



BLA 125521

BLA APPROVAL

Eli Lilly and Company
Attention: Brian E. Wagner, PharmD
Director, Global Regulatory Affairs
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Wagner:

Please refer to your Biologics License Application (BLA) dated and received March 23, 2015, and your amendments, submitted under section 351(a) of the Public Health Service Act for TALTZ (ixekizumab) injection prefilled syringe and autoinjector, 80 mg/mL.

LICENSING

We have approved your BLA for TALTZ (ixekizumab) injection effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce TALTZ under your existing Department of Health and Human Services U.S. License No. 1891. TALTZ is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture TALTZ drug substance at Eli Lilly S.A. in, Dunderrow Kinsale, County Cork, Ireland. The final formulated product will be manufactured, filled, labeled, and packaged at Eli Lilly and Company, Indianapolis, Indiana. The device will be assembled, packaged, and labeled at Eli Lilly and Company, Indianapolis, Indiana. You may label your product with the proprietary name, TALTZ, and market it in 80 mg/ml in a single-dose prefilled auto-injector or single-dose prefilled syringe to deliver 1 mL liquid solution subcutaneous injection.

DATING PERIOD

The dating period for TALTZ shall be 24 months from the date of manufacture when stored at 5 °C. 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) °C.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of TALTZ 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 TALTZ, or in the manufacturing facilities, will require the submission of information to your biologics license application 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 text.

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 [21 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the instructions for use, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels submitted on February 3, 2016, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)”. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved BLA 125521.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for TALTZ was not referred to an FDA advisory committee because this biologic is not the first in its class and the application did not raise significant public health questions on the role of the biologic in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 0 to less than 6 years because necessary studies are impossible or highly impracticable. This is because:

- The prevalence of psoriasis in the 0 to less than 6 years age group is low (with the highest prevalence published of 0.3%) and the proportion of children with a severe condition in need of a systemic treatment is 4%, giving a final prevalence of the condition to be about 1 per 10,000 in this age group.
- Live vaccinations (MMR, varicella) are usually given in this age group, limiting the treatment of this pediatric population with ixekizumab.

We are deferring submission of your pediatric studies for ages 6 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 study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(C) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

3049-1 Conduct a dose-ranging Pharmacokinetics (PK), Safety and Efficacy Study in pediatric subjects 6 to <18 years of age with moderate to severe psoriasis (with a duration of exposure to ixekizumab of at least one year).

Final Protocol Submission: 03/2017
Study Completion: 09/2021
Final Report Submission: 03/2022

Submit the protocol to your IND 100834, with a cross-reference letter to this BLA.

Reports of the required pediatric postmarketing study must be submitted as a 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 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 maternal, fetal and neonatal toxicity as well as an unexpected serious risk of malignancy, opportunistic infections, autoimmune disease, neurologic or demyelinating disease, and cardiovascular adverse events.

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:

- 3049-2 Conduct a retrospective cohort study using administrative databases to identify pregnancy outcomes in a cohort of women exposed to ixekizumab and a non-ixekizumab systemic medication exposure cohort. The outcomes will include major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age births. This study may use multiple data sources in order to obtain a sufficient sample size as women with psoriasis are counseled to avoid systemic treatments while trying to conceive and during the course of pregnancy.

The timetable you submitted on March 16, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2016
Study Completion:	12/2021
Final Report Submission:	06/2022

- 3049-3 Conduct a prospective registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to ixekizumab during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age births, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

The timetable you submitted on March 16, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 04/2017
Study Completion: 05/2029
Final Report Submission: 05/2030

3049-4 Conduct a prospective, observational study to assess the long-term safety of ixekizumab compared to other therapies used in the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy in the course of actual clinical care. The study's primary outcome is malignancy. Secondary outcomes include, but are not limited to, serious infection, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events. Describe and justify the choice of appropriate comparator population(s) for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate(s), with a pre-specified statistical analysis method. Specify concise case definitions and validation algorithms for both primary and secondary outcomes. For the ixekizumab-exposed and comparator(s), clearly define the study drug initiation period and any exclusion and inclusion criteria. Enroll patients over an initial 4-year period and follow for a minimum of 8 years from the time of enrollment.

The timetable you submitted on March 16, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 04/2017
Study Completion: 05/2029
Final Report Submission: 05/2030

Submit the protocol(s) to your IND 100834, with a cross-reference letter to this BLA. Submit 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).”**

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 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 SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

- 3049-5 Conduct a clinical study to assess whether ixekizumab alters the metabolism or pharmacokinetics of CYP substrates in psoriasis patients treated with ixekizumab.

The timetable you submitted on March 16, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 08/2016
Study Completion: 01/2018
Final Report Submission: 05/2018

Submit clinical protocols to your IND 100834 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.**”

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 3049-6 Perform a repeat microbial retention study for the (b) (4) using a suitable surrogate solution. Alternatively, perform the study using a modified process, a modified formulation, or a reduced exposure time for the challenge organism. Provide the summary data, the associated report, and justification for any modifications to the study. If any (b) (4) parameters are changed as a result of the study, update the BLA file accordingly.

The timetable you submitted on March 16, 2016, states that you will conduct this study according to the following schedule:

Study Completion: 11/2016
Final Report Submission: 12/2016

3049-7 Provide data from two additional commercial drug product batches to support the maximum hold time for pooled drug substance. The hold time study should include the maximum hold time at (b) (4) °C followed by the maximum hold time under ambient conditions. Provide data from two additional commercial drug product batches to support the maximum hold time for drug product prior to (b) (4). The supporting data should include bioburden and endotoxin testing results from samples (b) (4). Data from process simulations (b) (4) may be provided in lieu of data from drug product batches.

The timetable you submitted on March 16, 2016, states that you will conduct this study according to the following schedule:

Study Completion: 11/2016
Final Report Submission: 12/2016

Submit clinical protocols to your IND 100834 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**.”

GENERAL ADVICE

For PMR 3049-4, in your annual progress report of postmarketing studies, provide patient accrual and demographic summary data; and in your periodic postmarketing safety report as required under 21 CFR 600.80(c)(2), provide safety data for the reporting period, and cumulatively.

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 package insert to:

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

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

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

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

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 4206
Silver Spring, MD 20903

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

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics 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.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

FDA BENEFIT-RISK FRAMEWORK APPLICANT INTERVIEW

FDA has also contracted with Eastern Research Group, Inc. (ERG) to conduct an assessment of FDA's initial phase implementation of the Benefit-Risk Framework (BRF) in human drug review. A key element of this evaluation includes interviews with applicants following FDA approval of New Molecular Entity (NME) New Drug Applications (NDAs) and original Biologic License Applications (BLAs). The purpose of the interview is to assess the extent to which the BRF provides applicants with a clear understanding of the reasoning behind FDA's regulatory decisions for NME NDAs and original BLAs.

ERG will contact you to schedule a BRF applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final reports. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to this evaluation.

If you have any questions, call Paul Phillips, Regulatory Project Manager, at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Julie Beitz, MD
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIE G BEITZ
03/22/2016