

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022526Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memorandum

Date	August 18, 2015
From	Julie Beitz, MD
Subject	Office Director Decisional Memorandum
NDA #	022526
Applicant Name	Sprout Pharmaceuticals, Inc.
Date of Submission	February 14, 2015 (received on February 18, 2015)
PDUFA Goal Date	August 18, 2015
Proprietary Name / Established (USAN) Name	Addyi (flibanserin)
Dosage Forms / Strengths	Tablets / 100 mg
Proposed Indication	Treatment of hypoactive sexual desire disorder (HSDD)
Action:	Approval
Approved Indication	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: <ul style="list-style-type: none"> • A co-existing medical or psychiatric condition, • Problems within the relationship, or • The effects of a medication or other drug substance

Materials Reviewed/Consulted	Discipline Reviewers
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 DMEPA Division of Medication Error Prevention and Analysis
 DMPP Division of Medical Policy Programs
 DNP Division of Neurology Products
 DPMH Division of Pediatrics and Maternal Health
 DRISK Division of Risk Management
 OND Office of New Drugs
 OPDP Office of Prescription Drug Promotion
 OSE Office of Surveillance and Epidemiology
 OSI Office of Scientific Investigations

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Addyi (flibanserin) is a post-synaptic 5-HT_{1A} agonist and 5-HT_{2A} antagonist, and a new molecular entity. It also binds with moderate affinity to 5-HT_{2B}, 5-HT_{2C}, and dopamine D₄ receptors. I concur with the recommendation of the Division of Bone, Reproductive and Urologic Products to approve Addyi (flibanserin) tablets for the treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD) as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is not due to:

- A co-existing medical or psychiatric condition,
- Problems within the relationship, or
- The effects of a medication or other drug substance

Acquired HSDD refers to HSDD that develops in a woman who previously had no problems with sexual desire. Generalized HSDD refers to HSDD that occurs regardless of the type of stimulation, situation or partner. ADDYI is not indicated for the treatment of HSDD in postmenopausal women or in men, or to enhance sexual performance. To ensure that the benefits of the drug outweigh the risks of severe hypotension and syncope when taken with alcohol, Addyi will be approved with a REMS, or risk evaluation and mitigation strategy, with elements to assure safe use.

The recommended dose of Addyi is 100 mg administered orally once per day at bedtime.

HSDD is a multi-faceted disorder that encompasses a spectrum of symptoms of varying severity. Women with HSDD experience considerable distress or anxiety over their loss of sexual desire, rarely initiate sexual contact and often avoid intimate situations. Loss of sexual desire can result in loss of self-esteem and feelings of inadequacy, isolation and guilt, and can negatively impact the woman's relationship with her partner.

There is an unmet medical need for safe and effective treatments for women with HSDD. Certain psychological interventions can improve symptom severity and sexual satisfaction in women with HSDD. There is, however, a lack of controlled trials comparing different types of psychological interventions, or that are designed to assess the contribution of medications, such as flibanserin, to psychological interventions in women with HSDD. Future methodologically sound trials of sufficient size are needed to further evaluate the efficacy of treatment options for HSDD.

There are no FDA-approved drugs for the treatment of HSDD. Some women report improvements in their symptoms with over-the-counter products, such as supplements (e.g., DHEA), or off-label prescription therapies such as various testosterone products, combination estrogen and progesterone products, and antidepressants. The benefits of these therapies have not been established and are often outweighed by their attendant side effects.

The efficacy of Addyi (flibanserin) was established in three North American randomized, placebo-controlled trials involving 2409 premenopausal women.

These women had acquired, generalized HSDD by DSM-IV-TR criteria for a mean of 5 years, and were in stable monogamous, heterosexual relationships. Taken together, these trials showed that treatment with flibanserin 100 mg qhs for 6 months resulted in consistent, albeit small, improvements relative to placebo in the number of satisfying sexual events and in sexual desire, and reduced distress associated with low sexual desire. In supportive analyses, more flibanserin-treated women than placebo-treated women reported meaningful improvement across the three trials. Substantial placebo effects were noted for all efficacy endpoints in the submitted trials; this is not surprising since frequent interactions with partners and trial personnel, including use of daily diaries, may help keep sexual interest in participants at the forefront. No subgroup of premenopausal women with HSDD was identified that was more likely to derive a benefit from flibanserin treatment. The totality of evidence supports the conclusion that flibanserin is an effective treatment for premenopausal women with acquired, generalized HSDD. The assessment of female sexual dysfunction remains a challenging task. Further consensus is needed regarding meaningful and valid efficacy endpoints to be used in clinical trials of therapies for HSDD.

The safety profile of Addyi (flibanserin) has been characterized in several clinical pharmacology, drug-drug interaction, and controlled clinical trials. Product labeling will contain a Boxed Warning stating that the following are contraindicated:

- **Use of alcohol.** Use of alcohol with flibanserin can increase the risk of severe hypotension and syncope, and its use is contraindicated. Interpretation of the submitted alcohol interaction trial is limited by the observed inter-subject variability and the small number of female subjects enrolled. Thus, the extent of alcohol interaction in premenopausal women, who may be more sensitive to the effects of alcohol than men, has not been fully characterized. Before prescribing flibanserin, the healthcare provider should 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, and counsel patients who are prescribed flibanserin about the importance of avoiding alcohol use. To ensure that the benefits of the drug outweigh the risks of severe hypotension and syncope when taken with alcohol, flibanserin will be approved with a REMS.
- **Co-administration with strong or moderate CYP3A4 inhibitors.** Co-administration of flibanserin with a strong or moderate CYP3A4 inhibitor increases flibanserin concentrations, can increase the risks of severe hypotension and syncope, and is contraindicated. Flibanserin may be co-administered with weak inhibitors of CYP3A4, including oral contraceptives, although the incidence of hypotension, dizziness and fatigue is increased compared to contraceptive non-users.
- **Use in patients with hepatic impairment.** Flibanserin concentrations were increased in patients with mild hepatic impairment to a similar extent as those observed with co-administration of flibanserin and a strong CYP3A4 inhibitor. Use of flibanserin in patients with hepatic impairment is therefore contraindicated.

Product labeling will also include the following risks under Warnings and Precautions:

- **CNS depression.** Flibanserin is a CNS depressant. The risk of CNS depression is increased if flibanserin is taken during waking hours, or if flibanserin is taken with alcohol, other CNS depressants, or drugs that increase flibanserin concentrations. Although the driving simulation study did not detect

next-day psychomotor impairment when assessed at 9 hours after flibanserin dosing, product labeling will warn patients to not drive or engage in activities requiring full mental alertness or motor coordination for at least 6 hours after taking flibanserin.

- **Hypotension and syncope with flibanserin alone.** Flibanserin alone can cause hypotension and syncope. The risk of hypotension and syncope is increased if flibanserin is taken during waking hours, if a higher than the recommended dose is taken, or if flibanserin is used in patients with pre-existing conditions that predispose them to hypotension.
- **Mammary tumors in female mice.** In a two-year carcinogenicity study, mammary tumors developed in female mice at low multiples of human exposure. The mechanism for mammary tumor development in flibanserin-treated mice is not known, and the clinical significance of these findings, in the absence of similar findings in Wistar rats, is unclear. The submitted phase 3 trials cannot rule out a human carcinogenicity risk since the trials were only 24 months in duration.

In addition to product labeling, the risks of severe hypertension and syncope due interactions between flibanserin and moderate or strong CYP3A4 inhibitors will be further minimized through existing automated pharmacy systems that will alert the pharmacist about these interactions before flibanserin is dispensed.

Furthermore, to ensure that the benefits of flibanserin outweigh the increased risks of severe hypotension and syncope due to an interaction with alcohol, flibanserin will be approved with a REMS with elements to assure safe use. The elements to assure safe use will require prescribers and pharmacies that prescribe and dispense Addyi to be specially certified so that they understand they are required to counsel patients to avoid alcohol use while taking flibanserin. The Addyi REMS Program will require prescriber training and certification, and certification of pharmacies that will dispense only to patients with a prescription from a certified prescriber. A *Patient-Provider Agreement Form* will be used as a counseling tool for patients and a Medication Guide will be distributed each time the drug is dispensed. Knowledge, attitude and behavior surveys will evaluate the knowledge of certified prescribers, of authorized representatives and staff pharmacists in certified pharmacies, and of patients prescribed Addyi. There will be an implementation system and a timetable for assessments of the REMS.

A dedicated alcohol interaction trial conducted in women will not be required pre-approval. Rather, the applicant will be required to conduct three alcohol interaction trials post-approval under 505(o) to assess the risks to flibanserin users associated with taking varying doses of alcohol, with drinking alcohol at varying intervals related to flibanserin dosing, and with “real world” use of alcohol. In addition, the applicant will be required to conduct a prospective observational study to assess the risk of appendicitis in flibanserin users, a pregnancy exposure registry to assess maternal, fetal and infant outcomes in flibanserin users, an observational study of fetal outcomes in women exposed to flibanserin during pregnancy, and enhanced pharmacovigilance to assess and analyze serious adverse events associated with flibanserin use, including hypotension and syncope, accidents or injuries, and fatal outcomes.

There are no inspectional issues that preclude approval of this application.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p>Analysis of Condition</p>	<p>The DSM-IV-TR, published in July 2000, defined HSDD as the persistent or recurrent deficiency or absence of sexual fantasies and desire for sexual activity, which causes marked distress or interpersonal difficulty. The judgment of deficiency or absence is made by the clinician, taking into account factors that affect sexual functioning, such as age and the context of the person’s life.</p> <p>In May 2013, DSM-5 diagnostic criteria were published that merged female sexual desire and arousal disorders and defined a new disorder, female sexual interest/arousal disorder (FSI/AD). This disorder is characterized by a lack of sexual interest/arousal for a minimum of 6 months. As in the DSM-IV-TR, the problem should cause significant distress or impairment.</p> <p>One survey of over 30,000 US women found that 12% of individuals reported experiencing distressing sexual problems defined as a sexual problem and a score of at least 15 on the Female Sexual Distress Scale. Distressing sexual problems were reported most frequently in women aged 45-64 years.¹</p> <p>In October 2014, CDER convened a Patient-Focused Drug Development (PFDD) meeting on Female Sexual Dysfunction to discuss disease symptoms and their impact on daily life. Additional details are provided in Section 2 of this review.</p>	<p>HSDD is a multi-faceted disorder that encompasses a spectrum of symptoms of varying severity. Women with HSDD experience considerable distress or anxiety over their loss of sexual desire, rarely initiate sexual contact and often avoid intimate situations. Loss of sexual desire can result in loss of self-esteem and feelings of inadequacy, isolation and guilt, and can negatively impact the woman’s relationship with her partner.</p>
<p>Current Treatment Options</p>	<p>Psychological interventions have been used to treat sexual dysfunction in men and women, including sexual skills training, sex therapy, cognitive-behavioral therapy, marital therapy, systematic desensitization, and education interventions. In HSDD, cognitive-behavioral therapy alone or in combination with sexual skills training has been used. Psychological interventions improved symptom severity, and to a lesser</p>	<p>There is an unmet need for safe and effective treatments for women with HSDD.</p> <p>Certain psychological interventions can improve symptom severity and sexual satisfaction in women</p>

¹ Shifren JL, Monz BU, Russo PA, Segreti A, and Johannes CB. Sexual problems and distress in United States women – prevalence and correlates. *Obstet Gynecol* 2008; 112:970-978.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>extent, sexual satisfaction in three trials. The long-term effects of these interventions are unknown.²</p> <p>There are no FDA-approved drugs for the treatment of HSDD. At CDER’s 2014 PFDD meeting, participants provided their perspectives about a variety of approaches they used to treat low sexual desire, including over-the-counter products, and off-label prescription medications. These approaches offered limited benefits. Additional details are provided in Section 2 of this review.</p>	<p>with HSDD. There is, however, a lack of controlled trials comparing different types of psychological interventions, or that are designed to assess the contribution of medications, such as flibanserin, to psychological interventions in women with HSDD. Future methodologically sound trials of sufficient size are needed to further evaluate the efficacy of treatment options for HSDD.</p> <p>There are no FDA-approved drugs for the treatment of HSDD. Off-label prescription medications include various testosterone products, combination estrogen and progesterone products, and antidepressants. The benefits of these therapies have not been clearly established and are often outweighed by their attendant side effects. Over-the-counter products, such as supplements (e.g., DHEA), offer limited benefits.</p>
Benefit	<p>Flibanserin is a post-synaptic 5-HT_{1A} agonist and 5-HT_{2A} antagonist, and a new molecular entity. It also binds with moderate affinity to 5-HT_{2B}, 5-HT_{2C}, and dopamine D₄ receptors.</p> <p>The efficacy of Addyi (flibanserin) 100 mg qhs was established in three North American randomized, placebo-controlled trials of premenopausal women with acquired, generalized HSDD, Trials 511.71 and 511.75 submitted in the original</p>	<p>The efficacy of Addyi (flibanserin) was established in three North American randomized, placebo-controlled trials involving 2409 premenopausal women. These women had acquired, generalized HSDD by DSM-IV-TR criteria for a mean of 5 years, and were in stable monogamous, heterosexual relationships. On average, the women enrolled in</p>

² Fruhauf S, Gerger H, Schmidt HM, Munder T, and Barth J. Efficacy of psychological interventions for sexual dysfunction: A systematic review and meta-analysis. Arch Sex Behav 2013; 42:915-933.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>application, and Trial 511.147 submitted in the applicant’s Complete Response and reviewed in the second cycle. Key trial findings are summarized below.³</p> <ul style="list-style-type: none"> • <i>Cycle 1 (October 2009 – August 2010)</i> <p>Trials 511.71 and 511.75. These were 6-month, randomized, double-blind, placebo-controlled clinical trials conducted in the US and Canada. Both trials consisted of a 4-week baseline period followed by a 24-week blinded treatment period.</p> <p>The mean duration of HSDD in these women was approximately 5 years. The mean age of enrollees was 36 years. The majority of women were married and in their present relationship an average of 10 years. The trial protocols listed numerous exclusions precluding enrollment. In particular, women were not eligible for enrollment if they were taking a prohibited medication, had a history of major depressive disorder within 6 months of the screening visit or any psychiatric disorder that could influence sexual function, compliance or safety, or if they had a recent major life stress or relationship discord that could interfere with sexual activity. Alcohol use was permitted.</p> <p>Findings. Efficacy was assessed in a total of 655 women on flibanserin 100 mg qhs and 652 women on placebo. Both trials demonstrated a statistically significant change from baseline in the number of satisfying sexual events (SSEs), one of two co-primary endpoints, for flibanserin relative to placebo. However, a statistically significant improvement for flibanserin relative to placebo was not demonstrated for the change from baseline in the second co-primary endpoint, the eDiary sexual desire item measured daily over 24 weeks. While results on sexual desire as measured by the sexual desire domain of the Female Sexual Function Index (FSFI-SD) favored flibanserin, the Division and I did not agree that it was appropriate to disregard the negative results obtained with the pre-specified eDiary sexual desire item analyses in favor of the positive results obtained using another instrument.</p>	<p>these trials were having satisfying sex less than once weekly; feeling sexual desire infrequently or never and at a low, very low or nil level; and having distress about low sexual desire frequently.</p> <p>In these trials, women counted the number of SSEs, reported their sexual desire over the preceding four weeks (scored using the FSFI-SD on a range of 1.2 to 6.0), and reported their distress related to low sexual desire (scored using the FSDS-R Question 13 on a range of 0 to 4). On average, treatment with flibanserin increased the number of SSEs by 0.5 to 1 additional event per month over placebo, increased the sexual desire score by 0.3 to 0.4 over placebo, and decreased the distress related to low sexual desire score by 0.3 to 0.4 over placebo.</p> <p>Taken together, these trials showed that treatment with flibanserin 100 mg qhs for 6 months resulted in fairly consistent, albeit small, improvements relative to placebo in the number of satisfying sexual events, in sexual desire, and reduced distress associated with low sexual desire. Improvements in the number of SSEs and in sexual desire correlated when sexual desire was assessed using the FSFI-SD questionnaire, but not when sexual desire was assessed using a daily electronic diary.</p>

³ Additional details may be found in my September 27, 2013 review and in Section 2 of this review.

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	<p>Rather, the favorable results for the FSFI-SD could be viewed as exploratory, to be replicated in a future trial. In both trials, flibanserin treatment was associated with reduced HSDD-related distress, a secondary endpoint, evaluated by the Female Sexual Distress Scale-Revised (FSDS-R, Question 13).</p> <p>In the August 2010 Complete Response letter, FDA recommended that the applicant conduct an additional blinded, placebo-controlled clinical trial to assess the effects of flibanserin on SSEs and sexual desire (as co-primary endpoints), and HSDD-related distress (as a key secondary endpoint). The FSFI-SD could be used to assess sexual desire if the applicant demonstrated adequate content validity, including recall validity, and acceptable measurement properties. The trial should have less restrictive entry criteria compared to previously conducted HSDD clinical trials with respect to the presence of co-morbid conditions in enrolled subjects and use of concomitant medications.</p> <ul style="list-style-type: none"> • <i>Cycle 2 (March 2013 – September 2013)</i> <p>Trial 511.147. This was a 6-month, randomized, double-blind, placebo-controlled clinical trial that had been ongoing in the US at the time the 2010 Complete Response letter was issued.</p> <p>The mean duration of HSDD in these women was approximately 5 years. The mean age of enrollees was 36.5 years. The mean length of time in their present relationship was 11 years. Compared to the protocols for the previously submitted trials, the protocol for this trial listed fewer exclusions and prohibited medications that would preclude enrollment. Alcohol use was permitted.</p> <p>Findings. Efficacy was assessed in 532 women on flibanserin 100 mg qhs and 536 women on placebo. Flibanserin-treated women reported a significantly greater change in the number of SSEs per 28 days from baseline as compared to placebo-treated women. Flibanserin-treated women also showed a significantly greater improvement in FSFI-SD score (the pre-specified co-primary endpoint). In protocol-</p>	<p>There remains residual uncertainty with regard to the optimal recall period for assessing sexual desire in clinical trials. Daily diary assessments may result in “diary fatigue” whereas assessments performed less frequently (e.g., via self-administered monthly questionnaires) may be influenced by more recent events.</p> <p>Although the FSFI is generally considered the “gold standard” self-administered instrument that assesses various aspects of sexual function, there is a need for continued validation research given the many complex cognitive, affective and motivational elements that contribute to the construct of sexual desire in women.</p> <p>Substantial placebo effects were noted for all efficacy endpoints in the submitted trials; this is not surprising since the use of daily diaries and frequent interactions with partners and trial personnel may help keep sexual interest in participants at the forefront.</p> <p>No subgroup of premenopausal women with HSDD was identified that was more likely to derive a benefit from flibanserin treatment.</p> <p>Pre-specified supportive analyses were performed to assess the clinical meaningfulness of the efficacy findings across the three phase 3 trials. In general, approximately 10% more flibanserin-treated women than placebo-treated women reported</p>

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	<p>specified analyses, the applicant reported similar results with FSFI-SD 7-day and FSFI-SD 28-day recall assessments of sexual desire. Flibanserin-treated women also reported reduced distress, a key secondary endpoint, as captured by FSDS-R Question 13, relative to placebo-treated women.</p> <ul style="list-style-type: none"> • <i>Cycle 3 (February 2015 – August 2015)</i> <p>Exploratory subgroup analyses were performed to assess whether treatment effects varied depending on baseline number of SSEs, FSFI-SD scores and FSDS-R scores to determine whether a subgroup of women could be identified who were more likely to respond to treatment. No such subgroup was identified.</p> <p>Pre-specified supportive analyses were performed to assess the clinical meaningfulness of the efficacy findings across the three phase 3 trials. Responders were defined for each efficacy endpoint by anchoring change from baseline to end of treatment with their score on the Patient’s Global Impression of Improvement (PGI-I). The percentage of responders anchored to “much improved” or “very much improved” among flibanserin-treated women ranged from 21% to 48%, depending on the endpoint and the trial. The percentage of responders anchored to “much improved” or “very much improved” among placebo-treated women ranged from 14% to 38%. In general, approximately 10% more flibanserin-treated women than placebo-treated women reported meaningful improvement in satisfying SSEs, sexual desire, or reduced distress due to low sexual desire.</p> <p>Considering the totality of clinical trial evidence and results from supportive analyses of clinical meaningfulness, the majority (18 of 24) of Committee members at the June 4, 2015 meeting concluded that there was an unmet medical need for safe and effective therapies for women with HSDD, and that flibanserin was an effective treatment for premenopausal women with acquired, generalized HSDD.</p>	<p>meaningful improvements in satisfying sexual events, sexual desire or distress.</p> <p>In conclusion, across three controlled trials of flibanserin there were consistent, albeit small, treatment differences relative to placebo, and more flibanserin-treated women than placebo-treated women reported meaningful improvement. The totality of evidence supports the conclusion that flibanserin is an effective treatment for premenopausal women with acquired, generalized HSDD. The assessment of female sexual dysfunction remains a challenging task. Further consensus is needed regarding meaningful and valid efficacy endpoints to be used in clinical trials of therapies for HSDD.</p>

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Risk	<p>The safety of flibanserin 100 mg qhs was evaluated in a total of 2,997 generally healthy premenopausal women with acquired, generalized HSDD. Of these, 1672 received treatment for at least 6 months, and 850 received treatment for at least 12 months.</p> <p>The safety profile of flibanserin has been assessed in several clinical pharmacology, drug-drug interaction, and controlled clinical trials submitted over the course of the three review cycles. The major findings from these studies are summarized below:⁴</p> <p>Use of alcohol. The applicant conducted a single-center, randomized, double-blind, 5-treatment crossover study evaluating the effects of single doses of flibanserin 100 mg when given alone, or with 0.4 g/kg or 0.8 g/kg of 95% ethanol. These ethanol doses are equivalent to two and four 5 ounce glasses of wine containing 12% alcohol content in a 70 kg subject, respectively, and were consumed over 10 minutes in the morning after a light breakfast. Twenty-five subjects with a history of moderate alcohol consumption completed the study; 23 of the subjects were males.</p> <p>Syncope or hypotension requiring therapeutic intervention (ammonia salts and/or placement in supine or Trendelenburg position) occurred in 4/23 (17%) men administered flibanserin 100 mg with 0.4 mg/kg alcohol. In these men, systolic blood pressure reductions ranged from 28 to 54 mm Hg, and diastolic blood pressure reductions ranged from 24 to 46 mm Hg. Six of 24 (25%) of subjects co-administered flibanserin with 0.8 mg/kg experienced orthostatic hypotension when standing from a sitting position, one of whom required intervention. There were no events requiring intervention when flibanserin or alcohol were administered alone.</p> <p>The incidence of somnolence was 92% in subjects administered flibanserin 100 mg with 0.8 mg/kg alcohol, 74% in subjects administered flibanserin 100 mg with 0.4 mg/kg alcohol, and 67% when flibanserin 100 mg was administered alone. In the</p>	<p>The safety profile of Addyi (flibanserin) has been characterized in several clinical pharmacology, drug-drug interaction, and controlled clinical trials.</p> <p>Product labeling will include a Boxed Warning and contraindicate the following:</p> <p>1) Use of alcohol. Use of alcohol with flibanserin can increase the risks of severe hypotension and syncope seen with flibanserin alone, and its use is contraindicated. Interpretation of the submitted alcohol interaction trial is limited by the observed inter-subject variability, the small number of female subjects enrolled (N=2), the small number subjects per treatment group (N=5), and incomplete concentration-time profiles. Flibanserin was dosed in the morning and alcohol consumed quickly (over 10 minutes). In sum, the extent of alcohol interaction in premenopausal women, who may be more sensitive to the effects of alcohol than men, has not been fully characterized. Before prescribing flibanserin, the prescriber should 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, and counsel patients who are prescribed flibanserin about the importance of</p>

⁴ *ibid.*

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	<p>absence of flibanserin, the incidence of somnolence was 60% and 38% for the high and low alcohol dose cohorts, respectively.</p> <p>Mean flibanserin exposure (based on AUC_{0-4}) was similar for subjects taking the drug alone or with ethanol.</p> <p>In phase 3 trials of flibanserin in premenopausal women, alcohol use was permitted. There were no serious adverse events associated with alcohol use reported, however the frequency and quantity of alcohol use in these trials is unknown. In a phase 3 trial involving postmenopausal women, a 54 year old woman died of acute alcohol intoxication 14 days after starting flibanserin 100 mg qhs. Blood alcohol concentration at autopsy was 0.289 g/dL. The patient had a history of hypertension and hypercholesterolemia and baseline alcohol consumption of 1-3 drinks daily. The contribution of flibanserin to the fatal outcome in this patient cannot be ruled out.</p> <p>Co-administration with strong or moderate CYP3A4 inhibitors. In a study of 24 healthy female subjects, administration of flibanserin 50 mg with the strong CYP3A4 inhibitor ketoconazole 400 mg at steady state increased flibanserin single-dose exposure (AUC_{0-inf}) by 4.5-fold and C_{max} by 1.8-fold relative to the values for flibanserin alone. The terminal half-life of flibanserin increased to 16 hours. Dizziness, fatigue, nausea, vomiting and somnolence were more frequently reported with ketoconazole co-administration than with flibanserin alone.</p> <p>In a study of healthy female subjects, administration of flibanserin 100 mg with the moderate CYP3A4 inhibitor fluconazole 200 mg at steady state resulted in a 2.2-fold increase in flibanserin C_{max} and a 7.0-fold (AUC_{0-inf}) increase in single dose exposure. T_{max} values were similar for flibanserin alone or flibanserin + fluconazole. The flibanserin terminal half-life increased from 10 hours for flibanserin alone to 23 hours for flibanserin + fluconazole. Mean clearance of flibanserin decreased from 75.9 to 9.8 L/hr with fluconazole administration.</p> <p>Drug-related adverse events were reported in 85% (22/26) of subjects in the</p>	<p>avoiding alcohol use. Due to the alcohol interaction, flibanserin will be approved with a REMS.</p> <p>2) Co-administration with strong or moderate CYP3A4 inhibitors. Co-administration of flibanserin with a strong or moderate CYP3A4 inhibitor increased flibanserin plasma concentrations, was associated with increased risks of hypotension, syncope, and somnolence, and is contraindicated.</p> <p>Flibanserin may be co-administered with weak inhibitors of CYP3A4, including oral contraceptives, although the incidence of hypotension, dizziness and fatigue is increased compared to contraceptive non-users.</p> <p>3) Use in patients with hepatic impairment. Flibanserin concentrations were increased in subjects with mild hepatic impairment to a similar extent as those observed with co-administration of flibanserin with a strong CYP3A4 inhibitor. Use of flibanserin in patients with hepatic impairment is contraindicated.</p> <p>Product labeling will also include the following risks under Warnings and Precautions:</p> <p>1) CNS depression. Flibanserin is a CNS depressant. The risk of CNS depression is increased if flibanserin is taken during waking</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>flibanserin alone group, in 27% (4/15) of subjects in the fluconazole alone group, and in 100% (15/15) of subjects in the flibanserin + fluconazole group. Fatigue, dizziness, and nausea were the most commonly reported events; the onset of these events was near the flibanserin T_{max} in all cases. There were three reports of hypotension or syncope among the 15 subjects in the flibanserin + fluconazole group occurring at one hour after dosing with flibanserin 100 mg. One of these events was severe, requiring intravenous saline.</p> <p>Co-administration of flibanserin with oral contraceptives. In a meta-analysis of 17 users of oral contraceptives (mild CYP3A4 inhibitors), flibanserin AUC was 1.4-fold higher and C_{max} was 1.3-fold higher relative to 91 non-users. Women with hepatic or renal impairment were not included in this analysis.</p> <p>In controlled trials, 1466 women reported concomitant use of hormonal contraceptives at enrollment. The incidence of somnolence, dizziness and fatigue was higher in these women as compared to non-users.</p> <p>Use in patients with hepatic impairment. Single oral doses of flibanserin 50 mg were administered to 10 subjects with mild liver impairment (Child-Pugh score of 6 points), 4 subjects with moderate liver impairment (Child-Pugh score of 8-9 points), and 14 healthy subjects matched by age, weight, and gender. Flibanserin exposure was increased 4.5-fold in subjects with mild hepatic impairment, and the flibanserin half-life increased to 26 hours compared to 10 hours in healthy controls.</p> <p>CNS depression. In controlled trials of premenopausal women with HSDD, the incidence of CNS depression (including reports of somnolence, sedation and fatigue) was 21% in women taking flibanserin 100 mg qhs and 8% of placebo-treated women.</p> <p>At FDA's request, a driving simulation study was performed in 83 premenopausal women to assess next-day psychomotor impairment after bedtime dosing of flibanserin. The use of oral contraceptives was permitted. There was no evidence for driving impairment, or adverse psychomotor or cognitive effects at 9 hours after</p>	<p>hours, or if flibanserin is co-administered with alcohol, other CNS depressants, or drugs that increase flibanserin concentrations (such as strong or moderate CYP3A4 inhibitors). Although the driving simulation study did not detect next-day psychomotor impairment when assessed at 9 hours after flibanserin dosing, product labeling will warn patients to not drive or engage in activities requiring complete mental alertness or motor coordination for at least 6 hours after taking flibanserin.</p> <p>2) Hypotension and syncope with flibanserin alone. Flibanserin can cause hypotension and syncope. The risk of hypotension and syncope is increased if flibanserin is taken during waking hours, if a higher than approved dose is taken, or if flibanserin is used in patients with pre-existing conditions that predispose them to hypotension.</p> <p>3) Mammary tumors in female mice. In a two-year carcinogenicity study, mammary tumors developed in female mice at low multiples of human exposure. Prolactin levels were not increased in female mice suggesting that the mechanism of tumor induction is unlikely to be hormonal. Thus, the mechanism for mammary tumor development in flibanserin-treated mice is not known, and the clinical significance of these findings, in the absence of similar</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>single and multiple doses of flibanserin 100 mg taken daily at bedtime, or after single doses of flibanserin 200 mg taken at bedtime.</p> <p>Hypotension and syncope with flibanserin alone. In controlled trials of premenopausal women with HSDD taking flibanserin 100 mg qhs, hypotension was reported in 0.2% of flibanserin-treated women and in <0.1% of placebo-treated women. Syncope was reported in 0.4% of flibanserin-treated women and in 0.2% of placebo-treated women. Dizziness was reported in 11.4% of flibanserin-treated women and in 2.2% of placebo-treated women.</p> <p>Mammary tumors in female mice. In a two-year carcinogenicity study conducted in CD-1 mice, orally administered flibanserin produced a dose-related increase in the incidence of mammary tumors in female mice at doses that were approximately 3 and 10 times the recommended clinical dose based on AUC. No increases in mammary tumors were observed in male mice. No increase in mammary tumor incidence was observed in a two-year carcinogenicity study conducted in Wistar rats. To evaluate a potential hormonal mechanism related to the induction of the mammary tumors, prolactin levels were evaluated in female mice. There were no effects on prolactin levels at either 14 or 34 weeks at doses up to 10 times the recommended clinical dose based on AUC.</p> <p>Flibanserin was negative for mutagenesis <i>in vitro</i> in the Ames test and in Chinese hamster ovary cells. It was positive for chromosomal aberrations in cultured human lymphocytes but negative for chromosomal aberrations <i>in vivo</i> in the rat bone marrow micronucleus assay and for DNA damage in rat liver in the Comet assay.</p>	<p>findings in Wistar rats, is unclear. The submitted phase 3 trials cannot rule out a human carcinogenicity risk since the trials were only 24 weeks in duration. The finding of mammary tumors in female mice will be described in product labeling under Warnings and Precautions.</p>
<p>Risk Management</p>	<p>Labeling: Product labeling will include a Boxed Warning stating that flibanserin is contraindicated in the following settings:</p> <ul style="list-style-type: none"> • With alcohol use; • With co-administration of strong or moderate CYP3A4 inhibitors; and • In patients with hepatic impairment. 	<p>The Boxed Warning, Contraindications, and Warnings and Precautions sections of product labeling adequately address the serious risks that have been associated with the use of flibanserin in clinical trials.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>The Warnings and Precautions section will describe additional risks of CNS depression, hypotension and syncope with flibanserin alone, and the preclinical findings of mammary tumors in female mice.</p> <p>Automated pharmacy systems. In addition to the Boxed Warning, the risks of severe hypertension and syncope due to interactions between flibanserin and moderate or strong CYP3A4 inhibitors will be further minimized through existing automated pharmacy systems that will alert the pharmacist about these interactions before flibanserin is dispensed.</p> <p>REMS: A joint meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee was held on June 4, 2015. The Committee voted 18 to 6 in favor of flibanserin approval. All members voting in favor indicated that risk mitigation strategies beyond labeling were needed to ensure that the benefits of flibanserin outweighed its risks in premenopausal women with HSDD. Based on advice provided by Committee members and further discussions within the Agency, FDA determined that the applicant's proposed REMS, which consisted of a Medication Guide and a Communication Plan, was not adequate to mitigate the increased risks of severe hypotension and syncope associated with Addyi (flibanserin) due to an interaction with alcohol.</p> <p>The applicant submitted a revised proposed REMS with elements to assure safe use on June 29, 2015. The goals of the REMS are to mitigate the increased risks of severe hypotension and syncope due to an interaction between Addyi and alcohol by:</p> <ul style="list-style-type: none"> • Ensuring prescribers and pharmacists are educated about the increased risks of hypotension and syncope associated with Addyi due to an interaction with alcohol and the need to counsel patients about these risks; and • Informing patients about the increased risks of hypotension and syncope 	<p>In addition to product labeling, the risks of severe hypertension and syncope due to interactions between flibanserin and moderate or strong CYP3A4 inhibitors will be further minimized through existing automated pharmacy systems that will alert the pharmacist about these interactions before flibanserin is dispensed.</p> <p>Furthermore, Addyi will be approved with a REMS with elements to assure safe use to ensure that the benefits of the drug outweigh the increased risks of severe hypotension and syncope due to an interaction between Addyi and alcohol. The elements to assure safe use will require prescribers and pharmacies that prescribe and dispense Addyi to be specially certified so that they understand they are required to counsel patients to avoid alcohol while taking Addyi.</p> <p>The Addyi REMS Program will require prescriber training and certification, and certification of pharmacies that will dispense only to patients with a prescription from a certified prescriber. A <i>Patient-Provider Agreement Form</i> will be used as a counseling tool for patients and a Medication Guide will be distributed each time the drug is dispensed. Knowledge, attitude and behavior surveys will evaluate knowledge of certified prescribers, of authorized representatives and staff pharmacists in certified pharmacies, and of patients prescribed Addyi. There will also be an</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>associated with Addyi due to an interaction with alcohol.</p> <p>The REMS for Addyi will ensure that prescribers are specially certified and agree to counsel patients about the increased risks of severe hypotension and syncope associated with Addyi due to an interaction with alcohol, and the need to abstain from alcohol use during treatment with Addyi. In addition, certification of pharmacies that dispense Addyi is necessary to establish that Addyi has been prescribed only by certified prescribers. Certification of outpatient pharmacies will also entail pharmacist counseling of patients prior to dispensing Addyi of the need to abstain from alcohol while on treatment with Addyi. Inpatient pharmacies must also be enrolled and certified in order to purchase and dispense Addyi. Knowledge, attitude and behavior surveys will evaluate knowledge of certified prescribers, of authorized representatives and staff pharmacists in certified pharmacies, and of patients prescribed Addyi.</p> <p>The applicant will submit REMS assessments to the FDA at 6 months and 12 months from the date of the initial approval of the REMS, and annually thereafter. Additional details regarding the elements of the Addyi REMS Program are described in Section 2 below.</p> <p>Post-approval studies and clinical trials: Seven post-approval studies or clinical trials will be required under 505(o) namely: 1) three alcohol interaction trials in women, 2) an observational study to assess the risk of appendicitis in flibanserin users, 3) a pregnancy exposure registry, 4) an observational study to assess the risk of adverse fetal outcomes in women exposed to flibanserin during pregnancy, and 5) enhanced pharmacovigilance for adverse events of interest including hypotension, syncope, accidents or injuries, and fatal outcomes. Additional details regarding these required studies and clinical trials are provided in Section 2 below.</p>	<p>implementation system and a timetable for assessments of the REMS.</p> <p>A dedicated alcohol interaction trial in women will not be required pre-approval. Rather, the applicant will be required to conduct three post-approval alcohol interaction trials under 505(o). In addition, the applicant will be required to conduct a prospective observational study to assess the risk of appendicitis in flibanserin users, a pregnancy exposure registry to assess maternal and fetal outcomes in flibanserin users, an observational study of fetal outcomes in women exposed during pregnancy, and enhanced pharmacovigilance to assess and analyze serious adverse events of interest associated with Addyi use, including hypotension and syncope, accidents or injuries, and fatal outcomes.</p>

2. Additional Review Comments

2.1 Additional Efficacy Considerations

Co-administration with strong or moderate CYP3A4 inducers. Strong CYP3A4 inducers may substantially decrease the exposure to flibanserin. In a study of 24 healthy female subjects, rifampin 600 mg given once daily for 7 days prior to administration of flibanserin 100 mg decreased flibanserin exposure by 95%. In contrast, steady state etravirine, a moderate inducer of CYP3A4, decreased flibanserin exposure by approximately 21%.

2.2 Additional Safety Considerations

Accidental injury. In phase 3 trials, 42 (2.7%) of flibanserin-treated women and 47 (2.5%) of placebo-treated women reported accidental injuries. In 9/42 (24%) and in 3/47 (6%) of women in these groups, respectively, CNS depression (e.g., somnolence, fatigue or sedation) was reported within the preceding 24 hours.

Appendicitis. An unexplained imbalance in the number of reports of appendicitis was observed in phase 3 trials: six reports on various flibanserin doses (incidence of 0.2%) and none on placebo. FDA is aware of an increased risk of diverticulitis and gallbladder disorders identified during the review of eplivanserin (NDA 22423), a 5HT_{2a} antagonist; the product was not approved. Taken together, these findings may suggest a possible class effect related to both drugs' activity at the 5HT_{2a} receptor which is prevalent in the smooth muscle cells of the GI tract. However, given the low event rates the observed imbalance in flibanserin clinical trials may represent a chance finding. The applicant will be required to conduct a postmarketing observational study to further assess the risk of appendicitis in flibanserin users.

Abuse potential. Flibanserin is not recommended for scheduling under the Controlled Substances Act. Although flibanserin was associated with both sedative and stimulant (e.g., insomnia) effects in placebo-controlled clinical trials there were no reports of euphoria-related adverse effects. In the absence of a signal of euphoria, the sedative and stimulant effects of flibanserin are not indicative of abuse potential.

The safety of flibanserin use in specific populations can be summarized as follows:

Pregnancy. The available human data do not establish the presence or absence of a flibanserin-associated risk to pregnancy. In preclinical studies, fetal toxicity only occurred in the presence of significant maternal toxicity including reductions in weight gain and sedation. Adverse reproductive and developmental effects consisted of decreased fetal weight, structural anomalies and increases in fetal loss at exposures greater than 15 times exposures achieved with the recommended human dose.

Flibanserin is excreted in rat milk. There is no information regarding the presence of flibanserin in human milk, effects on the breastfed infant, or effects on milk production. Breastfeeding is not recommended during flibanserin treatment.

Pediatrics: Flibanserin is not indicated for use in pediatrics patients. The PREA pediatric study requirement is waived because pediatric studies would be impossible for highly impractical.

Race/Ethnicity: A cross-study comparison of flibanserin exposure found a 1.4-fold higher exposure in Japanese women with HSDD as compared to Caucasian women. When the mean flibanserin exposure in Japanese women was adjusted for weight, exposure was comparable to that of Caucasian women. This suggests that weight, rather than race, contributed to the observed differences in flibanserin exposure in the two populations.

CYP2C19 poor metabolizers. The magnitude of increase in flibanserin exposure seen with co-administration of fluconazole was not anticipated. Since fluconazole is also a moderate CYP2C9 inhibitor and a strong CYP2C19 inhibitor, it was hypothesized that flibanserin metabolism might be mediated by these other isoforms.

In a study of flibanserin 100 mg administered to 9 subjects who were CYP2C19 poor metabolizers, flibanserin exposure (AUC_{0-inf}) increased 1.5-fold and C_{max} increased 1.3-fold compared to 8 CYP2C19 extensive metabolizers. A similar effect is expected if flibanserin were administered with a CYP2C19 inhibitor. In this study, syncope occurred one hour after a single dose of flibanserin 100 mg in a premenopausal woman who was a CYP2C19 poor metabolizer.

2.3 Regulatory Review and Advisory Committee Meetings

- ***Cycle 1 (October 2009 – August 2010)***

NDA 022526 for flibanserin was originally submitted by Boehringer Ingelheim Pharmaceuticals, Inc., on October 27, 2009. A joint meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) and the Drug Risk and Safety Management Advisory Committee (DSaRM) was held on June 18, 2010. The Committee was asked to comment on the appropriateness of relying on post-hoc analyses of the FSFI-SD, a pre-specified secondary endpoint, instead of the eDiary assessment of sexual desire, one of two co-primary efficacy endpoints specified in the protocols for the two phase 3 controlled trials submitted. A majority (9 of 11) of the members did not agree with this approach. Committee members voted unanimously (11 vs. 0) against flibanserin approval, noting that the applicant had not demonstrated an acceptable overall benefit to risk profile for flibanserin.

On August 27, 2010, FDA issued a Complete Response letter stating that an additional efficacy trial would be required as well as studies to evaluate: 1) the pharmacokinetics of flibanserin 100 mg when co-administered with moderate CYP3A4 inducers/inhibitors or when taken with alcohol, 2) the risk of syncope-related events with supra-therapeutic doses, and 3) the abuse potential of flibanserin.

- ***Cycle 2 (March 2013 – September 2013)***

Ownership of the NDA was transferred to Sprout Pharmaceuticals, Inc. on January 20, 2012; the new applicant submitted a Complete Response on March 29, 2013, triggering a second review cycle. A second Complete Response letter was issued on September 27, 2013. Considering the findings from the three submitted phase 3 trials, FDA concluded that the observed treatment benefits were statistically significant but numerically small and did not convincingly outweigh the safety concerns identified, including adverse events related to CNS depression, syncope, and hypotension, and

exacerbation of these events when flibanserin was taken with alcohol, and co-administered with strong or moderate CYP3A4 inhibitors. In addition, FDA requested a dedicated driving simulation study to evaluate the potential for residual (next-day) psychomotor impairment from night time administration of flibanserin.

- ***Formal Dispute Resolution Request***

On December 3, 2013, the applicant submitted a formal dispute resolution request appealing the Complete Response action and the need for additional studies. Dr. John Jenkins, Director of OND, denied the appeal on February 7, 2014, stating that FDA's benefit-risk assessment was sound and that the benefits of flibanserin in premenopausal women with HSDD do not outweigh the safety concerns that have been identified. He advised that the applicant fully address the issues raised by the second Complete Response letter before resubmitting the application, and concurred with the Division's plans to discuss the application at an Advisory Committee meeting on the next review cycle.

- ***Cycle 3 (February 2015 – August 2015)***

The applicant submitted a Complete Response on February 14, 2015, received on February 18, 2015, triggering a third review cycle. A joint BRUDAC and DSaRM meeting was held on June 4, 2015. Committee members discussed the phase 3 efficacy findings, including pre-specified supportive analyses performed to assess the clinical meaningfulness of these findings. The Committee noted the large placebo effects for all efficacy endpoints (i.e., SSEs, sexual desire, and distress) and the small placebo-corrected treatment differences. Nevertheless, the majority of Committee members concluded that there was an unmet medical need for safe and effective therapies for HSDD, and that flibanserin was an effective treatment for women with acquired, generalized HSDD.

Several Committee members voiced concerns about the hypotension, syncope and CNS depression reported in flibanserin users, particularly in the presence of alcohol. They also noted the inadequate enrollment of women in the submitted alcohol interaction trial. Other concerns included: the likelihood of adverse effects due to the interaction of flibanserin with strong or moderate CYP3A4 inhibitors or co-administration with other CNS depressants; the clinical significance of the finding of mammary tumors in female mice; the potential off-label use of flibanserin, if approved, in postmenopausal or pregnant women; and the paucity of safety data in women with low body weight and of long-term safety data in general.

Six Committee members voted against NDA approval stating that the benefits of flibanserin treatment were outweighed by the risks, particularly those related to the alcohol interaction. The remaining 18 members voted for approval but with implementation of risk mitigation strategies beyond product labeling. There was broad support for prescriber certification to ensure that prescribers and patients were informed of the risks. Pharmacy certification was also recommended to further ensure that pharmacists were informed of the risks and would dispense to patients only after obtaining authorization (e.g., by calling the REMS coordinating center) to verify that the prescriber was certified in the REMS program. Three Committee members also recommended that informed consent be obtained.

Labeling recommendations included a Boxed Warning regarding the interaction with alcohol pending further study post-approval, a contraindication for alcohol use, and a recommendation to discontinue

treatment if symptoms of HSDD did not improve. There was broad support for a repeat dedicated alcohol interaction trial conducted in women.

2.4 Patient-Focused Drug Development (PFDD) Meeting

On October 27, 2014, CDER convened a Patient-Focused Drug Development (PFDD) meeting on Female Sexual Dysfunction to discuss disease symptoms, daily impacts and patient perspectives on available treatment options. Participants described a transition (either sudden or gradual) from a prior “fulfilling” sex life to a “total loss” of sexual desire or arousal. Many attributed the onset of symptoms to specific life events, including childbirth, hysterectomy or mastectomy. Women with HSDD experienced considerable distress or anxiety over their loss of sexual desire, rarely initiated sexual contact and often avoided intimate situations. Loss of sexual desire often resulted in loss of self-esteem, and feelings of inadequacy, isolation and guilt. Participants also noted the impact of their loss of sexual desire on relationships with their partners, including divorce and separation.⁵

Participants also provided their perspectives about a variety of approaches used to treat low sexual desire. Varying success was reported among women who underwent cognitive-behavioral or marital therapy. No success was reported with use of over-the counter products, including supplements such as DHEA (dehydroepiandrosterone) and Provestra (a blend of botanicals and vitamins), and male enhancement supplements. No success was reported among women who had tried manual pelvic floor physical therapy, massage, or acupuncture.

There are no FDA-approved drugs for the treatment of HSDD. Participants reported on a number of prescription medications that have been used off-label, including:

- *Hormonal therapy:* Testosterone topical creams or gels, injections, or implanted pellets have been prescribed, often to women with low levels of testosterone for their age range. Some participants described noticeable symptom improvement, while others noted variability in effectiveness, or waxing and waning effects. A few participants, however, did not notice benefit or experienced benefits only briefly. Side effects of testosterone therapy included acne, unwanted hair growth, and nausea. In addition, gels and creams were odorous and sticky, pellets required costly surgical procedures for insertion, and injections caused bruising and bleeding. Some participants reported improved sexual responsiveness with use of combination estrogen and progestin, and relief of symptoms associated with menopause or hysterectomy complications.
- *Antidepressants:* Several participants were prescribed antidepressants such as bupropion; most found these medications to be ineffective and made it more difficult to achieve orgasm.
- *Other medications:* Other therapies prescribed included muscle relaxants, analgesics, nerve injections, and sildenafil. Participants did not report any symptom improvement while on these therapies.

2.5 Postmarketing Requirements

The following postmarketing clinical trials and studies will be required under 505(o):

⁵ The Voice of the Patient: Female Sexual Dysfunction, June 2015. Public Meeting held October 27, 2014.

- 1) Three alcohol interaction trials conducted in women ages 18-44 to further assess the interaction of Addyi with alcohol in the following scenarios:
 - a. Addyi taken together with either 0.2, 0.4 or 0.6 g/kg alcohol (“worst case scenario”)
 - b. Addyi taken with alcohol at various intervals
 - c. Addyi taken at bedtime following alcohol with dinner (“real world setting”)
- 2) A prospective observational study to assess the risk of appendicitis in female users of flibanserin, ages 18-44.
- 3) A pregnancy exposure registry conducted in the US to estimate the incidence of congenital malformations and other adverse pregnancy outcomes among women 18 years of age and older who have been exposed to flibanserin during pregnancy. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, and other adverse pregnancy outcomes for a duration of 5 years. Annual interim status reports, including enrollment numbers, will be submitted to FDA.
- 4) A retrospective observational study to estimate the risk of adverse fetal outcomes among women exposed to flibanserin during pregnancy or within 30 days prior to conception.
- 5) Enhanced pharmacovigilance for adverse events of interest associated with Addyi use, including assessment and analysis of reports of hypotension, syncope, accidents or injuries, and fatal outcomes, for a duration of 5 years; interim reports to be submitted to FDA at 6 month intervals. Evaluation of these adverse events will include use of alcohol around the time of the event, timing of dosing, and use of concomitant medications.

2.6 Addyi REMS Program

In this third review cycle, the applicant proposed a REMS consisting of a Medication Guide for patients and a Communication Plan for prescribers. Based on recommendations from the Advisory Committee provided on June 4, 2015, and further discussion within the Agency, FDA determined that the applicant’s proposed REMS was not adequate to mitigate the increased risks of severe hypotension and syncope associated with Addyi due to an interaction with alcohol.

The applicant submitted an amended proposed REMS to include elements to assure safe use on June 29, 2015. The elements to assure safe use will require prescribers and pharmacies that prescribe and dispense Addyi to be specially certified so that they understand they are required to counsel patients to avoid alcohol while taking Addyi.

To become certified, a prescriber must complete and submit the *Addyi REMS Prescriber Enrollment Form* indicating that he/she has reviewed the full prescribing information for Addyi, completed the *Addyi REMS Prescriber and Pharmacy Training Program* and the *Addyi REMS Knowledge Assessment*. As a condition of certification, the prescriber must agree to follow the requirements of the Addyi REMS Program, including counseling patients about the increased risks of hypotension and syncope associated with Addyi due to an interaction with alcohol.

Pharmacy certification consists of designating an authorized representative who will complete the appropriate pharmacy enrollment form (e.g., multiple location pharmacy, individual pharmacy

location, or inpatient pharmacy enrollment form), the *Addyi REMS Prescriber and Pharmacy Training Program*, the *Addyi REMS Knowledge Assessment*, and ensure that:

- All pharmacy staff involved in the dispensing of Addyi are trained on the risks associated with Addyi;
- Processes are in place to ensure that pharmacy staff verify the prescriber is certified in the Addyi REMS Program, and that the staff counsels the patient to avoid alcohol use with Addyi prior to each dispensing of Addyi;
- Pharmacies will maintain appropriate documentation and comply with audits;
- Outpatient pharmacies will have a pharmacy management system in place to verify that the Addyi prescriber is REMS-certified; and
- Inpatient pharmacies will dispense only for inpatient use unless the pharmacy is enrolled as an outpatient pharmacy and can comply with the requirements for outpatient pharmacies as stipulated in the Addyi REMS Program.

The applicant will also ensure that authorized wholesalers and distributors comply with the requirements of the Addyi REMS Program by putting processes in place to verify, prior to distributing Addyi, that the pharmacy is certified. In addition, authorized wholesalers and distributors will maintain appropriate documentation and comply with audits.

Implementation and operational metrics of the Addyi REMS Program will include assessment of:

- Stakeholders' (prescribers, pharmacies, and distributors) utilization
- Addyi utilization
- REMS Support Center activities
- REMS Program compliance
- Barriers or delays in patient access
- Inappropriate patient access

Knowledge, attitude and behavior surveys will evaluate knowledge of certified prescribers, of authorized representatives and staff pharmacists in certified pharmacies, and of patients prescribed Addyi.

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/s/

JULIE G BEITZ
08/18/2015