NDA 209500/S-005 & S-006

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT

Intra-Cellular Therapies, Inc.
Attention: Nicole L. Bradley, PharmD
Executive Director, Regulatory Affairs
430 East 29th St, Suite 900
New York, NY 10016

Dear Dr. Bradley:

Please refer to your supplemental new drug application (sNDA) dated February 17, 2021, received February 17, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Caplyta (lumateperone) capsules.

These Prior Approval supplemental new drug applications provide for the addition of the following indication: depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 209500/S-005 and S-006**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric studies requirement for ages 0 to 9 years because necessary studies are impossible or highly impracticable. This is because it is difficult to diagnosis bipolar disorder in children younger than 10 years and the prevalence rate of bipolar disorder for children younger then 10 years of age is low.

We are deferring submission of your pediatric studies for ages 10 to 17 years for this application because pediatric studies should be delayed until additional safety or effectiveness data have been collected.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

4192-1 Conduct a GLP juvenile animal study to assess the toxicology of lumateperone to support clinical trials of lumateperone in the intended pediatric population ages 10 to 17 years.

Final Protocol Submission: n/a
Study Completion: n/a
Final Report Submission: 02/2022

4192-2 Conduct an open-label, multiple oral dose study to demonstrate the safety, tolerability, and pharmacokinetics of lumateperone in patients ages 10 to 17 years with major depressive episode with bipolar I or II disorder (bipolar depression).

Final Protocol Submission: 05/2022
Study Completion: 05/2023
Final Report Submission: 11/2023

4192-3 Conduct a randomized, double-blind, placebo-controlled study to assess the efficacy and safety of lumateperone for the treatment of major depressive episode associated with bipolar I or II disorder (bipolar depression) in patients aged 10 to 17 years.

Final Protocol Submission: 11/2023
Study Completion: 05/2027
Final Report Submission: 11/2027

4192-4 Conduct an open-label study to assess the long-term safety of lumateperone in patients aged 10 to 17 years with major depressive episode associated with bipolar I or II disorder (bipolar depression).

Final Protocol Submission: 11/2023
Study Completion: 11/2027
Final Report Submission: 05/2028

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 126701, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submission dated February 17, 2021, containing the final report for the following postmarketing requirement listed in the December 20, 2019 approval letter.

3760-5 Conduct a clinical pharmacokinetic trial to evaluate if UGT enzyme inhibitors alter the PK of lumateperone and its metabolites (including metabolites IC201337 and IC201338) using fully validated assays and to determine appropriate dosing recommendations for CAPLYTA with regard to use of concomitant UGT enzyme inhibitors.

We have reviewed your submission and conclude that the above requirement was fulfilled.

We remind you that there are postmarketing requirements and postmarketing commitments listed in the December 20, 2019 approval letter that are still open.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Tiffanie Taylor, Regulatory Project Manager, at Tiffanie.Taylor@fda.hhs.gov .

Sincerely,

{See appended electronic signature page}

Tiffany R. Farchione, MD
Director
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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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/

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