

BLA 761154

BLA APPROVAL

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O.Box 4310
Morgantown, WVA 26505

Attention: S. Wayne Talton
Head of Global Regulatory Affairs

Dear Mr. Talton:

Please refer to your biologics license application (BLA) dated July 12, 2019, received July 12, 2019, and your amendments, submitted under section 351(k) of the Public Health Service Act for Hulio (adalimumab-fkjp) injection, 20 mg/0.4 mL and 40 mg/0.8 mL.

LICENSING

We have approved your BLA for Hulio (adalimumab-fkjp) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Hulio under your existing Department of Health and Human Services U.S. License No. 2210. Hulio is indicated for:

1. Rheumatoid Arthritis (RA): Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.
2. Juvenile Idiopathic Arthritis (JIA): Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 4 years of age and older.
3. Psoriatic Arthritis (PsA): Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.
4. Ankylosing Spondylitis (AS): Reducing signs and symptoms in adult patients with active AS.
5. Adult Crohn's Disease (CD): Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.

Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab products.

6. Ulcerative Colitis (UC): Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of adalimumab products has not been established in patients who have lost response to or were intolerant to TNF blockers.
7. Plaque Psoriasis (Ps): The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture adalimumab-fkjp drug substance at Kyowa Hakko Kirin Co., Ltd., Takasaki Plant in Takasaki, Gunma, Japan. The final formulated drug product will be manufactured, filled, packaged, and assembled and secondary packaged at (b) (4)

(b) (4); secondary packaged and labeled at (b) (4)

(b) (4) You may label your product with the proprietary name, Hulio, and market it in a 40 mg/0.8 mL prefilled syringe and prefilled pen and 20 mg/0.4 mL prefilled syringe.

DATING PERIOD

The dating period for Hulio shall be 36 months from the date of manufacture when stored at 2 to 8 °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 Hulio 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 Hulio, 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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 (text for the Prescribing Information, Instructions for Use, and Medication Guide). 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 761154.**” Approval of this submission by FDA is not required before the labeling is used.

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

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>.

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

Rheumatoid Arthritis

At this time, we have determined that, with respect to Polyarticular Juvenile Idiopathic Arthritis (pJIA) in pediatric patients 0 to less than 2 years of age, no pediatric studies will be required under PREA for your BLA.

We are deferring the required pediatric assessment for pediatric patients 2 years to less than 4 years of age. See Deferred Pediatric Assessments below.

We are deferring the required pediatric assessment for patients < 15 kg. See Deferred Pediatric Assessments below.

Psoriatic Arthritis

At this time, we have determined that, with respect to this indication, no pediatric studies will be required under PREA for your BLA.

Ankylosing Spondylitis

At this time, we have determined that, with respect to this indication, no pediatric studies will be required under PREA for your BLA.

Crohn's Disease

At this time, we have determined that, with respect to Crohn's disease in pediatric patients less than 6 years of age, no pediatric studies will be required under PREA for your BLA.

We are deferring the required pediatric assessment for pediatric patients 6 years to 17 years of age. See Deferred Pediatric Assessments below.

Ulcerative Colitis

At this time, we have determined that, with respect to ulcerative colitis in pediatric patients less than 5 years of age, no pediatric studies will be required under PREA for your BLA.

We are deferring the required pediatric assessment for pediatric patients 5 to 17 years of age. See Deferred Pediatric Assessments below.

Plaque Psoriasis

At this time, we have determined that, with respect to this indication, no pediatric studies will be required under PREA for your BLA.

Deferred Pediatric Assessments

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.

- 3894-1 Assessment of Hulio (adalimumab-fkjp) for the treatment of polyarticular juvenile idiopathic arthritis (JIA) in patients ages 2 to less than 4 years of age.

The timetable you submitted on June 26, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: September 2021

- 3894-2 Assessment of Hulio (adalimumab-fkjp) for the treatment of Pediatric Crohn's disease (CD) in pediatric patients 6 years to 17 years of age.

The timetable you submitted on June 18, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: September 2021

- 3894-3 Assessment of Hulio (adalimumab-fkjp) for the treatment of pediatric ulcerative colitis (UC) in pediatric patients 5 years to 17 years of age.

The timetable you submitted on June 18, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: September 2021

- 3894-4 Develop a presentation that can be used to accurately administer Hulio (adalimumab-fkjp) to pediatric patients who weigh less than 15 kg.

The timetable you submitted on June 26, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: December 2023

Submit the protocol(s) to your IND 116471, 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 COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 3894-5 Develop and implement tests in appropriate format (functional bioassays or the use of FcγRIIIa and C1q binding as surrogates) for the Fc-domain-mediated effector functions of antibody-dependent cell mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) of FKB327; and to add these tests to the drug substance release specification. The updated drug substance release specification, test methods and supporting validation data will be submitted to FDA following 21 CFR 601.12 (b).

The timetable you submitted on June 18, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: September 2022

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*.³

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.⁴ Information and Instructions for completing the form can be found at FDA.gov.⁵

³ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

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

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

REPORTING REQUIREMENTS

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

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

BsUFA II 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 Original 351(k) BLAs under BsUFA II ('the Program'). The BsUFA II 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 BsUFA II applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential

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Silver Spring, MD 20993
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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.

If you have any questions, call Elaine Sit, Regulatory Project Manager, at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Nikolay P. Nikolov, MD
Director (Acting)
Division of Rheumatology and Transplant Medicine
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
 - Prescribing Information
 - Patient Package Insert or Medication Guide
 - 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/

NIKOLAY P NIKOLOV
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