



BLA 761054

BLA APPROVAL

Samsung Bioepis Co., Ltd.
c/o Quintiles, Inc.
4920 E. Greensboro Chapel Hill Road
Graham, NC 27253

Attention: Kamali Chance, MPH, PhD, RAC
Vice President, Head, Global Biosimilars Regulatory Strategy, Quintiles

Dear Dr. Chance:

Please refer to your Biologics License Application (BLA) dated and received March 21, 2016, submitted under section 351(k) of the Public Health Service Act for Renflexis (infliximab-abda) for Injection, 100 mg.

We acknowledge receipt of your major amendment dated December 9, 2016, which extended the goal date by three months.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2046 to Samsung Bioepis Co., Incheon, Republic of Korea, under the provisions of section 351(k) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Renflexis (infliximab-abda). Renflexis is indicated for:

- 1) Crohn's Disease:
 - 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 the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease.

2) Pediatric Crohn's Disease:

- reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.

3) Ulcerative Colitis:

- reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

4) Rheumatoid Arthritis:

- in combination with methotrexate, reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis.

5) Ankylosing Spondylitis:

- reducing signs and symptoms in patients with active ankylosing spondylitis

6) Psoriatic Arthritis:

- reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.

7) Plaque Psoriasis:

- treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture infliximab-abda drug substance at Biogen Manufacturing ApS, Hillerød, Denmark. The final formulated product will be manufactured, filled, labeled, and packaged at Patheon Italia SpA, Ferentino, Italy. You may label your product with the proprietary name, Renflexis, and will market it in 100 mg in a single-use 20 mL vial.

DATING PERIOD

The dating period for Renflexis shall be 30 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 30 months from the date of manufacture when stored at -60 to -80°C.

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

FDA LOT RELEASE

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

WAIVER OF HIGHLIGHTS SECTION

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 [21 601.14(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, 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, 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, before May 5, 2017, 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 761054.**” 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, 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 comments pertain to the Rheumatoid Arthritis indication:

We are waiving the pediatric study requirement for pediatric patients ages 2 through 4 years of age because this product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients.

We are also waiving the pediatric study requirements for pediatric patients less than 2 years of age because necessary studies are impossible or highly impracticable given that the disease is rarely diagnosed in this population.

The following comment pertains to the Ankylosing Spondylitis indication:

We are waiving the pediatric study requirements for pediatric patients ages 0 to 17 years for this indication because necessary studies are impossible or highly impracticable.

The following comment pertains to the Psoriatic Arthritis indication:

We are waiving the pediatric study requirements for pediatric patients ages 0 to 17 years for this indication because necessary studies are impossible or highly impracticable.

The following comment pertains to the Plaque Psoriasis indication:

We are waiving the pediatric study requirements for pediatric patients ages 0 to 17 years old for this indication because necessary studies for this product (i.e., dedicated studies limited to pediatric patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis) are impossible or highly impracticable.

The following comment pertains to the Crohn’s disease indication:

We are waiving the pediatric study requirements for pediatric patients less than 6 years of age because necessary studies for this product (i.e., dedicated studies limited to pediatric patients 2 to less than 6 years of age) are impossible or highly impracticable. Additionally, this condition is rare in patients less than 2 years of age.

The following comment pertains to Ulcerative Colitis indication:

We are waiving the pediatric study requirements for pediatric patients less than 6 years of age because necessary studies for this product (i.e., dedicated studies limited to pediatric patients 2 to less than 6 years of age) are impossible or highly impracticable. Additionally, this condition is rare in patients less than 2 years of age.

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

We remind you of your Product Quality postmarketing commitments (PMC's):

PMC #3209-1: Implement a test for FcγRIIIa binding affinity into the drug substance Release specification. Submit the proposed release specification as a CBE-30 supplement described under 21 CFR 601.12 (c).

The timetable you submitted on April 17, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/21/2018

PMC #3209-2: Implement the reducing CE-SDS purity test into the drug substance and drug product release specifications. Submit the proposed release specification as a CBE-30 supplement described under 21 CFR 601.12 (c).

The timetable you submitted on April 17, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/21/2018

PMC #3209-3: Re-evaluate and establish final in-process bioburden and endotoxin limits for the MabSelect SuRe viral inactivated neutralized (VIN) eluate at the end of hold prior to 0.2 μm filtration. In addition, provide the qualification test data for the bioburden and endotoxin samples. Submit the proposed limits as a CBE-30 supplement described under 21 CFR 601.12 (c).

The timetable you submitted on April 17, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/31/2018

PMC #3209-4: Re-evaluate and establish final endotoxin limits for the 10 mM sodium phosphate, 10 % sucrose, pH 6.2 solution and 10% polysorbate 80 solution. Submit the proposed limits as a CBE-30 supplement described under 21 CFR 601.12 (c).

The timetable you submitted on April 17, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 10/31/2019

PMC #3209-5: Repeat the container closure integrity test (CCIT) validation for the SB2 drug product using a positive control with a defect size of no more than 20 microns. Submit the CCIT validation study report as a CBE-30 supplement described under 21 CFR 601.12 (c).

The timetable you submitted on April 17, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 11/30/2017

PMC #3209-6: Qualify an in-process endotoxin test method and establish an in-process endotoxin action limit for the bioburden reduction filtration step of the SB2 drug product manufacturing process. Submit the proposed limit as a CBE-30 supplement described under 21 CFR 601.12 (c).

The timetable you submitted on April 17, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/15/2017

PMC #3209-7: Conduct endotoxin, bioburden, and sterility test method qualification study using one additional batch of SB2 drug product manufactured according to the commercial drug product manufacturing processes.

The timetable you submitted on April 17, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/15/2017

PMC #3209-8: Conduct the bubble point determination study of the sterilizing filter with two additional lots of SB2 drug product.

The timetable you submitted on April 17, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 11/30/2017

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 20903

If you have any questions, call Christine Ford, Regulatory Project Manager, at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, PhD
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
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/

BADRUL A CHOWDHURY
04/21/2017