CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761059Orig1s000

Trade Name: Hadlima injection

Generic or Proper Name: adalimumab-bwwd

Sponsor: Samsung Bioepis Co., Ltd.

Approval Date: July 23, 2019

Indication: 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.

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761059Orig1s000

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Officer/Employee List	**X**
Multidiscipline Review(s) • **Summary Review** • **Office Director** • **Cross Discipline Team Leader** • **Clinical** • **Non-Clinical** • **Statistical** • **Clinical Pharmacology**	**X**
Product Quality Review(s)	**X**
Clinical Microbiology / Virology Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

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APPROVAL LETTER

BLA 761059

BLA APPROVAL

Samsung Bioepis Co., Ltd.
c/o Cardinal Health, Inc.
7400 West 110th Street, Suite 300
Overland Park, KS 66210

Attention: David Rhein, RPh, PharmD
US Agent

Dear Dr. Rhein:

Please refer to your biologics license application (BLA) dated July 23, 2018, received July 23, 2018, and your amendments, submitted under section 351(k) of the Public Health Service Act for Hadlima (adalimumab-bwwd) injection 40 mg/0.8 mL.

LICENSING

We have approved your BLA for Hadlima (adalimumab-bwwd) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Hadlima under your existing Department of Health and Human Services U.S. License No. 2046. Hadlima is indicated for the following:

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 Hadlima drug substance (b) (4) (b) (4). The final formulated drug product will be manufactured, filled, labeled, and packaged at (b) (4), (b) (4). You may label your product with the proprietary name, Hadlima, and market it in 40 mg/0.8 mL prefilled syringe and autoinjector.

DATING PERIOD

The dating period for Hadlima shall be 36 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 (b) (4).

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Hadlima 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 Hadlima, 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 761059**." 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 < 30 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 by 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)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

3671-1 Assessment of Hadlima (adalimumab-bwwd) 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 July 8, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: September 2021

3671-2 Assessment of Hadlima (adalimumab-bwwd) for the treatment of Pediatric Crohn's disease (CD) in pediatric patients 6 years to 17 years of age.

The timetable you submitted on July 8, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: September 2021

3671-3 Assessment of Hadlima (adalimumab-bwwd) for the treatment of pediatric ulcerative colitis (UC) in pediatric patients 5 years to 17 years of age.

The timetable you submitted on July 8, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: December 2020

3671-4 Develop a presentation that can be used to accurately administer Hadlima (adalimumab-bwwd) to pediatric patients who weigh less than 30 kg.

The timetable you submitted on July 8, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: September 2021

Submit the protocol(s) to an IND, with a cross-reference letter to this BLA, if needed.

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 COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3671-5 Implement (b) (4) monitoring (b) (4) of the SB5 drug product.

The timetable you submitted on July 8, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: March 2020

3671-6 To implement an SB5 derived assay control for the complement dependent cytotoxicity (CDC), TNF-α reporter gene potency, and TNF-α FRET binding potency assays and to establish acceptance criteria for the assay control relative to the reference standard (RS). The final study report(s) will be submitted in accordance with 21 CFR 601.12.

The timetable you submitted on July 8, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: March 2020

3671-7 To implement a system suitability criterion (b) (4) (b) (4) and establish a tighter limit for %difference in the peak areas (b) (4) (b) (4). The final study report(s) will be submitted in accordance with 21 CFR 601.12.

The timetable you submitted on July 8, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: October 2019

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 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).

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

[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

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 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 Brandi Wheeler, Regulatory Project Manager, at (301)796-4495.

Sincerely,

{See appended electronic signature page}

Sally Seymour, MD
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
  - 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
07/23/2019 02:04:14 PM
Signed under the authority delegated by Dr. Sally Seymour, Division Director, DPARP.