DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

September 4, 2015

Our STN: BL 125555/0

BLA APPROVAL

Octapharma Pharmazeutika Produktionsges.m.b.H.
Attention: Mr. Stanley Ammons
Octapharma USA, Inc.
121 River Street, Suite 1201
Hoboken, NJ 07030

Dear Mr. Ammons:

We have approved your biologics license application for Antihemophilic Factor (Recombinant), effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Antihemophilic Factor (Recombinant) under your existing Department of Health and Human Services U.S. License No. 1646. Antihemophilic Factor (Recombinant) is indicated in adults and children with Hemophilia A for:

- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT00989196, NCT01125813 and NCT01341912.

Under this license, you are approved to manufacture Antihemophilic Factor (Recombinant) at your Octapharma AB Stockholm, Sweden facility. The sterile water for injection (solvent) pre-filled syringes will be manufactured by (b) (4) The final drug product will be labeled and packaged at the Octapharma (b) (4) facility in . You may label your product with the proprietary name, NUWIQ, and market it as approved in your license application.

We did not refer your application to the Blood Products Advisory Committee because our review of information submitted in your BLA, including the clinical study design and results, did not raise concerns or controversial issues, which would have benefited from an advisory committee discussion.

The dating period for Antihemophilic Factor (Recombinant) shall be 24 months from the date of manufacture when stored at +2 to +8 °C and protected from light. During the shelf life, the product may be kept at room temperature (up to 25 °C) for a single period not exceeding three months. After storage at room temperature, the product must be used or discarded, and must not be refrigerated again. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product in accordance with 21 CFR 610.50. Following the final sterile filtration, no reprocessing/reworking is allowed without prior approval from the Agency.

The dating period for your drug substance shall be [redacted] when stored at [redacted] The expiration date for the packaged product, the lyophilized powder plus solvent, shall be dependent on the shortest expiration date of any component.

You currently are not required to submit samples of future lots of Antihemophilic Factor (Recombinant) to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, 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.

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging, or labeling of Antihemophilic Factor (Recombinant), or in the manufacturing facilities.

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, 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 the Director, Office of Compliance and Biologics Quality, at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave
WO71-G112
Silver Spring, MD 20993-0002

Under 21 CFR 201.57(c)(18), patient labeling must be reprinted at the end of the package insert. We request that the text of information distributed to patients be printed in a minimum of 10-point font.

Please provide your final content of labeling in Structured Product Labeling (SPL) format and include the carton and container labels. In addition, please submit three original paper copies for carton and container final printed labeling. All final labeling should be submitted as Product Correspondence to this BLA at the time of use (prior to marketing) and include implementation information on FDA Form 356h.

In addition, please submit the final content of labeling (21 CFR 601.14) in SPL format via the FDA automated drug registration and listing system, (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. 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.

You may submit two draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertisement and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and you must submit distribution reports as described in 21 CFR 600.81. You should submit postmarketing adverse experience reports and distribution reports to the Office of Biostatistics and Epidemiology, at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave
WO71-G112
Silver Spring, MD 20993-0002

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

In addition, you must submit adverse event reports for any infectious disease transmission within 15 days after learning of the event. Infectious disease transmission refers to an adverse event that involves suspected or confirmed transmission of an infectious agent, whether the recipient develops the infectious disease or only has serologic or other evidence. If an infectious disease transmission event is serious and unexpected, you must submit a 15-day “alert report”, as required under 21 CFR 600.80 (c)(1)(i). Infectious disease transmission events that do not meet criteria for expedited submission require periodic reports and must be submitted as individual case reports within 15 days, as authorized under 21 CFR 600.80(c)(2)(i).

You should submit reports for all other non-expedited adverse events under the periodic reporting requirements specified in 21 CFR 600.80(c)(2).

PEDIATRIC REQUIREMENTS

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

We note that you have fulfilled the pediatric study requirement for all relevant pediatric age groups for this application.

AGREED UPON POSTMARKETING COMMITMENTS

We acknowledge your written commitments as described in your letter of September 3, 2015 as outlined below:

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B.

1. GENA-05: Evaluation of immunogenicity, efficacy and safety of Antihemophilic Factor (Recombinant) in previously untreated patients.

Final protocol submission date: November 2, 2012
Study/trial completion date: November 30, 2018
Final Report Submission date: April 30, 2019

2. GENA-13: Evaluation of long-term immunogenicity, tolerability, and efficacy of Antihemophilic Factor (Recombinant) in previously treated children.

Final protocol submission date: September 17, 2015
Study/trial completion date: June 30, 2016
Final Report Submission date: November 30, 2016

3. GENA-15: Extension for subjects who completed GENA-05.

Final protocol submission date: December 12, 2013
Study/trial completion date: November 30, 2018
Final Report Submission date: April 30, 2019

4. GENA-99: Post-licensure trial to document long-term immunogenicity, safety, and efficacy of Antihemophilic Factor (Recombinant) in patients treated in normal clinical practice.

Final protocol submission date: July 21, 2014
Study/trial completion date: June 30, 2019
Final Report Submission date: March 31, 2020

Please submit clinical protocols to your IND 13722, and a cross-reference letter to this BLA, STN BL 125555 explaining that these protocols were submitted to the IND.

If the information in any of the final study reports support a change in the labeling, the final study report should be submitted as a supplement. Supplements in support of labeling changes based on a postmarketing study report may be subject to a user fee. Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Study Commitment – Protocol**
- **Postmarketing Study Commitment – Correspondence**
- **Postmarketing Study Commitment – Final Study Report**
- **Supplement contains Postmarketing Study Commitments – Final Study Report**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. Label your annual report an "**Annual Status Report of Postmarketing Study Requirements/Commitments**" and submit it to the FDA each year within 60 days of the anniversary date of this letter until all Requirements and 506B Commitments are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing commitment;
- the original schedule for the commitment;
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted); and
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm).

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

We acknowledge your written commitment as described in your letter of September 1, 2015 as outlined below:

5. Octapharma commits to validate and implement the [redacted] received from FDA, for [redacted] analysis as a quality control

lot release test for NUWIQ and submit the data for approval by FDA as a a Prior Approval Supplement (PAS) by 04 September 2016 under a Supplement that contains Postmarketing Study Commitment – Final Study Report.

Final Report Submission: September 4, 2016

We request that you submit information concerning nonclinical and chemistry, manufacturing, and control postmarketing commitments and final reports to your BLA, STN BL 125555. Please refer to the sequential number for each commitment and the submission number as shown in this letter.

Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Study Commitment – Status Update**
- **Postmarketing Study Commitment – Final Study Report**
- **Supplement contains Postmarketing Study Commitment – Final Study Report**

For each postmarketing commitment not subject to the reporting requirements of 21 CFR 601.70, you may report the status to FDA as a "**Postmarketing Study Commitment – Status Update**." The status report for each commitment should include:

- the sequential number for each study as shown in this letter;
- the submission number associated with this letter;
- describe what has been accomplished to fulfill the non-506B PMC; and,
- summarize any data collected or issues with fulfilling the non-506B PMC.

When you have fulfilled your commitment, submit your final report as **Postmarketing Study Commitment – Final Study Report** or **Supplement contains Postmarketing Study Commitment – Final Study Report**.

PDUFA V 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 NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V 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 PDUFA V 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.

Sincerely,

Jay S. Epstein, MD
Director
Office of Blood Research and Review
Center for Biologics Evaluation and Research