



Our STN: BL 125416/0

Octapharma Pharmazeutika Produktionsges.m.b.H.
Attention: Mr. Stanley Ammons
Octapharma USA, Inc.
121 River Street, 12th floor
Hoboken, NJ 07030

Dear Mr. Ammons:

We have approved your biologics license application for Pooled Plasma (Human), Solvent/Detergent Treated effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Pooled Plasma (Human), Solvent/Detergent Treated under your existing Department of Health and Human Services U.S. License No. 1646. Pooled Plasma (Human), Solvent/Detergent Treated is indicated for: (1) Replacement of multiple coagulation factors in patients with acquired deficiencies due to liver disease and in patients undergoing cardiac surgery or liver transplantation; and (2) plasma exchange in patients with thrombotic thrombocytopenic purpura (TTP).

Under this license, you are approved to manufacture, fill, label and package Pooled Plasma (Human), Solvent/Detergent Treated final, formulated product at:

1. Octapharma Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235
A-1100 Vienna
Austria

or
2. Octapharma AB
Elersvägen 40
SE-11275 Stockholm
Sweden

You may label your product with the proprietary name, Octaplas™. The final product will be marketed in 200 ml doses filled into polyvinyl chloride blood bags.

The dating period for Pooled Plasma (Human), Solvent/Detergent Treated shall be 24 months from the date of manufacture when stored at $\leq -18^{\circ}\text{C}$ ($\leq -0.4^{\circ}\text{F}$), protected from light. 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.

Please submit samples of the product in final containers together with 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).

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for each change in the product, production process, quality controls, equipment, facilities, responsible personnel or labeling of Pooled Plasma (Human), Solvent/Detergent Treated.

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 the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Rockville, MD 20852-1448.

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 and FDA Form 2567, as appropriate.

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 Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Branch, HFM-602, 1401 Rockville Pike, Rockville, MD 20852-1448. 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)).

REPORTING OF ADVERSE EXPERIENCES

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 Center for Biologics Evaluation and Research, Office of Biostatistics and Epidemiology, HFM-210, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448. Prominently identify all adverse experience reports as described in 21 CFR 600.80. Pursuant to 21 CFR 600.2(f), for updated mailing address information, please refer to <http://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/default.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 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).

You must also submit adverse experience reports for both thromboembolic events and hyperfibrinolysis from the United States as 15-day alert reports under 21 CFR 600.80(c)(1)(i), for the first five years after licensure.

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 deferring submission of pediatric study #1 (below) until September 30, 2016 and pediatric study #2 (below) until October 31, 2017 because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported according to 21 CFR 601.70 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. The required studies are listed below:

1. An open-label, multicenter, clinical study to investigate safety, tolerability and efficacy of Octaplas™ in the management of pediatric patients <16 years old who require multiple plasma coagulation factors

Final Protocol Submission: July, 2013
Study Completion Date: February, 2016
Final Report Submission: September 30, 2016

2. A non-interventional, open-label, multicenter, clinical study to investigate safety, tolerability and efficacy of Octaplas™ in the management of pediatric patients <16 years old who require therapeutic plasma exchange

Final Protocol Submission: August, 2013
Study Completion Date: March, 2017
Final Report Submission: October 31, 2017

Please submit final study reports to this BLA. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated, “**Required Pediatric Assessments.**”

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute [section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)].

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of thromboembolism in the thrombotic thrombocytopenic purpura (TTP) patient population and risk of increased bleeding due to hyperfibrinolysis in the liver transplantation patient population.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Clinical studies to further assess these potential risks are needed because Octaplas™ contains lower levels of Protein S and alpha-2-plasmin inhibitor than found in FFP. The completed clinical studies are considered too small to reliably assess the potential for adverse events. Therefore, based on appropriate scientific data, we have determined that you are required to conduct the following studies:

3. Non-interventional 2-arm study to evaluate the safety of Octaplas™ versus FFP in patients treated for thrombotic thrombocytopenic purpura (TTP) with special emphasis on monitoring the occurrence of thromboembolic events (TEEs)

We acknowledge the timetable you submitted on November 29, 2012, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: August, 2013
Study Completion Date: December, 2017
Final Report Submission: July, 2018

4. Non-interventional 2-arm study to evaluate the safety of Octaplas™ versus FFP in patients undergoing orthotopic liver transplantation (LTX) with a special emphasis on hyperfibrinolysis

We acknowledge the timetable you submitted on November 29, 2012, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: October, 2013
Study Completion Date: April, 2017
Final Report Submission: November, 2017

Please submit the protocols to your IND 13956, with a cross-reference letter to this BLA. Please submit all final reports to this BLA and prominently identify them, as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as, 21 CFR 601.70, requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

We will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with

When you have fulfilled your commitment, please submit your final report as a PMC Submission – Final Study Report or Supplement Containing Postmarketing Study Commitment – Final Study Report.

Sincerely yours,

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

Enclosure