Our STN: BL 125587/0

BLA APPROVAL
August 2, 2018

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

Dear Mr. Ammons:

Please refer to your Biologics License Application (BLA) for immune globulin intravenous, human-ifas dated April 15, 2015, received April 15, 2015, submitted under section 351(a) of the Public Health Service Act (PHS Act).

We have approved your BLA for immune globulin intravenous, human-ifas effective this date. Octapharma Pharmazeutika Produktionsges.m.b.H. is hereby authorized to introduce or deliver for introduction into interstate commerce, immune globulin intravenous, human-ifas under their existing Department of Health and Human Services U.S. License No. 1646. Immune globulin intravenous, human-ifas is indicated for the treatment of primary humoral immunodeficiency (PI) in patients 2 years of age and older and chronic immune thrombocytopenic purpura (ITP) in adults.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT01012323, NCT01313507, and NCT01349790.

Under this license, you are approved to manufacture immune globulin intravenous, human-ifas drug substance at Octapharma OSA, 72 rue du Maréchal Foch, Lingolsheim, France. The final formulated product will be manufactured at Octapharma Pharmazeutika Produktionsges.m.b.H. (OPG), Oberlaaer Strasse 235, Vienna, Austria, and filled at Octapharma Pharmazeutika Produktionsges.m.b.H. (OPG), Oberlaaer Strasse 235, Vienna, Austria, labeled and packaged at the Octapharma Pharmazeutika Produktionsges.m.b.H. (OPG), Oberlaaer Strasse 235, Vienna, Austria, and Octapharma ODE, Otto-Reuter-Straße 3, Dessau-Roßlau, Germany.

You may label your product with the proprietary name PANZYGA and market it in the following presentations (fill sizes): 10 mL, 25 mL, 50 mL, 100 mL, 200 mL, and 300 mL vials.

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 trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

DATING PERIOD

The dating period for immune globulin intravenous, human-ifas shall be for 24 months from the date of manufacture when stored at $5^{o} \pm 3^{o}$ C . Within the 24 month time period, immune globulin intravenous, human-ifas may be stored at $\leq 25^{o}$ C for 9 months. If not used after storage for 9 months at $\leq 25^{o}$ C , the product should be discarded. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. 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 (b) (4) when stored at (b) (4) .

FDA LOT RELEASE

Please submit protocols showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

BIOLOGICAL PRODUCT DEVIATIONS

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, packaging, 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

MANUFACTURING CHANGES

You must submit information to your BLA 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 immune globulin intravenous, human-ifas, or in the manufacturing facilities.

LABELING

Under 21 CFR 201.57(c)(18), patient labeling must be referenced in section 17 PATIENT COUNSELING INFORMATION. Patient labeling must be available and may either be reprinted immediately following the full prescribing information of the package insert or accompany the prescription product labeling.

We hereby approve the draft package insert labeling submitted under amendment 72, dated August 2, 2018, and the draft carton and container labeling submitted under amendment 70, dated July 31, 2018.

WAIVER OF HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling, unless we notify you otherwise.

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 *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 Form FDA 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 advertising 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. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format —Postmarketing Safety Reports* at http://www.fda.gov/Drugs/DrugSafety/ucm400526.htm and FDA's Adverse Event

reporting System website http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm.

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 safety 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 are waiving the pediatric study requirement for ages zero to less than 2 years for PI because studies are impossible or highly impracticable due to the rarity of PI diagnosed in this age group. No additional pediatric studies for PI are required because the pediatric study assessment has been fulfilled with the data submitted in this application.

We are waiving the pediatric study requirement for ages zero to less than 1 year for ITP because studies in this age group are highly impracticable as occurrence of spontaneous remissions can result in a variable clinical course.

We are deferring submission of your pediatric study in ITP for ages ≥ 1 year to < 18 years of age because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported according to 21 CFR 601.28 and section 505B(a)(3)(B) of the FDCA. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

Label your annual report as an "**Annual Status Report of Postmarketing Study Requirement/Commitments**" and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements under section 506B of the FDCA are released or fulfilled. This required study is listed below:

1. Deferred pediatric study under PREA for the treatment of ITP will evaluate efficacy and safety of Panzyga in patients ages ≥ 1 year to < 18 years.

   Draft Protocol Submission: February 28, 2019

   Final Protocol Submission: June 30, 2019

   Study Completion Date: April 30, 2022

   Final Report Submission: October 31, 2022

Submit the protocol to your IND 14121, with a cross-reference letter to this BLA, STN BL 125587 explaining that this protocol was submitted to the IND.

Submit final study reports to this BLA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated as:

- **Required Pediatric Assessment**

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

We acknowledge your written commitments as described in your letter of July 18, 2018, as outlined below:

2. Octapharma commits to submitting information on the stability study I7P012 annually as a "Postmarketing commitment - Status Update". The final stability reports will be submitted as a "Postmarketing Commitment - Final Study Reports" by Oct 30, 2020. Octapharma will also report any confirmed out-of-specification results at the recommended storage conditions from the stability monitoring to the Agency within 45 days of the event(s).

   Final Report Submission: October 30, 2020

3. Octapharma commits to submitting the final validation report for the ongoing production (b) (4) .

   Final Report Submission: August 30, 2019

We request that you submit information concerning nonclinical and chemistry, manufacturing, and control postmarketing commitments and final reports to your BLA, STN BL 125587. Please refer to the sequential number for each commitment.

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

- **Postmarketing Commitment – Status Update**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing 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 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-section 506B PMC; and,
- summarize any data collected or issues with fulfilling the non-section 506B PMC.

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

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 biological products qualify for inclusion in the program 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 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, please contact the Regulatory Project Manager for this application.

Sincerely,

Wilson W. Bryan, MD
Director
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research