DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125561/0

BLA APPROVAL

Alexion Pharmaceuticals, Inc.
Attention: Sara Saltzman
Senior Director, Regulatory Affairs
352 Knotter Drive
Cheshire, CT 06410

Dear Ms. Saltzman:

Please refer to your Biologics License Application (BLA) received January 8, 2015, and your amendments, submitted under section 351(a) of the Public Health Service Act for Kanuma (sebelipase alfa).

We acknowledge receipt of your major amendment dated September 2, 2015, which extended the goal date by three months.

LICENSING

We have approved your BLA for Kanuma (sebelipase alfa) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Kanuma under your existing Department of Health and Human Services U.S. License No.1743. Kanuma is indicated for the treatment of patients with a diagnosis of Lysosomal Acid Lipase (LAL) deficiency.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture sebelipase alfa drug substance at (b) (4) . The final formulated product will be manufactured and filled at (b) (4) The final formulated product will be labeled, and packaged at (b) (4) . You may label your product with the proprietary name, Kanuma, and will market it in 20 mg/10 mL single-use vials.

DATING PERIOD

The dating period for Kanuma shall be 24 months from the date of manufacture when stored at 5 ± 3°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) °C.

Results of ongoing stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

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 Kanuma 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 Kanuma, 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) 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 labeling and immediate container label submitted on September 3, 2015, 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 – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)". Alternatively, 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 125561**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

RAREPEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV BLA 125561. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(l) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently marked, "Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher."

- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.

- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.

- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:
  - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population

aged 0 through 18 years),
o the estimated demand in the U.S. for the product, and
o the actual amount of product distributed in the U.S.

- You may also review the requirements related to this program at http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf1 (see Section 908 of FDASIA on pages 1094-1098 which amends the FD&C Act by adding Section 529). Formal guidance about this program will be published in the future.

ADVISORY COMMITTEE

Your application for Kanuma was not referred to an FDA advisory committee because the safety profile is acceptable for the treatment of patients with a diagnosis of Lysosomal Acid Lipase (LAL) deficiency and the application did not raise significant safety or efficacy issues that were unexpected for a biologic of this class.

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.

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

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2920-1 Evaluate the long-term, prospective clinical outcomes of treatment with sebelipase alfa in adult and pediatric patients with LAL deficiency, including but not limited to progression of liver and cardiovascular diseases and changes in anthropometric assessments (i.e., length/height z-scores, and weight z-scores). At a minimum, liver assessments will include results of liver biopsies and imaging studies, changes in liver synthetic function, evidence for clinical progression to end stage liver disease (e.g., assessed by the Model for End-Stage Liver Disease [MELD] score), receipt of liver transplantation, and fatal outcomes. Cardiovascular assessments will include incidence rates of non-fatal stroke, myocardial infarction, and cardiovascular death. Additional evaluations will include dosing regimens administered and reasons for any dose modifications. This trial will also collect data on the occurrence of any serious hypersensitivity reactions, such as anaphylaxis, as well as changes in antibody status (i.e., detection and titers of binding and neutralizing antibodies, and detection of IgE

antibodies). Eligible patients will be enrolled over an initial 3-year period and followed for a minimum of 10 years from the time of enrollment or until death, whichever comes first. This trial may be conducted as a separate study or as a sub-study within the Lysosomal Acid Lipase registry.

The timetable you submitted on December 3, 2015, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: March 31, 2016
Trial Completion: September 30, 2029
Final Report Submission: April 30, 2030

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

We also remind you of your additional postmarketing commitments:

Drug Substance Quality Microbiology

2920-2 Increase the bioburden test volume for (b) (4) samples to improve the sensitivity of the bioburden tests. In addition, provide bioburden qualification data for all in-process and drug substance samples from a total of three lots.

The timetable you submitted on December 3, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: January 31, 2016

2920-3 Provide endotoxin qualification data for the in-process drug substance samples from a total of three lots.

The timetable you submitted on December 3, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: January 31, 2016

2920-4 Improve the endotoxin method for the (b) (4) samples by optimizing the endotoxin test procedures.

The timetable you submitted on December 3, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: January 31, 2016

2920-5 Develop and validate a reliable endotoxin test for the unformulated drug substance sample. In addition, validate the (b) (4) and drug

substance endotoxin test using the modified endotoxin method involving the use of [redacted] sample preparation system. Provide the validation information and data.

The timetable you submitted on December 3, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: April 30, 2016

Drug Product Quality Microbiology

2920-6 Validate the [redacted] If the [redacted] is revised based on the validation study, update the BLA file accordingly.

The timetable you submitted on December 3, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: January 31, 2016

2920-7 Perform a microbial retention study to support the proposed [redacted] time limit for [redacted] Limit the validated time for [redacted] to [redacted] until the [redacted] time limit has been approved by the Agency.

The timetable you submitted on December 3, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: January 31, 2016

2920-8 Perform a study to confirm that the dye ingress test method used for drug product stability samples is capable of detecting small defects that could allow microbial ingress. The study should be performed with a range of small defect sizes [redacted] Revise the positive control defect size used for stability testing based on the results of the study and update the BLA file accordingly.

The timetable you submitted on December 3, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: January 31, 2016

2920-9 Conduct a study to understand the mechanism of endotoxin masking and/or interference in the drug product. Explore alternative test methods and develop a more suitable *in vitro* test method for the drug product.

The timetable you submitted on December 3, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: April 30, 2016

Drug Substance Quality

2920-10 Characterize the potential levels of [redacted] in the drug substance.

The timetable you submitted on December 3, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: March 31, 2016

2920-11 Develop and implement a drug substance release test to quantify the percent compositions of the [redacted] variants.

The timetable you submitted on December 3, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: January 31, 2017

2920-12 To improve control of the [redacted] glycan profile, identify for the current HPAEC-PAD method peaks representative of [redacted] and establish drug substance release specifications for the critical peaks or groups of peaks. Alternatively, develop an alternative method with better resolution to control the glycan profile, such as (but not limited to) the [redacted] characterization tests.

The timetable you submitted on December 3, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: April 30, 2017

2920-13 Conduct a study to improve the formulation to reduce or eliminate the potential for formation of visible [redacted] particles and other [redacted] aggregates. If a significantly improved formulation is identified, develop the improved formulation for the commercial product.

The timetable you submitted on December 3, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: February 29, 2016

Final Drug Product Quality

2920-14 Develop and implement an improved SDS-PAGE test or another purity test to quantitate high molecular weight product-related species with greater sensitivity and precision than the current SDS-PAGE test.

The timetable you submitted on December 3, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: January 31, 2017

2920-15 Implement the [redacted] (b) (4) test method for drug product release specifications.

The timetable you submitted on December 3, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: April 30, 2016

2920-16 Implement an assay for uptake of sebelipase alfa into [redacted] (b) (4) for drug product release specifications.

The timetable you submitted on December 3, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: June 30, 2016

2920-17 Develop and implement a [redacted] (b) (4) receptor binding assay for drug product release specifications.

The timetable you submitted on December 3, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: January 31, 2017

2920-18 Conduct studies to determine whether the [redacted] (b) (4) receptor binding assays are stability-indicating. Implement the stability-indicating assays into the drug product stability specifications with acceptance criteria supported by stability data.

The timetable you submitted on December 3, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: January 31, 2018

2920-19 Improve the enzyme activity assay to increase the range of sebelipase alfa dilutions over which the assay will yield consistent values for specific activity.

The timetable you submitted on December 3, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: January 31, 2016

2920-20 Evaluate and revise as warranted all release and stability specifications after manufacture of sufficient commercial batches for meaningful statistical analyses.

The timetable you submitted on December 3, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: December 31, 2016

2920-21 Conduct worst-case simulated or worst-case real world shipping studies for both the drug substance and the drug product to assess the potential impact of shipping conditions on product quality.

The timetable you submitted on December 3, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: October 31, 2016

2920-22 Characterize the potential of rhLAL to form oxidized variants and deamidated variants and determine whether variants identified are stability-indicating. Implement changes to the drug substance and drug product control strategies as warranted by the data.

The timetable you submitted on December 3, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: July 31, 2016

Submit clinical protocols to your IND 108460 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 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

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.

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.

If you have any questions, call Kevin Bugin, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:
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/

JULIE G BEITZ
12/08/2015