

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761100Orig1s000

Trade Name: Ontruzant
Generic or Proper Name: trastuzumab-dttb
Sponsor: Samsung Bioepis Co., Ltd
Approval Date: January 18, 2019

Indication: Adjuvant Breast Cancer:
Adjuvant treatment of HER2-overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer:

- as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
- as part of a treatment regimen with docetaxel and carboplatin
- as a single agent following multi-modality anthracycline based therapy.

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

Metastatic Breast Cancer:

- In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more

chemotherapy regimens for metastatic disease.

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

Metastatic Gastric Cancer:

- In combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease.

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

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APPROVAL LETTER



BLA 761100

BLA APPROVAL

Biologics Consulting Group, Inc.
Authorized U.S. Representative for Samsung Bioepis Co., Ltd
Attention: Norman W. Baylor, PhD, President and CEO
1555 King Street, Suite 300
Alexandria, VA 22314

Dear Dr. Baylor:

Please refer to your Biologics License Application (BLA) dated October 20, 2017, received October 20, 2017, and your amendment, submitted under section 351(k) of the Public Health Service Act for Ontruzant (trastuzumab-dttb) 150 mg for injection.

We acknowledge receipt of your major amendment dated July 30, 2018, which extended the goal date by three months.

LICENSING

We have approved your BLA for Ontruzant (trastuzumab-dttb) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Ontruzant, under your existing Department of Health and Human Services U.S. License No. 2046.

Ontruzant is indicated for:

Adjuvant Breast Cancer:

Adjuvant treatment of HER2-overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer:

- as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
- as part of a treatment regimen with docetaxel and carboplatin
- as a single agent following multi-modality anthracycline based therapy.

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

Metastatic Breast Cancer:

- In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer

- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

Metastatic Gastric Cancer:

- In combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease.

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Ontruzant (trastuzumab-dttb) at (b) (4). The final formulated product will be manufactured, filled, labeled and packaged at (b) (4). You may label your product with the proprietary name, Ontruzant, and market it in 150 mg for injection.

DATING PERIOD

The dating period for Ontruzant shall be 36 months from the date of manufacture when stored at $5 \pm 3^{\circ}\text{C}$. 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) from the date of manufacture when stored at (b) (4).

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Ontruzant 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 Ontruzant, 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 AND 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 CFR 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 Prescribing Information). 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 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 titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved BLA 761100.**” 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 the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric studies requirement for this application because necessary studies are impossible or highly impracticable in children. Breast cancer and gastric cancer occur, for the most part in the adult population. The incidence of these cancer types in pediatric patients is extremely rare, and as such, clinical pediatric studies are impossible or highly impracticable.

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

We remind you of your postmarketing commitments:

3532-1 Monitor [REDACTED] (b) (4)
[REDACTED] and provide [REDACTED] (b) (4)

The timetable you submitted on January 9, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/2019

3532-2 Conduct a study to determine the (b) (4) using SB3 drug product at the pump speed setting used for the PPQ batches.

The timetable you submitted on January 9, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2019

3532-3 Update the dye-ingress container closure integrity test used on the SB3 drug product vials to include vial reconstitution prior to visual inspection.

The timetable you submitted on January 9, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2019

3532-4 Perform a method validation study to confirm the suitability of the FcγRIIIa AlphaScreen assay for use as a potency assay for SB3 drug substance and drug product stability testing. Submit the results in a final study report to the BLA.

The timetable you submitted on January 9, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2019

3532-5 Perform a method validation study to confirm the suitability of the Size Exclusion-High Performance Liquid Chromatography assay for use as a purity assay in the detection of high molecular weight species for SB3 drug substance and drug product lot release and stability testing. Submit the results in a final study report to the BLA.

The timetable you submitted on January 9, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2019

3532-6 Perform a qualification study using production (b) (4) to confirm the suitability of (b) (4) assay for the detection of product-specific host cell protein impurities in SB3 drug substance. Submit the results in a final study report to the BLA.

The timetable you submitted on January 9, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2019

3532-7 Implement a two-tiered reference standard program that includes the qualification of a working reference standard to be used for SB3 primary reference standard stability testing, routine SB3 drug substance and drug product release and stability testing. Submit the qualification results of the working reference standard to the BLA in a prior-approval supplement.

The timetable you submitted on January 9, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2019

Submit clinical protocols to your IND 123158 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 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 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).

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 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 Fatima Rizvi, Regulatory Project Manager, at (240) 402-7426.

Sincerely,

{See appended electronic signature page}

Laleh Amiri-Kordestani, MD
Supervisory Associate Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
Prescribing Information
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/

LALEH AMIRI KORDESTANI
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