

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022526Orig1s000

OTHER ACTION LETTERS

Food and Drug Administration (FDA)
Center for Drug Evaluation and Research (CDER)
Office of New Drugs (OND)
Office of Drug Evaluation (ODE) III
Division of Bone, Reproductive, and Urologic Products (DBRUP)

Clinical Memorandum

September 17, 2015

To: NDA 022526

From: Christina Chang, M.D., M.P.H. – Clinical Team Leader, DBRUP

Through: Hylton Joffe, M.D., M.M.Sc. – Division Director, DBRUP

This memorandum serves to amend information contained in the September 27, 2013 Complete Response Letter (CRL), and related reviews.

In the CRL, item 1d under the **Clinical Safety** section documents the Division’s assessment concerning the incidences of accidental injuries temporally related to sedation that were observed in the Phase 3 clinical program for both flibanserin and placebo. Item 1d states:

“Flibanserin 100 mg nightly appears to be associated with an increased frequency of adverse events of hypotension, syncope and accidental injury, including reports of severe events. Although the phase 3 program is not large enough to assess the risk of major injury (e.g., motor vehicle accidents), sedation was reported more commonly in association with reports of injury in flibanserin-treated subjects as compared to placebo-treated subjects (74% vs. 37%).”

Based on further communication with the Applicant and re-analysis of the data, the Division determined that the two percentages stated in this paragraph and in the related reviews were incorrect. The paragraph should state:

“Flibanserin 100 mg nightly appears to be associated with an increased frequency of adverse events of hypotension, syncope and accidental injury, including reports of severe events. Although the phase 3 program is not large enough to assess the risk of major injury (e.g., motor vehicle accidents), sedation was reported more commonly in association with reports of injury in flibanserin-treated subjects as compared to placebo-treated subjects (**21% vs. 6%**).”

The revised percentages also apply to the corresponding text in the related reviews. The correct information is conveyed in the final, approved labeling.

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/s/

CHRISTINA Y CHANG
09/17/2015

HYLTON V JOFFE
09/17/2015



NDA 022526

COMPLETE RESPONSE

Sprout, Inc.
Attention: Richard Divan
Director, Regulatory Affairs
4208 Six Forks Road, Suite 1010
Raleigh, NC 27609

Dear Mr. Divan:

Please refer to your New Drug Application (NDA) dated and received October 27, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flibanserin Tablets.

We also refer to our Complete Response letter dated August 27, 2010 and your Complete Response Submission received March 29, 2013.

We also acknowledge receipt of your amendments dated November 20, December 17, 18, and 23, 2009, January 21, and 26, February 5, 19, 24, March 3, 9, 12, 16, April 13, 26, 28, 30(2), May 7, 12(2), 13, 14, 19, 25, 26, 27, June 8, 15, 16(2), 17, July 2, and 8, 2010, August 8, September 20, December 29, 2011, January 20, August 23, 2012, April 10, May 6, 17, 22, June 14, July 17, 18, August 1, 5, and September 12, 2013.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. You have consistently shown modest improvements in the placebo-adjusted treatment responses in premenopausal women with hypoactive sexual desire disorder (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.

We have detailed our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL EFFICACY

1. The efficacy of flibanserin is modest in the population of premenopausal women that was studied. Taken together, your three phase 3 trials showed that treatment with flibanserin 100 mg nightly over 6 months resulted in fairly consistent improvements in the number of satisfying sexual events and in sexual desire, and reduction in distress. Changes in the number of satisfying sexual events and sexual desire correlated when desire was assessed using the FSFI sexual desire domain, but not when desire was assessed daily using an

electronic diary. Based on anchoring to the patient global improvement questionnaire, the difference between the percentage of responders on flibanserin and the percentage of responders on placebo was about 10%. We are not convinced that the treatment benefits observed with flibanserin outweigh the identified substantial safety concerns.

2. You have not adequately established content validity for the FSFI sexual desire domain. As previously communicated, FDA is willing to accept the measurement of “desire” using a well-defined and reliable scale that adequately captures the components of this concept, consistent with FDA’s “Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims,” December 2009. Your Complete Response submission included two validation studies (Studies 511.144 and 511.151) that enrolled a total of 45 premenopausal women. With respect to the two items in the FSFI sexual desire domain, only 67% (10/15) of subjects in the first study and 53% (16/30) of subjects in the second study reported that the two questions together reflected all of their problems with sexual desire or interest. Open-ended concept elicitation interviews were not performed to determine if there are additional components of sexual desire that should be included as separate items in an assessment of sexual desire.
3. It is unclear how healthcare providers would identify appropriate candidates for flibanserin, if approved. In your September 12, 2013, amendment, you propose having healthcare providers use the “Decreased Sexual Desire Screener” to assess whether patients have HSDD. However, it does not appear that this instrument has been used in the context of flibanserin’s clinical development program. In addition, HSDD has been replaced by female sexual interest/arousal disorder in the newly revised Diagnostic and Statistical Manual of Mental Disorders (DSM). The impact of this change in DSM criteria on the appropriate selection of patients for treatment with flibanserin is unclear. The potential for widespread use in patients who are not necessarily appropriate candidates for this therapy is a major concern.
4. Co-administration of flibanserin with CYP3A4 inducers reduced flibanserin exposures. Specifically, flibanserin exposure was reduced by 96% and 21% in the presence of rifampin and etravirine, respectively.

To address these issues, we recommend that you:

1. Identify and assess the efficacy of flibanserin in a well-defined population of premenopausal women in whom a larger treatment effect size may be demonstrated. Such a population would be enriched with subjects with more severely reduced sexual desire or satisfying sexual events at baseline. Use of the newly established DSM-5 criteria to select patients for assessment of flibanserin efficacy should be considered.
2. If such a population is identified, propose ways that healthcare providers can easily and accurately select appropriate candidates for treatment. Any instrument(s) to be used by healthcare providers to identify patients in clinical practice who may be appropriate candidates for treatment should be assessed in the context of your flibanserin clinical trial(s).

3. Explore areas of improved measurement of sexual desire that may increase understanding of treatment benefit including:
 - a. Ensuring that the instrument used to assess the concept of sexual desire has adequate content validity and other measurement properties
 - b. Improving measurement of the concept of interest (e.g., use of an electronic diary; use of a shorter recall period, e.g., 24 hours).
4. Clarify how you would advise healthcare providers regarding flibanserin dosing with concomitant use of strong and moderate CYP3A4 inducers, if the drug is approved.

CLINICAL SAFETY

1. Central nervous system depression (e.g., fatigue, somnolence, and sedation) is reported frequently in patients taking flibanserin 100 mg nightly. These effects are more pronounced in settings that increase flibanserin exposures and when flibanserin is administered during the daytime rather than at bedtime. In addition, the long half-life of flibanserin raises concern for residual next-day impairment even if flibanserin is dosed at bedtime. We are concerned that labeling alone will not mitigate the safety concerns arising from situations that increase flibanserin exposures or if patients do not adhere to the dosing directions. These concerns are detailed further below:
 - a. Concomitant administration of centrally-acting medications (e.g., serotonin-norepinephrine reuptake inhibitors, alcohol, triptans) may adversely affect flibanserin tolerability and may compromise patient safety. We are concerned with the pronounced effect of concomitant use of alcohol, as two subjects in Study SPR-12-03 required medical intervention after experiencing orthostatic syncope and hypotensive episodes. In addition, we are not convinced that the submitted alcohol interaction study was adequately designed to assess the full extent of the risks associated with co-administration with flibanserin. For example, the study used a subjective visual analog scale for sedation and did not include objective endpoints for assessing impairment. This is an issue because subjective evaluations correlate poorly with objective impairment. In addition, sedation was assessed only up to four hours after dosing and the data show that the visual analog scale was maximally affected by flibanserin plus ethanol at this timepoint with an unknown time-course for recovery. We are also concerned that the study enrolled mostly men (23 of 25, 92%). Women, who are the only target population for flibanserin, may have a more pronounced effect to co-administered alcohol.
 - b. Co-administration of flibanserin with drugs that are strong or moderate CYP3A4 inhibitors leads to a marked increase in flibanserin exposure, poor tolerability and a higher frequency of syncope and hypotension, which may be severe, compared to flibanserin used alone. Of particular concern, three subjects who received flibanserin and fluconazole in Study SPR-12-01 experienced symptomatic hypotension; one

subject became unresponsive and required medical intervention for a profound hypotensive episode (64/41 mmHg).

- c. Central nervous system adverse effects such as dizziness and fatigue appear to be more pronounced when flibanserin is administered with hormonal contraceptives. This interaction may compromise the safety of flibanserin in young women, many of whom will likely be chronic users of hormonal contraceptives.
 - d. Flibanserin 100 mg nightly appears to be associated with an increased frequency of adverse events of hypotension, syncope and accidental injury, including reports of severe events. Although the phase 3 program is not large enough to assess the risk of major injury (e.g., motor vehicle accidents), sedation was reported more commonly in association with reports of injury in flibanserin-treated subjects as compared to placebo-treated subjects (74% vs. 37%). Your assessment of “Choice Reaction Time”, an endpoint that tests general alertness and motor speed (which are important for driving and activities requiring mental alertness), showed impairment for up to 3.5 hours after dosing. However, this study was not adequately designed to exclude impairment at later timepoints; the study results are also limited because of the lack of a positive control. Given the long half-life for flibanserin, we have substantial concern about the potential for residual next-day impairment after bedtime dosing, including driving impairment.
2. These additional concerns have been identified during the course of our review:
- a. A greater incidence of appendicitis among flibanserin users compared to placebo may represent a class effect of drugs with 5HT_{2A} antagonism.
 - b. It is unclear whether the increased incidence of mouse mammary tumors observed at flibanserin exposures three and ten times the recommended human dose represents a clinical risk of breast cancer. The absence of a mammary tumor signal in rats does not completely exclude human risk. We note that the duration of the clinical trials (up to 6 months) is insufficient to characterize the incidence of neoplasms related to chronic use of flibanserin.

To address these issues, we recommend that you:

1. Clarify how the following risks will be minimized in clinical practice, if flibanserin is approved:
 - a. Central nervous system effects (e.g., fatigue, dizziness, somnolence and sedation)
 - b. Syncope, hypotension and accidental injury
2. Propose strategies beyond labeling to ensure that flibanserin is not prescribed with moderate or strong CYP3A4 inhibitors, or taken with alcohol or other centrally-acting medications.
3. Propose a strategy to mitigate the risk to patients associated with concomitant use of flibanserin and hormonal contraceptive products.

4. Conduct a driving impairment study that incorporates the following general characteristics:
 - a. Employs either a driving simulator or an “on-the-road” study design
 - b. Includes a positive control and a placebo arm
 - c. Assesses drug effects at up to the highest doses and exposures that could be encountered in clinical use. This includes exposures that might be experienced by patients with specific intrinsic or extrinsic factors that could lead to higher systemic exposures.
 - d. Evaluates impairment after a single-dose and chronic exposure (at steady-state drug levels). Given the long half-life of flibanserin, we are concerned that a single bedtime dose may produce residual central nervous system effects into the next morning. Therefore, the driving impairment study following a single dose flibanserin exposure should be conducted on the morning following bedtime dosing.
5. Propose a plan to determine whether the excess incidence of appendicitis observed in the phase 3 placebo-controlled program is drug-related.
6. 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 at flibanserin exposures three and ten times the proposed human dose.

CLINICAL PHARMACOLOGY

1. Cumulative findings from the ketoconazole and fluconazole (strong and moderate CYP3A4 inhibitors) drug interaction studies and physiologically-based pharmacokinetic modeling suggest that other CYP enzymes are involved in the metabolism of flibanserin.

Data from your original submission showed that co-administration of flibanserin 50 mg with ketoconazole, a strong CYP3A4 inhibitor, resulted in a 4.6-fold increase in flibanserin exposure. Data provided in your resubmission showed that multiple doses of fluconazole resulted in a 2.2-fold increase in C_{max} and a 7.0-fold increase in the AUC_{0-inf} of flibanserin. The 7-fold increase in flibanserin exposure with fluconazole, a moderate CYP3A4 inhibitor, was not anticipated based on the presumed metabolic pathway of flibanserin (mainly through CYP3A4 and to a minor extent CYP2D6, as you have stated).

Fluconazole is identified as an inhibitor of multiple enzymes - CYP3A4 (moderate), CYP2C9 (moderate) and CYP2C19 (strong) according to FDA’s “Draft Guidance for Industry: Drug Interactions – Study Design, Data Analysis, Implications for Dosing and Labeling Recommendations,” February 2012. Your *in vivo* study results suggest that CYP2C9 and/or CYP2C19 may be involved in the metabolism of flibanserin.

2. Data from the digoxin-flibanserin drug interaction study suggest that flibanserin may be an inhibitor of P-glycoprotein (P-gp). Digoxin is a P-gp substrate and is commonly used as a probe in drug interaction studies to evaluate potential P-gp substrates and/or inhibitors.

The digoxin C_{max} increased by 46% and AUC_{0-inf} increased by 96% following multiple doses of flibanserin 100 mg co-administered with a single dose of digoxin 0.5 mg. A 2-fold increase in digoxin exposure suggests flibanserin may be a P-gp inhibitor. Due to the relatively narrow margin for safety, this increase in digoxin systemic exposure could shift a patient from being exposed to a safe maintenance dose to a toxic dose.

To address these issues, we recommend that you:

1. Propose a plan to assess the effect of CYP2C9 and CYP2C19 enzymes on the metabolism of flibanserin. In addition, identify other metabolic enzymes that may contribute to the metabolism of flibanserin and provide plans to address potential drug interactions.
2. Propose a strategy to mitigate the risk to patients associated with concomitant use of flibanserin and digoxin.
3. Propose a plan to address potential drug interactions between flibanserin and P-gp substrates.

ADDITIONAL COMMENTS

We have the following comments and recommendations that are not approvability issues:

1. We believe a future discussion of this application before an advisory committee is warranted to review the identified efficacy and safety concerns and your responses to these deficiencies. Specifically, we would seek advice on whether the demonstrated benefits of treatment with flibanserin outweigh the risks associated with its use in the proposed target population.
2. Although the submitted human abuse potential study does not provide conclusive data regarding the abuse potential of flibanserin, we have concluded, based on the available preclinical and clinical data, that there is no need to conduct a new human abuse potential study at this time.
3. Studies 511.130 and 511.156 assessing flibanserin efficacy and safety in postmenopausal women were not extensively reviewed during this review cycle because you are not currently proposing to market flibanserin in the postmenopausal population.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling 21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and

clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, “Formal Meetings Between the FDA and Sponsors or Applicants,” May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JULIE G BEITZ
09/27/2013



NDA 022526

COMPLETE RESPONSE

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Alexander Rochefort
Director, Drug Regulatory Affairs
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877

Dear Mr. Rochefort:

Please refer to your New Drug Application (NDA) dated and received October 27, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for flibanserin tablets 100 mg.

We acknowledge receipt of your amendments dated November 20, December 17, 18, and 23, 2009, January 21 and 26, February 5, 19, and 24, March 3, 9, 12, and 16, April 13, 26, 28, and 30 (2), May 7, 12 (2), 13, 14, 19, 25, 26, and 27, June 8, 15, 16 (2), and 17, and July 2 and 8, 2010.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

EFFICACY

1. There is lack of substantial evidence that flibanserin is effective for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women.

Two randomized placebo-controlled trials demonstrated a statistically significant change from baseline in the number of satisfying sexual events (SSEs), one of two co-primary endpoints, for flibanserin relative to placebo. However, a statistically significant improvement for flibanserin relative to placebo was not demonstrated for the change from baseline in the second co-primary endpoint, the eDiary sexual desire item measured daily over 24 weeks. Flibanserin treatment was associated with reduced HSDD-related distress, evaluated by the Female Sexual Distress Scale-Revised (FSDS-R). While results on sexual desire as measured by the sexual desire domain of the Female Sexual Function Index (FSFI-SD) favored flibanserin, we do not believe that it is appropriate to disregard the negative results obtained with the pre-specified eDiary sexual desire item analyses in favor of the positive results obtained using another instrument.

In addition, the entry criteria for subjects enrolled in these controlled clinical trials were very restrictive, precluding a full clinical evaluation of efficacy in the target population of women who experience HSDD.

We recommend that you conduct an additional blinded, placebo-controlled clinical trial to assess the effects of flibanserin on SSEs and sexual desire (as co-primary endpoints), and HSDD-related distress (as a key secondary endpoint). If you use an instrument other than the eDiary employed in the trials submitted in this NDA, the instrument that is used to measure sexual desire should have adequate content validity, including recall validity, and acceptable measurement properties when used to evaluate premenopausal women with HSDD, consistent with the concepts set forth in the FDA's "Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims," December 2009. You should provide evidence that the assessment schedule of the instrument that is used to measure sexual desire can adequately capture the subject's entire range of experiences over the assessment period (i.e., four weeks).

The trial should have less restrictive entry criteria compared to previously conducted HSDD clinical trials with respect to the presence of co-morbid conditions in enrolled subjects, and use of concomitant medications including dietary supplements. For example, women with mild forms of depression and anxiety should be included, as long as the HSDD is not a function of the underlying psychiatric diagnosis. Subjects taking commonly prescribed medications, including centrally acting drugs such as triptans, should also be enrolled.

We also recommend that you submit your trial protocol for a special protocol assessment prior to initiating this trial.

2. There is insufficient information to characterize the efficacy of the recommended dose of flibanserin in the presence of moderate CYP3A4 inducers.

Co-administration of flibanserin with a strong CYP3A4 inducer resulted in markedly reduced flibanserin plasma concentrations. We believe the magnitude of this effect is such that flibanserin efficacy in HSDD patients co-administered strong CYP3A4 inducers would be seriously compromised.

We recommend that you conduct a drug-drug interaction study to evaluate the effect of co-administration of a moderate CYP3A4 inducer on the pharmacokinetic profile of flibanserin 100 mg.

SAFETY

1. There is insufficient information to characterize the safety profile of the recommended 100 mg dose of flibanserin in premenopausal women with HSDD who have co-morbid conditions or ingest concomitant medications including dietary supplements, or alcohol. To address this deficiency, we recommend that you:
 - a. Enroll a broad population of premenopausal women with HSDD in ongoing or future placebo-controlled HSDD clinical trials of flibanserin. As stated above, we recommend that you enroll women with mild psychiatric conditions, assuming the HSDD is not a function of the underlying psychiatric diagnosis, and women taking commonly prescribed concomitant medications, including centrally acting drugs.

- b. Complete your ongoing 12-week, double-blind, placebo-controlled study to assess the safety of concomitant use of flibanserin 100 mg daily with selective serotonin or norepinephrine reuptake inhibitors. Special attention should be paid to the possibility of exacerbation of depression in subjects with a prior history of major depressive disorder.
 - c. Conduct a drug-drug interaction study to determine the effect of simultaneous administration of flibanserin 100 mg with alcohol. This study should assess the tolerability and effects on pharmacodynamic endpoints, such as blood pressure and orthostatic vital signs, in flibanserin-treated subjects ingesting alcohol as compared to subjects on flibanserin alone.
 - d. Conduct a pharmacokinetic, pharmacodynamic, safety study in healthy premenopausal women ingesting supra-therapeutic doses of flibanserin to assess the effect of such exposure on orthostatic vital signs and the risk of syncope.
 - e. Conduct a drug-drug interaction study to evaluate the pharmacokinetic profile and safety of flibanserin 100 mg when co-administered with moderate CYP3A4 inhibitors.
 - f. Submit the final report of a meta-analysis of phase 1 pharmacokinetic and safety data in women who received oral contraceptives and various doses of flibanserin concomitantly. A determination of the need for a drug-drug interaction study to evaluate the pharmacokinetic profile and safety of flibanserin 100 mg when co-administered with weak CYP3A4 inhibitors will be made after FDA has completed its review of your meta-analysis.
2. There is insufficient information to assess the risk of accidental injury associated with the use of flibanserin and to assess the root cause of these events (e.g., drug-related somnolence, syncope, depression-related inattention, or other causes).

We recommend that the incidence of accidental injury (e.g., falls, automobile accidents, etc.) be assessed in flibanserin- and placebo-treated subjects enrolled in ongoing and future HSDD clinical trials of flibanserin.

3. Flibanserin is active in the CNS, has sedative properties, and there is evidence that it produces physical dependence. These properties are suggestive of a drug with abuse potential. However, in the absence of a human abuse potential study, it is not possible to draw definitive conclusions about the abuse potential of flibanserin.

You should conduct a human abuse potential study in individuals with a history of sedative abuse and, pursuant to 21 CFR 314.50(d)(5)(vii), submit a proposal to schedule flibanserin in the Controlled Substances Act (CSA) and reasons for your proposal. We recommend that you submit the protocol for this study for review prior to initiating the study.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

SAFETY UPDATE

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7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

While not approvability issues, we request that you:

1. Evaluate whether flibanserin has agonist properties at the 5HT_{2B} receptor site. If flibanserin is found to have such properties, further assessment of its ability to induce valvulopathy, an adverse event known to be associated with this receptor site, would be warranted.
2. Provide clinical trial analysis datasets in an electronic format that would facilitate clinical and statistical review. Please refer to the document, "Study Data Specifications, Version 1.5.1," located on the FDA website:
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf>.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

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Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22526

ORIG-1

BOEHRINGER
INGELHEIM
PHARMACEUTICA
LS INC

FLIBANSERIN

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/s/

JULIE G BEITZ
08/27/2010