



BLA 761107

**BLA APPROVAL**

Novimmune S.A.  
c/o Advyzom LLC  
Attention: Liz Lucini, PharmD  
U.S. Agent, Vice President, Regulatory Affairs  
335 Snyder Avenue  
Berkeley Heights, NJ 07922

Dear Dr. Lucini:

Please refer to your Biologics License Application (BLA) dated March 20, 2018, received March 20, 2018, and your amendments, submitted under section 351(a) of the Public Health Service Act for GAMIFANT™ (emapalumab-lzsg) Injection, 10 mg/2 mL and 50 mg/10 mL.

We also refer to our approval letter dated November 20, 2018 which contained the following errors: storage temperature range and the Rare Pediatric Disease Voucher.

This replacement approval letter incorporates the correction of the errors. The effective approval date will remain November 20, 2018, the date of the original approval letter.

**LICENSING**

We are issuing Department of Health and Human Services U.S. License No. 2082 to Novimmune S.A., Geneva, Switzerland, 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 GAMIFANT™ (emapalumab-lzsg). GAMIFANT is indicated for the treatment of adult and pediatric (newborn and older) patients with primary hemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy.

**MANUFACTURING LOCATIONS**

Under this license, you are approved to manufacture emapalumab drug substance at (b) (4) [redacted]. The final formulated drug product will be manufactured, filled, labeled, and packaged at Patheon Italia S.p.A, Ferentino, Italy. You may

label your product with the proprietary name, GAMIFANT, and market it in 2 mL and 10 mL vials.

### **DATING PERIOD**

The dating period for GAMIFANT shall be 36 months from the date of manufacture when stored at 2°C to 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)°C. 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 GAMIFANT 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 GAMIFANT, 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 Medication Guide). 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 carton and container labeling submitted on November 9, 2018, 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 761107.**” Approval of this submission by FDA is not required before the labeling is used.

## **RARE PEDIATRIC 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 761107. 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)(1) 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),
- the estimated demand in the U.S. for the product, and
- 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.pdf> (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 emapalumab was not referred to an FDA advisory committee because evaluation of the safety data [when used in the treatment of adult and pediatric (newborn and older) patients with primary hemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy] did not raise significant safety or efficacy issues that were unexpected 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 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:

PMC 3520-1 To submit the complete final clinical study report from Study NI-0501-09: An Open-label, Single-arm, Multicenter Study to Broaden Access to Emapalumab, an Anti-Interferon gamma (Anti-IFN $\gamma$ ) Monoclonal Antibody, and to Assess its Efficacy, Safety, Impact on Quality of Life, and Long-term outcome in Pediatric Patients with Primary Hemophagocytic Lymphohistiocytosis. Include summary analysis of overall response and updated information on safety

The timetable you submitted on November 2, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2023

PMC 3520-2 Submit the complete final study report from Study NI-0501-06: A Pilot, open-label, single-arm, multicenter study to evaluate safety, tolerability, pharmacokinetics and efficacy of intravenous administration of NI-0501, an anti-interferon gamma (anti-IFN $\gamma$ ) monoclonal antibody in patients with systemic Juvenile Idiopathic Arthritis (sJIA) developing Macrophage Activating Syndrome/secondary HLH (MAS/sHLH). Include summary analysis of overall response and updated information on safety.

The timetable you submitted on November 2, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 08/2021

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

We remind you of your postmarketing commitments:

PMC 3520-3 To re-evaluate emapalumab drug substance lot release and stability specifications after 12 additional lots have been manufactured at the commercial scale. The corresponding data, the analysis and the statistical plans used to evaluate the specifications, and any proposed changes to the specifications should be provided in the final report.

The timetable you submitted on November 2, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2021

PMC 3520-4 To re-evaluate emapalumab drug product lot release and stability specifications after 12 additional lots have been manufactured at the commercial scale. The corresponding data, the analysis and the statistical plans used to evaluate the specifications, and any proposed changes to the specifications should be provided in the final report.

The timetable you submitted on November 2, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2020

PMC 3520-5 To complete the development of an assay to detect host-cell proteins with improved sensitivity, and to re-evaluate host cell protein release acceptance criteria following analysis of all clinical, PPQ, and commercial drug substance lots with the improved host cell protein assay. The corresponding validation report, data, analysis and the statistical plans used to evaluate the specifications,

and the proposed change to the specification should be provided in the final report.

The timetable you submitted on November 2, 2018, states that you will conduct this study according to the following schedule:

Interim Submission (Assay Validation Report): 12/2018  
Final Report Submission: 06/2019

PMC 3520-6 To complete investigations into the root-cause, prevalence and size distribution of the visible particles in your clinical, PPQ, and commercial drug substance lots, and based on these investigations, to propose a control strategy for visible particles in your final drug substance to ensure the drug product will be “free from visible particles”.

The timetable you submitted on November 2, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2019

PMC 3520-7 To perform a leachable study to evaluate the filled drug product container closure systems through the end of shelf-life when stored under the recommended conditions. Testing will be performed at regular intervals and will include appropriate methods to detect, identify, and quantify organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS). The complete data and risk evaluation for potential impact of leachables on product safety and quality will be submitted to the BLA.

The timetable you submitted on November 2, 2018, states that you will conduct this study according to the following schedule:

Interim Report Submission: 06/2019 (24 month data)  
Final Report Submission: 03/2020 (36 month data)

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 Natasha Kormanik, Regulatory Project Manager, at (240) 402-4227.

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  
Medication Guide

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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  
11/20/2018  
Dr. Farrell signing on behalf of Dr. Pazdur