



BLA 761055

BLA APPROVAL

Regeneron Pharmaceuticals, Inc.
Attention: Elisa Babilonia, PhD
Associate Director Regulatory Affairs
777 Old Saw Mill River Rd
Tarrytown, NY 10579

Dear Dr. Babilonia:

Please refer to your Biologics License Application (BLA) dated and received July 29, 2016, and your amendments, submitted under section 351(a) of the Public Health Service Act for DUPIXENT (dupilumab) injection, 150 mg/mL.

LICENSING

We have approved your BLA for DUPIXENT (dupilumab) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, DUPIXENT under your existing Department of Health and Human Services U.S. License No. 1760. DUPIXENT is indicated for the treatment of adult patients with moderate to severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture DUPIXENT drug substance (b) (4) at Regeneron Pharmaceuticals, Inc. in Rensselaer, New York. The final formulated product will be manufactured, filled, labeled, and packaged at Sanofi Winthrop, Le Trait, France. You may label your product with the proprietary name, DUPIXENT, and will market it in 300 mg/2 mL solution in a single-dose pre-filled syringe or 300 mg/2 mL solution in a single-dose pre-filled syringe with needle shield.

DATING PERIOD

The dating period for DUPIXENT shall be 24 months from the date of manufacture when stored at 5 ± 3 °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. The dating period for your (b) (4) shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

Results of ongoing stability studies should be submitted throughout the dating period as they become available, including the results of stability studies from the first three production lots.

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

FDA LOT RELEASE

You are not currently required to submit samples of future lots of DUPIXENT 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.

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 patient package insert). 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 **and** carton and immediate container labels submitted on February 27, 2017, 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 — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015)”. 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 761055.**” Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for DUPIXENT was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial 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, 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 DUPIXENT is indicated for the treatment of moderate to severe atopic dermatitis in patients whose disease is not adequately controlled with topical prescription therapies or for whom 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 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 601.28 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

- 3183-1 Conduct a randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab administered concomitantly with topical therapy in subjects 6 years to less than 12 years of age with severe atopic dermatitis.

Final Protocol Submission: 03/18
Study Completion: 06/19
Final Report Submission: 09/19

- 3183-2 Conduct a randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab monotherapy in subjects 12 years to less than 18 years of age with moderate to severe atopic dermatitis.

Final Protocol Submission: 01/18
Study Completion: 02/19
Final Report Submission: 05/19

3183-3 Conduct an open-label study to characterize the long-term safety (at least 1 year) of dupilumab in pediatric subjects 6 months to less than 18 years with moderate and/or severe atopic dermatitis.

Final Protocol Submission: 04/18
Study Completion: 12/22
Final Report Submission: 03/23

3183-4 Conduct a safety, pharmacokinetic (PK), and efficacy study in subjects 6 months to less than 6 years with severe atopic dermatitis.

Final Protocol Submission: 01/18
Study Completion: 08/21
Final Report Submission: 11/21

Submit the protocols to your IND 107969, with a cross-reference letter to this BLA.

Reports of these required pediatric postmarketing studies 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 adverse pregnancy and fetal outcomes.

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:

3183-5 A prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to dupilumab 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 23, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 12/18
Study Completion: 07/25
Final Report Submission: 07/26

- 3183-6 Conduct a retrospective cohort study using administrative databases to identify pregnancy outcomes in a cohort of women exposed to dupilumab and a non-dupilumab systemic medication or phototherapy 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 atopic dermatitis are counseled to avoid systemic treatments while trying to conceive and during the course of pregnancy.

The timetable you submitted on March 23, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 03/19
Study Completion: 10/25
Final Report Submission: 10/26

Submit clinical protocols to your IND 107969, with a cross-reference letter to this BLA. Submit all final reports 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 protocols 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 or FDA’s regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

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:

- 3183-7 Complete the ongoing drug-drug interaction clinical study R668-AD-1433 to determine the potential for dupilumab to alter the pharmacokinetics of CYP substrates in subjects with moderate to severe atopic dermatitis.

The timetable you submitted on March 23, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/17

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

We remind you of your postmarketing commitments:

- 3183-8 Revise the (b) (4) CFU/ (b) (4) mL bioburden limit for product sampled (b) (4) after data from 10 additional drug product batches has been analyzed.

The timetable you submitted on March 23, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/17

- 3183-9 Provide bioburden and sterility test qualification data from one additional batch of 150 mg/mL drug product. Submit the data in the first annual report.

The timetable you submitted on March 23, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission (may include in first annual report): 5/18

Submit clinical protocols to your IND 107969 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. 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 20993

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.

If you have any questions, call Matthew White, Senior Regulatory Project Manager, at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):
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
03/28/2017