BLA 761122

BLA APPROVAL

GlaxoSmithKline LLC
1250 S. Collegeville Road
Collegeville, PA 19426

Attention: Ron Chamrin
Manager, Global Regulatory Affairs

Dear Mr. Chamrin:

Please refer to your biologics license application (BLA) dated August 7, 2018, received August 7, 2018, and your amendments, submitted under section 351(a) of the Public Health Service Act for Nucala (mepolizumab) Liquid Formulation, Subcutaneous Injection via Autoinjector (AI) or Safety Syringe Device (SSD), 100 mg/mL.

LICENSING

We have approved your BLA for Nucala (mepolizumab) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Nucala under your existing Department of Health and Human Services U.S. License No.1727. Nucala is indicated for 1) the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype; 2) treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Nucala drug substance at (b) (4) The final formulated drug product will be manufactured, filled, labeled, and packaged at Glaxo Operations UK Ltd., County Durham, United Kingdom. You may label your product with the proprietary name, Nucala, and market it in 100 mg/mL, injection, in single-dose prefilled autoinjector or prefilled syringe.

DATING PERIOD

The dating period for Nucala shall be 24 months from the date of manufacture when stored at 2-8 °C; Nucala may be stored up to 7 days at 20-25°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 Nucala 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 Nucala, 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.

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, as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (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*.[2]

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 761122**." Approval of this submission by FDA is not required before the labeling is used.

[1] 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.

ADVISORY COMMITTEE

Your application for Nucala was not referred to an FDA advisory committee because this biologic is not the first in its class.

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

We remind you of your postmarketing commitments:

3620-1 Conduct a microbial retention study using mepolizumab drug product under conditions that do not impact viability of the challenge organism.

The timetable you submitted on April 23, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: October 2019

3620-2 Provide dose accuracy, injection time and activation force for the remaining 18 month and 24 month timepoints for ongoing stability protocol on the three (b) (4) batches used to verify of the autoinjector functionality after aging.

The timetable you submitted on May 10, 2019, states that you will conduct this study according to the following schedule:

Study Completion: November 2019
Final Report Submission: January 2020

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.

The following pertains to the EGPA indication:

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

The following pertains to Add-on maintenance treatment of patients with severe asthma and with an eosinophilic phenotype:

We are waiving the pediatric study requirement for patients less than 6 years of age because necessary studies are impossible or highly impracticable. This is because the disease (severe asthma with an eosinophilic phenotype) is unlikely to exist in sufficient numbers to allow for a study to be conducted.

We are deferring submission of your pediatric studies for ages 6 years to 11 years because this product is ready for approval for use in adults and review of the pediatric studies submitted in November 2018 has not been completed.

POSTMARKETING REQUIREMENTS UNDER 505(o)

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)(C) of the FDCA. These required studies are listed below.

3620-3 Conduct a 12 week, randomized, open-label, pharmacokinetic and pharmacodynamics study of Nucala (mepolizumab) in pediatric patients with asthma 6 years to 11 years of age (Part A of Study 200363).

The timetable you submitted on June 3, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	Submitted
Study Completion:	Submitted
Final Report Submission:	September 2019

3620-4 Conduct a 12 month long-term safety and pharmacodynamics extension study of Nucala (mepolizumab) in pediatric patients with asthma 6 years to 11 years of age (Part B of Study 200363).

The timetable you submitted on June 3, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	Submitted
Study Completion:	Submitted
Final Report Submission:	September 2019

Submit clinical protocol(s) to your IND 006971 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).

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 601.70requires 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.

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:

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 Patient Package Insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[3] Information and Instructions for completing the form can be found at FDA.gov.[4] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[5]

REPORTING REQUIREMENTS

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

[3] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[5] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

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

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.[6]

If you have any questions, call Ji Hyun LaRose, Regulatory Project Manager, at (301) 796-9017.

Sincerely,

{See appended electronic signature page}

Sally Seymour, MD

[6] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

Acting Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):

- 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/

BANU A KARIMI SHAH
06/06/2019 01:09:31 PM
signing with the delegated authority of Dr. Sally Seymour, Acting Division Director, DPARP