



Final Review

To: File (BLA 125416), Nancy Kirschbaum & Pratibha Rana

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Sponsor: Octapharma Pharmazeutika Produktionsges; m.b.h.

Product: Solvent/Detergent Treated Plasma for Transfusion [Octaplas[®]]

Subject: Final review of Characterization, Control of Critical Steps, Method Validation and Impurities sections in BLA under STN 125416

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1. Executive Summary

Octaplas is a solvent/detergent (S/D) treated blood group-specific plasma-for-transfusion product, which was developed as an alternative to single-donor fresh frozen plasma (FFP) in order to increase the safety of plasma for transfusion by minimizing the risk of virus transmission. Octaplas is prepared from 630 to 1,520 single-donor units of the same blood group. During the manufacturing process, whole cells and cell fragments/debris are removed by 1.0 µm size exclusion filtration. Subsequently, the plasma pool is treated with a combination of the solvent [1% Tri(n-butyl) phosphate (TNBP)] and detergent (1% Octoxynol-9) to inactivate any enveloped viruses. These S/D reagents are later removed by oil and solid phase extraction, respectively. After 0.2 µm sterile filtration, Octaplas is filled into 200-mL bags and rapidly deep-frozen.

Octaplas intended for US market is an updated version of the product that has been licensed under the original name of Octaplas and later as OctaplasLG from 2 to 10 years in European countries, Australia and Canada. OctaplasLG is the second generation product with

1. a shortened solvent-detergent treatment duration to preserve the activity of Protein S and alpha-2-plasma inhibitor and
2. addition of a ---(b)(4)--- affinity chromatography to reduce the load of prion proteins.

The main differences between OctaplasLG and the US version of Octaplas are use of the US-sourced plasma as a source material and extended and more stringent lot release specifications.

Control of critical manufacturing steps and intermediates is conducted through the use of action limits for process parameters such as ---(b)(4)-----
 --(b)(4)----- . If the measured values of the samples do not meet the limits, they will be adjusted accordingly.

Profile of the product- and process-related impurities which include ----(b)(4)----- solvent/detergent is reproducible from batch-to-batch. The levels of impurities are controlled with dedicated validated lot release tests. Activated coagulation factors are controlled with a classical ---(b)(4)-----

Potency of the product is controlled by a comprehensive ----(b)(4)-----
 -----(b)(4)-----
 -----(b)(4)----- . The adequate control of the manufacturing process has been confirmed by the consistency of batch-to-batch release data.

Based on the information submitted in the Characterization, Control of Critical Steps, Method Validation and Impurities sections of the BLA, I conclude that the quality attributes of the product and its manufacturing process are adequately controlled. Therefore, I recommend approval of this BLA.

2. Characterization

Elucidation of Structure and Other Characteristics

Composition

3.2.S.3.1.1 Composition

Names of Ingredients	Per 200 ml Bag	Function	Standard
Human plasma protein	9.0-14.0 g	Active ingredient	internal
Sodium citrate dihydrate	0.88 - 1.48 g	Anticoagulant	Ph.Eur., USP
Sodium dihydrogen-phosphate dihydrate	0.06 - 0.24 g	Buffer component	Ph.Eur., USP/NF
Glycine	0.80 - 1.20 g	Osmolality regulator	Ph.Eur., USP/NF

Physicochemical Characterization

- the total protein concentration is 45-70 mg/mL
- the protein distribution is within the range of normal human plasma
- the coagulation activity values are close to the corresponding values of normal human plasma
- Majority of coagulation factors and some inhibitors are included in specifications. Activities of these proteins are within or slightly below the normal range, with the exception of factor VIII (b)(4) (b)(4) and Protein S (≥ 0.4 IU/mL) and alpha₂-antiplasmin (A2AP, ≥ 0.4 IU/mL).
- no antimicrobial substance or preservative is added
- viral safety is improved through S/D treatment and immune neutralization (based on control in the titers of specific antibodies and virus load)
- potential removal of pathogenic prion proteins (PrP_{sc}) by affinity ligand chromatography
- free of blood cells and cell fragments

Final Release Specifications

For detailed results of the quality control parameters in Octaplas batches, see Table 1.

Table 1 Quality control parameters in Octaplas conformance batches

[--(b)(4)--]

[(b)(4)]

Note that the above specifications for coagulation factor activities and Proteins C and S are --(b)(4)-
----(b)(4)----- In addition, only the Octaplas intended for US
market is tested for ADAMTS13, Factors X, II and VII.

Additional Comparison Data

Quality of Octaplas manufactured from the US and European plasma (denoted as OctaplasLG) was
compared with the data presented for the predecessor product (Octaplas) manufactured without the
prion removal step and reduction of the S/D treatment time from 4-4.5 hours to 1-1.5 hours. Single-
donor FFP units were also tested for comparison. In Octaplas batches, ----(b)(4)-----
----- (b)(4)-----

----- However, levels of
Protein S and Plasmin Inhibitor in OctaplasLG were higher than those observed in the first
generation product Octaplas, which is consistent with the reduced S/D treatment exposure in the
OctaplasLG.

In conclusion, these findings demonstrate comparable activities of all major coagulation factors and
inhibitors, except for Protein S and Plasmin Inhibitor, in Octaplas (US) and FFP.

[(b)(4)]

Two (2) pages determined to be not releasable (b)(4)

[(b)(4)]

3. Critical Steps and Intermediates

This review is limited to the control of Critical Steps and Intermediates and does not cover the process validation which was the subject of the review for other members of the review team.

The values given in the in-process flow diagram (see Figure and Table below) are action limits. Control of critical manufacturing steps and intermediates is conducted through the use of action limits for process parameters such as ----(b)(4)-----

-- ----(b)(4)-----

The proposed action limit ranges are acceptable because they reflect and are justified by the relative simplicity of the manufacturing process which is designed to produce a minimally altered and aliquoted version of the starting material, i.e. a pooled plasma product. To this end, the manufacturing process is geared towards

----- (b)(4) -----

Two (2) pages determined to be not releasable (b)(4)

[(b)(4)]

4. Methods Validation/Qualification

In the course of the implementation of the manufacturing process of S/D-treated plasma products at Octapharma Stockholm (OAB), the corresponding validated analytical methods have been compared between QC OPG (Vienna) and QC OAB.

For the most part, these methods are well-known clinical coagulation laboratory assays and the remaining methods are well-developed techniques in use by Octapharma for control of other US- and/or EU-licensed plasma-derived products such as Factor VIII and Factor IX concentrates. Proper suitability controls were developed by Octapharma to ensure the validity of the methods.

With the exception of the ---(b)(4)----- (see below), QC OPG and QC OAB utilize similar methodology and equipment. Activities of coagulation factors and inhibitors are determined with commercially available kits -----(b)(4)-----
------(b)(4)-----

Full list of methods and their validation reports submitted in this BLA is provided in the table below:

[(b)(4)]

Table 1a below summarizes methods used for testing of in-process samples, which are referred by Octapharma as “method of preparation (MOP)” tests. Table 1b summarizes Product Specification methods.

[(b)(4)]

Table 1b: Test parameters requested by final product specification

Parameter	Sample	
Visual Control ⁵⁾	FC	(b)(4)
(b)(4)	FC	
	FC	
Total Protein	FC	
(b)(4)	FC	
	FC	
Sterility ¹⁾	FC	
Pyrogens ⁸⁾	FC	

Two (2) pages determined to be not releasable (b) (4)

5. Impurities

Evaluated Lots

The impurity profile was assessed using the (b)(4) OctaplasLG process validation batches:

----- (b)(4) -----

----- (b)(4) -----

List of Impurities and Sources

Product-related impurities:

- ----- (b)(4) ----- are present in recovered and Source Plasma
- -- (b)(4) -- is present in recovered and Source Plasma as an anticoagulant
- --- (b)(4) --- is present in recovered plasma as an anticoagulant

Process-related impurities:

- Sodium dihydrogen-phosphate dihydrate is added to the Octaplas plasma pool as a buffer to protect the plasma proteins from --- (b)(4) -----
- S/D reagents [Octoxynol and TNBP (tri-n-butyl phosphate)] are added after the removal of residual cells, cell fragments and cell debris, to inactivate enveloped viruses
- Castor oil is added subsequently to virus inactivation, to remove TNBP from plasma (i.e., oil extraction)
- Potential leachables of the C18 chromatographic resin (solid phase extraction on the C18 resin is used to remove Octoxynol from plasma after virus inactivation)

- Potential leachables of the ---(b)(4)----- resin (affinity ligand chromatography is used to remove potentially present prion proteins)
- Glycine is added before sterile filtration and filling, to adjust osmolality

Results

Product-related impurities

One (1) page determined to be not releasable (b)(4)

[(b)(4)]

Conclusions & Recommendation

The impurity profile has been determined for (b)(4) Octaplas process validation batches at the QC department using routine finished product release testing. The impurity profile of Octaplas was reproducible and the data demonstrate that the validation batches are well within the specified limits. The more detailed assessment of product safety with regards to the levels of Extractable and Leachables and process related impurities was provided by Pharmacology and Toxicology reviewer.

6. Conclusion

I recommend approval of this BLA.