DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761112

BLA APPROVAL

Ablynx NV
Strategic Drug Development Services, LLC
Attention: Scott A. Oglesby, PhD
US Agent for Ablynx NV
6518 Green Rise Road
Hillsborough, NC 27278

Dear Dr. Oglesby:

Please refer to your Biologics License Application (BLA) dated June 6, 2018, received June 6, 2018, and your amendments, submitted under section 351(a) of the Public Health Service Act for CABLIVI® (caplacizumab-yhdp), for injection, 11 mg/vial.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2085 to Ablynx NV, Zwijnaarde, Oost-Vlaanderen, Belgium under the provisions of section 351(a) 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 CABLIVI® (caplacizumab-yhdp). CABLIVI® is indicated for the treatment of adult patients with acquired thrombotic thrombocytopenic purpura (aTTP), in combination with plasma exchange and immunosuppressive therapy.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture caplacizumab-yhdp drug substance at (b) (4). The final formulated drug product will be manufactured, filled, labeled, and packaged at (b) (4) (b) (4). The solvent (sterile Water for Injection pre-filled syringes) will be manufactured, filled, and labeled at (b) (4). You may label your product with the proprietary name, CABLIVI , and market it in 11 mg single-dose vials for injection.

DATING PERIOD

The dating period for CABLIVI® shall be 48 months from the date of manufacture when stored at 2°C - 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). The dating period for your solvent shall be (b) (4) months from the date of manufacture when stored at (b) (4).

The expiration date for the packaged product, CABLIVI® plus solvent, vial adapter, needle, and alcohol swabs shall be dependent on the shortest expiration date of any component.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of CABLIVI® and each kit component 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 CABLIVI®, 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 and 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 CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on January 31, 2019, 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 761112**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for caplacizumab-yhdp was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for a biologic of this class or in the intended population.

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.

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

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

We remind you of your postmarketing commitments:

PMC 3568-1 To develop and implement an analytical method to determine polysorbate 80 (PS80) levels as an (b) (4) control on ALX-0081 drug product (DP) with appropriate upper and lower limits. The final report, including method validation reports and assessment of the acceptance criterion for polysorbate 80 based on method capabilities and available data, should be submitted as a Prior Approval Supplement.

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

Final Report Submission: 07/19

PMC 3568-2 To conduct a study to demonstrate that the pre-filled syringe plunger movement during air transport does not impact product sterility.

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

Final Report Submission: 08/19

PMC 3568-3 To repeat the (b) (4) bacterial retention study using a non-bactericidal surrogate solution with physical attributes comparable to the product.

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

Final Report Submission: 09/19

PMC 3568-4 To validate shipping of bulk drug substance (b) (4) (D) (4) during summer conditions.

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

Final Report Submission: 03/19

PMC 3568-5 To perform the testing for resistance to overriding for sWFI syringe in accordance to ISO-80369-7.

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

Final Report Submission: 08/19

Submit clinical protocols to your **IND 107609** 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

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 biological products 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 Laura Wall, Regulatory Project Manager, at 301-796-2237.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURES:
Content of Labeling
Prescribing Information
Instructions for Use

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/

ANN T FARRELL
02/06/2019 10:08:57 AM
Signing on behalf of Dr. Pazdur