CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217006Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 134612

MEETING PRELIMINARY COMMENTS

Otsuka Pharmaceutical Development & Commercialization, Inc.
Attention: Michelle Hillsman, MS
Senior Manager, Global Regulatory Affairs
508 Carnegie Center Drive
Princeton, NJ 08540

Dear Ms. Hillsman:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for aripiprazole (OPC-14597).

We also refer to your correspondence, dated and received December 10, 2021, requesting a meeting to discuss gaining final alignment of outstanding questions for NDA filing.

Our preliminary responses to your meeting questions are enclosed.

You should provide a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, email me at ann.sohn@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ann Sohn, PharmD, MS, LCDR USPHS
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	March 9, 2022, at 1:00 p.m. to 2:00 p.m. (EST)
Meeting Location:	Teleconference
Application Number:	IND 134612
Product Name:	Aripiprazole (OPC-14597)
Indication:	Treatment of schizophrenia and maintenance monotherapy treatment of bipolar I disorder in adults
Sponsor Name:	Otsuka Pharmaceutical Development & Commercialization, Inc.
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for March 9, 2022, 1:00p.m. to 2:00 p.m. (EST) between Otsuka Pharmaceutical Development & Commercialization, Inc. and the Division of Psychiatry. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0. BACKGROUND

The Sponsor is developing aripiprazole 2-month ready-to-use long-acting injectable (2M RTU LAI) for the treatment of schizophrenia and maintenance monotherapy treatment of bipolar I disorder in adults. Aripiprazole 2M RTU LAI is an extended-release aripiprazole formulation intended for administration every 2 months (8 weeks) via gluteal intramuscular (IM) injection by healthcare professionals. Aripiprazole 2M RTU LAI would not require reconstitution (720 mg or 960 mg in a pre-filled syringe).

FDA approved aripiprazole 1-month LAI (Abilify Maintena IM depot, 300 mg and 400 mg) on February 28, 2013, under NDA 202971 for the treatment of schizophrenia and

on February 27, 2017, for maintenance monotherapy treatment of bipolar I disorder in adults. The Sponsor refers to Abilify Maintena as aripiprazole 1M RTU LAI.

Type C Guidance Meetings were scheduled in 2017 and 2018 to discuss the development program for aripiprazole 2M LAI. On March 10, 2017, (under IND 67380) FDA agreed that pharmacokinetic (PK) bridging could be an acceptable approach for establishing effectiveness of aripiprazole 2M LAI, but that a new IND should be created for the 2-month administration. The initial discussion of trial design for Study 031-201-00181 is documented in the Type C meeting preliminary comments dated August 1, 2018. In their response, dated August 30, 2018, the Sponsor agreed to the FDA's recommendation for additional statistical criteria for comparative PK and incorporating additional safety/efficacy time points.

The Sponsor submitted a protocol for a single ascending dose (SAD) study of two dose levels of aripiprazole 2M LAI (780 and 1200 mg) under IND 134612, and the study was allowed to proceed. The Sponsor submitted simulation data on August 6, 2018, that suggested comparable C_{trough} aripiprazole concentrations were expected after multiple dosing with Abilify Maintena 400 mg monthly and aripiprazole 2M LAI 900 mg every 2 months. Thus, the 900-mg dose was selected for a proposed multiple dose trial, and the Sponsor submitted a protocol outline for this trial. FDA commented on the endpoints' need to ascertain PK similarity, the timing of clinical endpoints, the need for a comprehensive use-related risk analysis, and concerns from a device perspective that included the possibility of the needle clogging (b) (4) The Sponsor submitted the PK Study 031-201-279 protocol for review on November 15, 2018, and was allowed to proceed with no further comments from the FDA review team.

The Sponsor's clinical development program in support of aripiprazole 2M RTU LAI includes 3 trials:

- Study 031-201-00181: A pivotal open-label, multiple-dose, randomized, parallel-arm, multicenter trial designed to assess the safety, tolerability, and PK of multiple doses of either aripiprazole 2M RTU LAI 960 mg or aripiprazole 1M depot 400 mg injected into the gluteal muscle in adult subjects with schizophrenia or bipolar I disorder.

- Study 031-201-00104: A phase 1, open-label, single ascending dose, parallel-arm, multicenter trial designed to determine the safety, tolerability, and PK of a single dose of either 780 mg or 1200 mg of aripiprazole 2M RTU LAI injected into the gluteal muscle in adult subjects with schizophrenia.

- Study 031-201-00279: A phase 1, two-part, open-label, single- and multiple-dose, multicenter trial designed to assess the PK, safety, and tolerability of 420 mg aripiprazole 1M RTU LAI injected into the deltoid or gluteal muscle sites in adult subjects with schizophrenia or bipolar I disorder.

The Sponsor proposes to submit via the NDA 505(b)(1) pathway. The Sponsor's stated purpose for requesting this meeting is to gain final alignment on outstanding questions for the aripiprazole 2M RTU LAI NDA filing as outlined below:

- To confirm acceptability of the planned safety updates for the NDA submission
- To confirm acceptability of nonclinical data generated to assess the impact of stress factors and immune/inflammatory response modulators on the aripiprazole 2M RTU LAI release profile
- To confirm acceptability of the planned datasets for inclusion in the NDA submission
- To confirm acceptability of the NDA cross-referencing strategy to previous aripiprazole NDAs
- To confirm that a Summary of Clinical Efficacy (SCE) is not needed for the NDA
- To discuss the presentation of data in the planned US Prescribing Information (USPI) on aripiprazole 2M RTU LAI and other aripiprazole product data.

2.0. DISCUSSION

2.1. CLINICAL

Question 1: Does the Agency agree that no 120-day or final safety update will be needed for the NDA?

FDA Response to Question 1: *We agree that you do not need to provide a 120-day safety update if you have no additional data to report. However, you should submit documentation to explain whether or not you have additional information for review for the 120-day update.*

2.2. NONCLINICAL

Question 2: Does the Agency agree that these (nonclinical) conducted studies are acceptable to address the Agency's concerns around potential impacts on the aripiprazole 2M RTU LAI release profile?

FDA Response to Question 2: *The conducted studies appear acceptable to address the potential impacts on the aripiprazole 2M RTU LAI release profile. However, the final determination will be a matter of review of the final study reports that were recently submitted to the IND on January 21, 2022.*

2.3. REGULATORY

Question 3: Does the Agency agree that datasets only need to be submitted for the pivotal trial, and are not required for the supportive trials?

FDA Response to Question 3: *We do not agree. You should submit data from all supportive clinical trials that include safety monitoring. In addition, you should include in your submission the recommended analyses as communicated in the Agency's Type C meeting preliminary comments from August 1, 2018.*

Question 4: Does the Agency agree that this cross-referencing strategy (to Abilify Maintena, NDA 202971) would be appropriate for the planned 2M RTU LAI NDA?

FDA Response to Question 4: *Your proposal to reference information you have previously submitted to your Abilify Maintena NDA is acceptable.*

Question 5: Does the Agency agree that an SCE is not needed for this NDA?

FDA Response to Question 5: *We agree that you do not need to submit an SCE.*

Question 6: Does the Agency agree with:

a) The Sponsor's proposed incorporation of PK information from the pivotal 031-201-00181 trial in the USPI?

b) The Sponsor's proposal of summarizing demonstrated comparability between the aripiprazole 2M RTU LAI formulation and Abilify Maintena in the USPI based on bridging and/or popPK studies, while retaining relevant data from the current Abilify Maintena USPI?

FDA Response to Question 6: *Your proposal appears reasonable; however, it will be a matter of review.*

3.0. OTHER

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA; 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for

the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR; for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

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[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products—Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345,

Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[5] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[6]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials).

[5] https://www.fda.gov/media/84223/download
[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[7]

[7] https://www.fda.gov/media/85061/download

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANN J SOHN
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