

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022526Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: August 18, 2015

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Drug Name(s): Addyi (flibanserin)

Therapeutic Class: Serotonin 1A receptor agonist and a Serotonin 2A receptor antagonist

Dosage and Route: Film-coated tablets 100 mg

Application Type/Number: NDA 22526

Applicant/Sponsor: Sprout Pharmaceuticals, Inc.

OSE RCM #: 2015-521

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## **EXECUTIVE SUMMARY**

The purpose of this review is to document the Division of Risk Management's (DRISK) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for Addyi (flibanserin) tablets, NDA 22526, received from Sprout Pharmaceuticals, Inc. (Sprout) on June 29, 2015. The proposed indication for Addyi is for the treatment of hypoactive sexual desire disorder in premenopausal women. The REMS proposed by Sprout on June 29, 2015 is to mitigate the risk of hypotension and syncope due to an interaction with alcohol and included a Medication Guide, prescriber certification, pharmacy certification, implementation system, and timetable for submission of assessments.

Based on the currently available data and input from the Bone, Reproductive and Urologic Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee, and the REMS Oversight Committee, DRISK and the Division of Bone, Reproductive, and Urology Products have determined that a REMS is necessary to ensure the benefits outweigh the increased risk of hypotension and syncope associated with Addyi due to an interaction with alcohol.

The final agreed upon REMS for Addyi mitigates the aforementioned risks by:

- Ensuring prescribers and pharmacists are educated about the increased risk of hypotension and syncope associated with Addyi due to an interaction with alcohol and the need to counsel patients about this risk.
- Informing patients of the increased risk of hypotension and syncope associated with Addyi due to an interaction with alcohol.

The REMS includes the following elements: prescriber certification [elements to assure safe use (ETASU) A], pharmacy certification (ETASU B), implementation system, and a timetable for submission of assessments. Sprout's amended submission, received August 18, 2015 and appended to this review, contains the agreed upon REMS for Addyi and is considered acceptable by DRISK.

## **1 INTRODUCTION**

The purpose of this review is to document the Division of Risk Management's (DRISK) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for Addyi (flibanserin) tablets, NDA 22526, received from Sprout Pharmaceuticals, Inc. (Sprout) on June 29, 2015. The NDA was originally submitted on October 27, 2009, resubmitted on March 28, 2013 in response to a complete response (CR), and resubmitted on February 18, 2015 in response to a CR. The submission received on February 18, 2015 was amended on June 29, 2015 based on discussions with the Agency and advice from the joint the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee (AC) meeting held on June 4, 2015.

The REMS proposed by Sprout on June 29, 2014 is to mitigate the risk of hypotension and syncope due to an interaction with alcohol and included a Medication Guide (MG), prescriber certification, pharmacy certification, implementation system, and timetable for submission of assessments.

### **1.1 PRODUCT BACKGROUND**

Addyi (flibanserin) is a new molecular entity and is not marketed in any other country. It is primarily metabolized by CYP3A4 and, to a lesser extent, by CYP2C19. It has a mean terminal

half-life of approximately 11 hours. Per the Sponsor's clinical overview from the original NDA submission, flibanserin was originally developed to treat depression, based on anti-depressant-like effects in pre-clinical models. In Phase IIa depression trials, in which flibanserin failed to show efficacy on the primary endpoint for depression, virtually no sexual dysfunction was noted. In one of these 4 Phase IIb trials, flibanserin demonstrated a positive effect as measured by ASEX (Arizona Sexual Experiences Scale), which formed the basis for pursuing the indication of HSDD in women.

Flibanserin is a serotonin 1A receptor agonist and a serotonin 2A receptor antagonist with a proposed indication to treat hypoactive sexual desire disorder (HSDD) in premenopausal women. The precise mechanism of action of flibanserin for treatment of HSDD is unknown; however, its impact on HSDD is believed to be related to its effects on norepinephrine, serotonin, and dopamine activities in the central nervous system. Addyi is available as 100 mg tablets and the recommended dose is 100 mg taken orally once daily at bedtime.

## 1.2 DISEASE BACKGROUND

Estimates of HSDD in U.S. women vary widely, depending on the instruments used for assessment as well as menopausal status of the women studied. Two large survey studies have estimated the prevalence of HSDD in U.S. premenopausal women to be 7.7% to 14%,<sup>1,2</sup> potentially affecting 5.5 to 8.6 million U.S. women ages 20 to 49 years. The diagnostic criteria for HSDD are defined by the American Psychiatric Association in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR. HSDD is characterized by persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity, as judged by the clinician. The symptoms must not be better explained by an alternative disorder or substance (e.g., alcohol abuse, medication) and should lead to marked distress and interpersonal difficulty.

The American Psychiatric Association published an updated DSM, termed DSM-5 in May of 2013. DSM-5 has merged features from HSDD and female sexual arousal disorder as described in DSM-IV-TR and replaced these conditions with a new condition, Female Sexual Interest/Arousal Disorder (FSIAD). As with HSDD, patients with FSIAD must have associated distress and impairment and must not have an alternative explanation that better explains their symptoms. For this reason, HSDD will be defined in the approved PI and in the REMS materials.

As discussed at the FDA public meeting in October 2014, FSIAD is an important area of treatment focus for FDA however there are no approved treatments at this time. The approved therapies for female sexual disorders, (Osphena [ospemifene] and some estrogen products), are limited to addressing pain during sex associated with menopausal changes in the vulva/vagina. FDA recognizes that challenges exist in the drug development for FSIAD. These challenges include properly diagnosing FSIAD; for example, the diagnostic criteria are not objectively defined, and practitioners must exclude relationship difficulties. Additionally, outcome assessments present challenges with regard to what should be measured (what is meaningful to patients), how should the information be measured (via diaries or clinical visits) and how often

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<sup>1</sup> West SL, D'Aloisio AA, Agans RP, Kalsbeek WD, Borisov NN, et al. Prevalence of low sexual desire and hypoactive sexual desire disorder in a nationally representative sample of U.S. women. *Arch Intern Med* 2008;168:1441-9.

<sup>2</sup> Leiblum SR, Koochaki PE, Rodenberg CA, Barton IP, Rosen RC. Hypoactive sexual desire disorder in postmenopausal women: U.S. results from the Women's International Study of Health and Sexuality (WISHeS). *Menopause* 2006;13:46-56.

outcomes should be measured.<sup>3</sup> These have been challenges in the flibanserin clinical development program. As discussed, flibanserin was developed with an intention to treat HSDD, which at this time is not recognized as a singular disease in the current DSM.

### 1.3 REGULATORY HISTORY

The following is a summary of the regulatory history for flibanserin, which includes the 3 cycles of review, relevant to the REMS:

On December 2, 1996, the Agency received IND (b) (4) for flibanserin for the treatment of HSDD in premenopausal women.

On October 27, 2009, Boehringer Ingelheim (BI) submitted NDA 22526 for flibanserin for the treatment of HSDD.

On June 18, 2010, the Reproductive Health Drugs Advisory Committee convened to discuss flibanserin and determined that BI did not provide sufficient evidence to support: (1) the overall efficacy for flibanserin for treatment of HSDD compared to placebo [vote: Yes-1; No-10; Abstain-0] or (2) that the overall risk/benefit profile of flibanserin for the treatment of HSDD in premenopausal women is acceptable [vote: Yes-0; No-11; Abstain-0]

On August 27, 2010, the Agency issued a CR letter<sup>4</sup>, where the determination was made that the application could not be approved in its present form due to efficacy and safety deficiencies. The CR letter highlighted lack of substantial efficacy for treatment of HSDD as well as concerns with efficacy in the presence of moderate CYP3A4 inhibitors. Safety issues cited included a lack of data from patients with comorbid conditions and on concomitant medications and alcohol. There was also insufficient information to assess the risk of accidental injuries associated with flibanserin. The company was also requested to study flibanserin in an abuse potential study since it is characterized as a central nervous system (CNS) depressant. The CR letter included recommendations for a new Phase 3 study with sexual desire as co-primary endpoints and HSDD-related distress as a key secondary endpoint; the Agency requested that sexual desire assessments have adequate content validity, recall validity, and acceptable measurement properties consistent with recommendations in the 2009 "FDA Guidance for Industry: Patient-Reported Outcome Measures Use in Medical Product Development to Support Labeling Claims."

On February 17, 2012, BI sold flibanserin to Sprout and the Agency acknowledged the transfer of ownership of the NDA.

On April 26, 2012, a Type B pre-NDA meeting between Sprout and DBRUP was held to discuss the contents of a CR submission. An additional Phase 3, double-blinded, placebo-controlled pivotal efficacy study (511.147), was initiated during the first flibanserin review cycle and completed February 2011, six months after the initial CR action. The study, compared to studies 511.71 and 511.75, allowed for:

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<sup>3</sup> Chang, C., FDA/DBRUP Clinical Team Leader, Presentation on the Background of Female Sexual Interest/Arousal Disorder, FDA Public Meeting on Female Sexual Dysfunction Patient-Focused Drug Development, October 27, 2014.

<sup>4</sup> Bietz, J. Office of New Drug/DBRUP Complete Response Letter to Flibanserin NDA 22526 dated August 27, 2010.

- enrollment of a broader patient population
- more concomitant medication use
- sexual desire, measured by items 1 and 2 of the 19-item Female Sexual Function Index (FSFI), as a primary outcome measure

The study also included a sub-study for assessment of content and recall validity to compare 28-day versus 7-day recall. DBRUP advised that it would be a matter of review whether results from the new study (511.147) are adequate to support efficacy, since the co-primary efficacy endpoint (FSFI desire domain items 1 and 2), instruments, and recall periods (28 days versus 7 days), were not formally agreed to by DBRUP.<sup>5</sup>

On March 29, 2013, submitted their response to the DBRUP August 27, 2010 CR letter, resubmitting NDA 22526. Their resubmission did not include a REMS proposal.

On September 3, 2013, DRISK completed a Deferral of Risk Evaluation and Mitigation Strategies (REMS) Review of Flibanserin.<sup>6</sup>

On September 27, 2013, DBRUP issued a CR letter<sup>7</sup> to the Sponsor for flibanserin stating “you have consistently shown modest improvements in the placebo-adjusted treatment responses in premenopausal women with HSDD, as assessed using the Female Sexual Function Index (FSFI) sexual desire domain, and the number of satisfying sexual events. However, we are not convinced that these treatment effects offset the identified substantial safety concerns.”

The following summarizes highlights of safety concerns and deficiencies, as detailed in the CR letter:

- Central nervous system (CNS) depression (fatigue, somnolence, and sedation) occurred in 21% of subjects taking flibanserin 100 mg nightly.
- Increased frequency of syncope and accidental injury, including serious events, compared to placebo
- Drug-drug interactions with centrally-acting drugs (e.g. serotonin-norepinephrine reuptake inhibitors, alcohol, triptans), strong or moderate CYP3A4 inhibitors as well as alcohol
- Marked increase in flibanserin exposure, poor tolerability and a higher frequency of syncope and hypotension when flibanserin is administered with drugs that are strong or moderate CYP3A4 inhibitors (e.g., hormonal contraceptives)
- Greater incidence of appendicitis among flibanserin users compared to placebo

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<sup>5</sup> As discussed by the Study Endpoints and Labeling Development (SEALD) team for flibanserin NDA 22526, use of patient reported outcomes (PROs) has been problematic throughout drug development of treatment of Female Sexual Dysfunction and different subgroups including HSDD. The main issues have been what questions to ask and what recall time to use (1, 7, 14, 28 days). The Division has fairly consistently favored use of electronic diaries and short recall time (24-72 hour range) for collection of accurate data, especially for satisfactory sexual events and sexual desire/interest. Study 511.147 used an electronic diary to capture data but did not use the diary for measuring the change in sexual desire. Instead, the 19-item FSFI paper instrument was completed every 4 weeks at clinic visits. (See Page 21-23 of DBRUP Clinical and Safety Review of flibanserin NDA 22526 dated August 29, 2013 for detailed discussion.

<sup>6</sup> Vega, A. Deferral of Risk Evaluation and Mitigation Strategies (REMS) Review for Flibanserin dated September 3, 2013.

<sup>7</sup> Bietz, J., DBRUP Complete Response Letter for Flibanserin NDA 22526 dated September 27, 2013

- Studies on mice demonstrated an increased incidence of mammary tumors at doses three times the recommended for humans
- Human studies of flibanserin's abuse potential were not interpretable

DBRUP recommendations related to the deficiencies cited above included:

- The Sponsor should show how risks will be minimized in clinical practice including CNS effects (fatigue, dizziness, somnolence and sedation), and syncope, hypotension and accidental injury
- Propose strategies beyond labeling to ensure flibanserin is not prescribed with moderate or strong CYP3A4 inhibitors, or taken with alcohol or other centrally-acting medications
- Conduct a driving impairment study
- Propose a plan to determine whether the excess incidence of appendicitis observed in the Phase 3 placebo-controlled program is drug-related
- Propose a plan to assess the clinical risk of breast cancer in light of the non-clinical findings of dose-dependent mammary tumors in mice

On November 18, 2013, a Type A End of Review meeting was held between DBRUP and the Sponsor to discuss the September 27, 2013 CR letter and path forward for the NDA.<sup>8</sup>

On December 3, 2013, the Sponsor filed a formal dispute resolution request (FDRR) to DBRUP's September 27, 2013 CR action for flibanserin NDA 22526.

On February 7, 2014, the Office of New Drugs (OND) responded to the Sponsor's FDRR (Appeal Denied Letter)<sup>9</sup> denying the appeal in support of issues identified by DBRUP in their September 27, 2013 CR action.

On March 12, 2014, a Type A meeting was held to discuss a path forward to address deficiencies noted in the CR letter. Key among the issues addressed were a planned driving study to assess next-day impairment, drug-drug interaction studies to assess the effect of CYP2C9 and/or CYP2C19 enzymes on the metabolism of flibanserin. Guidance was provided on the planned studies. Additionally, guidance was provided, in collaboration between DBRUP and DRISK, to Sprout's questions about risk mitigation strategies. Sprout proposed a communication plan (CP) REMS. DBRUP and DRISK provided guidance that, although this would be a review issue at the time of submission, a CP may have limitations given the safety issues identified with flibanserin.<sup>10</sup>

On January 15, 2015, a Type B meeting was held to discuss the Sponsor's plan to address the concerns raised in the September 17, 2013 CR letter and the Agency's February 7, 2014 Appeal Denial Letter, in conjunction with the sponsor's planned NDA resubmission.<sup>11</sup>

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<sup>8</sup> DBRUP End of Review Type A meeting with Sprout Pharmaceuticals for Flibanserin NDA 22526 held on November 18, 2013.

<sup>9</sup> Jenkins, J. Office of New Drugs Appeal Denial for Sprout Pharmaceuticals FDRR for DBRUP September 27, 2013 CR action for Flibanserin NDA 22526, dated February 7, 2014.

<sup>10</sup> Division of Bone, Reproductive and Urologic Products (DBRUP) Memorandum of Meeting Minutes for the March 12, 2014 Type A Meeting with Sprout for Flibanserin (NDA 22526) dated April 10, 2014

<sup>11</sup> Division of Bone, Reproductive and Urologic Products (DBRUP) Memorandum of Meeting Minutes for the January 15, 2015 Type B Meeting with Sprout for Flibanserin (NDA 22526) dated February 10, 2015

On February 18, 2015, Sprout resubmitted their application (Seq. No. 0062). Their resubmission addressed issues cited in the September 17, 2013 CR and included the results of the recommended driving study (Study SPR-14-01), a pharmacogenetics study which addressed potential involvement of cytochrome P450 enzymes CYP2C9 and CYP2C19 in the metabolism of flibanserin (Study SPR-14-06), a proposed REMS with a MG and CP and updates to the U.S. Prescribing Information (USPI). As this is the current submission under review, some results from the studies are briefly discussed here:

- Study SPR-14-01 evaluated safety, tolerability, pharmacokinetics, and pharmacodynamics of flibanserin when given at a standard dose (100 mg), and at a supratherapeutic dose (200 mg). Results showed that therapeutic and supra-therapeutic doses of flibanserin had no negative effect on the measures of next-day simulated driving performance that were evaluated.
- In female subjects that were poor metabolizers of CYP2C9, concentrations of flibanserin 100 mg once a day decreased about 19%, compared to those in extensive metabolizers of CYP2C9. However, flibanserin concentrations increased about 1.5 fold when flibanserin 100 mg was administered to CYP2C19 poor metabolizers compared to CYP2C19 extensive metabolizers. One poor metabolizer experienced syncope one hour after the single 100 mg dose of flibanserin. This subject had about twice the flibanserin concentration than those with normal CYP2C19 enzyme activity.

This submission also included validation of the instruments used in measuring the efficacy results along with a discussion of Sprout's current understanding of hypotension and syncope related to flibanserin, rare adverse events of appendicitis and breast cancer, and risk mitigation activities that they plan to undertake post-approval.

On March 24, 2015 DBRUP and DRISK presented REMS options for flibanserin to the REMS Oversight Committee (ROC)<sup>12</sup> meeting, an AC comprised of CDER Senior Management. ROC recommended risk management options, including labeling alone, a CP REMS, and REMS with elements to assure safe use (ETASU) options (prescriber and pharmacy certification), be presented for consideration by the AC.

On June 4, 2015, the joint BRUDAC/DsARM AC was held to discuss the flibanserin application. The AC panel was asked to discuss the clinical significance of the efficacy findings from the clinical program. They were also asked to discuss their level of concern with hypotension and syncope when flibanserin was used alone and also when used with alcohol. The panel was asked to vote on if they recommended approval with labeling alone, if they recommended approval with risk mitigation beyond labeling or if they did not recommend approval. Overall, the AC panel voted to approve 18 to 6 but only with risk mitigation beyond labeling. For most panelists voting for approval, this included REMS with ETASU. Although the REMS recommendations were not always concrete (the panel has varying exposures and experiences with REMS), approximately eight of the panelists recommended prescriber certification, eight recommended pharmacy certification and five recommended patient consent of some type (some of these recommendations are overlapping).

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<sup>12</sup> As per the 21 century review process, all REMS with elements to assure safe use (ETASU) are discussed at the REMS Oversight Committee (ROC) which consists of senior level management from the Offices of New Drugs, Surveillance and Epidemiology, and Regulatory Policy.

On June 11, 2015, DBRUP had a teleconference with Sprout where they advised Sprout to resubmit a REMS that considers the options presented at the AC and the advice recommended by the AC.

On June 18, 2015, Sprout submitted a document outlining arguments against an ETASU REMS.

On June 23, 2015 DBRUP and DRISK had a teleconference with Sprout to reiterate that they should consider the AC recommendations including ETASU D as several panel members had proposed a patient/prescriber agreement form (PPAF). The Applicant inquired about whether the (b) (4) tool should be included in the REMS. The Agency stated that we have not reached a final decision regarding whether the tool is appropriate for inclusion in the REMS.

On June 29, 2015 (officially in EDR on July 2), Sprout submitted an updated REMS proposal to include ETASU A and B, both prescriber and pharmacy certification. They included their communication plan materials and other previously proposed materials under these ETASU.

On June 30, 2015, another ROC meeting was held to discuss REMS options. The options presented included ETASU D, documentation of safe use in the form of a PPAF with Prescriber and Pharmacy Certification or with Pharmacy Certification were presented. REMS goals were also discussed. DRISK and DBRUP were considering whether hypotension and syncope with flibanserin alone or only with alcohol use should be mitigated by the REMS. ROC recommended hypotension and syncope with alcohol use should be the risks mitigated by the REMS and that ETASU A and B should be implemented (prescriber and pharmacy certification).

On July 2, 2015, Sprout submitted revised materials for the REMS.

On July 17, 2015, the Agency sent edited materials and comments to Sprout (DRISK Review dated July 20, 2015). The Agency requested ETASU A and B as well as materials to support these ETASU PPAF and counseling tool, enrollment forms, and training materials).

On July 21, 2015 Sprout submitted revised materials to the Agency. These materials reflected their request for removing alcohol as a contraindication from the proposed label. These materials also reflected their request to have the PPAF removed from the REMS program. This submission is reviewed here.

On July 24, 2015 Sprout had a teleconference with the Agency to discuss alcohol as a contraindication and the inclusion of the PPAF in the REMS. They were told these would be required. In addition, they discussed some changes proposed to the label regarding mammary tumors in animal studies and the case of death in a post-menopausal patient.

On July 27, 2015 the Agency sent the proposed label as well as REMS materials for the Sponsor to review and provide comments.

On July 28, 2015 Sprout submitted edited materials to the Agency (submitted via gateway on July 29, 2015).

On July 30, 2015 Sprout had a teleconference with the Agency to discuss labeling. This discussion focused mainly on the placement and wording of the mammary tumor data.

On August 3, 2015 the Agency sent REMS materials and labeling to the Sponsor. Efforts were made to align the REMS materials to the label.

On August 4, 2015, the Sponsor returned these materials with suggestions and edits. They also added more details, as requested, to their operating procedures in the Supporting Document.

On August 6, 2015, the Agency sent edited materials back to the Sponsor. Work was done to improve the Patient-Provider Agreement Form and align pharmacy enrollment forms.

On August 10, 2015, The Sponsor submitted edited documents back to the Agency. They complied with some requests but wanted to add some information to the Training Program Slides and suggested other edits for the REMS document and enrollment forms. (b) (4)

(b) (4)

## 2 MATERIALS REVIEWED

### 2.1 SUBMISSIONS

- Sprout Pharmaceuticals, Inc. Response to September 27, 2013 Complete Response Letter/Resubmission of NDA 22526 for Flibanserin submitted February 17, 2015 (Seq. No. 0062)
- Sprout Pharmaceuticals, Inc. REMS amendment to NDA 22526 for Flibanserin submitted June 18, 2015 (Seq. No. 0073)
- Sprout Pharmaceuticals, Inc. REMS amendment to NDA 22526 for Flibanserin submitted July 2, 2015 (Seq. No. 0075)
- Sprout Pharmaceuticals, Inc. REMS amendment to NDA 22526 for Flibanserin submitted July 21, 2015 (Seq. No. 0079)
- Sprout Pharmaceuticals, Inc. REMS amendment to NDA 22526 for Flibanserin submitted August 11, 2015 (Seq. No. 0081)
- Sprout Pharmaceuticals, Inc. REMS amendment to NDA 22526 for Flibanserin submitted August 17, 2015 (Seq. No. 0084)
- Sprout Pharmaceuticals, Inc. REMS amendment to NDA 22526 for Flibanserin submitted August 18, 2015 (Seq. No. 0086)

### 2.2 OTHER MATERIALS INFORMING OUR REVIEW

- Boehringer Ingelheim Original Submission (ORIG-1) of flibanserin NDA 22526 submitted October 27, 2009 (Seq. No. 0000)
- Reproductive Health Drugs Advisory Committee meeting held June 18, 2010 for flibanserin NDA 22526, including meeting material, agenda, slide presentations (FDA and Boehringer Ingelheim), meeting minutes and transcripts:  
<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/ucm215436.htm> Bietz, J. Office of New Drug Evaluation III Director, Complete Response (first cycle) to Flibanserin NDA 22526 dated August 27, 2010.
- Sprout Pharmaceuticals, Inc. Response to August 27, 2010 Complete Response Letter/Resubmission of NDA 22526 for Flibanserin submitted March 28, 2013 (Seq. No. 0039)
- Easley, O. and Davis, D., DBRUP Clinical and Safety Review of flibanserin NDA 22526 dated August 29, 2013

- Bietz, J. Office of New Drug Evaluation III Director, Complete Response (second cycle) to Flibanserin NDA 22526 dated September 27, 2013
- Sprout Pharmaceuticals, Inc. Formal Dispute Resolution Request (FDRR) for flibanserin NDA 22526 submitted December 3, 2013 (Seq. No. 0052)
- Jenkins, J., Office of New Drugs Director, Formal Dispute Resolution Request Final Response (Appeal Denied) letter dated February 7, 2014
- Williamson, C., Regulatory Project Manager, DBRUP Memorandum of Meeting Minutes for the March 12, 2014 Type A Meeting for Flibanserin dated April 10, 2014
- Sprout Pharmaceuticals, Inc. Pre-NDA Type B Meeting Briefing Document for the scheduled January 15, 2015 meeting, submitted via hard copy to DBRUP on December 15, 2014.
- Williamson, C., Regulatory Project Manager, DBRUP Memorandum of Meeting Minutes for the January 15, 2015 Type A Meeting for Flibanserin February 10, 2015
- FDA Briefing Document Joint Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee June 4, 2015
- Dunn S. REMS Review for Addyi (flibanserin), dated July 20, 2015
- Dunn S. REMS Review for Addyi (flibanserin), dated July 29, 2015
- Dunn S. REMS Review for Addyi (flibanserin), comments emailed August 4, 2015 and review in DARRTS on August 18, 2017
- Dunn S. REMS Review for Addyi (flibanserin), comments emailed August 6, 2015 and review in DARRTS on August 18, 2017
- Dunn S. REMS Review for Addyi (flibanserin), comments emailed August 13, 2015 and review in DARRTS on August 18, 2017
- Dunn S. REMS Review for Addyi (flibanserin), comments emailed August 18, 2015 and review in DARRTS on August 18, 2017

### 3 SUMMARY OF THE CLINICAL DEVELOPMENT PROGRAM AND EFFICACY

Phase III efficacy studies of pharmaceutical compounds for the treatment of sexual dysfunctions utilize patient-reported outcome (PRO) measures to form the basis for assessment of efficacy. The NDA has been submitted to the Agency three times. Each submission is described here. Please see Regulatory History, Section 1.3 for further details on the submission contents and CR Letter content.

#### **2009-2010**

There were five studies used to support the initial NDA submission which are summarized in the table below

Study	Design
511.70	Randomized, placebo controlled efficacy study There were two co-primary endpoints for studies: 1) change in satisfying sexual event (SSEs) from the four week baseline to Weeks 21-24; and 2) the eDiary sexual desire score change for the same four week time period.
511.71	Randomized, placebo controlled efficacy study There were two co-primary endpoints for studies : 1) change in SSEs from the four week baseline to Weeks 21-24; and 2) the eDiary sexual desire score change for the same four week time period

511.75	Randomized, placebo controlled efficacy study There were two co-primary endpoints for studies : 1) change in SSEs from the four week baseline to Weeks 21-24; and 2) the eDiary sexual desire score change for the same four week time period.
511.74	Randomized withdrawal study in which patients first completed a 6-month open label (OL) flibanserin treatment period after which responders entered a 6-month double-blind, placebo-controlled, randomized withdrawal period
511.84	A 52 week open-label extension study (still ongoing at the time of the original submission) that enrolled patients from 511.70, 511.71, 511.75, and 511.74

There were also two long term extension studies (511.68 and 511.69).

Of note, during their first review, the review team did consider some adverse events of interest (depression, syncope, suicidality and accidents) from the previous data in patients with Major Depressive Disorder (MDD) due to the original plan to develop treatment for MDD; however, this was not part of the main database.

The original submission included safety data of flibanserin in 5007 premenopausal women with HSDD from all the studies described above. Of these, 1138 (39.4%) subjects treated with flibanserin 100 mg once at bedtime (qhs) for at least six months, and 205 (7.1%) subjects treated with flibanserin 100 mg qhs for at least one year. Please see DBRUP 2010 review of Efficacy and Safety for flibanserin for complete details.<sup>13</sup> DBRUP found that there was statistically significant difference between flibanserin and placebo for the increase in SSEs and change in the distress endpoint. DBRUP was not certain if this small statistical significance would translate into clinical significance. The review team concluded that the overall benefit/risk ratio was not favorable and issued a CR for the application. As discussed in the Regulatory History section, the CR cited concomitant alcohol ingestion, accidental injuries and concerns with abuse potential as major safety issues.

### **2013**

In March of 2013, the Sponsor submitted complete and final study reports for 14 additional studies completed since the filing of the original application in 2009.<sup>14</sup> The March 29, 2013 resubmission included efficacy data from a new randomized double blind placebo controlled Phase 3 study (511.147). This study allowed for enrollment of a broader patient population with concomitant medication use. Additionally, this new study included sexual desire as a primary outcome measure with Female Sexual Function Index (FSFI) desire questions and a 28 day recall period. There was also a substudy for a seven day FSFI recall.

The March 2013 submission also included data from two Phase 3 studies in postmenopausal women (511.130 and 511.156); 1 Phase 3 study in women with co-administration of an SSRI or SNRI (511.114); 7 Phase 1 studies that address specific safety issues such as concurrent CYP3A4 inhibitor interactions and abuse potential (511.146, 511.158, SPR-12-01, SPR-12-02,

<sup>13</sup> Davis, D. (efficacy) and Easley, O. (safety) DBRUP Review of Efficacy and Safety for flibanserin NDA 22526 dated August 27, 2010.

<sup>14</sup> Sprout Pharmaceuticals Response to Complete Response Resubmission of Flibanserin NDA 22526, Sections 2.2, 2.5, 2.7.3 and 2.7.4 dated March 29, 2013.

SPR-12-03, SPR-12-04, SPR-12-05); and long-term safety data from open-label studies (511.84, 511.118, 511.133). In total there was incremental safety and efficacy data from over 3000 patients/subjects in the resubmission.

Of note, one of the studies in this submission, the SPR-12-03 study was a pharmacodynamic/pharmacokinetic study with alcohol. It was a single-center, randomized, double-blind, single-dose, crossover study of the effect of concomitant alcohol intake on flibanserin tolerability and safety in healthy adult subjects with a history of moderate alcohol intake (average of approximately 5 to 21 units of alcohol per week). Twenty-five subjects (23 males and 2 females) were studied. There was an increase in several adverse events (AEs) in this study. This will be discussed in the following safety section.

At the point of the 2013 resubmission, over 7000 women received at least one dose of flibanserin over the entire flibanserin development program. Of these 7000 women, 4860 women received it for the HSDD indication. The three pivotal studies in the resubmission showed a statistically significant difference between flibanserin and placebo on the endpoints of SSEs, FSFI-desire score (but not daily desire measured by an eDiary) and Female Sexual Distress Scale-Revised (FSDS-R) Q13 distress score. Flibanserin resulted in a placebo-corrected mean increase of 0.8 to 1.0 more SSEs per 28-day period. DBRUP notes that using the median result to measure efficacy which is preferred with this type of data, flibanserin resulted in a placebo corrected mean increase of 0.5 to 1.0 more SSEs per month. When desire was measured by the FSFI desire domain (the other co-primary endpoint but only for Study 511.147), flibanserin resulted in a placebo-corrected mean increase in desire of 0.3 to 0.4 on a scale of 1.2 to 6.0. This was statistically significant; but it was only the result from one of the key Phase 3 studies. Overall, treatment differences were numerically small and the clinical significance is unknown.<sup>15</sup>

DBRUP's efficacy evaluation of the flibanserin resubmission concluded that they "believe that the risk/benefit profile for flibanserin 100 mg taken at bedtime is not favorable. Low sexual desire and distress are the hallmark of HSDD, so it seems imperative that a statistically significant and clinically meaningful change in these two endpoints should be clearly demonstrated. We do not believe that the difference between placebo and flibanserin response merits approval given the safety issues with flibanserin compared to placebo treatment."<sup>16</sup> See DBRUP clinical review for further details.<sup>3</sup>

## **2015**

The current resubmission addressed deficiencies listed in the Agency's September 27, 2013 CR Letter and associated meetings between the Sponsor and the Agency cited above in Section 1.3, Regulatory History. The submission incorporated requested safety information to include the Driving Study (SPR-14-01) to demonstrate next-day driving effects for flibanserin and a pharmacogenetics study (SPR-14-06) to study effects of impaired CYP2C9 or CYP2C19 function on the clearance of flibanserin. As discussed in Section 1.2, there were no issues with next day driving effects and some effect of CYP2C9/CYP2C19 clearance on flibanserin found.

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<sup>15</sup> Sewell, C. and Easley, O. DBRUP Review of NDA 22526 dated July 20, 2015.

<sup>16</sup> Davis, D. and Easley, O. DBRUP Clinical Review of flibanserin NDA 22526 dated August 29, 2013.

At this time, the total HSDD clinical development program includes 6439 premenopausal and postmenopausal women in Phase 1, Phase 2 and Phase 3 studies that received at least one dose of flibanserin.

## 4 SAFETY CONCERNS OF INTEREST

Hypotension and syncope associated with the use of flibanserin, including an interaction with alcohol and an interaction with CYP3A4 inhibitors, is a safety concern of interest for flibanserin based on DBRUP's evaluation of the safety database described above. Additionally there were events related to CNS depression and accidental injuries, appendicitis, and potential breast cancer (based on an animal model) events that were selected as safety concerns of interest.

### 4.1 HYPOTENSION AND SYNCOPE

There is a higher incidence of hypotension and syncope, including one serious adverse event (SAEs), associated with therapeutic doses of flibanserin as compared to placebo. The mechanism that causes these events and a definitive relationship between the hypotension and syncope is unknown. The sections below describe the available data from the clinical studies regarding the risk of hypotension and syncope alone (See Section 4.1.1), the risk of hypotension and syncope due to an interaction with alcohol (See Section 4.1.2), the risk of hypotension and syncope due to an interaction with CYP3A4 inhibitors (See Section **Error! Reference source not found.**), and the potential risk of hypotension and syncope in patients with hepatic impairment (See Section 4.1.4).

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#### 4.1.1 Hypotension and Syncope with Flibanserin Alone

The following describes cases of hypotension and syncope from clinical studies that were not due to an interaction with alcohol, CYP3A4 inhibitors, or in patients with hepatic impairment. The cases may include other potential contributing factors, which are described further below. Time to onset for these events is overall unpredictable; they occurred at varying times after treatment initiation, ranging from hours to days or weeks.

##### Phase 1 Studies

Syncope with flibanserin treatment alone occurred in three patients, including one patient who also experienced hypotension concurrently. All three patients recovered without sequelae, including one patient who was treated with intravenous fluids. There was one patient who did not require treatment and one patient for whom treatment was not recorded.

##### Phase 3 Studies

In the Phase 3 studies, there were six reports of syncope in patients treated with 100 mg of flibanserin, of which four were thought to be possibly drug-related. The overall rate of syncope in the Phase 3 studies is 0.4% (n=6) compared to 0.2% (n=4) in placebo. One of these cases was a SAE. This patient, who had a history of orthostatic hypotension, suffered a concussion, was hospitalized, treated with intravenous fluids, and recovered without sequelae. Another case included a patient receiving hormonal contraceptives, which has been found to increase flibanserin exposure by approximately 40%. In addition, three of the patients had identified as "drinkers" at baseline. Alcohol use was not excluded from the Phase 3 studies; therefore, alcohol could not be ruled out as a contributing factor in these cases (see Section 4.1.2 for further details)

Due to the events seen, hypotension and syncope will be labeled as a Warning and Precaution (W&P) in the USPI to inform healthcare professionals and in the MG to inform patients about this risk. If patient were to have an episode of hypotension and syncope during the operation of a vehicle or in other similar circumstances, this could lead to an accident or a more severe AE outcome. This was a concern that was discussed by members of the AC as well. Therefore, to minimize potential accidental injury the label includes text instructing patients to take flibanserin at bedtime and that patients should not drive or engage in other activities requiring full alertness until at least 6 hours after taking flibanserin and until they know how flibanserin affects them. (see Section 4.2).

#### **4.1.2 Hypotension and Syncope due to an Interaction with Alcohol**

##### Phase 1 Study: Interaction with Alcohol

Syncope and hypotension events occurred in a dedicated interaction study of flibanserin 100 mg and alcohol. This study was conducted in 25 healthy, moderate drinkers, including 23 men and 2 women. Hypotension or syncope requiring therapeutic intervention (ammonia salts and/or placement in supine or Trendelenberg position) occurred in four (17%) of the 23 subjects co-administered flibanserin and 0.4 g/kg alcohol (this was the low dose arm; the alcohol was equivalent of two 12 ounce cans of beer). Events occurred within 1.5 to 4 hours after the co-administration of alcohol and flibanserin. Though only one patient had syncope (two episodes), all patients experienced hypotension and needed intervention (Table 1). The magnitude of the systolic blood pressure reductions ranged from about 28 to 54 mmHg and the magnitude of the diastolic blood pressure reductions ranged from about 24 to 46 mmHg.

**Table 1: Individual Adverse Events of Symptomatic Hypotension, Flibanserin-ETOH Dose-Dose Interaction (DDI) Study, SPR-12-03**



In the same study, six (25%) of the 24 subjects co-administered flibanserin and 0.8 g/kg alcohol (equivalent of four 12 ounce cans of beer) experienced orthostatic hypotension when standing from a sitting position. The magnitude of the systolic blood pressure reductions ranged from 22 to 48 mmHg, and the diastolic blood pressure reductions ranged from 0 to 27 mmHg. One of these subjects required therapeutic intervention (ammonia salts and placement supine with the foot of the bed elevated). There were no events requiring therapeutic intervention when flibanserin or alcohol was administered alone.

### Phase 3 Studies

The Sponsor conducted two Phase 3 studies in post-menopausal women prior to the second resubmission. In one of these studies there was a death of a 54 year old woman who had been on flibanserin for two weeks. She was found on her bed, face down. On autopsy the death was deemed due to alcohol poisoning and her blood alcohol content was 0.289 g/100mL. The autopsy report also noted coronary artery disease. A relationship between this patient's death and use of flibanserin is unknown

In order to ensure the benefits of Addyi outweigh the increased risk of hypotension and syncope associated with Addyi due to an interaction with alcohol, a REMS is necessary (see Section 5).

#### **4.1.3 Hypotension and Syncope with CYP3A4 and CYP2C19 inhibitors**

### Phase 1 Studies

Syncope with a strong CYP3A4 inhibitor occurred in four patients. Three of these patients had hypotension with these episodes. All four patients recovered without sequelae, including one patient who was treated with an ammonia inhalant and intravenous fluids, one patient did not require treatment, and one patient for whom treatment was not recorded.

Syncope with a poor metabolizer of CYP2C19 occurred in one patient. This patient did not have hypotension. She recovered after a 20 minute rest.

Due to the events seen, the increased risk of hypotension and syncope associated with flibanserin due to an interaction with strong and moderate CYP3A4 inhibitors will be a contraindication for Addyi. Additionally, the label will include a boxed warning and W&P regarding the drug-drug interaction. CYP2C19 inhibitors are listed as a Drug Interaction due to the risk of syncope, hypotension and CNS depression.

Existing safety nets in the healthcare system can help ensure these interactions are identified and a healthcare provider (HCP) is alerted. These include DDI screening at the physician and pharmacy level. Because the number of moderate to severe CYP3A4 inhibitors is extensive and continues to grow, and patients can receive prescriptions from multiple prescribers, the healthcare system relies on DDI screening technology to identify and prevent serious DDIs. The healthcare system's existing DDI screening technology includes screening performed by electronic medical records before prescribing, by insurance companies during prescription claim adjudication and by pharmacy management systems that perform a drug utilization review prior to dispensing every prescription. Further assurance is provided by 42 CFR 456.705 which requires states to establish detailed information for how pharmacies document the prospective drug utilization review performed by pharmacists.

#### 4.1.4 Potential for Hypotension and Syncope in Patients with Hepatic Impairment

While hypotension and syncope did not occur in patients with hepatic impairment, the study in subjects with hepatic impairment using 50 mg of flibanserin demonstrated that flibanserin exposure increased 4.6 fold compared to those with normal hepatic function. This is a comparable increase in exposure seen with moderate and strong CYP3A4 inhibitors. Therefore, DBRUP is concerned that there is the potential for hypotension and syncope similar to that seen with the CYP3A4 inhibitors.

Due to the comparable impact of hepatic impairment as seen with moderate and strong CYP3A4 inhibitors on flibanserin exposure, the increased risk of hypotension and syncope associated with flibanserin use in hepatic impairment will be a contraindication for Addyi. Additionally, the label will include a boxed warning and W&P regarding the risk in patients with hepatic impairment.

#### 4.2 CNS DEPRESSION

Events consistent with CNS depression (i.e., fatigue, somnolence, sedation) were the most common AEs in the clinical program and occurred in nearly 21% of subjects receiving flibanserin 100 mg at bedtime and at a rate three times greater than placebo. Fatigue also occurred at a higher rate (9.2% of patients treated with flibanserin vs. 5% in the placebo group). However, the CNS AEs were generally not SAEs. Most patients experienced the AE and became tolerant in seven to 14 days.<sup>17</sup>

Study SPR-14-01 evaluated safety, tolerability, pharmacokinetics, and pharmacodynamics of flibanserin when given at a standard dose (100 mg), and at a supratherapeutic dose (200 mg). Results showed that therapeutic and supra-therapeutic doses of flibanserin had no negative effect on the measures of next-day simulated driving performance that were evaluated.

There is a slightly greater incidence of accidental injury in the flibanserin 100 mg at bedtime dose group compared to placebo across pre-menopausal HSDD safety databases. These events may be confounded by the risks of syncope and hypotension and CNS depression. To determine whether accidental injury might be related to risks involving syncope, hypotension and those of CNS depression, DBRUP conducted a search in the HSDD database for events of accidental injury then determined the proportion of these patients who reported an adverse event within 24 hours of the accident that coded to a MedDRA preferred term of *dizziness*, *somnolence*, *fatigue*, *hypotension*, *circulatory collapse*, or *sedation*. As shown in Table 2, of the patients who reported accidental injury, nearly three times as many reported corresponding CNS depression with flibanserin compared to placebo.

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<sup>17</sup> Sprout Pharmaceuticals USPI NDA 22526, Sequence 0085 dated August 18, 2015.

**Table 2: Proportion of subjects experiencing concomitant accidental injury and CNS depression, phase 3, placebo-controlled pre-menopausal HSDD studies**

N (%)  
\*CNS depression  
collapse

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Due to the events seen, CNS depression will be labeled as a W&P in the USPI to inform healthcare professionals and in the MG to inform patients about this risk. Patients are also instructed to take flibanserin at bedtime to minimize potential accidental injury due to the hypotension and syncope related AEs (see Section 4.1.1) and CNS depression.

### 4.3 OTHER SAEs, SIGNIFICANT AEs AND ADDITIONAL SAFETY CONCERNS

There were two deaths in the safety database. One occurred in post-menopausal woman who had been consuming alcohol and was discussed above. The other death was due to an airplane crash. There were two cases of concussion and two cases of road traffic accidents compared to none in placebo that were all categorized as SAEs. One event of concussion was discussed earlier; it was an SAE that occurred with hypotension and syncope. The second event of concussion was a result of a road traffic accident.

*Reviewer's Comment:*

*The occurrence of the concussions and traffic accidents are concerning due to the CNS depression, hypotension and syncope risks with flibanserin.*

The other SAEs observed in the clinical program occurred in very few patients, did not display an imbalance with treatment groups and did not indicate a relationship to flibanserin treatment. However, there were also six SAEs of appendicitis compared to none in placebo. Appendicitis is a potential risk associated with the use of flibanserin and is not well understood at this time. DBRUP notes that the etiology of the increased incidence of appendicitis in pre-menopausal flibanserin-treated subjects remains unclear and could be due to chance alone or may represent a class effect of drugs that are antagonists at the 5HT<sub>2A</sub> receptor. The Sponsor has proposed to conduct a post-approval observational pharmacoepidemiologic safety study for this AE; the Agency is going to require this study as a post-marketing requirement (PMR). Additionally, the risk of appendicitis will be included in the Adverse Reactions section of the USPI.

Also of note, a potential safety signal emerged with a two year mouse carcinogenicity study that revealed dose-dependent mammary tumors at flibanserin exposures three and ten times the proposed human dose. There were no events of breast cancer in the pre-menopausal phase 3 controlled clinical studies, the duration of the studies. Breast cancer is a potential risk associated with use of flibanserin and is not well understood at this time. (b) (4)

The Sponsor proposed conducting a post-approval observational pharmacoepidemiologic safety study using administrative healthcare claims data to assess any risk for less common adverse events such as breast cancer. DBRUP did not feel that this would be methodologically feasible and is not requiring this study.

## 5 EVALUATION OF THE NEED FOR A REMS FOR ADDYI

After much discussion with DBRUP and ROC as well as evaluating the AC input, the Agency has determined the risks of hypotension and syncope due to the interaction with alcohol require a REMS to ensure the benefits outweigh the risks.

### **Benefit**

HSDD is a chronic condition characterized by “a deficiency or absence of sexual fantasies and desire for sexual activity” causing “marked distress or interpersonal difficulty.” Estimates of HSDD in U.S. women vary widely, depending on the instruments used for assessment of the condition, as well as menopausal status of the women studied. Two survey studies have estimated the prevalence of HSDD in U.S. premenopausal women to be 7.7% to 14%,<sup>18,19</sup> potentially affecting 5.5 to 8.6 million U.S. women ages 20 to 49. Currently, there are no approved pharmacotherapies for treating female HSDD.

HSDD can cause significant distress and treating this disorder must be balanced with benefit and the seriousness of the risk of syncope and hypotension associated with flibanserin. The outcomes of these adverse effects have the potential to result in life-threatening accidental injuries in relatively healthy premenopausal women treated with flibanserin. Flibanserin consistently showed statistical significance in improving both SSE and distress. Flibanserin resulted in a placebo-corrected mean increase of 0.8 to 1.0 more SSEs per 28-day period. Overall, the clinical significance of the efficacy results is difficult to ascertain. In addition, the effect of this drug may not be observed with initial doses and treatment should be discontinued if there is no improvement after 8 weeks as not all patients will respond to therapy. These efficacy considerations were factored into the Agency’s benefit/risk assessment and the need for a REMS to mitigate this risk.

### **Risk**

First, the increased risk of hypotension and syncope associated with the use of flibanserin due to an interaction with alcohol are of particular concern due to both the absolute incidence in the dedicated alcohol study (16%), the magnitude of effect on changes in blood pressure, and the need for intervention by a healthcare professional (e.g., positioning or ammonia inhalant, see Section 4.1.2)). In addition, in the Phase 3 studies there was a higher rate of hypotension and syncope that could have been complicated by alcohol use since alcohol use was not excluded from the study

Second, the mechanism of the association between flibanserin and the increased risk of hypotension and syncope due to the interaction with alcohol is not well understood. Furthermore, flibanserin is a new molecular entity with a novel mechanism of action (5-HT<sub>1A</sub> receptor agonist and a 5-HT<sub>2A</sub> receptor antagonist). Therefore, this AE profile is unique to this product and it is likely that it will not be a part of the common medical knowledge base. Additionally, DBRUP has raised concerns that the events in the alcohol interaction study occurred in male subjects in a predominantly male study; potential cases could be more frequent or worse in female subjects that generally have smaller body mass index and blood volume. Furthermore, the alcohol

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<sup>18</sup> West SL, D’Aloisio AA, Agans RP, Kalsbeek WD, Borisov NN, et al. Prevalence of low sexual desire and hypoactive sexual desire disorder in a nationally representative sample of U.S. women. *Arch Intern Med* 2008;168:1441-9.

<sup>19</sup> Leiblum SR, Koochaki PE, Rodenberg CA, Barton IP, Rosen RC. Hypoactive sexual desire disorder in postmenopausal women: U.S. results from the Women’s International Study of Health and Sexuality (WISHeS). *Menopause* 2006;13:46-56.

interaction study in mostly male subjects has not been followed up by a study in premenopausal females, which is the indicated population. This concerning risk has not been well characterized in the indicated population and further information is needed. Therefore, to better characterize this risk of the alcohol interaction with flibanserin, DBRUP is recommending that the Sponsor conduct a post-approval study in women.

Third, the indicated population is a population in which alcohol use is expected (see Table 3). Given the large percentage of casual and binge drinkers in the indicated patient population, this is a concern. Since alcohol is contraindicated with flibanserin, patients prescribed flibanserin will have to willing and able to abstain from alcohol use during the period of treatment. Therefore, risk mitigation beyond labeling must be considered to ensure prescribers are aware of this risk prior to prescribing and that patients are informed prior to receiving their first prescription of the need to abstain from alcohol use during the length of treatment.

**Table 3: Premenopausal Women Alcohol Drinking Statistics 2013**

<b>Women Age</b>	<b>% Current Drinker</b>	<b>% Binge Drinker (5 or more drinks on the same occasion)</b>
18 – 25	56.9%	31.4%
26+	50.1%	14.7%

SAMHSA 2013 National Survey on Drug Use and Health (NSDUH) 2012-2013

<http://www.samhsa.gov/data/sites/default/files/NSDUHresultsPDFWHTML2013/Web/NSDUHresults2013.pdf>

### **Risk/Benefit assessment**

In summary, the increased risk of hypotension and syncope associated with flibanserin due to an interaction with alcohol requires risk mitigation beyond labeling to ensure the benefits outweigh the risks. This recommendation is based on the following:

- The rate of hypotension and syncope in the alcohol interaction study was very high and concerning for the Agency and the AC panel.
- The mechanism of the interaction between alcohol and flibanserin is unknown.
- Risk factors for more severe events (body size, amount of alcohol consumption) are not known.
- The alcohol interaction study did not evaluate the risk in the indicated population; therefore, the magnitude of the risk is unknown in premenopausal women.
- Alcohol use is expected in the indicated population. Preventing alcohol consumption is challenging as alcohol use is pervasive in our society. Abstaining from alcohol use altogether is difficult as there are both social pressures to drink, personal reasons, and the drug itself is addictive.
- Flibanserin is a chronic medication taken daily. It is unknown how dosage interruptions will impact efficacy if flibanserin is used intermittently to avoid an interaction with alcohol.
- Non-responders will be exposed to the drug and the potential adverse events for up to 8 weeks before a treatment effect is expected and before a determination can be made about possible benefit for an individual patient.

### **How the risks resulting from alcohol interactions are mitigated for other approved drugs**

There are other drugs that interact with alcohol, however alcohol is not contraindicated in those product labels. Most CNS depressants (e.g. opioids, sedative/hypnotics, antidepressants) interact with alcohol due to additive CNS depression leading to respiratory depression, syncope, etc. This is an expected adverse event when two CNS depressants are taken together and is routinely communicated through labeling. Other common AEs with alcohol include additive hepatotoxicity with certain drugs. This interaction is also routinely communicated through labeling since alcohol is a well-known hepatotoxin. One of the most well-known alcohol/drug reactions is a disulfiram-like reaction with metronidazole. However, metronidazole differs from flibanserin, most importantly, it is an acute medication taken for short term and abstaining from alcohol during treatment for a week is much easier than for a chronic condition.

Currently there is one REMS program that addresses a contraindication with alcohol. The Xyrem REMS has both prescriber and pharmacy certification as well as documentation of safe use to prevent in inappropriate prescribing, misuse, abuse, and diversion of Xyrem. Informing the HCPs of the contraindication with alcohol is one of the objectives used to meet this goal. The safety concern was identified based on postmarketing reports, in which the causal relationship between Xyrem and alcohol could not be ruled out. Furthermore, the outcomes of the cases included serious respiratory depression and death. Therefore, the Agency determined that the REMS for Xyrem require screening for alcohol use when prescribed Xyrem.

## **6 RISK MANAGEMENT PROPOSED BY THE SPONSOR**

In their resubmission dated February 18, 2015, Sprout proposed a REMS for flibanserin comprising a MG and CP. However, after the Advisory Committee meeting and discussions with the Agency, Sprout amended their REMS proposal on June 29, 2015, which included a MG, prescriber certification and pharmacy certification. The following summarizes the Sponsor's proposed REMS submission, received on June 29, 2015.

### **6.1 GOALS**

The Sponsor proposed the following goals for the REMS:



## 6.2 REMS ELEMENTS

### 6.2.1 Medication Guide

The Sponsor proposed that a MG be dispensed with each flibanserin prescription in accordance with 21 CFR 208.24.

### 6.2.2 Elements to Assure Safe Use

#### 6.2.2.1 Prescriber Certification

The Sponsor proposed HCPs who prescribe flibanserin will be specially certified. The HCP will become certified when he or she completes and submits the Addyi REMS Prescriber Certification and Enrollment form indicating that he or she has reviewed the Full Prescribing Information (PI) for Addyi, the Addyi MG, completed the Addyi REMS Prescriber Training Program and has agreed to follow the requirements of the REMS program, including counseling patients about the risk of hypotension and/or syncope; [REDACTED] (b) (4)

The following tools were proposed as part of Prescriber Certification:

- Addyi REMS Prescriber Training Module
- Prescriber Certification and Enrollment Form
- The Decreased Sexual Desire Screener
- The Addyi Appropriate Use and Counseling Checklists
- Addyi REMS Program website

In addition, the Sponsor will target communications about the REMS to the following HCPs and professional organizations:

[REDACTED] (b) (4)

#### 6.2.2.2 Pharmacy Certification

The Sponsor will ensure that Addyi will only be dispensed by certified pharmacies. To become certified, each pharmacy must designate an Authorized Representative to internally coordinate and oversee the Addyi REMS Program. The Authorized Representative must complete the Addyi REMS Pharmacy Training Program, knowledge assessment questions and [REDACTED] (b) (4)

The following tools were proposed as part of Pharmacy Certification:

[REDACTED] (b) (4)



### 6.2.3 Implementation System

The Sponsor proposed to establish an implementation system for the Addyi REMS to monitor and evaluate whether the ETASU are meeting the program’s goals. The Sponsor proposed the following components for the implementation system:

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### 6.2.4 Timetable of Submission of Assessments

The Sponsor will submit REMS Assessments to the FDA at 6 and 12 months after REMS approval and annually thereafter.

## 7 FDA’S PROPOSED REMS

The Agency has determined the risks of hypotension and syncope due to the interaction with alcohol require a REMS to ensure the benefits outweigh the risks of flibanserin.<sup>20</sup> While the REMS will not prevent all events of hypotension and syncope due to an alcohol interaction, it will increase assurance that prescribers and patients are aware and consider the risk before prescribing flibanserin or taking flibanseirn.

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<sup>20</sup> DBRUP FDA Briefing Document for Joint BRUDAC/DSaRM Advisory Committee Meeting for NDA 22526 Flibanserin June 4, 2015 Risk Management Options for Flibanserin Associated Hypotension and Syncope Pages 116-124.

## **7.1 GOAL**

The Agency had determined the following goal and objectives are necessary for the Addyi REMS:

To mitigate the increased risk of hypotension and syncope associated with Addyi due to an interaction with alcohol by:

- Ensuring prescribers and pharmacists are educated about the increased risk of hypotension and syncope associated with Addyi due to an interaction with alcohol and the need to counsel patients about this risk.
- Informing patients of the increased risk of hypotension and syncope associated with Addyi due to an interaction with alcohol.

*Rationale for the proposed goal:* The objectives help to ensure the goal of the REMS is met. The key risk mitigation strategy is to increase assurance that patients are informed about the risks and only receive flibanserin if they are aware of the need to abstain from alcohol use during flibanserin treatment. In order to support this, prescribers and pharmacies must be certified in the REMS program by completing education about the risks and agreeing to counsel patients appropriately. To accomplish these goals, the REMS will include prescriber certification and pharmacy certification.

## **7.2 REMS ELEMENTS**

DRISK and DBRUP, with advice from the ROC and the AC, have determined that the minimally necessary elements to ensure the benefits outweigh the increase risk of hypotension and syncope associated with the use of flibanserin due to an interaction with alcohol include prescriber certification (ETASU A), pharmacy certification (ETASU B), an implementation system, and timetable for submission of assessments. A summary of the rationale for each element are described further below.

### **7.2.1 Medication Guide**

The Agency does not agree with the Sponsor's proposal to include a MG as an element of the REMS. While the MG is intended to communicate the most important information for a patient to be aware of and must be provided to the patient at the point of dispensing by the pharmacist, the Addyi MG contains other important information that is not the focus of the REMS. Additionally, receipt of the MG does not ensure patients have read the MG or discussed its contents with their healthcare provider. Therefore, the Agency is proposing a Patient-Provider Agreement Form (see Section 7.2.2.1) as the primary patient education tool under the REMS for use by prescribers, which will provide focused information to patients regarding the increased risk of hypotension and syncope due to an interaction with alcohol (see Section 7.2.2.1).

### **7.2.2 Elements to Assure Safe Use**

#### **7.2.2.1 Prescriber Certification (ETASU A)**

The Sponsor proposed prescriber certification which included a Prescriber Training Program, including knowledge assessment, Prescriber Enrollment form, and additional educational materials (The Decreased Sexual Desire Screener, Addyi Appropriate Use and Counseling Checklists and the Addyi REMS Program website), and targeted communication to potential prescribers and professional societies. The REMS program requirements proposed by the

Sponsor for prescribers include training for prescribers and counseling of patients regarding the risk of concern.

While DBRUP and DRISK agree with the Sponsor that prescriber certification is necessary to ensure prescribers are informed about the increased risk of hypotension and syncope associated with Addyi due to an interaction with alcohol, DBRUP and DRISK believe only outpatient prescribers need to undergo the certification process. Prescribers that want to continue patients on Addyi in an inpatient setting do not need to be certified because patients are managed in a medically supervised setting and are unlikely to be exposed to alcohol in the inpatient setting.

The prescriber certification is a one-time certification process, which can be completed online or via printed materials. Addyi will be the first drug approved for HSDD, a condition that is no longer in the DSM manual, and is likely to be treated by a variety of prescriber specialties with varied experience in treating sexual dysfunction. Additionally, DBRUP and DRISK agree with Sprout that the prescriber, as a condition of certification, must inform patients of the need to avoid alcohol use during treatment with flibanserin. This is an essential requirement since the risk of hypotension and syncope due to alcohol is directly related to patient behavior.

DBRUP and DRISK do not agree with the Sponsor's proposal regarding the tools to support prescriber certification. The review team determined that the Decreased Sexual Desire Screener and Addyi Appropriate Use and Counseling Checklists were determined to be outside the scope for the goals and objectives of the program. Additionally, the targeted communication to potential prescribers and professional societies was not a necessary element of the REMS to needed to help mitigate the risk. Therefore, the tools recommended by the review team to support prescriber certification include the following:

- *Addyi REMS Program Prescriber Enrollment Form*: used by prescribers to capture enrollment information
- *Addyi REMS Program Prescriber and Pharmacy Training*: used by prescribers to review the risk messages relevant to the increased risk of hypotension and syncope associated with Addyi due to the interaction with alcohol (see Section 7.3.1 for key risk messages for prescribers)
- *Addyi REMS Program Knowledge Assessment*: used by the Addyi REMS Program to ensure prescribers have reviewed and understand the *Addyi REMS Program Prescriber and Pharmacy Training*
- *Addyi REMS Program Website*: used by prescribers to access REMS materials and complete prescriber certification process
- *Addyi REMS Program Patient-Provider Agreement Form (PPAF)*: used by prescribers to counsel patients about the increased risk of hypotension and syncope associated with Addyi due to the interaction with alcohol (see Section 7.3.1 for key risk messages for patients). The completed PPAF is maintained in the patient's records and the prescriber must provide the patient with the portion of the PPAF designated for patient receipt. Additionally, this tool is available as an optional tool for pharmacists to use to counsel patients prior to dispensing.

The review team considered whether the PPAF needed to be submitted to the REMS program upon completion as evidence of documentation of safe use (ETASU D), which would be linked to dispensing (i.e., a pharmacist would not dispense Addyi unless the patient had a completed PPAF in a REMS database). The review team's proposed Addyi REMS to the ROC included this requirement. The rationale for this requirement was to provide assurance for the patient's

receipt of counseling due to the likelihood of alcohol use in this patient population and the dependency on patient behavior. However, advice provided by the ROC was that documentation of safe use would be unduly burdensome given the size of the anticipated indicated patient population and due to concerns about maintaining a patient database for this diagnosis. Therefore, the ROC agreed with the inclusion of a PPAF in the REMS; however, it should not be linked to distribution under documentation of safe use conditions (ETASU D).

The DRISK Risk Management Analyst and Team Leader continue to believe the Addyi REMS Program should include a documentation of safe use requirement in order to ensure patients are informed of the serious risks by requiring completion of a PPAF. However, at this time, the Agency will not be including a documentation of safe use as an element to assure safe use component of the REMS.

The Sponsor has agreed to the Agency's proposed recommendations to the prescriber certification requirements.

#### **7.2.2.2 Pharmacy Certification (ETASU B)**

The Sponsor proposed pharmacy certification, which included a Pharmacy Training Program, including knowledge assessment, pharmacy enrollment forms (b) (4) utilization of the pharmacy management system to electronically verify prescriber certification prior to dispensing, and targeted communication (b) (4). The REMS program requirements proposed by the Sponsor for pharmacies include training for pharmacies and counseling of patients regarding the risk of concern.

DBRUP and DRISK agree with the Sponsor that pharmacy certification is necessary to ensure relevant staff involved in the dispensing process at pharmacies are informed about the increased risk of hypotension and syncope associated with Addyi due to an interaction with alcohol. The pharmacy certification will be completed by an authorized representative and only require re-enrollment in the program if there are changes to the authorized representative. The pharmacy certification process can be completed online or via printed materials and utilizes the same training materials used for certified prescribers. Additionally, pharmacy certification requires the pharmacist to verify the patients only receive flibanserin pursuant to a prescription by a certified prescriber. Furthermore, the REMS also requires certified pharmacies to counsel patients prior to dispensing Addyi regarding the need to abstain from alcohol use during treatment with flibanserin (the PPAF is available as an optional tool to certified pharmacies for counseling). This will provide ongoing reminders to patients about this serious risk. Counseling patients about adverse events and drug interactions is within the scope of pharmacy practice.

The review team also agrees with the Sponsor's proposal to utilize the pharmacy management systems to electronically verify prescriber certification prior to dispensing, which reduces the burden of the REMS on the healthcare system. Since flibanserin will be a chronic treatment for HSDD, it is expected this medication will be dispensed primarily by outpatient retail pharmacies. Most retail outpatient pharmacies and all of the major chain pharmacies have the capability to use automatic electronic verification systems (i.e. switch systems). The review team recommended inclusion of an alternate mechanism for verification for pharmacies that do not utilize pharmacy management systems. The Addyi REMS will include a call center for pharmacies to call and verify prescriber certification. In addition, the Sponsor has agreed to

incorporate an online tool within 6 months of approval, which will allow certified pharmacies to access the database of certified prescribers.

The tools recommended by the review team to support pharmacy certification include the following:

- *Addyi REMS Program Multiple Location Pharmacy Enrollment Form*: used by outpatient pharmacies that will utilize the pharmacy management system and need to enroll multiple pharmacy locations under a single authorized representative
- *Addyi REMS Program Individual Location Pharmacy Enrollment Form*: used by an outpatient pharmacy that needs to enroll a single pharmacy location under a single authorized representative. Pharmacies have the option of using the pharmacy management system or phone verification for prescriber certification.
- *Addyi REMS Program Inpatient Pharmacy Enrollment Form*: used by inpatient pharmacies that may only dispense Addyi for inpatient use.
- *Addyi REMS Program Prescriber and Pharmacy Training*: used by the authorized representative and relevant pharmacy staff to review the risk messages relevant to the increased risk of hypotension and syncope associated with Addyi due to the interaction with alcohol (see Section 7.3.1 for key risk messages for pharmacists)
- *Addyi REMS Program Knowledge Assessment*: used by the Addyi REMS Program to ensure the authorized representative has reviewed and understand the *Addyi REMS Program Prescriber and Pharmacy Training*

Note, the PPAF is available as an optional tool for pharmacists to use to counsel patients prior to dispensing.

The Sponsor has agreed to the review team's proposed recommendations to the pharmacy certification requirements.

### **7.2.3 Implementation System**

The implementation system includes the requirements necessary to monitor and evaluate prescriber and pharmacy certification. It includes the requirements for distributors; audit requirements for certified pharmacies, and wholesaler distributors; and program infrastructure necessary to support the respective ETASU. The Sponsor has agreed to the review team's proposed recommendations to the implementation system.

### **7.2.4 Timetable for Submission of Assessments**

The Sponsor proposed submission of REMS Assessments to FDA at 6 months and 12 months from the date of the approval of the Addyi REMS, and then annually thereafter. DBRUP and DRISK agree with the Sponsor's proposed timetable. This timetable for the submission of assessments is consistent with the timetable included for other REMS with ETASU.

## **7.3 ADDYI REMS PROGRAM KEY RISK MESSAGES AND ASSESSMENT PLAN**

### **7.3.1 Addyi REMS Program Key Risk Messages**

The Agency and Applicant have agreed upon the following Addyi REMS Program key risk messages. These messages are conveyed in the Addyi REMS educational materials (*Addyi REMS Program Prescriber and Pharmacy Training*, *Addyi REMS Program Knowledge*

*Assessment and the Addyi REMS Program PPAF*) and will be used to develop stakeholder surveys. The results of these surveys will be reported in the Applicant's Assessment reports to the Agency. Assessing stakeholder knowledge of these key risk messages, along with other assessment plan metrics, will be used to determine if the goals of the Addyi REMS are being achieved.

#### Addyi Risk Messages for Prescribers:

*Risk Message #1:* Alcohol is contraindicated for patients taking Addyi.

- Alcohol use is contraindicated with Addyi because the interaction can lead to hypotension and syncope, which may be severe.

*Risk Message #2:* Prescribers must use the patient-provider agreement form (PPAF) to counsel their patients about the increased risk of hypotension and syncope associated with Addyi due to an interaction with alcohol prior to an initial prescription for Addyi being provided to the patient.

- The *Patient-Provider Agreement Form* is an important tool for prescribers to use with patients and should be used to counsel patients at the office visit.
- This form should be included in the patient's chart.
- The bottom portion can be torn off for the patient to take home.
- This form can also be used for pharmacy counselling.

#### Addyi Risk Messages for Pharmacists

*Risk Message #1:* Alcohol is contraindicated for patients taking Addyi.

- Alcohol is contraindicated with Addyi because the interaction can lead to hypotension and syncope, which may be severe.

*Risk Message #2:* Certified pharmacies must counsel patients prior to dispensing every prescription about the need to avoid alcohol with Addyi.

- The *Patient-Provider Agreement Form* is an important tool and can be used by the pharmacist to counsel patients at the pharmacy.

#### Addyi Risk Message for Patients

*Risk Message #1:* Patients who are taking Addyi treatment must not drink alcohol.

*Risk Message #2:* Drinking alcohol while using Addyi can lead to low blood pressure and loss of consciousness (fainting) can be severe and require intervention by a healthcare provider.

### **7.3.2 Addyi REMS Assessment Plan**

The Agency and Applicant have agreed upon the following Addyi REMS Program Assessment Plan. The assessment plan primarily addresses compliance with REMS requirements and knowledge of the risks addressed in the Addyi REMS. The Addyi REMS Support Center report may provide additional data on program implementation and may identify challenges with stakeholder participation in the Addyi REMS. Analyses of adverse events of interest will not be captured in the REMS Assessment but through routine pharmacovigilance.

The REMS assessment plan must include, but is not limited to, the following:

**A. REMS Program implementation and operational metrics**

All metrics will include the current reporting period and cumulative data. Whenever appropriate, data will be provided in tabular format.

1. *Stakeholders (prescribers, pharmacies, and distributors) utilization*
  - a. Numbers of each stakeholder, status of certification, and method of certification.
  - b. Distribution of certified prescribers by degree, clinical specialty, practice setting, geographic region.
  - c. Distribution of certified pharmacies by pharmacy type (inpatient, outpatient multiple location, outpatient individual location), geographic region, title of authorized representative.
  - d. Distribution of authorized distributors and wholesalers by geographic region.
  - e. Listing and categorization of reasons enrollment is incomplete for each stakeholder group (e.g., pharmacy unable to configure a pharmacy management system, missing information on enrollment form, incomplete knowledge assessment).
  
2. *Addyi utilization*
  - a. Total number of orders (bottles or packages) shipped to pharmacies stratified by pharmacy type.
  - b. Number of outpatient prescriptions dispensed stratified by method of dispensing authorization (PMS or non-electronic) and prescriber specialty.
  - c. Based upon available third-party patient audits a summary of ages of patients who are dispensed product and the duration of use; a description of the source of audits will be provided in each assessment.
  
3. *REMS Support Center report*
  - a. Number of contacts by stakeholder type (patient, prescriber, pharmacy, other).
  - b. Summary of frequently asked questions (FAQ) by stakeholder type.
  - c. Listing and categorization of REMS-related problems (e.g., technical, process, inability to find certified prescriber) by stakeholder type and a description of any corrective actions resulting from issues identified.
  
4. *REMS Program Compliance (beginning at the 12-month assessment)*
  - a. Audits: Summary of audit findings for audits conducted during the reporting period, including any corrective actions taken to address findings, the status of corrective actions, and any resulting preventative actions taken.
  - b. Number of prescriber, pharmacy and distributors de-certified and reasons for de-certification.
  - c. Number of Addyi prescriptions dispensed that were written by non-certified prescribers and any action taken and outcome of action (e.g., provision of educational program materials, prescriber becoming certified).

- d. Number of prescriptions dispensed by non-certified outpatient pharmacies and the actions taken to prevent future occurrences.
- e. Number of shipments sent to non-certified pharmacies, sources of report, and actions taken to prevent future occurrences.
- f. Number of times an Addyi prescription was dispensed because a pharmacy bypassed REMS, and if any event occurred, a description of how the events were identified and any corrective actions taken.
- g. Non-compliance with safe use, source of report, and any corrective action or resolution from reports to the REMS Support Center or the Applicant directly.

5. *Barriers or delays in patient access*

- a. Number of times all entities are certified, but system generated a prescription rejection notice.
- b. Lack of certified prescribers and/or pharmacies in a patient's local area (based on reports to the Addyi REMS Support center or to the Applicant directly).
- c. Unintended system interruptions and resolutions.
- d. For electronic verification: number of times a "back up" system was used to validate a prescription and source of problem (e.g., switch level, pharmacy level, REMS database).

6. *Inappropriate patient access*

- a. Number of times inpatient pharmacy dispenses Addyi for outpatient use (as identified through audits or reports to the Addyi REMS Support Center).
- b. Number of times one or all entities were not certified but system verified dispensing and generated an authorization code.

**B. Evaluation of knowledge through Knowledge, Attitude and Behavior (KAB) surveys**

1. *Prescribers*

- a. An evaluation of knowledge of certified prescribers of the increased risk of severe hypotension and syncope associated with Addyi due to an interaction with alcohol and knowledge of Addyi REMS program requirements.
- b. An evaluation of prescriber practice or behavior with regards to counseling patients about the increased risk of severe hypotension and syncope associated with Addyi due to an interaction with alcohol.

2. *Pharmacies*

- a. An evaluation of knowledge of authorized representatives and staff pharmacists in certified pharmacies of the increased risk of severe hypotension and syncope associated with Addyi due to an interaction with alcohol and knowledge of Addyi REMS program requirements.

- b. For staff pharmacists: An evaluation of pharmacist practice or behavior with regards to counseling patients about the increased risk of severe hypotension and syncope associated with Addyi due to an interaction with alcohol.
- 3. *Patients*
  - a. An evaluation of knowledge of patients of the increased risk of severe hypotension and syncope associated with Addyi due to an interaction with alcohol.
  - b. An evaluation of patients' recall of counseling by prescriber, pharmacist, or both, on the increased risk of severe hypotension and syncope associated with Addyi due to an interaction with alcohol.
- C. Overall REMS evaluation**
  - a. As required for assessments of an approved REMS under section 505-1(g)(3) Sprout will include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.
- D. Knowledge Assessments at time of enrollment (to be provided in the 6 and 12 month assessments only)**
  - a. Numbers of certified prescribers, authorized pharmacy representatives, and staff pharmacists who successfully completed the knowledge assessment, including the method of completion (web or paper), and the number of attempts to successfully complete the knowledge assessment.
  - b. Summary of the most frequently missed *Addyi REMS Knowledge Assessment* questions, stratified by prescriber and pharmacy type.
    - i) Description of any potential comprehension or perception issues identified.
    - ii) Proposed REMS materials revisions to address comprehension or perception issues identified, if necessary
- E. REMS Program implementation (to be provided in 6 and 12 month assessments only)**
  - a. Product Launch Date
  - b. Date when REMS materials became available to HCPs on the website and via the call center
  - c. The dates HCPs could become certified online, by mail, by fax
  - d. Addyi REMS website utilization
  - e. Date when the REMS website went live
  - f. Number of unique site visits

## 8 CONCLUSION AND RECOMMENDATIONS

In conclusion, a REMS with ETASU is necessary for Addyi (flibanserin) to ensure the benefits outweigh the increased risk of hypotension and syncope due to an interaction with alcohol. The goal of the Addyi REMS is to mitigate the increased risk of hypotension and syncope associated with Addyi due to an interaction with alcohol by (1) ensuring prescribers and pharmacists are educated about the increased risk of hypotension and syncope associated with Addyi due to an interaction with alcohol and the need to counsel patients about this risk and (2) informing

patients of the increased risk of hypotension and syncope associated with Addyi due to an interaction with alcohol.

Therefore, a REMS with ETASU (A and B), implementation system, and a timetable for submission of assessments is required to ensure the benefits of Addyi outweigh the risks. Sprout's amended submission, received August 18, 2015 and appended to this review, contains the agreed upon REMS for Addyi and is considered acceptable by DRISK.

## **9 ATTACHMENTS**

Addyi REMS and appended materials

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/s/  
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KIMBERLY LEHRFELD

08/18/2015

Entered into DARRTS for Somya Dunn

REEMA J MEHTA

08/18/2015

I concur.

CYNTHIA L LACIVITA

08/18/2015

Concur

**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW**

Date: August 18, 2015

Reviewer(s): Somya Dunn, M.D., Risk Management Analyst  
Division of Risk Management (DRISK)

Joan Blair, R.N., M.P.H., Health Communications Analyst  
DRISK

Team Leader: Kim Lehrfeld, Pharm.D,  
DRISK

Deputy Division Director (Acting): Reema Mehta, Pharm.D, M.P.H.  
DRISK

Drug Name(s): Flibanserin (proposed proprietary name ADDYI)

Therapeutic Class: 5-HT<sub>1A</sub> Agonist and a 5-HT<sub>2A</sub> antagonist

Dosage and Route: Film-coated tablets 100 mg

Application Type/Number: NDA 22526

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## 1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK) comments on the proposed risk evaluation and mitigation strategy (REMS) for Addyi (flibanserin) tablets, NDA 22526, received from Sprout Pharmaceuticals (Sprout) on August 16, 2015. The proposed indication for Addyi is for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women. The NDA has been submitted three times and the 2015 submission is the third cycle. The first two cycles received a Complete Response (CR).

## 2 COMMENTS FOR THE SPONSOR

### Addyi REMS Materials:

- Training Slides: There should not be color in the font on any of the slides. (b) (4). The PPT version has some duplicative slides (7 and 8). Make sure these duplications are not in any final versions.
- Please note minor editorial track changes in the following MS Word versions of the enrollment forms.
  - Addyi REMS Program Multiple Locations Outpatient Pharmacy Enrollment Form
  - Addyi REMS Program Individual Location Outpatient Pharmacy Enrollment Form
  - Addyi REMS Program Inpatient Pharmacy Enrollment Form
  - Addyi REMS Prescriber Enrollment Form
- All other materials are acceptable and considered final:

### Addyi REMS Website:

#### General Comments:

- Note: We did not mark up the Website screenshots in the PDF document.
- Rename the titles of only the pdf links under Materials for Prescribers and Materials for Pharmacies to: **Addyi REMS Program Prescriber and Pharmacies Training (including a knowledge assessment)**. The title of the training program does NOT need to be changed elsewhere in the REMS materials or website - only on the webpages that provide a list of links to the pdf materials for each stakeholder group and note the training program.
- **Make sure all materials listed on the REMS website are titled accurately.**
  - For example, the word "Program" should be added after "REMS" as needed throughout the text of the entire website, e.g. Addyi REMS **Program** Patient-Provider Agreement Form on page 2 and under the appropriate button for prescribers and pharmacies, to note a few. It has been changed when the materials are listed for the stakeholders on the right side of the appropriate webpages, but is not noted other places.

#### Home Page (PDF screenshots page 1):

- Ensure that the four links in the horizontal grey banner are centered vertically. Those related to the pharmacies are lower.

Prescriber Training, Enrollment, and Certification (PDF screen shot page 6)

- Use **bold** font to highlight just these three words in the three easy steps:
  1. **Read**
  2. **Review**
  3. **Enroll**

Pharmacy Training, Enrollment, and Certification Landing Page (PDF screen shots pages 30-32)

- The Agency recommends that you use Option A, which is noted on slide 27 of the power point version of the screenshots and pages 30-32 on the pdf version of the screenshots.
- Use **bold** font to highlight the three easy steps:
  1. **Read**
  2. **Review**
  3. **Enroll**
- Revise the text as **highlighted** below:

"Read the Addyi REMS Program Prescriber and Pharmacy Training Program and the Prescribing Information for Addyi. The Addyi REMS Program Prescriber and Pharmacy Training Program and Prescribing Information are available for download from this website (www.AddyiREMS.com) or they can be requested by calling the Addyi REMS Support Center (XXX-XXX-XXXX). You can also launch the Training **Program\*\*** (**including the Knowledge Assessment**) and enrollment process by clicking the appropriate button **at the bottom of this webpage**. (See **Option 1: Online** below for a description of the different pharmacies)"

*Note: The addition of the highlighted text above clarifies that the knowledge assessment is included as part of the training program and that the only buttons that are "clickable" are those at the very bottom of the webpage.*

- Move \*\*Note the training program is also available to pharmacy staff to meet the training requirements of the Addyi REMS Program and the Pharmacy Staff Training Program "button" to below Option 2: Fax. As is, it looks like pharmacy staff have to enroll or become certified in the program, which is not accurate.
- On page 33 (grayed out under the "You have chosen ...." Box), the links to online training are arranged as 2 X 2 boxes. This is different than the screen shots on pages 30-32. If possible, that arrangement would be preferable since it is more compact and may allow stakeholders to see both Option #1 and Option #2 on one screen. Consider arranging this way.

**Resubmission Instructions:**

Submit both the individual clean PDF and clean MS Word versions of all documents in this submission. Note, the website can be submitted only as PDF.

Submit one final, clean, compiled PDF of the Addyi REMS document and all appended REMS materials. Include only the documents listed below. NOTE: the Supporting Document is NOT on this list.

- Addyi REMS Document
- Addyi REMS Program Prescriber and Pharmacy Training
- Addyi REMS Program Knowledge Assessment (without the answers)
- Addyi REMS Program Prescriber Enrollment Form
- Addyi REMS Program Patient-Provider Agreement Form
- Addyi REMS Program Individual Location Pharmacy Enrollment Form
- Addyi REMS Program Multiple Locations Pharmacy Enrollment Form
- Addyi REMS Program Inpatient Pharmacy Enrollment Form
- Addyi REMS Program Website (see the attached PDF Website which has the knowledge assessment answers screen shots, duplicate pages and ISI/legal disclaimer information removed)

Please submit by noon Tuesday 8/18. If the application for Addyi is approved, these materials will be posted on the FDA REMS website and attached to the approval letter.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SOMYA V DUNN  
08/18/2015

KIMBERLY LEHRFELD  
08/18/2015

**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW**

Date: August 13, 2015

Reviewer(s): Somya Dunn, M.D., Risk Management Analyst  
Division of Risk Management (DRISK)

Joan Blair, R.N., M.P.H., Health Communications Analyst  
DRISK

Team Leader: Kim Lehrfeld, Pharm.D,  
DRISK

Deputy Division Director (Acting): Reema Mehta, Pharm.D, M.P.H.  
DRISK

Drug Name(s): Flibanserin (proposed proprietary name ADDYI)

Therapeutic Class: 5-HT<sub>1A</sub> Agonist and a 5-HT<sub>2A</sub> antagonist

Dosage and Route: Film-coated tablets 100 mg

Application Type/Number: NDA 22526

---

## 1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK) comments on the proposed risk evaluation and mitigation strategy (REMS) for Addyi (flibanserin) tablets, NDA 22526, received from Sprout Pharmaceuticals (Sprout) on August 10, 2015. The proposed indication for Addyi is for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women. The NDA has been submitted three times and the 2015 submission is the third cycle. The first two cycles received a Complete Response (CR).

## 2 SUMMARY OF SPONSOR'S REMS SUBMISSION AND DRISK COMMENTS

### 2.1 ELEMENTS TO ASSURE SAFE USE

Review of these materials is based on the Sponsor submission from August 10, 2015 and references the correspondence with comments and edits provided for the Sponsor from the Agency on August 6, 2015.<sup>1</sup>

**General Comment:** The Addyi REMS materials were all renamed as follows:

- o Addyi REMS Program Prescriber and Pharmacy Training
- o Addyi REMS Program Knowledge Assessment
- o Addyi REMS Program Prescriber Enrollment Form
- o Addyi REMS Program Patient-Provider Agreement Form
- o Addyi REMS Program Individual Location Pharmacy Enrollment Form
- o Addyi REMS Program Multiple Locations Pharmacy Enrollment Form
- o Addyi REMS Program Inpatient Pharmacy Enrollment Form
- o Addyi REMS Program Website

#### REMS Document

The Sponsor continued to propose revising the pharmacy AE reporting requirements to align with current practice for pharmacies. The Sponsor provided the following summary of a communication from (b) (4) which explained the chain pharmacies concerns about the current proposed AE reporting requirement attestation in the Pharmacy Enrollment Form.

1. Being asked to attest to 100% compliance from all in store staff to report an AE, when there is no way for HQ to monitor whether or not all store staff report every AE, every time represents a significant risk at the HQ level. (Even at the store level, a pharmacist manager can't ensure staff do it when they aren't there.)
2. Whether casual discussions or counseling sessions, when a patient mentions they may have had an AE, the pharmacist must then remember to report the discussion. Pharmacists get interrupted all the time. At the pharmacist's level - it's the remembering to report all AEs that is a stickler, and then also

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<sup>1</sup> Dunn S. DRISK REMS Review for Addyi (flibanserin). Dated August 6, 2015. DARRTSed August 18, 2015.

- remembering to report to Sprout rather than MedWatch for this one REMS, but not other REMS.
3. Then, what happens when a patient gets the REMS drug from one chain, but discusses the potential AE to a pharmacist at another chain?
  4. When you have an action that is not involved within a technology, is a requirement outside of workflow, with no reminders within workflow, then it can't be known (or proven) whether a discussion happened that would have warranted reporting and that the reporting took place.
  5. Finally, when something needs attesting to, that infers it will be monitored and potentially be a non-compliance hit it seems that they would not be able to defend something that can't be traced back to an initiating event.

*Reviewer Comment: The Agency considered the above rationale and agrees that revising the requirement to ensure pharmacy staff understands the importance of reporting hypotension and syncope where an interaction with alcohol cannot be ruled out is sufficient. Therefore, the following AE reporting requirement language was revised in the REMS document as follows:*

Ensure all relevant staff involved in the dispensing of Addyi understand the importance of reporting any adverse event of hypotension and syncope where an interaction with alcohol cannot be ruled out to Sprout Pharmaceuticals or MedWatch.

*This language was also revised on all Addyi REMS Program Pharmacy Enrollment Forms. See appended, redlined Addyi REMS Program Pharmacy Enrollment Forms.*

#### **Prescriber Certification: Patient Provider Agreement Form**

The Sponsor revised the PPAF as communicated in previous DRISK comments. Only minor, editorial and formatting revisions were proposed to this material.

#### **Pharmacy Certification: Pharmacy Enrollment Forms**

The Sponsor revised the Pharmacy Enrollment Forms as communicated in previous DRISK comments, although they noted their continued concern with the AE reporting requirement attestation.

*Reviewer Comment: As discussed earlier in this review, the Agency revised the AE reporting requirements in the REMS document. The following revision was made to all three Pharmacy Enrollment Forms.*

I will ensure that all relevant staff involved in the dispensing of Addyi understand the importance of reporting any adverse event of hypotension and syncope where an interaction with alcohol cannot be ruled out to either Sprout Pharmaceuticals (XXX-XXX-XXXX) or MedWatch (XXX-XXX-XXXX).

*The only other revisions proposed were minor, editorial and formatting revisions.*

## **Prescriber and Pharmacy Certification: The Addyi REMS Prescriber and Pharmacy Training Program with Knowledge Assessment (KA)**

The Sponsor revised the Pharmacy Enrollment Forms as communicated in previous DRISK comments. However, they proposed revising the 3 steps in the Addyi REMS Program Certification Process from “Read, Review, Enroll” (b) (4)

*Reviewer Comment:* This change is not acceptable to the Agency. (b) (4)

. The slides were further revised to align with the most recent labeling changes. Specifically Slide 7 was deleted and replaced with 2 new slides. See appended, redlined Prescriber and Pharmacist Training Program and Knowledge Assessment for details.

### **REMS Website**

See **Section 3: Comments for the Sponsor, Addyi REMS Program** for detailed website comments.

## **3 COMMENTS FOR THE SPONSOR**

### **Addyi REMS Program Materials:**

- Slightly reduce the size of the Addyi logo and move to the left corner of each REMS material.
- Change titles of materials per track changes. Also, changes have been made to the content of the documents. Please see each document for specific edits made. A list of the revised titles is below.
  - Addyi REMS Program Prescriber and Pharmacy Training
  - Addyi REMS Program Knowledge Assessment
  - Addyi REMS Program Prescriber Enrollment Form
  - Addyi REMS Program Patient-Provider Agreement Form
  - Addyi REMS Program Individual Location Pharmacy Enrollment Form
  - Addyi REMS Program Multiple Locations Pharmacy Enrollment Form
  - Addyi REMS Program Inpatient Pharmacy Enrollment Form
  - Addyi REMS Program Website
- Add the phone number of the Addyi REMS Support Center to all REMS materials (near the Addyi REMS website URL), so stakeholders have easy access to additional information, should internet access not be available. *We note that this information is included on most of the forms already.*
- Please note that the knowledge assessment should never be a stand-alone document anywhere in the Addyi REMS Program or as a pdf link in the list of materials for

healthcare providers. It should only be attached at the end of the training program, as it is the final integral part of the training program. Please remove all pdf links to the knowledge assessment on the website. We understand that the answers to the knowledge assessment questions are only available to staff at the Addyi REMS Support Center and will not be available on the Addyi REMS website or as a pdf standalone document for distribution

- All phone numbers, fax numbers and website addresses must be populated on all materials in your next submission.

### **Addyi REMS Program Website:**

#### **General Comments:**

- Note: We did not mark up the Website screenshots in the PDF document but we did send the original back to you since we reference page numbers below.
- Please change all references to the "Full Prescribing Information" to "Prescribing Information."
- Make sure all materials listed on the REMS website are titled accurately

#### **Home Page (PDF screenshots pgs 1-2):**

- Replace (b) (4) with "What is the Addyi REMS Program?" Include the following text below heading:
  - **What is the Addyi REMS Program?**
    - A REMS is a strategy to manage known or potential serious risks associated with a drug product and is required by the FDA to ensure the benefits of a drug outweigh its risks. The purpose of the Addyi REMS Program is to inform prescribers, outpatient pharmacies, inpatient pharmacies, and patients about the increased risks of:
      - **Hypotension** and **Syncope** due to an interaction with alcohol
- Replace (b) (4) with "Addyi REMS Program Requirements"
- Update the "Indications" and the "Limitations of Use" content at the bottom of the home page per the revised PI.
- As noted previously, place a prominent REMS link to the AddyiREMS.com website on the product website.

#### **Prescriber Training, Enrollment, and Certification (PDF screen shots pgs 6-7)**

- The three easy steps do not align with the requirements of the REMS Program. They should be reverted back to how they were before:
  1. Read
  2. Review
  3. Enroll

- You must also add in small font at the bottom of the three steps: \*For online enrollment first sign-up by creating an account and providing all requested contact information

Pharmacy Training, Enrollment, and Certification Landing Page (PDF screen shots pgs 27-28)

- Refer to a mocked-up, Word version of this webpage on the next 2 pages.
- The three easy steps do not align with the requirements of the REMS Program. They should be reverted back to how they were before:
  1. Read
  2. Review
  3. Enroll
- You must also add in small font at the bottom of the three steps: \*For online enrollment first sign-up by creating an account and providing all requested contact information
- As noted previously, please indicate if the Addyi REMS Support Center will maintain a record of individual pharmacy staff members who have completed the training. An individual pharmacy staff member should have access to a confirmation of completed training (i.e. Certificate of Completion) that has their name and the date of completion that can be printed. This can be provides to an Authorized Representative to fulfill the documentation of training of pharmacy staff to meet the REMS requirements. Describe this in your REMS Supporting Document.

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/s/  
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SOMYA V DUNN  
08/18/2015

KIMBERLY LEHRFELD  
08/18/2015

**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW**

Date: August 6, 2015

Reviewer(s): Somya Dunn, M.D., Risk Management Analyst  
Division of Risk Management (DRISK)  
  
Joan Blair, R.N., M.P.H., Health Communications Analyst  
DRISK

Team Leader: Kim Lehrfeld, Pharm.D,  
DRISK

Deputy Division Director  
(Acting): Reema Mehta, Pharm.D, M.P.H.  
DRISK

Drug Name(s): Flibanserin (proposed proprietary name ADDYI)

Therapeutic Class: 5-HT<sub>1A</sub> Agonist and a 5-HT<sub>2A</sub> antagonist

Dosage and Route: Film-coated tablets 100 mg

Application Type/Number: NDA 22526

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## 1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK) comments on the proposed risk evaluation and mitigation strategy (REMS) for Addyi (flibanserin) tablets, NDA 22526, received from Sprout Pharmaceuticals (Sprout) on August 4, 2015. The proposed indication for Addyi is for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women. The NDA has been submitted three times and the 2015 submission is the third cycle. The first two cycles received a Complete Response (CR).

## 2 SUMMARY OF SPONSOR'S REMS SUBMISSION AND DRISK COMMENTS

### 2.1 ELEMENTS TO ASSURE SAFE USE

Review of these materials is based on the Sponsor submission from August 4, 2015 and references the correspondence with comments and edits provided for the Sponsor from the Agency on August 3, 2015.<sup>1</sup>

**General Comment:** In order to align with the labeling, "avoid alcohol use" was revised to "abstain from alcohol use" in the REMS document and all REMS appended materials.

#### **Prescriber Certification: PPAF**

The Sponsor proposed the following revisions:

- Change [REDACTED] (b) (4) to [REDACTED] (b) (4) low blood pressure."

*Reviewer Comment:* After consultation between DRISK, Division of Medical Policy's Patient Labeling Team and DBRUP, the Agency recommends using the word "severe" as this is more understandable to patients [REDACTED] (b) (4) and this aligns with the PI. This term should be used in the Prescriber/Pharmacy Training Program as well.

- Change "loss of consciousness" to "fainting."

*Reviewer Comment:* After consultation between DRISK, Division of Medical Policy's Patient Labeling Team and DBRUP, the Agency recommends using both terms, "fainting (loss of consciousness)." This will align with the revised MG. In addition, FDA recommended some minor editorial changes and formatting changes which are described in the appended, redlined PPAF.

#### **Pharmacy Certification: Pharmacy Enrollment Forms**

1. The Sponsor stated they found the following statement which was added to the Pharmacy Enrollment Forms confusing:

For outpatient use, Addyi is only available from certified outpatient prescribers and certified outpatient pharmacies through the Addyi REMS Program. For

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<sup>1</sup> Dunn S. DRISK REMS Review for Addyi (flibanserin). Dated August 3, 2015. DARRTSed August 18, 2015.

inpatient use, Addyi is only available from certified inpatient pharmacies through the Addyi REMS Program.

*Reviewer Comment: The statement was revised to ensure continuity of care for patients prescribed Addyi who are admitted to inpatient facilities. The REMS only requires prescribers to be certified for outpatient prescribing; inpatient prescribers do not need to be certified to continue existing patients on their flibanserin therapy. The revised statement improves transparency regarding this requirement by setting and reduces interruptions in therapy in an inpatient setting.*

2. The Sponsor also requested a change in the attestation related to AE reporting. They stated that their proposed change “is a consistent change being requested across the Pharmacy Enrollment documents. In discussions with pharmacists this language more closely matches their current practice of reporting AEs.”

FDA proposed attestation:

I will report any adverse events of hypotension or syncope to Sprout Pharmaceuticals at XXXXXXX where an interaction with alcohol cannot be ruled out.

Sponsor proposed attestation:



*Reviewer Comment: We do not agree with this revision. We agree that the language the Sponsor proposed is more in-line with how pharmacists report AE for most drugs. However, for Addyi which is being approved under a REMS, pharmacists are expected to report AE as a condition of certification.*

### **Prescriber and Pharmacy Certification: The Addyi REMS Prescriber and Pharmacy Training Program with Knowledge Assessment (KA)**

The Sponsor proposed revisions to a knowledge assessment question to improve pharmacist comprehension.

*Reviewer Comment: DRISK agreed that the question was confusing as previously written and revised it as follows:*

How often must pharmacists counsel patients about the need to avoid alcohol ?	a. Never b. Only if the patient asks about alcohol use	c. With the first prescription only d. With every prescription
---	---	---

The Sponsor also revised slide 7 of the Prescriber and Pharmacist Training Program to reflect labeling.

*Reviewer Comment: This slide was further revised to align with more recent labeling changes. See appended, redlined Prescriber and Pharmacist Training Program and Knowledge Assessment for details.*

### 3 COMMENTS FOR THE SPONSOR

1. The Agency has provided responses to the Sponsor's 2 outstanding issues in the Addyi REMS Pharmacy Enrollment Forms (see attached).
2. Update the draft Addyi REMS website and the Training Slides, submitted on August 4, 2015, to align with the PI being provided to you today. The Agency has aligned all other Addyi REMS materials (see attached) with the PI provided today.
3. Any additional changes to the attached materials should be provided back to the Agency as redlines to the attached materials and in a table format with rationale (as you provided to the Agency on August 4, 2015.)
4. Update the ISI to align with the PI.
5. Provide the updated REMS materials and ISI by COB on August 10, 2015.

### ATTACHMENTS

- 1 Addyi REMS Individual Location Outpatient Pharmacy Enrollment Form
- 2 Addyi REMS Patient-Provider Agreement Form
- 3 Addyi REMS Document
- 4 Addyi REMS Inpatient Pharmacy Enrollment Form
- 5 Addyi REMS Multiple Locations Outpatient Pharmacy Enrollment Form
- 6 Addyi REMS Prescriber Enrollment Form
- 7 Addyi REMS Knowledge Assessment Slides
- 8 Addyi REMS Prescriber and Pharmacy Training Program

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/s/

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SOMYA V DUNN  
08/18/2015

KIMBERLY LEHRFELD  
08/18/2015

**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Office of Surveillance and Epidemiology**  
**Office of Medication Error Prevention and Risk Management**  
**RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW**

Date: August 3, 2015

Reviewer(s): Somya Dunn, M.D., Risk Management Analyst  
Division of Risk Management (DRISK)

Joan Blair, R.N., M.P.H., Health Communications Analyst  
DRISK

Team Leader: Kim Lehrfeld, Pharm.D.  
DRISK

Deputy Division Director  
(Acting): Reema Mehta, Pharm.D., M.P.H.  
DRISK

Drug Name(s): Flibanserin (proposed proprietary name ADDYI)

Therapeutic Class: 5-HT<sub>1A</sub> Agonist and a 5-HT<sub>2A</sub> antagonist

Dosage and Route: Film-coated tablets 100 mg

Application  
Type/Number: NDA 22526

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## 1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK) comments on the proposed risk evaluation and mitigation strategy (REMS) for Addyi (flibanserin) tablets, NDA 22526, received from Sprout Pharmaceuticals (Sprout) on July 28, 2015. The proposed indication for Addyi is for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women. The NDA has been submitted three times and the 2015 submission is the third cycle. The first two cycles received a Complete Response (CR).

### 1.1 BACKGROUND

Flibanserin is a new molecular entity and is not marketed in any other country. Flibanserin is a 5-HT<sub>1A</sub> receptor agonist and a 5-HT<sub>2A</sub> receptor antagonist with a proposed indication to treat HSDD in premenopausal women. The precise mechanism of action of flibanserin for treatment of HSDD is unknown; however, its impact on HSDD is believed to be related to its effects on norepinephrine, serotonin, and dopamine activities in the central nervous system. The recommended dose for flibanserin is 100 mg taken orally once daily at bedtime.

The diagnostic criteria for HSDD are defined by the American Psychiatric Association in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR. HSDD is characterized by persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity, as judged by the clinician. The symptoms must not be better explained by an alternative disorder or substance (e.g., alcohol abuse, medication) and should lead to marked distress and interpersonal difficulty.

The American Psychiatric Association published an updated DSM, termed DSM-5 in May of 2013. DSM-5 has merged features from HSDD and female sexual arousal disorder as described in DSM-IV-TR and replaced these conditions with a new condition, Female Sexual Interest/Arousal Disorder. As with HSDD, patients with Female Sexual Interest/Arousal Disorder must have associated distress and impairment and must not have an alternative explanation that better explains their symptoms. For this reason, HSDD will be defined in the approved Prescribing Information and in the REMS materials.

### 1.2 REGULATORY HISTORY

The following is a summary of the regulatory history relevant to the REMS:

On December 2, 1996, FDA received the Investigational New Drug (IND) Application (IND (b) (4)) for flibanserin for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women.

On October 27, 2009, Boehringer Ingelheim (BI) submitted NDA 22526 for flibanserin for the treatment of HSDD.

On June 18, 2010, the FDA Reproductive Health Drugs Advisory Committee convened to discuss flibanserin, NDA 22526. The Committee determined that BI did not provide

sufficient evidence to support: (1) the overall efficacy for flibanserin for treatment of HSDD compared to placebo [vote: Yes-1; No-10; Abstain-0] or (2) that the overall risk/benefit profile of flibanserin for the treatment of HSDD in premenopausal women is acceptable [vote: Yes-0; No-11; Abstain-0]

On August 27, 2010, the Agency issued a Complete Response (CR) letter<sup>1</sup>, where the determination was made that the application could not be approved in its present form with efficacy and safety deficiencies. The CR letter highlighted lack of substantial efficacy for treatment of HSDD as well as concerns with efficacy in the presence of moderate CYP3A4 inhibitors. Safety issues cited included a lack of data from patients with comorbid conditions and on concomitant medications and alcohol. There was also insufficient information to assess the risk of accidental injuries associated with flibanserin. The company was also requested to study flibanserin in an abuse potential study since it is characterized as a CNS depressant. The CR letter included recommendations for a new Phase 3 trial with sexual desire as co-primary endpoints and HSDD-related distress as a key secondary endpoint; the Agency requested that sexual desire assessments have adequate content validity, recall validity, and acceptable measurement properties consistent with recommendations in the 2009 guidance on Patient-Reported Outcomes.

On February 17, 2012, BI sold flibanserin to Sprout Pharmaceuticals, Inc. (SPI) and the Agency acknowledged the transfer of ownership of the NDA.

On April 26, 2012, a Type B pre-NDA meeting between the Sponsor and DBRUP was held to discuss the contents of a CR submission. An additional Phase 3, double-blinded, placebo-controlled pivotal efficacy study (511.147), was initiated during the first flibanserin review cycle and completed February 2011, six months after the initial CR action. The study, compared to studies 511.71 and 511.75, allowed for:

- enrollment of a broader patient population
- more concomitant medication use
- sexual desire, measured by items 1 and 2 of the 19-item Female Sexual Function Index (FSFI), as a primary outcome measure

The study also included a sub-study for assessment of content and recall validity to compare 28-day versus 7-day recall. DBRUP advised that it would be a matter of review whether results from the new study (511.147) are adequate to support efficacy, since the co-primary efficacy endpoint (FSFI desire domain items 1 and 2), instruments, and recall periods (28 days versus 7 days), were not formally agreed to by DBRUP<sup>2</sup>.

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<sup>1</sup> Bietz, J. Office of New Drug/DBRUP Complete Response Letter to Flibanserin NDA 22526 dated August 27, 2010.

<sup>2</sup> As discussed by the Study Endpoints and Labeling Development (SEALD) team for flibanserin NDA 22526, use of patient reported outcomes (PROs) has been problematic throughout drug development of treatment of Female Sexual Dysfunction and different subgroups including HSDD. The main issues have been what questions to ask and what recall time to use (1, 7, 14, 28 days). The Division has fairly consistently favored use of electronic diaries and short recall time (24-72 hour range) for collection of accurate data, especially for satisfactory sexual events and sexual desire/interest. Study 511.147 used an

On March 29, 2013, submitted their response to the DBRUP August 27, 2010 CR letter, resubmitting NDA 22526. Their resubmission did not include a REMS proposal.

On September 3, 2013, DRISK completed a Deferral of Risk Evaluation and Mitigation Strategies (REMS) Review of Flibanserin<sup>3</sup>.

On September 27, 2013, DBRUP issued a CR letter<sup>4</sup> to the sponsor for flibanserin stating “you have consistently shown modest improvements in the placebo-adjusted treatment responses in premenopausal women with HSDD, as assessed using the Female Sexual Function Index (FSFI) sexual desire domain, and the number of satisfying sexual events. However, we are not convinced that these treatment effects offset the identified substantial safety concerns.”

The following summarizes highlights of safety concerns and deficiencies, as detailed in the CR letter:

- Central nervous system (CNS) depression (fatigue, somnolence, and sedation) occurred in 21% of subjects taking flibanserin 100 mg nightly.
- Increased frequency of syncope and accidental injury, including serious events, compared to placebo
- Drug-drug interactions with centrally-acting drugs (e.g. serotonin-norepinephrine reuptake inhibitors, alcohol, triptans), strong or moderate CYP3A4 inhibitors as well as alcohol
- Marked increase in flibanserin exposure, poor tolerability and a higher frequency of syncope and hypotension when flibanserin is administered with drugs that are strong or moderate CYP3A4 inhibitors (e.g., hormonal contraceptives)
- Greater incidence of appendicitis among flibanserin users compared to placebo
- Studies on mice demonstrated an increased incidence of mammary tumors at doses three times the recommended for humans
- Human studies of flibanserin’s abuse potential were not interpretable

DBRUP recommendations related to the deficiencies cited above included:

- The sponsor should show how risks will be minimized in clinical practice including CNS effects (fatigue, dizziness, somnolence and sedation), and syncope, hypotension and accidental injury
- Propose strategies beyond labeling to ensure flibanserin is not prescribed with moderate or strong CYP3A4 inhibitors, or taken with alcohol or other centrally-acting medications
- Conduct a driving impairment study

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electronic diary to capture data but did not use the diary for measuring the change in sexual desire. Instead, the 19-item FSFI paper instrument was completed every 4 weeks at clinic visits. (See Page 21-23 of DBRUP Clinical and Safety Review of flibanserin NDA 22526 dated August 29, 2013 for detailed discussion.

<sup>3</sup> Vega, A. Deferral of Risk Evaluation and Mitigation Strategies (REMS) Review for Flibanserin dated September 3, 2013.

<sup>4</sup> Bietz, J., DBRUP Complete Response Letter for Flibanserin NDA 22526 dated September 27, 2013

- Propose a plan to determine whether the excess incidence of appendicitis observed in the Phase 3 placebo-controlled program is drug-related
- Propose a plan to assess the clinical risk of breast cancer in light of the non-clinical findings of dose-dependent mammary tumors in mice

On November 18, 2013, a Type A End of Review meeting was held between DBRUP and the sponsor to discuss the September 27, 2013 CR letter and path forward for the NDA.<sup>5</sup>

On December 3, 2013, the Sponsor filed a formal dispute resolution request (FDRR) to DBRUP's September 27, 2013 CR action for flibanserin NDA 22526.

On February 7, 2014, the Office of New Drugs (OND) responded to the sponsor's FDDR (Appeal Denied Letter)<sup>6</sup> denying the appeal in support of issues identified by DBRUP in their September 27, 2013 CR action.

On March 12, 2014, a Type A meeting was held to discuss a path forward to address deficiencies noted in the CR letter. Key among the issues addressed were a planned driving study to assess next-day impairment, drug-drug interaction studies to assess the effect of CYP2C9 and/or CYP2C19 enzymes on the metabolism of flibanserin. Guidance was provided on the planned studies. Additionally, guidance was provided, in collaboration between DBRUP and DRISK, to Sprout's questions about risk mitigation strategies. Sprout proposed a Communication Plan (CP) REMS. DBRUP and DRISK provided guidance that, although this would be a review issue at the time of submission, a CP may have limitations given the safety issues identified with flibanserin.<sup>7</sup>

On January 15, 2015, a Type B meeting was held to discuss the Sponsor's plan to address the concerns raised in the September 17, 2013 CR letter and the Agency's February 7, 2014 Appeal Denial Letter, in conjunction with the sponsor's planned NDA resubmission.<sup>8</sup>

On February 18, 2015, Sprout resubmitted their application (Seq. No. 0062). Their resubmission addressed issues cited in the September 17, 2013 CR and included the results of the recommended driving study (Study SPR-14-01), a pharmacogenetics study which addressed potential involvement of cytochrome P450 enzymes CYP2C9 and CYP2C19 in the metabolism of flibanserin (Study SPR-14-06), a proposed REMS with a MG and CP and updates to the U.S. Prescribing Information (USPI). As this is the current submission under review, some results from the studies are briefly discussed here:

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<sup>5</sup> DBRUP End of Review Type A meeting with Sprout Pharmaceuticals for Flibanserin NDA 22526 held on November 18, 2013.

<sup>6</sup> Jenkins, J. Office of New Drugs Appeal Denial for Sprout Pharmaceuticals FDRR for DBRUP September 27, 2013 CR action for Flibanserin NDA 22526, dated February 7, 2014.

<sup>7</sup> Division of Bone, Reproductive and Urologic Products (DBRUP) Memorandum of Meeting Minutes for the March 12, 2014 Type A Meeting with Sprout for Flibanserin (NDA 22526) dated April 10, 2014

<sup>8</sup> Division of Bone, Reproductive and Urologic Products (DBRUP) Memorandum of Meeting Minutes for the January 15, 2015 Type B Meeting with Sprout for Flibanserin (NDA 22526) dated February 10, 2015

- Study SPR-14-01 evaluated safety, tolerability, pharmacokinetics, and pharmacodynamics of flibanserin when given at a standard dose (100 mg), and at a supratherapeutic dose (200 mg). Results showed that therapeutic and supra-therapeutic doses of flibanserin had no negative effect on the measures of next-day simulated driving performance that were evaluated.
- In female subjects that were poor metabolizers of CYP2C9, concentrations of ADDYI 100 mg qd decreased about 19%, compared to those in extensive metabolizers of CYP2C9. However, flibanserin concentrations increased about 1.5 fold when flibanserin 100 mg was administered to CYP2C9 poor metabolizers compared to CYP2C9 extensive metabolizers. One poor metabolizer experienced syncope one hour after the single 100 mg dose of flibanserin. This subject had about twice the flibanserin concentration than those with normal CYP2C9 enzyme activity.

This submission also included validation of the instruments used in measuring the efficacy results along with a discussion of Sprout's current understanding of hypotension and syncope related to flibanserin, rare adverse events of appendicitis and breast cancer, and risk mitigation activities that they plan to undertake post-approval.

On March 24, 2015 DBRUP and DRISK presented REMS options for flibanserin to the REMS Oversight Committee (ROC) meeting. The meeting included a presentation of the safety and efficacy findings of flibanserin from DBRUP and DRISK's presentation of Sprout's proposed REMS and both DRISK and DBRUP's recommended REMS elements. ROC recommended risk management options, including labeling alone, a Communication Plan REMS, and REMS with ETASU options (prescriber and pharmacy certification), be presented for consideration by the AC.

On June 4, 2015, the joint BRUDAC/DSaRM AC was held to discuss the flibanserin application. The AC panel was asked to discuss the clinical significance of the efficacy findings from the clinical program. They were also asked to discuss their level of concern with hypotension and syncope when flibanserin was used alone and also when used with alcohol. The panel was asked to vote on if they recommended approval with labeling alone, if they recommended approval with risk mitigation beyond labeling or if they did not recommend approval. Overall, the AC panel voted to approve 18 to 6 but only with risk mitigation beyond labeling. For most panelists voting for approval, this included REMS with ETASU. Although the REMS recommendations were not always concrete (the panel has varying exposures and experiences with REMS), approximately eight of the panelists recommended prescriber certification, eight recommended pharmacy certification and five recommended patient consent of some type (some of these recommendations are overlapping).

On June 11, 2015 DBRUP had a teleconference with Sprout where they advised Sprout to resubmit risk mitigation plans and to consider the options presented at the AC.

On June 18, 2015, Sprout submitted a document outlining arguments against an ETASU REMS.

On June 23, 2015 DBRUP and DRISK had a teleconference with Sprout to reiterate that they should consider the AC recommendations including ETASU D as several panel members had proposed a PPAF. The Applicant inquired about whether the Decreased Sexual Desire Screener (DSDS) tool should be included in the REMS. The Agency stated that we have not reached a final decision regarding whether the tool is appropriate for inclusion in the REMS.

On June 29, 2015 (officially in EDR on July 2) Sprout submitted an updated REMS proposal to include ETASU A and B, both prescriber and pharmacy certification. They included their communication plan materials and other previously proposed materials under these ETASU.

On June 30, 2015, another ROC meeting was held to discuss REMS options. The options presented included ETASU D, documentation of safe use in the form of a patient/prescriber agreement form (PPAF) with Prescriber and Pharmacy Certification or with Pharmacy Certification were presented. REMS goals were also discussed. DRISK and DBRUP were considering whether hypotension and syncope with flibanserin alone or only with alcohol use should be mitigated by the REMS. ROC recommended hypotension and syncope with alcohol use should be the risks mitigated by the REMS and that ETASU A and B should be implemented (prescriber and pharmacy certification).

On July 2, 2015, Sprout sent edited and updated materials for the REMS.

On July 17, 2015, the Agency sent edited materials and comments to Sprout (Interim Comments #1). The Agency requested ETASU A and B as well as materials to support these ETASU ( (b) (4) Agreement Form (PPAF) and counseling tool, enrollment forms, and training materials).

On July 21, 2015 Sprout submitted edited materials to the Agency. These materials reflected their request for removing alcohol as a contraindication from the proposed label. These materials also reflected their request to have the PPAF removed from the REMS program. This submission is reviewed here.

On July 24, 2015 Sprout had a teleconference with the Agency to discuss alcohol as a contraindication and the inclusion of the PPAF in the REMS. They were told these would be required. In addition, they discussed some changes proposed to the label regarding mammary tumors in animal studies and the case of death in a post-menopausal patient.

On July 27, 2015 the Agency sent the proposed label as well as REMS materials for the Sponsor to review and provide comments.

On July 28, 2015 Sprout returned edited materials to the Agency (submitted via gateway on July 29, 2015).

On July 30, 2015 Sprout had a teleconference with the Agency to discuss labeling. This discussion focused mainly on the placement and wording of the mammary tumor data.

## **2 MATERIALS REVIEWED**

- Sprout Pharmaceuticals, Inc. REMS Amendment to NDA 22526 for Flibanserin, submitted July 29, 2015 (Seq. No. 0077)

- Office of Prescription Drug Promotion (OPDP) Consult for Flibanserin, Lynn Panholzer July 29, 2015.

### **3 SUMMARY OF SPONSOR'S REMS SUBMISSION AND DRISK COMMENTS**

#### **3.1 GOALS**

The Sponsor revised the goals based on the comments provided by DRISK on July 17, 2015.<sup>9</sup>

#### **3.2 ELEMENTS TO ASSURE SAFE USE**

Review of these materials is based on the Sponsor submission from July 29, 2015 and references the correspondence with comments and edits provided for the Sponsor from the Agency on July 27, 2015.<sup>10</sup>

##### **REMS Document**

In the previous correspondence, the Sponsor was asked to revise their audit plan requirements for wholesalers/distributors and certified pharmacies in the REMS document. They were also asked to replace [REDACTED] <sup>(b) (4)</sup> with their company name and revert back to previous language since their changes were determined by the Agency to be editorial changes. Furthermore, FDA advised the Sponsor to add the Patient-Provider Agreement Form (PPAF) back into the REMS since the FDA has determined it is a necessary component to ensure the benefits outweigh the increased risk of hypotension and syncope due to an interaction with alcohol. The Sponsor complied with these requests. Only minor edits were made to this document during this round of reviews.

##### **Prescriber Certification: PPAF**

The Sponsor submitted this form with edits. They removed some of the instructional wording that was on the form and replaced this with a list of items for the prescriber. They also redesigned the form to have a shorter prescriber section followed by patient agreement section. This is followed by a repeat of the patient messages, after a perforation on the form, which HCPs can tear off and provide to patients to take home.

##### Reviewer Comment

*DRISK agrees to the general reorganization of the form and agrees to the removal of some of the instructions. The form was further reorganized by the Agency into distinct sections for the prescriber, pharmacist and patient. While the intention of the Agency was that the pharmacists can use the form to counsel patients, this revision clarifies that expectation. However, when used by the*

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<sup>9</sup> Dunn S. DRISK REMS Review for Addyi (flibanserin). Dated, July 20, 2015.

<sup>10</sup> Dunn S. DRISK REMS Review for Addyi (flibanserin). Dated July 29, 2015.

*pharmacist, no signature or charting is required. In addition, after consultation with the Office of Medical Policy's (OMP) Patient Labeling Team (PLT) and DBRUP, more patient-friendly wording was incorporated into the patient section which aligns with the revised Medication Guide (which will be part of labeling but not a component of the REMS).*

**Prescriber Certification: Prescriber Enrollment Form**

The Sponsor sent this form back with minor edits.

Reviewer Comment

*The only substantive change to this document was to [REDACTED] (b) (4)*

*[REDACTED] The following attestation was inserted to align with the REMS document:*

**I will maintain the completed Addyi REMS Patient-Provider Agreement Form in the patient's records and provide the portion of the Patient-Provider Agreement designated for the patient receipt.**

*Sponsor will be asked to send a mocked up final version for review.*

**Pharmacy Certification: Pharmacy Enrollment Forms**

The Sponsor sent back all three pharmacy enrollment forms with minor edits:

- Addyi REMS Multiple Locations Pharmacy Enrollment Form
- Addyi REMS Individual Location Pharmacy Enrollment Form
- Addyi REMS Inpatient Pharmacy Enrollment Form

Reviewer Comment

*Minor revisions were made to these forms in order to align with each other. In addition, introductory text was added to clarify that the outpatient prescribers must be certified in the Addyi REMS, while inpatient prescribers do not have to be certified. Continuity of care can only be achieved if both inpatient and outpatient pharmacies enroll in the Addyi REMS Program. Therefore, increasing transparency for the authorized representatives of pharmacies will help ensure they understand the REMS requirements and how the requirements differ for inpatient and outpatient pharmacies.*

*Additionally, the Sponsor will be asked to create mocked up pdf versions of these documents.*

**Prescriber and Pharmacy Certification: The Addyi REMS Prescriber and Pharmacy Training Program with Knowledge Assessment (KA)**

In the Sponsor's July 21 submission, the Sponsor had removed all references to alcohol as a contraindication in the REMS materials [REDACTED] (b) (4)

*[REDACTED] This was not acceptable. Therefore, the Sponsor was asked to incorporate recommendations made with the last set of revisions the Agency sent (July 27, 2015) to the slides in the first set of*

recommendations (July 17, 2015) and they complied with this. Now, alcohol appears again as contraindication [REDACTED] (b) (4). Finally, the Sponsor revised the REMS materials to reflect the current version of the label.

In the last correspondence from the Agency, Sponsor was also given new questions for the KA that were developed by the Agency. [REDACTED] (b) (4)

[REDACTED]. They incorporated these as requested.

Reviewer Comment

*The training program slides must continue to be amended to align with the label. Minor edits were made to the training and KA slides and are in the Notes section of slides. The Sponsor will be asked to create mocked up final versions of these documents.*

### 3.3 ADDYI REMS WEBSITE

The website the Sponsor submitted did align with the guidance for the website that was sent with the previous Agency/Sponsor correspondence on July 27<sup>th</sup>/July 28<sup>th</sup>. Some changes still need to be made. The Sponsor refers to the REMS program training and enrollment as [REDACTED] (b) (4). The role of the authorized representative for inpatient pharmacy is not clear. There are also inconsistencies noted with attestations from the enrollment forms and some text in the website.

Reviewer Comment

*The Sponsor will be asked [REDACTED] (b) (4) to describe the training, enrollment, and certification process and to make sure that other text noted on the website are consistent with text in all of the Addyi REMS enrollment forms. ] They need to provide screenshots to show all steps that the authorized representative of an inpatient pharmacy goes through to take the training, knowledge assessment, enrollment, and final certification. In addition, they will need to provide screenshots to show all steps that the pharmacy staff would go through to take the training and knowledge assessment. In this round of revisions, the Agency will provide another document with comments/guidance on the website.*

### 3.4 REMS SUPPORTING DOCUMENT

A revised REMS Supporting Document (SD) was submitted and was consistent with the Sponsor's proposed program. An assessment plan was provided for them; this has been incorporated. They were also asked to elaborate on their operating procedures in the last set of correspondence. They have now clarified who they are contracting their call center and database to. In the previous correspondence, the Sponsor was asked to add the Key Risk Message Map to their SD. This was done.

Reviewer Comment

*The Sponsor needs to further clarify how their support center will work, the hours and operating procedures. They also need to clarify how many times the provider can take the KA. This will be communicated in this round of comments.*

#### **4 DISCUSSION OF OPDP REVIEW OF REMS MATERIALS**

##### **OPDP Consult and Review:**

OPDP was consulted on March 4, 2015 to review the REMS materials. Lynn Panholzer was the reviewer. They submitted and DARRTED their review on July 29, 2015.

DRISK notes that OPDP provided several comments on the REMS materials - most of which DRISK agreed and these have been addressed either in the materials as described above or in the materials themselves (redlined versions to Sponsor).

The following provides an explanation as to why DRISK did not accept all of the specific recommendations offered by OPDP. These will be shared with OPDP to ensure their understanding of our rationale.

##### **OPDP recommended:**

1. Addyi REMS (b) (4) Agreement Form
  - The form inadequately communicates the indication of Addyi to prescribers by omitting the limitations of use from the draft PI, as follows:
    - Efficacy and safety of ADDYI have not been established in postmenopausal women or men.
    - Efficacy and safety of ADDYI have not been established in women with low sexual desire caused by a co-existing medical or psychiatric condition, problems within the relationship, or the effects of a medication or other drug substance.
    - Efficacy and safety of ADDYI have not been established for other female sexual disorders.

We recommend that the form be revised to include the full approved indication for the drug, including limitations of use.

***DRISK Response:** The PPAF should remain one page in length for ease of use and for inclusion into the patient's chart. The limitations of use do not relate to the risk message of the Addyi REMS. Therefore, we do not believe the Limitations of Use should be included in the PPAF. The Limitations of Use are included in the training program for healthcare providers and is located on the home page of the Addyi REMS website.*

2. We are concerned that the patient counseling points, in the context of informing patients about the interaction between Addyi and alcohol, may misleadingly minimize the risks of Addyi. (b) (4)

(b) (4)

We recommend that the form be revised to correct these potentially misleading and dangerous impressions. (b) (4)

(b) (4)

***DRISK Response:*** *OND and OSE believe that the REMS goal should only focus on hypotension and syncope WITH the use of alcohol.* (b) (4)

(b) (4)

3. Training Program Slides:

(b) (4)

***DRISK Response:*** *The slides reviewed by OPDP were a version that was predominantly created by the Sponsor based off of changes they wanted to make*

to the label. (b) (4) is no longer part of the training program, as it was originally submitted by the sponsor and rejected by DRISK. (b) (4)

The Addyi REMS focuses only on the increased risk of hypotension and syncope due to an interaction with alcohol. (b) (4)

(b) (4) In addition, as noted above, the Addyi REMS only addresses the risk of hypotension and syncope WITH alcohol.

#### 4. Addyi REMS Prescriber and Pharmacy Training Program

##### Addyi REMS Program Website

- o Slide 4: “Complete the Addyi Prescriber Training Program in 3 (b) (4) easy steps . . .” (underline emphasis added).

We are concerned that the phrase (b) (4) is promotional in tone and minimizes the importance of the REMS training requirement. We recommend that it be deleted.

**DRISK Response:** The REMS materials and website have been revised (b) (4) but we have allowed the sponsor to retain the word "easy." The training program, knowledge assessment, and enrollment process is relatively short and easy compared with other REMS programs.

### 5 DISCUSSION AND CONCLUSIONS

Overall, DRISK is in agreement with the Sponsor regarding the ETASU necessary for inclusion in the Addyi REMS Program. We are also now all in agreement with the Sponsor on the inclusion of the PPAF, Prescriber and Pharmacist Training Program and KA. The Sponsor complied with requested changes to REMS materials and the REMS document. Some edits and changes for clarity were made with this set of revisions. We are also requesting some updates/clarification to the website and the SD. Finally, we have incorporated OPDP recommendations as needed.

### 6 COMMENTS FOR THE SPONSOR

Retain the separate MS Word files for each of the REMS materials. Submit revised MS Word clean versions of the materials as they will be considered final - other than screenshots of the website and the Supporting Document--by tomorrow 8/4/15. The Agency needs to review the updated, complete set of screenshots before the Addyi REMS website is considered final.

**Please submit pdf mocked up versions of each of the materials for FDA's review** for those materials that are considered final. **Accept track changes provided by FDA on each of the documents.** Track changes proposed by Sprout and not rejected by the Agency may be considered acceptable for the final submission.

Final language in all REMS materials should reflect what is in the approved REMS document and the **text of all REMS materials must match the final label**. Please make additional changes to the REMS materials to reflect the label and REMS document as needed.

Note that REMS materials are not appropriate for use in a promotional manner.

**General Comment for all REMS Materials:**

Ensure consistent wording and exact titles of the REMS materials throughout all of the REMS materials, REMS document, and REMS supporting document Patient-Provider Agreement Form. Please also ensure consistency with the PI. Accept all changes to the materials and consider them as final versions.

**REMS Document**

See the REMS Document for edits.

**REMS Supporting Document**

See the Supporting Document for edits, questions and comments.

**Addyi REMS Multiple Locations Pharmacy Enrollment Form**

Accept all track changes and consider the form as final. Please create a pdf mockup version of this form for FDA review.

**Addyi REMS Individual Location Pharmacy Enrollment Form**

See the Addyi REMS Individual Location Pharmacy Enrollment Form for two additional minor revisions as track changes. Please create a pdf mockup version of this form for FDA review.

**Addyi REMS Inpatient Pharmacy Enrollment Form**

Please create a pdf mockup version of this form for FDA review.

**Addyi REMS Prescriber Enrollment Form**

See the Addyi REMS Prescriber Enrollment Form for two additional minor revisions as track changes. Please create a pdf mockup version of this form for FDA review.

**Addyi REMS Patient-Provider Agreement Form (PPAF)**

See the PPAF for edits and provide a clean MS Word and pdf/mockup version to the Agency for review. This form should be designed as a ONE page form.

**Addyi REMS Prescriber and Pharmacy Training Program**

Note minor changes in red text, plus comments for the sponsor in the notes section at the bottom of the power point slides. Please submit a pdf/mockup printed version of this training program for FDA's review - as it will appear for those who print out a copy for their review.

**Addyi REMS Knowledge Assessment**

Note minor changes in red text, including comments in the notes section at the bottom of both power point slides. Please submit a pdf/mockup printed version of this knowledge assessment for FDA's review. The Knowledge Assessment cannot be a stand-alone material for the REMS program, including the website. It must be attached to the Training Slides.

### **Addyi REMS Website**

New comments regarding FDA's review of the website are included on the attached document, which outlines specific changes and asks one question.

**Please submit updated screenshots of all of the Addyi REMS webpages for FDA's review in your next submission.**

### **Addyi ISI**

The Agency will provide specific comments on the ISI later this week when the revised label is provided.

## **ATTACHMENTS**

- 1 Addyi REMS Patient-Provider Agreement Form
- 2 Addyi REMS Document
- 3 Addyi REMS Individual Location Outpatient Pharmacy Enrollment Form
- 4 Addyi REMS Inpatient Pharmacy Enrollment Form
- 5 Addyi REMS Multiple Locations Outpatient Pharmacy Enrollment Form
- 6 Addyi REMS Prescriber Enrollment Form
- 7 Addyi REMS Website
- 8 Addyi REMS Website Guidance Document
- 9 Addyi REMS Knowledge Assessment Slides
- 10 Addyi REMS Prescriber and Pharmacy Training Program

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SOMYA V DUNN  
08/18/2015

KIMBERLY LEHRFELD  
08/18/2015

**Risk Evaluation and Mitigation Strategy (REMS) Memorandum**

**U.S. FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
Office of Drug Evaluation III  
Division of Bone, Reproductive and Urologic Products**

**NDA/BLA #s:** 022526  
**Product:** Addyi (flibanserin), 100 mg oral tablet  
**APPLICANT:** Sprout  
**FROM:** Christine P. Nguyen, MD  
Deputy Director for Safety  
**DATE:** August 17, 2015

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use (ETASUs) is necessary for Addyi (flibanserin) to ensure that the benefits of the drug outweigh the increased risk of severe hypotension and syncope associated with Addyi (flibanserin) due to an interaction with alcohol. During the review of this application, FDA determined that the Applicant's proposed REMS, which consisted of a Medication Guide and a communication plan, was not adequate to mitigate these risks. Severe hypotension and syncope can occur with Addyi (flibanserin) alone and with use of CYP 3A4 inhibitors which will be mitigated through labeling and existing mechanisms within the health care system. In addition, the risk of severe hypotension and syncope appears to be significantly increased when Addyi (flibanserin) is taken concomitantly with alcoholic beverages based on data from a clinical trial conducted in predominantly male subjects, and this risk cannot be mitigated through current labeling or aforementioned mechanisms. This clinically significant interaction between Addyi (flibanserin) and alcohol is challenging to mitigate because Addyi (flibanserin) requires daily administration on a chronic basis, and alcohol use, is prevalent in the real world setting. According to the Center for Disease Control and Prevention, in the United States from 2006 to 2010, approximately 50% and 15% of non-pregnant women aged 18 – 44 years reported drinking alcohol and binge drinking, respectively, within the 30 days of taking the self-reported survey.<sup>1</sup>

Due to this interaction between Addyi (flibanserin) and alcohol, ETASU A and ETASU B are required to ensure that the drug's benefits outweigh the increased serious risk of severe hypotension and syncope. The REMS for Addyi (flibanserin) will ensure that prescribers are specially certified and understand that alcohol use is contraindicated with Addyi (flibanserin), and that they must agree to counsel patients about the increased risk of severe hypotension and syncope associated with Addyi (flibanserin) due to an interaction with alcohol, and the need to abstain from alcohol use during treatment with Addyi (flibanserin). In addition, certification of pharmacies that dispense Addyi (flibanserin) is necessary to establish that Addyi (flibanserin) has been prescribed only by certified prescribers. Pharmacy certification will also entail pharmacy counseling of patients prior to dispensing Addyi (flibanserin) of the need to abstain from alcohol intake while on treatment with Addyi (flibanserin).

In reaching this determination, we considered the following:

- A. Addyi (flibanserin) will be indicated for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women. Estimates of HSDD in U.S. women vary widely, depending on the instruments used for assessment as well as menopausal status of the women studied. Two large survey studies have estimated the prevalence of HSDD in U.S. premenopausal women to be 7.7% to 14%,<sup>2,3</sup> potentially affecting 5.5 to 8.6 million U.S. women ages 20 to 49 years.
- B. According to the Diagnostic and Statistical Manual Disorders (DSM)-IV, HSDD is characterized by “a deficiency or absence of sexual fantasies and desire for sexual activity” that causes “marked distress or interpersonal difficulty,” and this sexual dysfunction is not better accounted for by other causes, such as mood disorders or a medical condition. The marked distress or interpersonal difficulty resulting from HSDD can lead to poor quality of life and relationship difficulties. There is no FDA-approved treatment for HSDD.
- C. The Applicant conducted three double-blind, placebo-controlled efficacy trials to support the efficacy of Addyi (flibanserin). All three trials showed statistically significant improvement with Addyi (flibanserin) compared to placebo in number of satisfying sexual events (SSEs). The first two trials failed on their co-primary sexual desire endpoint (the daily sexual desire score). The descriptive data from these first two trials, however, showed improvement with Addyi (flibanserin) over placebo on secondary endpoints of desire assessed with the Female Sexual Function Index (FSFI) and distress related to low desire. These data were considered supportive of drug benefit on sexual desire. The third trial used the FSFI desire domain as the pre-specified co-primary endpoint for sexual desire and showed statistically significant improvement with Addyi (flibanserin) over placebo for both the FSFI desire co-primary and the secondary distress endpoint. Across these trials, the placebo-corrected treatment effect

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<sup>1</sup> <http://www.cdc.gov/ncbddd/fasd/kf-alcohol-use2006-2010.html>

<sup>2</sup> West SL, D'Aloisio AA, Agans RP, Kalsbeek WD, Borisov NN, et al. Prevalence of low sexual desire and hypoactive sexual desire disorder in a nationally representative sample of U.S. women. *Arch Intern Med* 2008;168:1441-9.

<sup>3</sup> Leiblum SR, Koochaki PE, Rodenberg CA, Barton IP, Rosen RC. Hypoactive sexual desire disorder in postmenopausal women: U.S. results from the Women's International Study of Health and Sexuality (WISHeS). *Menopause* 2006;13:46-56.

with Addyi (flibanserin) ranges from increases of 0.5 – 1.0 SSE per month (baseline 2 – 3 SSEs/month); improvement of 0.3-0.4 points on the Sexual Desire Score by FSFI-desire domain (baseline score 1.8 -1.9); decrease of 0.3 to 0.4 points on distress score (baseline score of 3.2 - 3.4). FDA's responder Analysis anchoring these efficacy endpoints to the Patient Global Impression of Improvement indicated that 7-13% of subjects (placebo-corrected) reported the treatment difference to be meaningful.

- D. Flibanserin 100 mg is to be taken daily, on a chronic basis, as long as a woman remains premenopausal and has a diagnosis of HSDD.
- E. The most important safety concern for Addyi (flibanserin) in the treatment of women with HSDD warranting risk mitigation under the REMS is the increased risk of severe hypotension and syncope associated with Addyi (flibanserin) due to an interaction with alcohol. These serious risks may result in potentially serious and life-threatening injuries.

In a dedicated alcohol interaction study conducted in 25 subjects (23 men and 2 premenopausal women), severe hypotension or syncope requiring therapeutic intervention (ammonia salts and/or placement in supine or Trendelenberg position) occurred in 4 of the subjects co-administered Addyi (flibanserin) 100 mg and 0.4 g/kg alcohol (equivalent of two 12 ounce cans of beer containing 5% alcohol content, two 5 ounce glasses of wine containing 12% alcohol content, or two 1.5 ounce shots of 80-proof spirit in a 70 kg person, consumed over 10 minutes in the morning) compared to no such events when Addyi (flibanserin) or alcohol were administered alone. In these 4 subjects, all of whom were men, the magnitude of the systolic blood pressure reductions ranged from 28 to 54 mmHg and the magnitude of the diastolic blood pressure reductions ranged from 24 to 46 mmHg. In addition, 6 (25%) of the 24 subjects co-administered Addyi (flibanserin) 100 mg and 0.8 g/kg alcohol experienced orthostatic hypotension when standing from a sitting position. The magnitude of the systolic blood pressure reductions in these 6 subjects ranged from 22 to 48 mmHg, and the diastolic blood pressure reductions ranged from 0 to 27 mmHg. Although this study was primarily performed in men, it is expected that these risks will be similar, if not exacerbated in the target population of women who will use flibanserin.

To mitigate the risks due to the interaction between Addyi and alcohol, a variety of strategies were assessed. As use of alcoholic beverages in the target population of premenopausal women is expected to be common, a broader strategy to maximize provider, pharmacy and patient understanding of the risk communication to not drink alcoholic beverages while taking Addyi is necessary. The use of an ETASU along with other risk mitigation strategies (i.e. Medication Guide) has been demonstrated to augment correct identification of the primary drug risk as reported in a recent analysis of Medication Guide Assessments.<sup>4</sup> Given these factors along with the seriousness of the hypotensive and syncopal events documented in the clinical trial that evaluated the interaction of Addyi and alcohol, it was determined that ETASU were necessary.

E. Addyi (flibanserin) is a new molecular entity.

<sup>4</sup> Knox C., Hampp C., Willy M., Winterstein A., and Dal Pan, G. Patient understanding of drug risks: an evaluation of medication guide assessments. *Pharmacoepidemiology and Drug Safety* 2015; 24: 518-25.

The Addyi (flibanserin) REMS will consist of elements to assure safe use, including that prescribers will be specially certified and pharmacies that dispense Addyi (flibanserin) are specially certified, an implementation system, and a timetable for submission of assessments of the REMS.

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/s/  
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CHRISTINE P NGUYEN  
08/17/2015

**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Office of Surveillance and Epidemiology**  
**Office of Medication Error Prevention and Risk Management**  
**RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW**

Date: July 29, 2015

Reviewer(s): Somya Dunn, M.D., Risk Management Analyst  
Division of Risk Management (DRISK)

Joan Blair, R.N., M.P.H., Health Communications Analyst,  
DRISK

Team Leader: Kim Lehrfeld, Pharm.D, DRISK

Deputy Division Director (Acting): Reema Mehta, Pharm.D, M.P.H., DRISK

Drug Name(s): Flibanserin (proposed proprietary name ADDYI)

Therapeutic Class: 5-HT<sub>1A</sub> Agonist and a 5-HT<sub>2A</sub> antagonist

Dosage and Route: Film-coated tablets 100 mg

Application Type/Number: NDA 22526

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## 1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK) comments on the proposed risk evaluation and mitigation strategy (REMS) for Addyi (flibanserin) tablets, NDA 22526, received from Sprout Pharmaceuticals (Sprout) on July 21, 2015. The proposed indication for Addyi is for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women. The NDA has been submitted three times and the 2015 submission is the third cycle. The first two cycles received a Complete Response (CR).

### 1.1 BACKGROUND

Flibanserin is a new molecular entity and is not marketed in any other country. Flibanserin is a 5-HT<sub>1A</sub> receptor agonist and a 5-HT<sub>2A</sub> receptor antagonist with a proposed indication to treat HSDD in premenopausal women. The precise mechanism of action of flibanserin for treatment of HSDD is unknown, however, its impact on HSDD is believed to be related to its effects on norepinephrine, serotonin, and dopamine activities in the central nervous system. The recommended dose for flibanserin is 100 mg taken orally once daily at bedtime.

The diagnostic criteria for HSDD are defined by the American Psychiatric Association in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR. HSDD is characterized by persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity, as judged by the clinician. The symptoms must not be better explained by an alternative disorder or substance (e.g., alcohol abuse, medication) and should lead to marked distress and interpersonal difficulty.

The American Psychiatric Association published an updated DSM, termed DSM-5 in May of 2013. DSM-5 has merged features from HSDD and female sexual arousal disorder as described in DSM-IV-TR and replaced these conditions with a new condition, Female Sexual Interest/Arousal Disorder. As with HSDD, patients with Female Sexual Interest/Arousal Disorder must have associated distress and impairment and must not have an alternative explanation that better explains their symptoms. For this reason, HSDD will be defined in the approved PI and in the REMS materials.

### 1.2 REGULATORY HISTORY

The following is a summary of the regulatory history relevant to the REMS:

On December 2, 1996, FDA received the Investigational New Drug (IND) Application (IND (b) (4)) for flibanserin for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women.

On October 27, 2009, Boehringer Ingelheim (BI) submitted NDA 22526 for flibanserin for the treatment of HSDD.

On June 18, 2010, the FDA Reproductive Health Drugs Advisory Committee convened to discuss flibanserin, NDA 22526. The Committee determined that BI did not provide sufficient evidence to support: (1) the overall efficacy for flibanserin for treatment of

HSDD compared to placebo [vote: Yes-1; No-10; Abstain-0] or (2) that the overall risk/benefit profile of flibanserin for the treatment of HSDD in premenopausal women is acceptable [vote: Yes-0; No-11; Abstain-0]

On August 27, 2010, the Agency issued a Complete Response (CR) letter<sup>1</sup>, where the determination was made that the application could not be approved in its present form with efficacy and safety deficiencies. The CR letter highlighted lack of substantial efficacy for treatment of HSDD as well as concerns with efficacy in the presence of moderate CYP3A4 inhibitors. Safety issues cited included a lack of data from patients with comorbid conditions and on concomitant medications and alcohol. There was also insufficient information to assess the risk of accidental injuries associated with flibanserin. The company was also requested to study flibanserin in an abuse potential study since it is characterized as a CNS depressant. The CR letter included recommendations for a new Phase 3 trial with sexual desire as co-primary endpoints and HSDD-related distress as a key secondary endpoint; the Agency requested that sexual desire assessments have adequate content validity, recall validity, and acceptable measurement properties consistent with recommendations in the 2009 guidance on Patient-Reported Outcomes.

On February 17, 2012, BI sold flibanserin to Sprout Pharmaceuticals, Inc. (SPI) and the Agency acknowledged the transfer of ownership of the NDA.

On April 26, 2012, a Type B pre-NDA meeting between the Sponsor and DBRUP was held to discuss the contents of a CR submission. An additional Phase 3, double-blinded, placebo-controlled pivotal efficacy study (511.147), was initiated during the first flibanserin review cycle and completed February 2011, six months after the initial CR action. The study, compared to studies 511.71 and 511.75, allowed for:

- enrollment of a broader patient population
- more concomitant medication use
- sexual desire, measured by items 1 and 2 of the 19-item Female Sexual Function Index (FSFI), as a primary outcome measure

The study also included a sub-study for assessment of content and recall validity to compare 28-day versus 7-day recall. DBRUP advised that it would be a matter of review whether results from the new study (511.147) are adequate to support efficacy, since the co-primary efficacy endpoint (FSFI desire domain items 1 and 2), instruments, and recall periods (28 days versus 7 days), were not formally agreed to by DBRUP<sup>2</sup>.

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<sup>1</sup> Bietz, J. Office of New Drug/DBRUP Complete Response Letter to Flibanserin NDA 22526 dated August 27, 2010.

<sup>2</sup> As discussed by the Study Endpoints and Labeling Development (SEALD) team for flibanserin NDA 22526, use of patient reported outcomes (PROs) has been problematic throughout drug development of treatment of Female Sexual Dysfunction and different subgroups including HSDD. The main issues have been what questions to ask and what recall time to use (1, 7, 14, 28 days). The Division has fairly consistently favored use of electronic diaries and short recall time (24-72 hour range) for collection of accurate data, especially for satisfactory sexual events and sexual desire/interest. Study 511.147 used an electronic diary to capture data but did not use the diary for measuring the change in sexual desire. Instead, the 19-item FSFI paper instrument was completed every 4 weeks at clinic visits. (See Page 21-23 of

On March 29, 2013, submitted their response to the DBRUP August 27, 2010 CR letter, resubmitting NDA 22526. Their resubmission did not include a REMS proposal.

On September 3, 2013, DRISK completed a Deferral of Risk Evaluation and Mitigation Strategies (REMS) Review of Flibanserin<sup>3</sup>.

On September 27, 2013, DBRUP issued a CR letter<sup>4</sup> to the sponsor for flibanserin stating “you have consistently shown modest improvements in the placebo-adjusted treatment responses in premenopausal women with HSDD, as assessed using the Female Sexual Function Index (FSFI) sexual desire domain, and the number of satisfying sexual events. However, we are not convinced that these treatment effects offset the identified substantial safety concerns.”

The following summarizes highlights of safety concerns and deficiencies, as detailed in the CR letter:

- Central nervous system (CNS) depression (fatigue, somnolence, and sedation) occurred in 21% of subjects taking flibanserin 100 mg nightly.
- Increased frequency of syncope and accidental injury, including serious events, compared to placebo
- Drug-drug interactions with centrally-acting drugs (e.g. serotonin-norepinephrine reuptake inhibitors, alcohol, triptans), strong or moderate CYP3A4 inhibitors as well as alcohol
- Marked increase in flibanserin exposure, poor tolerability and a higher frequency of syncope and hypotension when flibanserin is administered with drugs that are strong or moderate CYP3A4 inhibitors (e.g., hormonal contraceptives)
- Greater incidence of appendicitis among flibanserin users compared to placebo
- Studies on mice demonstrated an increased incidence of mammary tumors at doses three times the recommended for humans
- Human studies of flibanserin’s abuse potential were not interpretable

DBRUP recommendations related to the deficiencies cited above included:

- The sponsor should show how risks will be minimized in clinical practice including CNS effects (fatigue, dizziness, somnolence and sedation), and syncope, hypotension and accidental injury
- Propose strategies beyond labeling to ensure flibanserin is not prescribed with moderate or strong CYP3A4 inhibitors, or taken with alcohol or other centrally-acting medications
- Conduct a driving impairment study
- Propose a plan to determine whether the excess incidence of appendicitis observed in the Phase 3 placebo-controlled program is drug-related

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DBRUP Clinical and Safety Review of flibanserin NDA 22526 dated August 29, 2013 for detailed discussion.

<sup>3</sup> Vega, A. Deferral of Risk Evaluation and Mitigation Strategies (REMS) Review for Flibanserin dated September 3, 2013.

<sup>4</sup> Bietz, J., DBRUP Complete Response Letter for Flibanserin NDA 22526 dated September 27, 2013

- Propose a plan to assess the clinical risk of breast cancer in light of the non-clinical findings of dose-dependent mammary tumors in mice

On November 18, 2013, a Type A End of Review meeting was held between DBRUP and the sponsor to discuss the September 27, 2013 CR letter and path forward for the NDA.<sup>5</sup>

On December 3, 2013, the Sponsor filed a formal dispute resolution request (FDRR) to DBRUP's September 27, 2013 CR action for flibanserin NDA 22526.

On February 7, 2014, the Office of New Drugs (OND) responded to the sponsor's FDDR (Appeal Denied Letter)<sup>6</sup> denying the appeal in support of issues identified by DBRUP in their September 27, 2013 CR action.

On March 12, 2014, a Type A meeting was held to discuss a path forward to address deficiencies noted in the CR letter. Key among the issues addressed were a planned driving study to assess next-day impairment, drug-drug interaction studies to assess the effect of CYP2C9 and/or CYP2C19 enzymes on the metabolism of flibanserin. Guidance was provided on the planned studies. Additionally, guidance was provided, in collaboration between DBRUP and DRISK, to Sprout's questions about risk mitigation strategies. Sprout proposed a Communication Plan (CP) REMS. DBRUP and DRISK provided guidance that, although this would be a review issue at the time of submission, a CP may have limitations given the safety issues identified with flibanserin.<sup>7</sup>

On January 15, 2015, a Type B meeting was held to discuss the Sponsor's plan to address the concerns raised in the September 17, 2013 CR letter and the Agency's February 7, 2014 Appeal Denial Letter, in conjunction with the sponsor's planned NDA resubmission.<sup>8</sup>

On February 18, 2015, Sprout resubmitted their application (Seq. No. 0062). Their resubmission addressed issues cited in the September 17, 2013 CR and included the results of the recommended driving study (Study SPR-14-01), a pharmacogenetics study which addressed potential involvement of cytochrome P450 enzymes CYP2C9 and CYP2C19 in the metabolism of flibanserin (Study SPR-14-06), a proposed REMS with a MG and CP and updates to the U.S. Prescribing Information (USPI). As this is the current submission under review, some results from the studies are briefly discussed here:

- Study SPR-14-01 evaluated safety, tolerability, pharmacokinetics, and pharmacodynamics of flibanserin when given at a standard dose (100 mg), and at a supratherapeutic dose (200 mg). Results showed that therapeutic

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<sup>5</sup> DBRUP End of Review Type A meeting with Sprout Pharmaceuticals for Flibanserin NDA 22526 held on November 18, 2013.

<sup>6</sup> Jenkins, J. Office of New Drugs Appeal Denial for Sprout Pharmaceuticals FDRR for DBRUP September 27, 2013 CR action for Flibanserin NDA 22526, dated February 7, 2014.

<sup>7</sup> Division of Bone, Reproductive and Urologic Products (DBRUP) Memorandum of Meeting Minutes for the March 12, 2014 Type A Meeting with Sprout for Flibanserin (NDA 22526) dated April 10, 2014

<sup>8</sup> Division of Bone, Reproductive and Urologic Products (DBRUP) Memorandum of Meeting Minutes for the January 15, 2015 Type B Meeting with Sprout for Flibanserin (NDA 22526) dated February 10, 2015

- and supra-therapeutic doses of flibanserin had no negative effect on the measures of next-day simulated driving performance that were evaluated.
- In female subjects that were poor metabolizers of CYP2C9, concentrations of ADDYI 100 mg qd decreased about 19%, compared to those in extensive metabolizers of CYP2C9. However, flibanserin concentrations increased about 1.5 fold when flibanserin 100 mg was administered to CYP2C19 poor metabolizers compared to CYP2C19 extensive metabolizers. One poor metabolizer experienced syncope one hour after the single 100 mg dose of flibanserin. This subject had about twice the flibanserin concentration than those with normal CYP2C19 enzyme activity.

This submission also included validation of the instruments used in measuring the efficacy results along with a discussion of Sprout's current understanding of hypotension and syncope related to flibanserin, rare adverse events of appendicitis and breast cancer, and risk mitigation activities that they plan to undertake post-approval.

On March 24, 2015 DBRUP and DRISK presented REMS options for flibanserin to the REMS Oversight Committee (ROC) meeting. The meeting included a presentation of the safety and efficacy findings of flibanserin from DBRUP and DRISK's presentation of Sprout's proposed REMS and both DRISK and DBRUP's recommended REMS elements. ROC recommended risk management options, including labeling alone, a Communication Plan REMS, and REMS with ETASU options (prescriber and pharmacy certification), be presented for consideration by the AC.

On June 4, 2015, the joint BRUDAC/DsARM AC was held to discuss the flibanserin application. The AC panel was asked to discuss the clinical significance of the efficacy findings from the clinical program. They were also asked to discuss their level of concern with hypotension and syncope when flibanserin was used alone and also when used with alcohol. The panel was asked to vote on if they recommended approval with labeling alone, if they recommended approval with risk mitigation beyond labeling or if they did not recommend approval. Overall, the AC panel voted to approve 18 to 6 but only with risk mitigation beyond labeling. For most panelists voting for approval, this included REMS with ETASU. Although the REMS recommendations were not always concrete (the panel has varying exposures and experiences with REMS), approximately eight of the panelists recommended prescriber certification, eight recommended pharmacy certification and five recommended patient consent of some type (some of these recommendations are overlapping).

On June 11, 2015 DBRUP had a teleconference with Sprout where they advised Sprout to resubmit risk mitigation plans and to consider the options presented at the AC.

On June 18, 2015, Sprout submitted a document outlining arguments against an ETASU REMS.

On June 23, 2015 DBRUP and DRISK had a teleconference with Sprout to reiterate that they should consider the AC recommendations including ETASU D as several panel members had proposed a PPAF. The Applicant inquired about whether the Decreased

Sexual Desire Screener (DSDS) tool should be included in the REMS. The Agency stated that we have not reached a final decision regarding whether the tool is appropriate for inclusion in the REMS.

On June 29, 2015 (officially in EDR on July 2) Sprout submitted an updated REMS proposal to include ETASU A and B, both prescriber and pharmacy certification. They included their communication plan materials and other previously proposed materials under these ETASU.

On June 30, 2015, another ROC meeting was held to discuss REMS options. The options presented included ETASU D, documentation of safe use in the form of a patient/prescriber agreement form (PPAF) with Prescriber and Pharmacy Certification or with Pharmacy Certification were presented. REMS goals were also discussed. DRISK and DBRUP were considering whether hypotension and syncope with flibanserin alone or only with alcohol use should be mitigated by the REMS. ROC recommended hypotension and syncope with alcohol use should be the risks mitigated by the REMS and that ETASU A and B should be implemented (prescriber and pharmacy certification).

On July 2, 2015, Sprout sent edited and updated materials for the REMS.

On July 17, 2015, the Agency sent edited materials and comments to Sprout (Interim Comments #1). The Agency requested ETASU A and B as well as materials to support these ETASU (b) (4) Agreement Form (PPAF) and counseling tool, enrollment forms, and training materials).

On July 21, 2015 Sprout submitted edited materials to the Agency. These materials reflected their request for removing alcohol as a contraindication from the proposed label. These materials also reflected their request to have the PPAF removed from the REMS program. This submission is reviewed here.

On July 24, 2015 Sprout had a teleconference with the Agency to discuss alcohol as a contraindication and the inclusion of the PPAF in the REMS. They were told these would be required. In addition, they discussed some changes proposed to the label regarding mammary tumors in animal studies and the case of death in a post-menopausal patient.

## **2 MATERIALS REVIEWED**

Sprout Pharmaceuticals, Inc. REMS Amendment to NDA 22526 for Flibanserin, submitted July 21, 2015 (Seq. No. 0076)

## **3 SUMMARY OF SPONSOR'S REMS SUBMISSION AND DRISK COMMENTS**

### **3.1 GOALS**

The Sponsor revised the goals based on the comments provided by DRISK on July 17, 2015.<sup>9</sup>

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<sup>9</sup> Dunn S. DRISK REMS Review for Addyi (flibanserin). Dated, July 20, 2015.

### 3.2 ELEMENTS TO ASSURE SAFE USE

#### REMS Document

The proposed REMS document submitted by the Sponsor included ETASU A (prescriber certification) and ETASU B (pharmacy certification). The following is a summary of the notable changes proposed by Sprout in the REMS document.

- The Sponsor revised the requirements in implementation system to link the requirements to commercial availability.

#### Reviewer Comment

*REMS requirements should be linked to the approval of the REMS. We request that the Sponsor clarify when they expect the drug to be commercially available so that we can determine if we need to extend the 30 day period to accommodate.*

- The Sponsor revised the audit plan for wholesalers/distributors to (b) (4)

#### Reviewer Comment

*This change is not acceptable; audits should be done on all wholesalers/distributors.*

- The Sponsor revised the audit plan for certified pharmacies to (b) (4) a maximum of 100 certified pharmacies.

#### Reviewer Comment

*DRISK amended the audit plan to 100 certified pharmacies or 1% of certified pharmacies (whichever is greater). This Agency proposed amendment was based on Agency experience with the number of certified pharmacies participating in other REMS programs with restricted distribution and retail availability.*

- The Sponsor proposed editorial changes to language in the REMS document; the Agency did not accept these changes if it did not change the meaning of the document or was not consistent with Agency current practice (e.g., use of “Applicant” vs. “Sprout Pharmaceuticals”)
- The Sponsor removed the PPAF from the REMS and disagreed with the inclusion the PPAF for the following reasons:

- (b) (4)

- [REDACTED] (b) (4)
- [REDACTED]
- [REDACTED]
- [REDACTED]

Reviewer Comment

*DRISK does not agree with the Sponsor's assertions and believes the PPAF is a necessary component of the REMS for flibanserin. The PPAF is included in the REMS as a tool to assist prescribers in their efforts to inform patients about the risk of the alcohol interaction. The PPAF will support ETASU A and importantly, the REMS will not require a checkpoint prior to dispensing to ensure that the PPAF is completed. Thus, the PPAF should not be construed as part of an ETASU D. This is consistent with advice provided by the Advisory Committee members and with the preliminary comments shared by the Agency during the teleconference on July 8, 2015. Furthermore, inclusion of this tool under ETASU A is consistent with other approved REMS programs (e.g., Truvada® REMS, Prescribing Program for Lotronex®, and Mycophenolate REMS®). This was discussed further with the Sponsor during the July 24<sup>th</sup> teleconference and Sprout agreed with the inclusion of the PPAF in the REMS.*

**Prescriber Certification: Addyi REMS [REDACTED] (b) (4) Agreement Form (PPAF)**

The Sponsor did not submit this form with edits as they did not want to include this form in the REMS.

The Agency resent the PPAF to the Sponsor with minor editorial revisions for inclusion in the REMS program under ETASU A Prescriber Certification on July 24, 2015. The Agency is also changing the name to "Patient-Provider Agreement Form" since this form can be used for pharmacy counseling.

**Pharmacy Certification: Pharmacy Enrollment Forms**

The Sponsor sent back all three pharmacy enrollment forms with minor edits:

- Addyi REMS Multiple Locations Pharmacy Enrollment Form
- Addyi REMS Individual Location Pharmacy Enrollment Form
- Addyi REMS Inpatient Pharmacy Enrollment Form

Reviewer Comment

*The Sponsor will be asked to review the tracked changes on these forms.*

## **Prescriber and Pharmacy Certification: The Addyi REMS Prescriber and Pharmacy Training Program with Knowledge Assessment**

As noted, the Sponsor did not want to include the PPAF in their REMS program. Therefore, their edited materials reflected this. The slides that discussed the PPAF were omitted from the Sponsor resubmission. In addition, DBRUP is requesting that hypotension and syncope due to an interaction with alcohol be a Contraindication in the label. The Sponsor disagreed with this and amended the label to reflect their new proposal which was to have this risk as Warning and Precaution. The Agency proposed training module included slides on the Contraindication. The Sponsor changed the module to reflect their version of the label.

The Knowledge Assessment submitted by the Sponsor contained four questions.



### Reviewer Comment

*The training program slides must be amended to reflect the original program where a PPAF was required and alcohol use would be contraindicated in the label.*

*The Knowledge Assessment questions did not capture the main risk messages for all the stakeholders. These should be revised as follows:*

1. Why is alcohol contraindicated with Addyi?
  - a) Hepatotoxicity
  - b) Teratogenicity
  - c) Hypotension and syncope
  - d) Hypersensitivity reaction
2. What is the purpose of the Addyi REMS (b) (4) Agreement Form?
  - a) For prescribers to use it to counsel patients at the office visit
  - b) For patient charting
  - c) For the patient to take home the important safety messages
  - d) For pharmacy counseling
  - e) All of the above
3. Pharmacies must counsel patients about the need to avoid alcohol

- a) Never
  - b) Only if the patient asks about alcohol use
  - c) With the first prescription only
  - d) With every prescription
4. What is the primary counseling message for the patient?
- a) Do not drink alcohol while taking Addyi until you know how alcohol affects you
  - b) Limit your alcohol use while taking Addyi
  - c) You must not drink alcohol while taking Addyi
  - d) Do not drink alcohol at night when you take your daily Addyi

### 3.3 ADDYI REMS WEBSITE

The Sponsor submitted an updated website to align with the Agency recommendations from July 17, 2015. This website included updates for some of the REMS materials as requested, such as enrollment forms and the training program. However, many changes need to be made. For example, the PPAF will be included in the REMS program as discussed. The home page also needs adjusting to provide clarity and links for materials. The home page must also provide an overview of the safe use conditions of the Addyi REMS Program. In addition, an easy link/box "Search for a Certified Pharmacy Near You" should be on the home page as well as the ***Prescriber Training, Enrollment, and Certification*** main page. (b) (4)

#### Reviewer Comment

*The Sponsor will receive a detailed list created by the Agency on all the changes they need to make to the website (Attachment 9). This details page by page all the changes that must take place.* (b) (4)

### 3.4 REMS SUPPORTING DOCUMENT

The REMS Supporting Document (SD) was submitted and was consistent with the Sponsor's proposed program. However, it lacked details to describe how the program will be implemented. The Sponsor will be provided questions to address in the SD to provide sufficient details regarding implementation and operationalization of the REMS program, including the Risk Message Map that includes the key messages communicated by the REMS materials. The key messages, as agreed upon with DBRUP include:

#### **ADDYI Risk Message for Prescriber:**

Risk Message #1: Alcohol is contraindicated for patients taking Addyi.

- Alcohol use is contraindicated with Addyi because the interaction can lead to hypotension and syncope, which may be life-threatening.

Risk Message #2: Prescribers must use the <sup>(b) (4)</sup> agreement <sup>(b) (4)</sup> (PPAF) to counsel their patients about the increased risk of hypotension and syncope associated with Addyi due to an interaction with alcohol whenever prescribing Addyi.

- The Patient-Provider Agreement Form is an important tool for prescribers to use with patients and should be used to counsel patients at the office visit.
- This form should be copied for the patient's chart.
- The bottom portion can be torn off for the patient to take home.
- This form can also be used for pharmacy counselling.

### **ADDYI Risk Message for Pharmacists**

Risk Message #1: Alcohol is contraindicated for patients taking Addyi.

- Alcohol use is contraindicated with Addyi because the interaction can lead to hypotension and syncope, which may be life-threatening.
- Risk Message #2: Certified pharmacies must counsel patients prior to dispensing every prescription about the need to avoid alcohol during treatment with Addyi.
- The Patient-Provider Agreement Form is an important tool and can be used by the pharmacist to counsel patients at the pharmacy.

### **ADDYI Risk Message for Patients**

Risk Message #1: Patients who are taking Addyi treatment must not drink alcohol.

Risk Message #2: Drinking alcohol while using Addyi can lead to low blood pressure and fainting, which may be life-threatening.

<sup>(b) (4)</sup>

- Revision of the expectation that Agency will provide comments on the assessment submission from no later than 3 months following assessment submission to within 6 months of assessment submission.

#### **4 DISCUSSION AND CONCLUSIONS**

Overall, DRISK is in agreement with the Sponsor regarding the ETASU necessary for inclusion in the Addyi REMS Program. Additionally, DRISK believes the program must include reference to the interaction with alcohol as a contraindication and all the materials must reflect this contraindication to align with the labeling for Addyi. In addition, there must be a PPAF to support prescriber certification. The Knowledge Assessment questions have been edited to reflect the Risk Message Mapping done by the Agency. The edited Addyi REMS document, enrollment forms and other materials will be provided to the Sponsor.

#### **5 COMMENTS FOR THE SPONSOR**

##### **REMS Document**

High level comments are included here, but detailed edits and comments are contained in the attachments. See all attached redlined documents.

- The implementation system was revised to link the requirements to the approval of the REMS. Clarify when you expect Addyi to be commercially available.
- The audit plan for wholesalers/distributors must be done for all wholesalers/distributors; therefore, the REMS document was revised to reflect this change.
- The proposed change to remove the (b) (4) Agreement Form (PPAF) was not accepted per the teleconference between the Agency and Sprout on July 24, 2015; therefore, the REMS document was revised to reflect this change.

##### **Prescriber Certification: Addyi REMS (b) (4) Agreement Form (PPAF)**

Revise the name of the (b) (4) Agreement Form to the Patient-Provider Agreement Form. The revised name of the form should be placed wherever appropriate.

##### **Pharmacy Certification: Pharmacy Enrollment Forms**

See all three forms for comments and edits:

- Addyi REMS Individual Location Outpatient Pharmacy Enrollment Form
- Addyi REMS Multiple Locations Outpatient Pharmacy Enrollment Form
- Addyi REMS Inpatient Pharmacy Enrollment Form

##### **Prescriber and Pharmacy Certification: The Addyi REMS Prescriber and Pharmacy Training Program with Knowledge Assessment**

The Training Program slides must align with the slides sent on July 17, 2015 as alcohol will be a contraindication and the PPAF will be part of the REMS. We also refer you to comments in the "NOTES" section of the slides for recommended changes to the slides. For the slide (#11) that discusses the PPAF, revise the last bullet to read:

- Pharmacists may use this form as an optional tool for counseling patients

The following Knowledge Assessment questions should be used for the post-training knowledge assessment, which aligns with the Risk Message Map included in the REMS Supporting Document:

5. Why is alcohol contraindicated with Addyi?
  - e) Hepatotoxicity
  - f) Teratogenicity
  - g) Hypotension and syncope
  - h) Hypersensitivity reaction
6. What is the purpose of the Addyi REMS (b) (4) Agreement Form?
  - f) For prescribers to use it to counsel patients at the office visit
  - g) For patient charting
  - h) For the patient to take home the important safety messages
  - i) For pharmacy counseling
  - j) All of the above
7. Pharmacies must counsel patients about the need to avoid alcohol
  - e) Never
  - f) Only if the patient asks about alcohol use
  - g) With the first prescription only
  - h) With every prescription
8. What is the primary counseling message for the patient?
  - e) Do not drink alcohol while taking Addyi until you know how alcohol affects you
  - f) Limit your alcohol use while taking Addyi
  - g) You must not drink alcohol while taking Addyi
  - h) Do not drink alcohol at night when you take your daily Addyi

### **Addyi REMS Website**

The website must be revised to include the PPAF.

The home page must be revised to include the following: (1) an overview of the safe use conditions of the Addyi REMS program; and (2) links for all REMS materials

An easy link/box "Search for a Certified Pharmacy Near You" should be included on the home page and the Prescriber Training, Enrollment, and Certification main page.

(b) (4)

See Attachment 10 (Addyi REMS Website Guidance Document) for additional comments on the website.

### **REMS Supporting Document**

The REMS Supporting Document (SD) lacks sufficient details to describe how the program will be implemented. See Attachment 8 (REMS SD) for guidance on additional details that should be described in the SD, including the Risk Message Map that includes the key messages communicated by the REMS materials.

(b) (4)

### **Other comments:**

Retain the individual and separate MS Word files for each of the REMS materials, submitting revised MS Word and pdf mocked up versions of each of the materials for FDA's review. **Accept track changes provided by FDA on each of the documents including the SD** and note new ones for our review. Track changes proposed by Sprout and not rejected by the Agency may be considered acceptable in the next submission. Please also provide clean and track change versions of all of the REMS materials by COB July 28, 2015.

**Final language in all REMS materials should reflect what is in the approved REMS document and the text of all REMS materials must match the current draft label and ultimately, the final label.** Make additional changes to the REMS materials to reflect the label and REMS document as needed.

Please note the following materials that are part of the Addyi REMS Program and are attached.

### **ATTACHMENTS**

1. Addyi REMS Document
2. Addyi REMS Individual Location Outpatient Pharmacy Enrollment Form
3. Addyi REMS Multiple Locations Outpatient Pharmacy Enrollment Form
4. Addyi REMS Inpatient Pharmacy Enrollment Form
5. Addyi REMS Prescriber Enrollment Form
6. Addyi REMS Prescriber and Pharmacy Training Program

7. Addyi REMS Knowledge Assessment Slides
8. Addyi REMS Supporting Document (to Sponsor only)
9. Addyi REMS Website
10. Addyi REMS Website Guidance Document

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/s/  
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SOMYA V DUNN  
07/29/2015

REEMA J MEHTA  
07/29/2015  
I concur.

**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Office of Surveillance and Epidemiology**  
**Office of Medication Error Prevention and Risk Management**  
**REMS MODIFICATION INTERIM COMMENTS**

Date: July 17, 2015

Reviewer(s): Somya Dunn, M.D., Risk Management Analyst  
Division of Risk Management (DRISK)

Joan Blair, R.N., M.P.H., Health Communications Analyst,  
DRISK

Team Leader: Kim Lehrfeld, Pharm.D, DRISK

Deputy Division Director (Acting): Reema Mehta, Pharm.D, M.P.H., DRISK

Acting Deputy Director Reema Mehta, PharmD, MPH  
Division of Risk Management

Drug Name(s): Flibanserin (proposed proprietary name ADDYI)

Therapeutic Class: 5-HT<sub>1A</sub> Agonist and a 5-HT<sub>2A</sub> antagonist

Dosage and Route: Film-coated tablets 100 mg

Application Type/Number: NDA 22526

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## **1 INTRODUCTION**

This review documents the rationale and interim comments for the proposed REMS Amendment (REMS) for flibanserin proposed proprietary name Addyi. Flibanserin is Sprout Pharmaceutical's (Sprout) NDA 22526, for the proposed indication of treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women. The NDA has been submitted three times and the 2015 submission is the third cycle. The first two cycles received a Complete Response (CR).

The most concerning risks identified by the Division of Bone, Reproductive and Urologic Products (DBRUP) and DRISK are the increased risks of hypotension and syncope that occur with flibanserin with concomitant alcohol use.

On June 29, 2015 (officially in EDR on July 2) Sprout submitted an updated REMS proposal to include prescriber certification and pharmacy certification. They included their communication plan materials and other previously proposed materials under these elements to assure safe use (ETASU). This review evaluates the Sponsor's submission.

### **1.1 BACKGROUND**

Flibanserin is a new molecular entity and is not marketed in any other country. Flibanserin is a 5-HT<sub>1A</sub> receptor agonist and a 5-HT<sub>2A</sub> receptor antagonist with a proposed indication to treat HSDD in premenopausal women. The precise mechanism of action of flibanserin for treatment of HSDD is unknown, however, its impact on HSDD is believed to be related to its effects on norepinephrine, serotonin, and dopamine activities in the central nervous system. The recommended dose for flibanserin is 100 mg taken orally once daily at bedtime.

The diagnostic criteria for HSDD are defined by the American Psychiatric Association in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR. HSDD is characterized by persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity, as judged by the clinician. The symptoms must not be better explained by an alternative disorder or substance (e.g., alcohol abuse, medication) and should lead to marked distress and interpersonal difficulty.

The American Psychiatric Association published an updated DSM, termed DSM-5 in May of 2013. DSM-5 has merged features from HSDD and female sexual arousal disorder as described in DSM-IV-TR and replaced these conditions with a new condition, Female Sexual Interest/Arousal Disorder. As with HSDD, patients with Female Sexual Interest/Arousal Disorder must have associated distress and impairment and must not have an alternative explanation that better explains their symptoms. For this reason, HSDD will be defined in the approved PI and in the REMS materials.

### **1.2 REMS REGULATORY HISTORY**

On December 2, 1996, FDA received the Investigational New Drug (IND) Application (IND (b) (4)) for flibanserin for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women.

On October 27, 2009, Boehringer Ingelheim (BI) submitted new drug application (NDA 22526) for flibanserin for the treatment of HSDD.

On June 18, 2010, the FDA Reproductive Health Drugs Advisory Committee convened to discuss flibanserin, NDA 22526. The Committee determined that BI did not provide sufficient evidence to support: (1) the overall efficacy for flibanserin for treatment of HSDD compared to placebo [vote: Yes-1; No-10; Abstain-0] or (2) that the overall risk/benefit profile of flibanserin for the treatment of HSDD in premenopausal women is acceptable [vote: Yes-0; No-11; Abstain-0]

On August 27, 2010, the Agency issued a Complete Response (CR) letter<sup>1</sup>, where the determination was made that the application could not be approved in its present form with efficacy and safety deficiencies. The CR letter highlighted lack of substantial efficacy for treatment of HSDD as well as concerns with efficacy in the presence of moderate CYP3A4 inhibitors. Safety issues cited included a lack of data from patients with comorbid conditions and on concomitant medications and alcohol. There was also insufficient information to assess the risk of accidental injuries associated with flibanserin. The company was also requested to study flibanserin in an abuse potential study since it is characterized as a CNS depressant. The CR letter included recommendations for a new Phase 3 trial with sexual desire as co-primary endpoints and HSDD-related distress as a key secondary endpoint; the Agency requested that sexual desire assessments have adequate content validity, recall validity, and acceptable measurement properties consistent with recommendations in the 2009 guidance on Patient-Reported Outcomes.

On February 17, 2012, BI sold flibanserin to Sprout Pharmaceuticals, Inc. (SPI) and the Agency acknowledged the transfer of ownership of the NDA.

On April 26, 2012, a Type B pre-NDA meeting between the Sponsor and DBRUP was held to discuss the contents of a CR submission. An additional Phase 3, double-blinded, placebo-controlled pivotal efficacy study (511.147), was initiated during the first flibanserin review cycle and completed February 2011, six months after the initial CR action. The study, compared to studies 511.71 and 511.75, allowed for:

- enrollment of a broader patient population
- more concomitant medication use
- sexual desire, measured by items 1 and 2 of the 19-item Female Sexual Function Index (FSFI), as a primary outcome measure

The study also included a sub-study for assessment of content and recall validity to compare 28-day versus 7-day recall. DBRUP advised that it would be a matter of review whether results from the new study (511.147) are adequate to support efficacy, since the co-primary efficacy endpoint (FSFI desire domain items 1 and 2),

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<sup>1</sup> Bietz, J. Office of New Drug/DBRUP Complete Response Letter to Flibanserin NDA 22526 dated August 27, 2010.

instruments, and recall periods (28 days versus 7 days), were not formally agreed to by DBRUP<sup>2</sup>.

On March 29, 2013, submitted their response to the DBRUP August 27, 2010 CR letter, resubmitting NDA 22526. Their resubmission did not include a REMS proposal.

On September 3, 2013, DRISK completed a Deferral of Risk Evaluation and Mitigation Strategies (REMS) Review of Flibanserin<sup>3</sup>.

On September 27, 2013, DBRUP issued a CR letter<sup>4</sup> to the sponsor for flibanserin stating “you have consistently shown modest improvements in the placebo-adjusted treatment responses in premenopausal women with HSDD, as assessed using the Female Sexual Function Index (FSFI) sexual desire domain, and the number of satisfying sexual events. However, we are not convinced that these treatment effects offset the identified substantial safety concerns.”

The following summarizes highlights of safety concerns and deficiencies, as detailed in the CR letter:

- Central nervous system (CNS) depression (fatigue, somnolence, and sedation) occurred in 21% of subjects taking flibanserin 100 mg nightly.
- Increased frequency of syncope and accidental injury, including serious events, compared to placebo
- Drug-drug interactions with centrally-acting drugs (e.g. serotonin-norepinephrine reuptake inhibitors, alcohol, triptans), strong or moderate CYP3A4 inhibitors as well as alcohol
- Marked increase in flibanserin exposure, poor tolerability and a higher frequency of syncope and hypotension when flibanserin is administered with drugs that are strong or moderate CYP3A4 inhibitors (e.g., hormonal contraceptives)
- Greater incidence of appendicitis among flibanserin users compared to placebo
- Studies on mice demonstrated an increased incidence of mammary tumors at doses three times the recommended for humans
- Human studies of flibanserin’s abuse potential were not interpretable

DBRUP recommendations related to the deficiencies cited above included:

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<sup>2</sup> As discussed by the Study Endpoints and Labeling Development (SEALD) team for flibanserin NDA 22526, use of patient reported outcomes (PROs) has been problematic throughout drug development of treatment of Female Sexual Dysfunction and different subgroups including HSDD. The main issues have been what questions to ask and what recall time to use (1, 7, 14, 28 days). The Division has fairly consistently favored use of electronic diaries and short recall time (24-72 hour range) for collection of accurate data, especially for satisfactory sexual events and sexual desire/interest. Study 511.147 used an electronic diary to capture data but did not use the diary for measuring the change in sexual desire. Instead, the 19-item FSFI paper instrument was completed every 4 weeks at clinic visits. (See Page 21-23 of DBRUP Clinical and Safety Review of flibanserin NDA 22526 dated August 29, 2013 for detailed discussion.

<sup>3</sup> Vega, A. Deferral of Risk Evaluation and Mitigation Strategies (REMS) Review for Flibanserin dated September 3, 2013.

<sup>4</sup> Bietz, J., DBRUP Complete Response Letter for Flibanserin NDA 22526 dated September 27, 2013

- The sponsor should show how risks will be minimized in clinical practice including CNS effects (fatigue, dizziness, somnolence and sedation), and syncope, hypotension and accidental injury
- Propose strategies beyond labeling to ensure flibanserin is not prescribed with moderate or strong CYP3A4 inhibitors, or taken with alcohol or other centrally-acting medications
- Conduct a driving impairment study
- Propose a plan to determine whether the excess incidence of appendicitis observed in the Phase 3 placebo-controlled program is drug-related
- Propose a plan to assess the clinical risk of breast cancer in light of the non-clinical findings of dose-dependent mammary tumors in mice

On November 18, 2013, a Type A End of Review meeting was held between DBRUP and the sponsor to discuss the September 27, 2013 CR letter and path forward for the NDA.<sup>5</sup>

On December 3, 2013, the Sponsor filed a formal dispute resolution request (FDRR) to DBRUP's September 27, 2013 CR action for flibanserin NDA 22526.

On February 7, 2014, the Office of New Drugs (OND) responded to the sponsor's FDDR (Appeal Denied Letter)<sup>6</sup> denying the appeal in support of issues identified by DBRUP in their September 27, 2013 CR action.

On March 12, 2014, a Type A meeting was held to discuss a path forward to address deficiencies noted in the CR letter. Key among the issues addressed were a planned driving study to assess next-day impairment, drug-drug interaction studies to assess the effect of CYP2C9 and/or CYP2C19 enzymes on the metabolism of flibanserin. Guidance was provided on the planned studies. Additionally, guidance was provided, in collaboration between DBRUP and DRISK, to Sprout's questions about risk mitigation strategies. Sprout proposed a Communication Plan (CP) REMS. DBRUP and DRISK provided guidance that, although this would be a review issue at the time of submission, a CP may have limitations given the safety issues identified with flibanserin.<sup>7</sup>

On January 15, 2015, a Type B meeting was held to discuss the Sponsor's plan to address the concerns raised in the September 17, 2013 CR letter and the Agency's February 7, 2014 Appeal Denial Letter, in conjunction with the sponsor's planned NDA resubmission.<sup>8</sup>

On February 18, 2015, Sprout resubmitted their application (Seq. No. 0062). Their resubmission addressed issues cited in the September 17, 2013 CR and included the

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<sup>5</sup> DBRUP End of Review Type A meeting with Sprout Pharmaceuticals for Flibanserin NDA 22526 held on November 18, 2013.

<sup>6</sup> Jenkins, J. Office of New Drugs Appeal Denial for Sprout Pharmaceuticals FDRR for DBRUP September 27, 2013 CR action for Flibanserin NDA 22526, dated February 7, 2014.

<sup>7</sup> Division of Bone, Reproductive and Urologic Products (DBRUP) Memorandum of Meeting Minutes for the March 12, 2014 Type A Meeting with Sprout for Flibanserin (NDA 22526) dated April 10, 2014

<sup>8</sup> Division of Bone, Reproductive and Urologic Products (DBRUP) Memorandum of Meeting Minutes for the January 15, 2015 Type B Meeting with Sprout for Flibanserin (NDA 22526) dated February 10, 2015

results of the recommended driving study (Study SPR-14-01), a pharmacogenetics study which addressed potential involvement of cytochrome P450 enzymes CYP2C9 and CYP2C19 in the metabolism of flibanserin (Study SPR-14-06), a proposed REMS with a MG and CP and updates to the U.S. Prescribing Information (USPI). As this is the current submission under review, some results from the studies are briefly discussed here:

- Study SPR-14-01 evaluated safety, tolerability, pharmacokinetics, and pharmacodynamics of flibanserin when given at a standard dose (100 mg), and at a supratherapeutic dose (200 mg). Results showed that therapeutic and supra-therapeutic doses of flibanserin had no negative effect on the measures of next-day simulated driving performance that were evaluated.
- In female subjects that were poor metabolizers of CYP2C9, concentrations of ADDYI 100 mg qd decreased about 19%, compared to those in extensive metabolizers of CYP2C9. However, flibanserin concentrations increased about 1.5 fold when flibanserin 100 mg was administered to CYP2C19 poor metabolizers compared to CYP2C19 extensive metabolizers. One poor metabolizer experienced syncope one hour after the single 100 mg dose of flibanserin. This subject had about twice the flibanserin concentration than those with normal CYP2C19 enzyme activity..

This submission also included validation of the instruments used in measuring the efficacy results along with a discussion of Sprout's current understanding of hypotension and syncope related to flibanserin, rare adverse events of appendicitis and breast cancer, and risk mitigation activities that they plan to undertake post-approval.

On March 24, 2015 DBRUP and DRISK presented REMS options for flibanserin to the REMS Oversight Committee (ROC) meeting. The meeting included a presentation of the safety and efficacy findings of flibanserin from DBRUP and DRISK's presentation of Sprout's proposed REMS and both DRISK and DBRUP's recommended REMS elements. ROC recommended risk management options, including labeling alone, a Communication Plan REMS, and REMS with ETASU options (prescriber and pharmacy certification), be presented for consideration by the AC.

On June 4, 2015, the joint BRUDAC/DsARM AC was held to discuss the flibanserin application. The AC panel was asked to discuss the clinical significance of the efficacy findings from the clinical program. They were also asked to discuss their level of concern with hypotension and syncope when flibanserin was used alone and also when used with alcohol. The panel was asked to vote on if they recommended approval with labeling alone, if they recommended approval with risk mitigation beyond labeling or if they did not recommend approval. Overall, the AC panel voted to approve 18 to 6 but only with risk mitigation beyond labeling. For most panelists voting for approval, this included REMS with ETASU. Although the REMS recommendations were not always concrete (the panel has varying exposures and experiences with REMS), approximately eight of the panelists recommended prescriber certification, eight recommended pharmacy certification and five recommended patient consent of some type (some of these recommendations are overlapping).

On June 11, 2015 DBRUP had a teleconference with Sprout where they advised Sprout to resubmit risk mitigation plans and to consider the options presented at the AC.

On June 18, 2015, Sprout submitted a document outlining arguments against an ETASU REMS.

On June 23, 2015 DBRUP and DRISK had a teleconference with Sprout to reiterate that they should consider the AC recommendations including ETASU D as several panel members had proposed a PPAF. The Applicant inquired about whether the Decreased Sexual Desire Screener (DSDS) tool should be included in the REMS. The Agency stated that we have not reached a final decision regarding whether the tool is appropriate for inclusion in the REMS.

On June 29, 2015 (officially in EDR on July 2) Sprout submitted an updated REMS proposal to include ETASU A and B, both prescriber and pharmacy certification. They included their communication plan materials and other previously proposed materials under these ETASU.

On June 30, 2015, another ROC meeting was held to discuss REMS options. The options presented included ETASU D, documentation of safe use in the form of a patient/prescriber agreement form (PPAF) with Prescriber and Pharmacy Certification or with Pharmacy Certification were presented. REMS goals were also discussed. DRISK and DBRUP were considering whether hypotension and syncope with flibanserin alone or only with alcohol use should be mitigated by the REMS. ROC recommended hypotension and syncope with alcohol use should be the risks mitigated by the REMS and that ETASU A and B should be implemented (prescriber and pharmacy certification).

### **1.3 MATERIALS REVIEWED**

Sprout Pharmaceuticals, Inc. REMS Correspondence to NDA 22526 for Flibanserin submitted July 2, 2015 (Seq. No. 0075)

## **2 REMS ELEMENTS PROPOSED BY THE SPONSOR WITH AGENCY RECOMMENDATIONS**

### **2.1 GOALS**

The Sponsor proposed the following goals:

-  (b) (4)
- 

- 

*Agency Comments:*

The REMS will mitigate the increased risk of hypotension and syncope due to an interaction with alcohol. [redacted] (b) (4)  
 [redacted]. The revised goal should read:

The goal of the Addyi REMS is to mitigate the increased risks of hypotension and syncope associated with Addyi due to an interaction with alcohol by:

- Ensuring prescribers and pharmacists are educated of 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.
- Informing patients of the increased risks of hypotension and syncope associated with Addyi due to an interaction with alcohol.

**2.1.1 Medication Guide**

The Sponsor submitted a Medication Guide (MG) but this document will not be part of the REMS. The MG will be part of the product labeling. The REMS will include a hypotension and syncope focused patient education material, the Addyi REMS [redacted] (b) (4)  
 [redacted] Agreement Form (see section 2.1.2).

**2.1.2 Elements to Assure Safe Use**

**REMS Document**

The REMS document submitted by the Sponsor contains both prescriber and pharmacy certification. These are acceptable. However, the format submitted is not consistent with the Agency’s current thinking for REMS documents. The REMS document also contains reference to various materials that will not be part of the REMS program. These are addressed below.

**Prescriber Certification: Prescriber Enrollment Form**

This form was submitted by the Sponsor. Editorial revisions as track changes were made to this form to organize and clarify the material as well as create

comprehensive attestations for the program. In addition, it was renamed the *Addyi REMS Prescriber Enrollment Form*.

### **The Addyi Appropriate Use and Counseling Checklist**

This checklist will not be part of the REMS. The information regarding considerations for prescribing that are relevant to the goal of the REMS is included in the training portion of the program and in the prescriber portion of the new Addyi REMS [REDACTED] <sup>(b) (4)</sup> *Agreement Form*.

### **The Decreased Sexual Desire Screener**

This document will not be part of the REMS [REDACTED] <sup>(b) (4)</sup>.

### **The Addyi REMS [REDACTED] <sup>(b) (4)</sup> Knowledge Assessments**

The current proposal from the Sponsor is consistent with the goals and tools that they submitted with their REMS. Many of these tools and materials are not consistent with the new Addyi REMS goals. Therefore, the Agency significantly revised the Sponsor's submitted training program and renamed it the *Addyi REMS Prescriber and Pharmacy Training Program*. The training is for both prescribers and pharmacies, as the new title indicates. It is designed to primarily be completed online, but should also be provided as a pdf printable version on the website should prescribers and pharmacies wish to take the training off line.

The Agency will request a knowledge assessment proposal with the REMS revisions. Review of the Knowledge Assessment will be completed during the next review cycle of the REMS materials once the other REMS materials are closer to being finalized.

#### *Additional Agency Recommendations for Prescriber Certification:*

### **Addyi REMS [REDACTED] <sup>(b) (4)</sup> Agreement Form**

This new material serves several purposes, including a patient counseling tool, prescriber agreement form, and patient agreement form outlining the risks associated with Addyi. This tool is designed to use in the prescriber's office and also serve as a charting documentation. It can also be used by pharmacists to counsel patients.

## Pharmacy Certification: Pharmacy Enrollment Forms

The Sponsor submitted (b) (4). Again, Agency revisions were made (b) (4) to organize and clarify the material as well as create comprehensive attestations for the program.



Additionally, the Sponsor did not propose to certify inpatient pharmacies. In order to ensure continuity of care for patients admitted to inpatient facilities, inpatient pharmacies must have access to flibanserin. However, inpatient prescribers will not be required to be certified in the Addyi REMS program and inpatient pharmacies will not be required to verify prescriber certification prior to dispensing. Inpatient pharmacy requirements have been added to the REMS document and the *Addyi REMS Inpatient Pharmacy Enrollment Form* was created.

### Letters: Dear Professional Organization Letters for Prescriber and Pharmacy, Dear Healthcare Provider Letter

These letters will not be part of the REMS program. The information needed for prescribers and pharmacists will be part of the *Addyi REMS Prescriber and Pharmacy Training Program* and also contained in the *Prescriber Enrollment Form* and *Pharmacy Enrollment Forms*.

### Timetable for Submission of Assessments

The Sponsor's timetable was appropriate. The Agency edited the wording to comply with the Agency's current thinking.

### 3 REMS ASSESSMENT PLAN

The REMS Assessment Plan is under discussion. However, a draft version is provided for the Sponsor for their review.

### 4 REMS SUPPORTING DOCUMENT

The REMS Supporting Document (SD) was submitted but was consistent with the Sponsor's proposed program. The Agency is requesting extensive changes to the program. Therefore the Sponsor will be asked to revise the SD.

## **2 DISCUSSION AND CONCLUSIONS**

Overall, DRISK agrees with the Sponsor's proposal in that the Addyi REMS Program should contain both prescriber and pharmacy certification. This includes the necessary enrollment forms as well as training materials. However, the program must focus on the increased risk of hypotension and syncope due to an interaction with alcohol. The proposed REMS document, training materials have been revised by the Agency to support this goal. Therefore, some of the Sponsor's proposed materials have been eliminated from the program and some have been edited for content. The newly designed *Addyi REMS Prescriber and Pharmacy Training Program* will be aimed at both prescribers and pharmacies. The *Addyi REMS* (b) (4) *Agreement Form* will be an important tool to support the goal. The pharmacy enrollment forms have been revised to account for all the types of pharmacies and methods of enrolling and checking prescriber certification. The edited Addyi REMS document, enrollment forms and other materials will be provided to the Sponsor for their review.

## **3 RECOMMENDATIONS**

Comments for the Sponsor:

### **Goals**

The REMS will mitigate the increased risk of hypotension and syncope due to an interaction with alcohol. Informing healthcare providers about patient selection and other specific instruction to providers are not to be part of this goal. The revised goal should read:

The goal of the Addyi REMS is to mitigate the increased risks of hypotension and syncope associated with Addyi due to an interaction with alcohol by:

- Ensuring prescribers and pharmacists are educated of 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.
- Informing patients of the increased risks of hypotension and syncope associated with Addyi due to an interaction with alcohol.

### **Medication Guide**

The Medication Guide (MG) will not be part of the REMS. The MG will be part of the product labeling. Therefore, you must submit it with your labeling revisions. It should not be submitted with REMS materials. The REMS will include a hypotension and syncope focused patient education material, the Addyi REMS (b) (4) Agreement Form which is described below.

### **REMS Document**

The REMS document contains both prescriber and pharmacy certification. These are acceptable. However, the format submitted is not consistent with the Agency's current thinking for REMS documents. Your proposed REMS document also contains reference to various materials that will not be part of the approved Addyi REMS program. These are addressed below.

**Prescriber Certification: Prescriber Enrollment Form**

Editorial revisions as track changes were made to this form to organize and clarify the material as well as create comprehensive attestations for the program. In addition, it was renamed the *Addyi REMS Prescriber Enrollment Form*.

**The Addyi Appropriate Use and Counseling Checklist**

This checklist will not be part of the REMS. The information regarding considerations for prescribing that are relevant to the goal of the REMS is included in the training portion of the program and in the prescriber portion of the new *Addyi REMS* (b) (4) *Agreement Form*.

**The Decreased Sexual Desire Screener**

This document will not be part of the REMS (b) (4)

**The Addyi REMS** (b) (4) **Knowledge Assessments**

The Agency revised the submitted training program and renamed it the *Addyi REMS Prescriber and Pharmacy Training Program*. The training is for both prescribers and pharmacies, as the new title indicates. It is designed to primarily be completed online, but should also be provided as a pdf printable version on the website should prescribers and pharmacies wish to take the training off line.

FDA's review of the Knowledge Assessment will be completed during the next review cycle of the REMS materials once the other REMS materials are more final. Please **submit a revised 3-4 question Knowledge Assessment** appropriate for both prescribers and pharmacists that reflects the revised REMS, REMS materials, and updated content from the *Addyi REMS Prescriber and Pharmacy Training Program*

**Additional Agency Recommendations: Addyi REMS** (b) (4) **Agreement Form**

This new material serves several purposes, including a patient counseling tool, prescriber agreement form, and patient agreement form outlining the risks associated with Addyi. This tool is designed to use in the prescriber's office and also serve as a charting documentation. It can also be used by pharmacists to counsel patients.

**Pharmacy Certification: Pharmacy Enrollment Forms**

Agency revisions were made to the submitted forms to organize and clarify the material as well as create comprehensive attestations for the program.

Your enrollment forms did not indicate that pharmacies without pharmacy management systems that transmit electronically for insurance claims could enroll in the Addyi REMS program. For example, closed healthcare system pharmacies (e.g. Kaiser and the Veterans Administration (VA)) do not transmit to external insurance companies for reimbursement. The Independent Pharmacy Enrollment Form has been revised to allow pharmacies to indicate if they have electronic transmission capabilities or not. An alternative way for these pharmacies to verify prescriber certification and receive a predispose authorization will need to be developed and implemented in the Addyi REMS program. Verification should be able to be accomplished in multiple ways; for example, by the certified pharmacy staff calling the Addyi REMS program or through the Addyi REMS website.

Additionally, you did not propose to certify inpatient pharmacies. In order to ensure continuity of care for patients admitted to inpatient facilities, inpatient pharmacies must have access to flibanserin. However, **inpatient prescribers will not be required to be certified in the Addyi REMS program** and inpatient pharmacies will not be required to verify prescriber certification prior to dispensing. Inpatient pharmacy requirements have been added to the REMS document and the *Addyi REMS Inpatient Pharmacy Enrollment Form* was created.

#### **Letters: Dear Professional Organization Letters for Prescriber and Pharmacy, Dear Healthcare Provider Letter**

These letters will not be part of the REMS program. The information needed for prescribers and pharmacists will be part of the Addyi REMS Prescriber and Pharmacy Training Program and also contained in the Prescriber Enrollment Form and Pharmacy Enrollment Forms.

#### **Timetable for Submission of Assessments**

Your timetable was appropriate. The Agency edited the wording to comply with the Agency's current thinking.

#### **REMS Assessment Plan**

The REMS Assessment Plan is under discussion. However, a draft version is provided for the Sponsor for their review.

#### **REMS Supporting Document**

You submitted a Supporting Document but it was consistent with the REMS program you proposed. Given the extensive changes to the program, the REMS Supporting Document must be revised and submitted to the Agency with your next submission.

#### **Addyi REMS Website**

FDA's review of the website will be completed during the next submission of the REMS materials to reflect the updated REMS, REMS materials, and Prescriber and Pharmacy

Training Program. Submit updated screenshots of all of the Addyi REMS webpages for FDA's review in your next submission. Demonstrate via screenshots how a health care provider and pharmacy will complete the training, knowledge assessment, and become enrolled as a prescriber or pharmacy.

**Other comments:**

Please note and retain the individual and separate MS Word files for each of the REMS materials, submitting revised MS Word and pdf mocked up versions of each of the materials for FDA's review. Please accept track changes provided by FDA on each of the documents and note new ones for our review. Provide clean and track change versions of all of the REMS materials by **COB JULY 21, 2015**.

Final language in all REMS materials should reflect what is in the approved REMS document and the text of all REMS materials must match the current draft label and ultimately, the final label. Please make additional changes to the REMS materials to reflect the label and REMS document as needed.

Please note that the following materials will not be included in the Addyi REMS Program:

- *Dear Healthcare Provider Letter*
- *Dear Pharmacist Letter*
- *Dear Professional Society Letters for Pharmacists*
- *Dear Professional Society Letters and for Prescribers*

Note the following materials that are part of the Addyi REMS Program. Some are revised versions of what was originally submitted to the Agency and some are new materials:

**4 ATTACHMENTS**

- Addyi REMS Document
- Addyi REMS Individual Location Outpatient Pharmacy Enrollment Form
- Addyi REMS Multiple Location Outpatient Pharmacy Enrollment Form
- Addyi REMS Inpatient Pharmacy Enrollment Form
- Addyi REMS Prescriber Enrollment Form
- Addyi REMS Patient-Prescriber Agreement Form
- Addyi REMS Prescriber and Pharmacy Training Program
- Addyi REMS DRAFT Assessment Plan

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SOMYA V DUNN  
07/17/2015

KIMBERLY LEHRFELD  
07/20/2015

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management  
Deferral of Risk Evaluation and Mitigation Strategies (REMS) Review**

Date: September 3, 2013

Reviewer(s): Amarilys Vega, MD, MPH, Medical Officer,  
Division of Risk Management (DRISK)

Team Leader: Cynthia LaCivita, Pharm D, Team Leader, DRISK

Subject: Risk management assessment deferral

Drug Name(s): Flibanserin

Therapeutic Class: 5-HT<sub>1A</sub> agonist and a 5-HT<sub>2A</sub> antagonist

Dosage and Route: Film-coated tablets 100 mg

Application Type/Number: NDA/22526

Submission Number: Original submission /Seq. No. 0039 (41)

Applicant/sponsor: Sprout Pharmaceuticals Inc.

OSE RCM #: 2013-861 and 2013-871

\*\*\* This document contains proprietary and confidential information that should not be released to the public. \*\*\*

## 1 INTRODUCTION

This review documents DRISK's defer to comment on if a Risk Evaluation and Mitigation Strategy (REMS) is necessary for flibanserin. Sprout Pharmaceuticals is seeking approval for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women.

Sprout Pharmaceuticals did not submit a REMS or risk management plan with their March 29, 2013 submission.

As of the time when this review was completed, flibanserin have not been approved in any other country.

### 1.1 BACKGROUND

*Hypoactive sexual desire disorder (HSDD)*. HSDD is defined as a persistent or recurrent deficiency or absence of sexual fantasies and thoughts, and/or desire for, or receptivity to sexual activity, which causes marked distress or interpersonal difficulties and is not caused by a medical condition or drug. HSDD is thought to be the most prevalent form of female sexual dysfunction, affecting up to 1 in 10 US women.<sup>1</sup> Currently, there is no FDA-approved treatment for HSDD.

*Flibanserin*.<sup>2</sup> Serotonin (also known as 5-hydroxytryptamine or 5-HT) is a neurotransmitter which regulates smooth muscle in the cardiovascular system and the gastrointestinal tract and promotes platelet aggregation.<sup>3</sup> Flibanserin's preferential activity is at post-synaptic serotonin receptors (5-HT<sub>1A</sub> receptor agonist and a 5-HT<sub>2A</sub> receptor antagonist) and has moderate affinity for 5-HT<sub>2B</sub>, 5-HT<sub>2C</sub>, and dopamine D4 receptors. Flibanserin's mechanism of action in HSDD is unknown but its pharmacologic effects on serotonin, dopamine, and norepinephrine are considered to be responsible for its clinical effects in patients with HSDD.

Flibanserin is supplied as a 100 mg immediate release film-coated tablet. The recommended human daily dose of flibanserin is 100 mg once daily at bedtime.

### 1.2 REGULATORY HISTORY

Following is the regulatory history of flibanserin, in pertinent part:

- **December 2, 1996:** FDA approves Investigational New Drug (IND) Application (b) (4) for flibanserin for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women.
- **October 27, 2009:** Boehringer Ingelheim submits to FDA New Drug Application 22-526 for flibanserin for the treatment of HSDD.
- **June 18, 2010:** Advisory Committee meeting. The committee determined that the Applicant did not provide sufficient evidence to support: (1) the overall efficacy for flibanserin for the treatment of HSDD compared to placebo (vote: Yes- 1; No – 10; Abstain- 0) or (2) that the

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<sup>1</sup> Simon JA.: Low Sexual Desire – Is it all in Her Head? Pathophysiology, Diagnosis, and Treatment of Hypoactive Sexual Desire Disorder. Postgrad Med. 2010 Nov;122(6):128-36.

<sup>2</sup> Flibanserin, Introduction and Clinical Overview, Sprout Pharmaceutical, dated March 19, 2013.

<sup>3</sup> Sanders-Bush E., Hazelwood L. (2011). Chapter 13. 5-Hydroxytryptamine (Serotonin) and Dopamine. In L.L. Brunton, B.A. Chabner, B.C. Knollmann (Eds), Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12e. Retrieved July 11, 2013 from <http://www.accessmedicine.com/content.aspx?aID=16662305>.

overall risk/benefit profile of flibanserin for the treatment of HSDD in premenopausal women is acceptable (vote: Yes-0; No-11; Abstain-0).

- **August 27, 2010:** FDA issues a Complete Response letter.
- **February 17, 2012:** Boehringer Ingelheim sold flibanserin to Sprout Pharmaceuticals, Inc. and on February 17, 2012 FDA acknowledged the transfer of ownership of the NDA to Sprout Pharmaceuticals.
- **March 29, 2013:** Sprout Pharmaceuticals submits their response to the August 27, 2010 Complete Response letter and resubmits NDA 22-526 to FDA.

Important upcoming dates:

- **September 29, 2013:** PDUFA date.

## 2 MATERIALS REVIEWED

### 2.1 DATA AND INFORMATION SOURCES

- Flibanserin Advisory Committee meeting minutes, dated June 18, 2010
- Flibanserin Complete Response letter, August 27, 2010
- Flibanserin Clinical Overview, dated November 08, 2012.
- Flibanserin Summary of Clinical Efficacy, dated October 30, 2012.
- Flibanserin Summary of Clinical Safety, dated November 06, 2012.
- Clinical Review, Daniel Davis, M.D. (efficacy) and Olivia Easley, M.D. (safety), dated August 29, 2013.
- General Advice Letter, Hylton V. Joffe, M.D., M.M.Sc., dated August 30, 2013.

## 3 REVIEW FINDINGS

The following safety concerns were identified.<sup>4</sup>

- Central nervous system (CNS) depression (fatigue, somnolence, and sedation) occurred in 21% of subjects taking flibanserin 100 mg nightly. CNS adverse effects were more pronounced with concomitant administration of hormonal contraceptives.
- Increased frequency of syncope and accidental injury, including serious events, compared to placebo.
- Drug-drug interactions with centrally-acting drugs (e.g., serotonin-norepinephrine reuptake inhibitors, alcohol, triptans), strong or moderate CYP3A4 inhibitors as well as alcohol.
- Adverse impact on tolerability of flibanserin with concomitant administration of centrally-acting drugs (e.g., serotonin-norepinephrine reuptake inhibitors, alcohol, triptans).
- Marked increase in flibanserin exposure, poor tolerability and a higher frequency of syncope and hypotension when flibanserin is administered with drugs that are strong or moderate CYP3A4 inhibitors (e.g., hormonal contraceptives).
- Treatment discontinuation rate (15%) was twice that observed in placebo.
- Greater incidence of appendicitis among flibanserin users compared to placebo.

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<sup>4</sup> General Advice Letter, Hylton V. Joffe, M.D., M.M.Sc., dated August 30, 2013.

- Studies in mice demonstrated an increased incidence of mammary tumors at doses three times the recommended human.
- Human studies of flibanserin’s abuse potential were deemed interpretable.

The Division of Bone, Reproductive, and Urologic Products (DBRUP) considers that flibanserin does not have a favorable benefit:risk profile.

*“We believe that the risk/benefit profile for Flibanserin 100 mg taken at bedtime is not favorable. Low sexual desire and distress are the hallmark of HSDD, so it seems imperative that a statistically significant and clinically meaningful change in these two endpoints be clearly demonstrated. We do not believe that the difference between the placebo and flibanserin response merits approval given the safety issues with flibanserin compared to the placebo treatment.”<sup>5</sup>*

#### **4 CONCLUSION AND RECOMMENDATIONS**

The benefit:risk profile of flibanserin 100 mg tablets for the treatment of HSDD is unfavorable. DBRUP plans to issue a Complete Response (CR) letter. Therefore, DRISK defers comment on the management of the risks associated with flibanserin and labeling at this time. A final discussion on the appropriate risk management strategy will be undertaken after the sponsor submits a satisfactory response to the CR letter. Please contact DRISK if you have any questions.

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<sup>5</sup> Clinical Review, Daniel Davis, M.D. (efficacy) and Olivia Easley, M.D. (safety), dated August 29, 2013, page 10.

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/s/  
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AMARILYS VEGA  
09/03/2013

CYNTHIA L LACIVITA  
09/03/2013  
Concur