APPLICATION NUMBER:

207202Orig1s000

OTHER ACTION LETTERS
NDA 207202

COMPLETE RESPONSE

Otsuka Pharmaceutical Development &
Commercialization, Inc.
Attention: Michael Fahmy
Director, Global Regulatory Affairs
2440 Research Boulevard
Rockville, MD 20850

Dear Mr. Fahmy:

Please refer to your New Drug Application (NDA) dated and received June 26, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for aripiprazole with ingestible event marker (IEM).

We have completed our review of this application 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.

PRODUCT QUALITY & CLINICAL

You have submitted clinical testing in the OSMITTER 316-13-206A and 316-13-206B studies to measure the accuracy of IEM detection and determine the data latency throughout the MIND1 system. Both of these studies demonstrate that the system performance is substantially degraded by addition of the drug tablet. FDA recognizes that the 206A study included product development information but, because it did not use versions of the patch or IEM intended for commercial release, we have only listed deficiencies and provided feedback for the 206B study. FDA identified the following deficiencies with the 206B study:

- This study used only placebo + IEM for testing and did not include any data for the proposed combination aripiprazole + IEM.
- Data latency between the Patch and Otsuka app raise concerns about timely notification to the patient as described above.
- None of the time points included co-ingestion of the combination product with food.
Considering the risk of dosing errors that the product presents to the patient and the variable results seen with the placebo product in 316-13-206B study, we request that you carry out a similar study that unambiguously tests the to-be-marketed formulation under the conditions in which it is likely to be used. We request that the study have a predetermined and justified endpoint, e.g., positive detection rate after a certain time period following ingestion. We recommend that the tablets studied represent or bracket the commercial tablet sizes and strengths, that you study with and without food, and that you consider using aged tablets. The Agency is prepared to provide advice and feedback on such a study.

You may also consider removing [b/(4)] so that the app functions more as a diary to record administrations; this would be more in line with the proposed label claim.

**PRODUCT QUALITY**

The proposed comparability protocol (CP) is not approved as it cannot be evaluated due to the user interface (Human Factors) deficiencies identified. We recommend that, if you continue to pursue a CP, it should be included in a resubmission/response to the CR.

We acknowledge receipt of full commercial drug product manufacturing batch records at the Otsuka Tokushima preapproval inspection; please submit these for each dosage strength to the application.

**HUMAN FACTORS**

A. General Comment

We find that the Patient Interface Human Factors (HF) validation study report does not provide sufficient data to conclude that the patient user interface supports safe and effective use of this
product by the Major Depressive Disorder, Bipolar I Disorder or Schizophrenia patient populations. There were multiple failures and difficulties observed with critical tasks. These failures can lead to dosing errors (e.g., missed dose or extra dose) and/or render the system ineffective.

Improvements to the user interface are needed to mitigate the risk for medication errors and ensure the product can be used by intended users for intended uses and environments. We recommend you re-evaluate the critical task failures and difficulties and their associated root causes, update your risk analysis accordingly, implement additional risk mitigation strategies, and demonstrate their effectiveness by conducting another HF validation study. We provide some label and labeling recommendations below that we recommend are implemented with any other changes you plan to make to the user interface so they can also be validated in your HF validation study.

B. Labels and Labeling

1. General Comment
   a. We recommend that you consider providing printed patient labeling that provides a brief overview of the system, instructions for critical use elements of the app, including system set up, critical patch tasks, description of some of the app features, cautions, etc. Based on the results of your HF validation study, we believe that printed patient labeling will be helpful to some patients and may minimize the risk for some errors seen in your HF validation study (e.g., patients trying to activate the patch through the smartphone screen instead of interacting with the patch itself).

   b. The recommendations for the container labels and carton labeling provided below pertain to the proposed labels and labeling submitted on June 26, 2015. We acknowledge that the conditionally approved Proprietary Name changed to “Abilify Mycic” after the June 26, 2015, submission. For clarity, the recommendations below reference the modifier however, they should be understood to also apply to your intended modifier “Mycic.”

2. Carton Labeling
   a. To help minimize the risk of wrong strength selection errors, increase the prominence of the statement of strength on the top panel of the labeling. Additionally, add the statement of strength to the front panel (see the example below).
b. Reference the entire conditionally acceptable proprietary name, "Abilify Mycere," in order to minimize potential confusion.

3. Patch Pouch Label

4. Top Card, Patch Box Front Panel, and Pill Bottle Tray

   To help minimize confusion, place the word "[redacted]" in front of the numbers so that patients are clear that a sequence of steps is being referred to rather than the number of tablets to take (a failure observed in your HF validation study). For example:

   1: The App
   2: The Patches
   3: The Tablets

5. Patch Box Front Panel and Patch Pouch Labeling

   The statement "Patches do not contain medication" does not have sufficient prominence and could be overlooked. Relocate the statement to a central location on the patch box
front panel in order to give it more prominence. Additionally, add the statement to the Patch Pouch label to decrease the chance of this information being overlooked.

**PRESCRIBING INFORMATION**

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm) and [Pregnancy and Lactation Labeling Final Rule](http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm) websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. 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](http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm)

**CARTON AND CONTAINER LABELING**

The recommendations for the container labels and carton labeling provided in the Human Factors section above pertain to the proposed carton and container labeling submitted on June 26, 2015 and should be addressed and implemented prior to conducting another HF validation study.

**PROPRIETARY NAME**

Please refer to correspondence dated, February 24, 2016, which addresses the proposed proprietary name, Abilify Mycite. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

**FACILITY INSPECTIONS**

During a recent inspection of the OTSUKA PHARMACEUTICAL CORPORATION LTD, FEI: 3003808559 manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

**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.

You may request a meeting or teleconference 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 FDA and Sponsors or Applicants,” May 2009 at
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, email Simran Parihar, PharmD, Regulatory Health Project Manager, at simran.parihar@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell Mathis, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MITCHELL V Mathis
04/26/2016