



BLA 761104

**BLA APPROVAL**

AstraZeneca AB  
c/o AstraZeneca Pharmaceuticals LP  
Attention: Jessica Allmond, MAS, RAC  
Director, Global Regulatory Affairs  
One MedImmune Way  
Gaithersburg, MD 20878

Dear Ms. Allmond:

Please refer to your Biologics License Application (BLA) dated January 29, 2018, received January 29, 2018, and your amendments, submitted under section 351(a) of the Public Health Service Act for LUMOXITI™ (moxetumomab pasudotox-tdfk) for injection, 1 mg/vial.

**LICENSING**

We have approved your BLA for LUMOXITI™ (moxetumomab pasudotox-tdfk) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, LUMOXITI™ under your existing Department of Health and Human Services U.S. License No. 2059. LUMOXITI™ is indicated for treatment of adult patients with relapsed or refractory hairy cell leukemia (HCL) who received at least two prior systemic therapies, including treatment with a purine nucleoside analog (PNA).

**MANUFACTURING LOCATIONS**

Under this license, you are approved to manufacture moxetumomab pasudotox-tdfk drug substance at [REDACTED] (b) (4). The final formulated vial drug product will be manufactured, filled, labeled and packaged at [REDACTED] (b) (4). The final IV Solution Stabilizer for LUMOXITI™ will be manufactured, filled, labeled and packaged at [REDACTED] (b) (4). You may label your product with the proprietary name, LUMOXITI™, and market it as a 1 mg lyophilized cake or powder in a single-dose vial for injection. You may label the IV Solution Stabilizer as “IV Solution Stabilizer for LUMOXITI™” and market it as a 1 mL single-dose vial for use with LUMOXITI™.

## **DATING PERIOD**

The dating period for LUMOXITI™ shall be 48 months from the date of manufacture when stored at 2-8 °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) from the date of manufacture when stored at (b) (4).

The dating period for IV Solution Stabilizer for LUMOXITI™ shall be 48 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the IV Solution Stabilizer for LUMOXITI™.

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

Results of ongoing stability studies should be submitted to the annual report.

## **FDA LOT RELEASE**

You are not currently required to submit samples of future lots of LUMOXITI™ and IV Solution Stabilizer for LUMOXITI™ 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 LUMOXITI™ and of IV Solution Stabilizer for LUMOXITI™, 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.

## **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, Medication Guide, Healthcare Provider Instructions for Use). 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 carton and immediate container labels for LUMOXITI™ submitted on August 22, 2018 and for the IV Solution Stabilizer carton label submitted on September 11, 2018, 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, Revision 3)*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved BLA 761104.**” Approval of this submission by FDA is not required before the labeling is used.

### **ADVISORY COMMITTEE**

Your application for LUMOXITI™ was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the biologic in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

### **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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify a signal of serious risk of adverse events in patients who are 65 years of age and older and in those with moderate renal impairment.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

PMR 3477-1 Conduct a study to provide evidence characterizing 1) the safety of moxetumomab pasudotox in patient who are 65 years of age and older and 2) the safety of moxetumomab pasudotox in patients who have moderate renal impairment. Submit interim and complete final reports and data of adverse events, including outcomes, management and discussion of potential mitigating strategies, with data collection 2 years post-approval and 5-years post-approval respectively.

The timetable you submitted on August 20, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 10/2018  
Final Protocol Submission: 01/2019  
Interim Analysis Submission: 03/2021  
Final Report Submission: 03/2024

Submit clinical protocol(s) to your IND 115709 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 601.70 requires 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.

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

We remind you of your postmarketing commitments:

PMC 3477-2 Conduct a low endotoxin recovery study to determine the ability of the kinetic chromogenic test to detect bacterial endotoxin spiked in the undiluted moxetumomab pasudotox drug product at (b) (4) for up to (b) (4)

The timetable you submitted on September 6, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/19

PMC 3477-3 Develop an alternative method for endotoxin release testing of the IVSS which can overcome the low endotoxin recovery (LER) phenomenon. Demasking buffers may be used in combination with the LAL bacterial endotoxin test to mitigate LER.

The timetable you submitted on September 6, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 08/19

PMC 3477-4 Submit updated limits for long term stability timepoints up to the 24-month timepoint for Drug Substance stored at (b) (4) °C. The limits will be established using the stability data from 5 Drug Substance Lots. A maximum of two lots in the years when the manufacturing occurs will be placed on stability at (b) (4) °C. A justification for the limits will be provided.

The timetable you submitted on September 6, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/26

**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.

As agreed to in your submission dated September 5, 2018, you will submit for a period of 5 years, all serious cases of hemolytic uremic syndrome (HUS) events and capillary leak syndrome (CLS) events reported with moxetumomab pasudotox as 15-day Alert reports (as described under 21 CFR 600.80(c)(1)) and provide detailed analyses of serious and non-serious events reported from clinical study and postmarketing reports in the periodic safety report. The analyses should show cumulative data relative to the date of approval of moxetumomab pasudotox as well as relative to the prior periodic safety reports. Medical literature reviews for case reports/case series of HUS events and CLS events reported with moxetumomab pasudotox should also be provided in the periodic safety report.

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

### **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 <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

### **POST APPROVAL FEEDBACK MEETING**

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Wanda Nguyen, Regulatory Project Manager, at (301) 796-2808.

Sincerely,  
*See appended electronic signature page*

Richard Pazdur, MD  
Office Director  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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ENCLOSURE:  
Content of Labeling

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**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.**  
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/s/  
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ANN T FARRELL  
09/13/2018  
Signing on behalf of Dr. Pazdur

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