CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761180Orig1s000

Trade Name:	ADBRY
Generic or Proper Name:	tralokinumab
Sponsor:	LEO Pharma AS
Approval Date:	December 27, 2021
Indication:	For the treatment of moderate-to-severe atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

CENTER FOR DRUG EVALUATION AND RESEARCH

761180Orig1s000

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	**X**
Labeling	**X**
REMS	
Officer/Employee List	**X**
Integrated Review(s)	**X**
Product Quality Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	**X**
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761180Orig1s000

APPROVAL LETTER

BLA 761180

BLA APPROVAL

LEO Pharma A/S
c/o LEO Pharma Inc.
Attention: Encarnacion Suarez, PharmD
Senior Director, US Regulatory Affairs
7 Girlada Farms, 2nd Floor
Madison, NJ 07940

Dear Dr. Suarez:

Please refer to your biologics license application (BLA) dated and received April 27, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for Adbry (tralokinumab) injection.

We acknowledge receipt of your resubmission dated July 2, 2021, which constituted a complete response to our April 23, 2021, action letter.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2169 to LEO Pharma A/S, Ballerup, Denmark, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Adbry. Adbry is indicated for the treatment of moderate-to-severe atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Adbry can be used with or without topical corticosteroids.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture tralokinumab drug substance at AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center in Frederick, Maryland. The final formulated drug product will be manufactured, filled, labeled, and packaged at Catalent Indiana, LLC, Bloomington, Indiana. You may label your product with the proprietary name, Adbry, and market it in 150 mg/1 mL accessorized prefilled syringe (APFS).

DATING PERIOD

The dating period for Adbry shall be 36 months from the date of manufacture when stored at 5 ± 3 °C, 14 days at room temperature (≤ 30°C) after storage at long-term conditions (5 ± 3 °C) for up to 36 months. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at -(b) (4)

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Adbry to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Adbry, or in the manufacturing facilities, will require the submission of information to your BLA for our review and written approval, consistent with 21 CFR 601.12.

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, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert, and Instructions for Use). 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 (October 2009)*.[2]

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

The SPL will be accessible via publicly available labeling repositories.

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 BLA 761180**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Adbry was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for a biologic of this class.

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

We are waiving the pediatric study requirement for ages less than 6 months because necessary studies are impossible or highly impracticable. This is because Adbry is indicated for the treatment of moderate-to-severe atopic dermatitis in patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable, and it will be impractical to make this determination in patients younger than 6 months of age.

We are deferring submission of your pediatric studies for ages 6 months to less than 18 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 under section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

4015 – 1 Study LP0162-1334 (ECZTRA 6) : Efficacy and safety (phase 3, randomized, double blind, placebo controlled, parallel-group, monotherapy) study in adolescents 12 to <18 years of agewith moderate-to-severe atopic dermatitis (AD) who are candidates for systemic treatment.

Final Protocol Submission: 06/15/2018
Study Completion: 03/30/2021
Final Report Submission: 03/30/2022

4015 – 2 Study LP0162-1335: A pharmacokinetic (PK) and safety [randomized, single (observer) blinded, parallel-group, monotherapy] dose-ranging study in pediatric subjects 2 to <12 years of age with moderate-to-severe atopic dermatitis (AD) who are candidates for systemic AD treatment (studied sequentially in 2 cohorts: 6 to <12 years and 2 to <6 years).

Final Protocol Submission: 03/31/2022
Study Completion: 09/30/2025
Final Report Submission: 03/31/2026

4015 – 3 Study LP0162-1336: An efficacy and safety (phase 3, randomized, double-blind, placebo-controlled, parallel-group) study with tralokinumab and placebo in combination with topical corticosteroid (TCS) therapy in pediatric subjects 2 to <12 years of age with moderate-to-severe atopic dermatitis (AD) who are candidates for systemic AD treatment (studied simultaneously in 2 cohorts: 6 to <12 years and 2 to <6 years).

Draft Protocol Submission: 5/31/2023
Final Protocol Submission: 09/30/2023
Study Completion: 03/31/2027
Final Report Submission: 09/30/2027

4015-4 Study LP0162-1381: An efficacy, safety, and pharmacokinetic (PK) (phase 2, single-arm, open-label, monotherapy) study in infants and pediatric subjects 6 months to <2 years of age with moderate-to severe atopic dermatitis (AD) who are candidates for systemic AD treatment.

Draft Protocol Submission: 02/28/2027
Final Protocol Submission: 06/30/2027
Study Completion: 12/31/2028
Final Report Submission: 06/30/2029

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 protocols to your IND 123797, with a cross-reference letter to this BLA.

Reports of these required pediatric postmarketing studies must be submitted as a biologics license application (BLA) or as a supplement to your approved BLA 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 Federal Food, Drug, and Cosmetic Act (FDCA) OR 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 identify an unexpected serious risk of adverse pregnancy and fetal outcomes.

Furthermore, the active postmarket risk identification and analysis system as available 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:

4015-5	A prospective, pregnancy exposure registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to tralokinumab during pregnancy to an unexposed control population.

The timetable you submitted on December 16, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/01/2022
Final Protocol Submission:	10/31/2022
Study Completion:	09/30/2034
Final Report Submission:	09/30/2035

[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.

4015-6 An additional pregnancy study that uses a different design from the Pregnancy Registry (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to tralokinumab during pregnancy compared to an unexposed control population.

The timetable you submitted on December 16, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/01/2022
Final Protocol Submission:	10/31/2022
Study Completion:	06/30/2030
Interim/Other:	06/30/2027
Final Report Submission:	12/30/2030

Submit clinical protocol(s) to your IND 123797 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your BLA. 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).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

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 21 CFR 601.70 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 601.70 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 601.70. 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 NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4015-7 The applicant commits to conduct a real-time shipping study of commercial product as a Post Marketing Commitment (PMC).

The timetable you submitted on December 16, 2021, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2022

Submit clinical protocols to your IND 123797 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. 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. 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]

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

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80).

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

POST APPROVAL FEEDBACK MEETING

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.

If you have any questions, call Strother D. Dixon, Senior Regulatory Project Manager, at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Julie G. Beitz, MD
Director
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
  - Instructions for Use
- Carton and Container Labeling

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/

JULIE G BEITZ
12/27/2021 03:53:13 PM