 inhibitors increases flibanserin exposure which can lead to severe hypotension and syncope. Therefore, concomitant use of flibanserin and strong or moderate CYP3A4 inhibitors is contraindicated. Consult the package insert for recommendation durations of wash-out periods for stopping or starting interacting combinations. Concomitant use of flibanserin with multiple weak CYP3A4 inhibitors including nonprescription drugs or herbal supplements could lead to clinically significant increased flibanserin exposure and risk for hypotension and syncope. o **Hepatic Impairment:** Flibanserin concentrations are greatly increased in patients with hepatic impairment which can lead to severe hypotension and syncope. Therefore, concomitant use of flibanserin is contraindicated in patients with any degree of hepatic impairment. • **ADDYI REMS Program:** Flibanserin is only available through the restricted REMS program because of the risk of hypotension and syncope when flibanserin is combined with alcohol. Prescribers and pharmacies must be certified with the program. Prescribers must enroll and complete training, and pharmacies can only dispense the drug written by a certified prescriber.

	Further information is available at www.AddyiREMS.com or 844-746-5745. • **CNS depression:** Flibanserin alone causes CNS depression. The risk of CNS depression is enhanced in situations where flibanserin exposure is increased or when flibanserin is taken during waking hours or with alcohol or other medications that cause CNS depression. Patients should not engage in activities that require full alertness such as driving until they know how flibanserin affects them. • **Mammary tumors in female mice:** Results from a 2 year carcinogenicity study found a statistically significant increase in the incidence of malignant mammary tumors in female mice exposed to flibanserin in 3 to 10 times the recommended dose. These findings were not observed in rats or male mice. The clinical significance is unknown.

Safety Considerations[1,2]

Alcohol interaction: In a dedicated pharmacodynamic study, healthy subjects (23 men and 2 women) considered moderate alcohol drinkers were co-administered 100 mg of flibanserin along with the equivalent of 2 standard alcoholic drinks. Four of 25 subjects (16%; all men) experienced clinically significant events of hypotension and syncope requiring medical intervention. Reductions in blood pressure ranged from 28 to 54 mm Hg systolic and 24 to 45 mm Hg diastolic. Of note, the potential interaction of flibanserin with alcohol was not prospectively evaluated in the phase 3 clinical trials, and the use of alcohol was not restricted nor the quantities or frequencies of use recorded.[2] The impact of alcohol in women and in patients naïve to alcohol treated with flibanserin has not been sufficiently studied.

Hypotension and syncope: In clinical trials with premenopausal women, hypotension was reported in 0.2% of flibanserin-treated patients (vs. <0.1% with placebo), and syncope was reported in 0.4% of flibanserin-treated patients (vs. 0.2% with placebo). The number of events was small, but there was an excess of events with flibanserin. Further, situations where flibanserin exposure is increased (e.g., due to drug interactions, impaired metabolism) or is combined with alcohol enhances the risk of hypotension and syncope.

CNS depression: In clinical trials with premenopausal women, 21% of flibanserin treated patients (vs. 8% with placebo) experienced somnolence, sedation, or fatigue. The risk of CNS depression is enhanced when flibanserin is taken during waking hours, combined with alcohol or other CNS depressants, or when flibanserin exposure is increased.

- Accidental injury: Among women who reported accidental injury in clinical trials, symptoms consistent with CNS depression (e.g., somnolence, fatigue, or sedation) were reported within the prior 24 hours more often in flibanserin treated patients compared to placebo (21% vs. 6%).
- Driving impairment: In a dedicated randomized, placebo-controlled, cross-over study conducted in 83 healthy, premenopausal women, flibanserin did not impair driving performance as assessed 9 hours after a single 100 mg dose, a single 200 mg dose,, and multiple doses of 100 mg once daily.

Adverse Reactions

Common adverse reactions[1]	Incidence >5%: Dizziness, somnolence, nausea, fatigue
Death/Serious adverse reactions[2,11]	Death: One death occurred in a 54 year old, postmenopausal flibanserin-treated patient. The woman was found unresponsive, and on autopsy she was found to have acute alcohol intoxication and atherosclerotic cardiovascular disease. Because the combination of alcohol and flibanserin may cause severe hypotension and CNS depression, the contribution of flibanserin in the woman's death could not be excluded. Serious adverse events: Serious adverse events that occurred in more than one flibanserin-treated patient included appendicitis, intervertebral disc protrusion, cholelithiasis, concussion, and road traffic accidents. Appendicitis: There was an excess of appendicitis cases reported in the premenopausal trials with flibanserin (0.2% vs. 0); however, the clinical

	significance of this finding is unclear.
Discontinuations due to adverse reactions[1]	Overall, discontinuations due to adverse events occurred more frequently with flibanserin 100 mg dosed at bedtime compared to placebo (13% vs. 6%).The most common reactions leading to discontinuation (and that occurred more frequently in flibanserin treated patients) were dizziness, nausea, somnolence, and anxiety.

Discontinuations due to adverse events in individual phase 3 trials:

Trial	FLIB	PBO
DAISY[3]	25 BID: 7.6% 50 BID: 17.1% 100 QHS: 15.7%	10.8%
VIOLET[4]	50 QHS: 7.8% 100 mg QHS: 11.4%	3.4%
BEGONIA[5]	100 QHS: 9.6%	3.7%

Drug Interactions

Drug-Drug Interactions[1]

See package insert for more detailed information. Flibanserin is primarily metabolized by CYP3A4 and by CYP2C19 to a lesser extent. Flibanserin is also a CNS depressant.

- Alcohol: Concomitant use is contraindicated due to increased risk of hypotension, syncope, and CNS depression.
- CNS depressants: Concomitant use should be discussed with the patient due to the increased risk of CNS depression.
- Moderate or strong CYP3A4 inhibitors: Concomitant use is contraindicated due to the increased exposure to flibanserin and risk of hypotension and syncope. For example, in a pharmacokinetic drug interaction study with fluconazole 100 or 200 mg (strong CYP3A4 inhibitor), 3 patients (20%) experienced clinically significant syncopal/hypotensive events that resulted in early discontinuation of the study. Exposure was noted to be increased by 7-fold.
- Weak CYP3A4 inhibitors: Concomitant use of flibanserin and multiple weak CYP3A4 inhibitors may increase the risk of adverse reactions and should be discussed with the patient. Of note, a post-hoc analysis of oral contraceptive (weak CYP3A4 inhibitor) users from the premenopausal clinical trials found a greater incidence of CNS depressive effects reported in patients on flibanserin plus oral contraceptives compared to flibanserin alone. A similar observation was not identified in the placebo group.
- Strong CYP2C19 inhibitors: Concomitant use should be discussed with the patient due to the potential for increased flibanserin exposure hypotension, syncope, and CNS depression.
- CYP3A4 inducers: Concomitant use is associated with significantly reduced exposure to flibanserin and is not recommended.
- Digoxin or other P-glycoprotein (P-gp) substrates: Concomitant use may increase digoxin or other P-gp substrate exposure and the risk for toxicity of drugs that have a narrow therapeutic index. Increased monitoring of the P-gp substrate (e.g., digoxin) is recommended.

Risk Evaluation

As of September 2015:

	Comments				
Sentinel event advisories	• None • Sources: ISMP, FDA, TJC				
Look-alike/sound-alike error potentials	NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment

Flibanserin 100mg tab	None	None	None	Filgrastim Flurbiprofen Lorcaserin Cycloserin
Addyi	None	None	None	Advil Abilify Adderall

Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

- **FDA approval:** Flibanserin was approved on its third submission to FDA. In the first two reviews, FDA determined that the risk/benefit ratio was unfavorable. Additional concerns raised by FDA in the second review included the use of the FSFI sexual desire domain as an endpoint, the significant interaction with flibanserin and alcohol that has not been adequately studied in the target population, the potential for clinically significant drug interactions with CYP3A4 inhibitors, and the possible relationship between accidental injury and CNS depressive effects of flibanserin. FDA also expressed concern for how providers would appropriately identify candidates for flibanserin given the changes in the DSM diagnostic criteria from what was used for identifying candidates for the clinical trials.

  There was controversy during the FDA review process, with various individuals and advocacy groups supporting approval of flibanserin for a condition with limited treatment options and no approved medications. Some made claims of gender bias against FDA, siting the several options available for men versus none for women. Opponents of the drug's approval stated that the drug has marginal benefit with significant harms for use in otherwise healthy women. FDA maintained that their decisions were being made solely on the efficacy and safety profile of the drug.

  In the third review, FDA concluded that flibanserin has a positive risk/benefit profile. FDA considered the lack of therapeutic alternatives available for a condition that may substantially affect the well-being of some women and recognized that some women will derive a clinically relevant effect from the use of flibanserin. Clear labeling, the REMS program, and several postmarketing requirements will address the major risks and concerns with the use of flibanserin.
- **Postmarketing requirements include the following:**
  - Pharmacovigilance study assessing the risks of hypotension, syncope, accidents or injuries, and fatal outcomes
  - Observational study evaluating the risk of appendicitis
  - Pregnancy registry and maternal-fetal outcomes study to evaluate pregnancy outcomes and birth defects
  - Clinical trial to evaluate the interaction between flibanserin and alcohol in the target female population
- **HSDD in DSM-4 and DSM-5:** The clinical trials evaluating flibanserin enrolled women based on a diagnosis of acquired, generalized HSDD as defined in the DSM-4. In the current DSM-5 (released in 2013), HSDD is no longer a stand-alone condition. Female sexual interest/arousal disorder (FSIAD) is the new condition described in DSM-5 and combines features from HSDD and female sexual arousal disorder from DSM-4. Note the FDA indication for flibanserin is for women with acquired, generalized HSDD, matching the patient inclusion criteria from clinical trials.

Dosing and Administration[1]

- Dosing: The recommended dose of flibanserin is 100 mg orally once daily at bedtime. Administration during the waking hours rather than bedtime can increase the risks for hypotension, syncope, accidental injury, and CNS depression (including somnolence and sedation).
- Missed doses: If a dose of flibanserin is missed, the patient should be instructed to take the next dose at bedtime on the next day and not to double up on doses.

- Discontinuation: If there is no improvement in symptoms after 8 weeks of flibanserin use, the drug should be discontinued.
- Management of moderate or strong CYP3A4 inhibitor interactions: If initiating use of flibanserin following moderate or strong CYP3A4 inhibitor use, start flibanserin 2 weeks after the last dose of the CYP3A4 inhibitor. If initiating a moderate or strong inhibitor of CYP3A4 following flibanserin use, start the CYP3A4 inhibitor 2 days after the last dose of flibanserin.

Special Populations (Adults)[1]

	Comments
Elderly	• Flibanserin is only indicated in premenopausal women. No studies have been conducted to evaluate the impact of age on flibanserin exposure.
Pregnancy	• Flibanserin has not been studied in pregnant women. In animals, fetal toxicity only occurred in the presence of significant maternal toxicity and at higher exposure than the recommended human dose. Animal studies cannot rule out the potential for fetal harm.
Lactation	• Flibanserin is excreted in rat milk. It is not known whether flibanserin is present in human milk. Because of the potential for serious adverse reactions in a breastfed infant, breastfeeding is not recommended during flibanserin treatment.
Renal Impairment	• In pharmacokinetic studies, flibanserin exposure was slightly increased (1.1-1.2 fold) in patients with moderate or severe renal impairment following single doses of 50 mg. There is no recommended dose adjustment or precautions for use for patients with renal impairment included in the manufacturer's labeling.
Hepatic Impairment	• Per pharmacokinetic study, mild hepatic impairment was associated with a 4.5 fold increase in systemic flibanserin exposure which increases the risk of hypotension, syncope, and CNS depression. Flibanserin is contraindicated in patients with any degree of hepatic impairment.
CYP2C19 Poor Metabolizers	• Increased flibanserin exposure occurred in CYP2C19 poor metabolizers, and syncope occurred in a patient who was a known CYP2C19 poor metabolizer. The package labeling recommends closer monitoring of these patients.
Pharmacogenetics/genomics	• No data identified.

Projected Place in Therapy

- According to the American College of Obstetricians and Gynecologists (ACOG), HSDD is the most common female sexual dysfunction, with estimated prevalence between 5.4% and 13.6%. There is a peak in women between 40 and 60 years of age and in women who have undergone surgical menopause. In younger women, HSDD is often secondary to another issue (e.g., relationship problems, medications, medical conditions).[12]
- The ACOG Practice Bulletin on female sexual dysfunction was published 2011, before flibanserin was approved.[12] ACOG recognizes transdermal testosterone as an effective, short-term treatment of HSDD; however, transdermal testosterone for women is not FDA approved and is not readily available in the U.S. in the low doses studied in women. Most studies evaluated the use of testosterone for HSDD in the postmenopausal population. In addition to adverse cosmetic effects (e.g., hirsutism, acne), safety concerns with the use of testosterone in women include adverse lipid profile changes, increased cardiovascular risk, and a possible association with breast cancer.
- Nonpharmacologic options that may be useful in the management of female sexual dysfunction in general may include the treatment of associated conditions, counseling, and lifestyle changes.
- Overall, there is moderate quality of evidence for the use of flibanserin for the treatment of acquired, generalized HSDD in premenopausal women. A modest effect has been shown in the various measured endpoints in multiple clinical trials, though the pre-defined, co-primary endpoints were not met in all of the clinical trials. Two unpublished studies failed to find a benefit of flibanserin in the primary endpoints. Keeping

in mind the sizable placebo effect seen in the clinical trials, roughly 10% more flibanserin patients reported global improvement in their condition after 24 weeks of treatment compared to placebo. The studied population was narrowly defined by the restrictive inclusion and exclusion criteria limiting the generalizability to other women. Flibanserin is commonly associated with CNS side effects, and more patients on flibanserin stopped therapy due to adverse effects compared to placebo.

- Serious safety concerns exist including clinically significant hypotension and syncope and CNS depression, which may be enhanced in certain settings. Drug interactions, hepatic impairment, and predisposition to hypotension and syncope need to be assessed before use. Additional postmarketing data requirements defined by FDA evaluating these and other concerns (e.g., pregnancy outcomes) will provide more information on the safety of flibanserin.
- The diagnosis of acquired, generalized HSDD associated with marked distress or interpersonal difficulty and not due to other reasons (co-existing medical or psychiatric condition; relationship problems; or the effects of medication or other substance) should be made by a trained, experienced clinician. Patients should understand the benefits and risks and be willing to abstain from alcohol completely. If there is no improvement in eight weeks, flibanserin should be discontinued.

Prepared August 2016. Contact person: Lisa Longo, Pharm.D., BCPS, National Pharmacy Benefits Management Services

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.