

NDA 209500

**NDA APPROVAL**

Intra-Cellular Therapies, Inc.  
Attention: Michael K. Olchaskey, PharmD  
Senior Vice President, Head of Regulatory Affairs  
430 East 29th Street  
Alexandria Center for Life Science, Suite 900  
New York, NY 10016

Dear Dr. Olchaskey:

Please refer to your new drug application (NDA) dated September 27, 2018, received September 27, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Caplyta (lumateperone) capsules.

We acknowledge receipt of your major amendment dated July 25, 2019, which extended the goal date by three months.

This new drug application provides for the use of Caplyta (lumateperone) capsules for the treatment of Schizophrenia.

### **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.<sup>1</sup> Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information) as well as annual reportable changes not included in the enclosed labeling. 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*.<sup>2</sup>

The SPL will be accessible via publicly available labeling repositories.

<sup>1</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

<sup>2</sup> 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>.

## **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.**” Approval of this submission by FDA is not required before the labeling is used.

## **ADVISORY COMMITTEE**

Your application for Caplyta was not referred to an FDA advisory committee because there were no issues that would benefit from advisory committee discussion.

## **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 study requirement for ages 0 to 12 years because necessary studies are impossible or highly impracticable. This is because of the very low incidence of schizophrenia in this age range.

We are deferring submission of your pediatric studies for ages 13 to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act/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 Federal Food, Drug, and Cosmetic Act/FDCA. These required studies are listed below.

- 3760-1 Conduct an open-label, multiple oral dose study to demonstrate the safety, tolerability, and pharmacokinetics of lumateperone in patients ages 13 to 17 years diagnosed with schizophrenia.

Final Protocol Submission:	04/2020
Study Completion:	10/2021
Final Report Submission:	04/2022

**U.S. Food and Drug Administration**  
Silver Spring, MD 20993  
[www.fda.gov](http://www.fda.gov)

3760-2 Conduct a randomized, double-blind, placebo-controlled study to assess the efficacy and safety of lumateperone for the treatment of schizophrenia in patients aged 13 to 17 years.

Final Protocol Submission:	12/2022
Study Completion:	06/2027
Final Report Submission:	12/2027

3760-3 Conduct an open-label study to assess the long-term safety of lumateperone in patients aged 13 to 17 years diagnosed with schizophrenia.

Final Protocol Submission:	12/2022
Study Completion:	12/2027
Final Report Submission:	06/2028

Submit the protocols to your IND 079690 with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (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.

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to 1) identify an unexpected serious risk associated with the presence of lumateperone in human milk, 2) assess the serious risk of toxicity due to Glucuronosyl Transferase (UGT) Enzyme Inhibitors, and 3) identify unexpected serious risks of drug interactions.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies and trials:

- 3760-4 Perform a lactation study (milk only) in lactating women who have received therapeutic doses of lumateperone using a validated assay to assess concentrations of lumateperone and its metabolites in breast milk.

The timetable you agreed to on December 19, 2019, states that you will conduct this study/trial according to the following schedule:

Final Protocol Submission:	12/2020
Study/Trial Completion:	06/2022
Final Report Submission:	12/2022

- 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.

The timetable you agreed to on December 19, 2019, states that you will conduct this study/trial according to the following schedule:

Final Protocol Submission:	06/2020
Study/Trial Completion:	12/2020
Final Report Submission:	06/2021

- 3760-6 Conduct a standard in vitro assay to determine:
- Substrate potential of ITI-007 for OATP1B1/1B3;
  - Inhibitor potential of ITI-007 towards P-gp and BCRP;
  - Inhibitor potential of all major metabolites (IC200131, IC200161, IC200565, IC201308, IC201309, and IC200056-enol-glu), if have not been evaluated, towards
    - transporters P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1, and MATE2K;
    - inhibitor/inducer potential towards major CYPs, except CYP3A (in vivo study with midazolam has been conducted).

The timetable you agreed to on December 19, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2020
Study/Trial Completion:	12/2020
Final Report Submission:	06/2021

Submit clinical protocols to your IND 079690 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

**Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

### **POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments:

3760-7: Conduct a placebo-controlled, randomized withdrawal maintenance study of lumateperone in patients with schizophrenia.

The timetable you agreed to on December 19, 2019, states that you will conduct this study/trial according to the following schedule:

Final Protocol Submission:	12/2020
Study/Trial Completion:	12/2023
Final Report Submission:	06/2024

- 3760-8: Develop new strengths of 10.5 mg and 21 mg of CAPLYTA to meet the need for dose adjustment in patients with moderate to severe hepatic impairment or in patients who are taking concomitant strong or moderate CYP3A4 inhibitors.

The timetable you agreed to on December 19, 2019, states that you will conduct this study/trial according to the following schedule:

Final Protocol Submission:	Not applicable
Study/Trial Completion:	Not applicable
Final Report Submission:	12/2021

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 079690 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and*

*Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*<sup>3</sup>

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.<sup>4</sup> Information and Instructions for completing the form can be found at FDA.gov.<sup>5</sup> For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.<sup>6</sup>

## **REPORTING REQUIREMENTS**

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

## **MEDWATCH-TO-MANUFACTURER PROGRAM**

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.<sup>7</sup>

## **POST APPROVAL FEEDBACK MEETING**

New molecular entities and new biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

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<sup>3</sup> 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>.

<sup>4</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

<sup>5</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

<sup>6</sup> <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>

<sup>7</sup> <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>

If you have any questions, call Jasmeet (Mona) Kalsi, Regulatory Project Manager, at (240) 402 – 8977 or e-mail [Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Ellis Unger, MD  
Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURES:

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

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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.**  
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