



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Pharmacology/Toxicology Review
Division of Hematology
Office of Blood Research & Review

To: BL 125416/2 (x-ref, Octagam, STN # 125062)
Reviewer: M. Keith Wyatt, Ph. D., Pharmacologist, CBER\OBRR\DH
Through: Anne M. Pilaro, Ph. D., Supervisory Toxicologist, CBER\OBRR\DH
Applicant: Octapharma USA

Product: Octaplas LG™, pooled (human) plasma, solvent detergent treated

Indication: Management of perioperative bleeding and substitution of intentionally removed plasma

Purpose: To identify, quantify and assess risk of ---(b)(4)- column leachates in OctaplasLG™

Date received: July 5, 2012

Recommendation:

The analytical and extractables/leachables data provided by the Applicant in response to the FDA information request (IR) sent on June 19, 2012 do not adequately address the safety of potential leachable components of the ---(b)(4)----- column ---(b)(4)----- matrix. Specifically, ---(b)(4)----- is a potent contact allergen, and has resulted in organ toxicities (chiefly liver, lung and kidney) following systemic exposures. The safety of repeated and/or large volume human exposures during administration of the product to patients with thrombotic thrombocytopenic purpura (TTP) has not been qualified by data from either the literature or from dedicated animal toxicity studies with the leachate/extractable materials. Additional information, including an assessment of the risk of repeated exposure to these components is needed from the Applicant to address this deficiency. Therefore, the Pharmacology/Toxicology discipline has drafted additional comments to be sent to the Applicant, requiring the Applicant to provide the results of an additional and more comprehensive evaluation of the toxicity of the leachable and extractable materials from the --(b)(4)---- column matrix. The Applicant will also be requested to use these and other available data to provide a risk assessment,

to ensure the safety of TTP patients chronically treated with Octaplas LG™ prepared using the --(b)(4)-- column.

Reviewer comment: The --(b)(4)-column is not as effective at removing prions from human plasma as the Applicant would like to claim. Based on this finding, as well as the concerns about the safety of --(b)(4)-- that leach from the --(b)(4)-- matrix, the risk and benefit of using the --(b)(4)-- column during OctaplasLG™ manufacture may not be justified.

Letter-ready comments to convey to the Applicant in the action letter. The Applicant should respond by close of business on September 18, 2012:

1. Regarding the extraction procedures and toxicity results using --(b)(4)----- resin extract (Study#116-006-EMD), and your July 5, 2012 response to the FDA IR letter dated June 19, 2012:

- a) The composition of the ---(b)(4)--- column matrix tested in Study ---(b)(4)--- ---(b)(4)---..." dated 05 July, 2012 was not provided in the report, and you state that it remains confidential. However, this information is not sufficient to evaluate the safety of the extractable and leachable components of the matrix. Identify the composition of the matrix tested in this assay, and provide information to the BLA that shows that the tested material is representative of the ---(b)(4)--- matrix used in the ---(b)(4)--- column.
- b) Provide the identity and concentration of all chemical compounds and impurities present in the ---(b)(4)-- column extracts, i.e. for all peaks present in the chromatograms that were included in the Study "---(b)(4)-----..." dated 05 July, 2012.
- c) Identify the location in the current BLA where the extractables and leachables data can be found for the ---(b)(4)-- columns that were used to support the approval of OctaplasLG in Australia and the specified European countries. If these data have not been submitted to the BLA, please provide them immediately.
- d) Toxicology data were presented in the risk assessment provided in the July 5, 2012 response to the FDA IR, but the no observable adverse effect levels (NOAELs) for ---(b)(4)-----
---(b)(4)----- were not included. In order to estimate the safety in patients who may be exposed to these components during OctaplasLG™ treatment, provide the NOAEL for each component and use these levels to calculate tolerable daily intakes and a margin of safety for each leachate listed.

Provide a risk assessment of the safety of repeated exposure to the leachable/extractable components of the - (b)(4)- column and ---(b)(4)- matrix, as would be expected from repeated use in the thrombotic thrombocytopenia purpura (TTP) clinical setting. This risk assessment should address both acute and from repeat-dose studies in rats and from

chronic Octaplas LG™ dosing by the clinically relevant intravenous route of administration and be based on experimental data that you have generated, as well as any available information from the published literature. Provide an estimate of the anticipated frequency that patients with TTP will require repeated treatment with OctaplasLG™, and determine the lifetime risk of OctaplasLG™ containing these leachates in this patient population.

Review of the Applicant's data sent in response to the June 19, 2012 IR letter:

The following original IR question (referred to as Question 2, below) was transmitted to the Applicant on June 19, 2012. The Applicant's response to Question 2 was received by FDA on July 5, 2012, and did not provide sufficient information to address the IR. Both the IR and the response are presented below, as abstracted from the Applicant's submission.

Question 2

Regarding (b)(4) report titled, (b)(4)

(b)(4) Safety, Leachables and Extractables:

- although the report presented some data on extractables and potential leachables, there was no explanation of the data as they related to potential toxicity if leached into the product
- line listings in appendix 1 are illegible

Please provide a meaningful discussion of the safety of the (b)(4)

(b)(4)

Response:

Please find enclosed an updated report titled (b)(4)

(b)(4) Safety, Leachables and Extractables" dated July 5th, 2012 as

[Attachment Q2_1](#) to this response document.

This report contains now a discussion of the safety of the (b)(4)

(b)(4) matrix. Newly included text is highlighted in yellow.

In addition Appendix 1 has been reworked and is presented as a table.

Introduction:

Octapharma (the Applicant) has developed Octaplas LG™, a solvent detergent-treated plasma-derived product for the management of several indications including bleeding during fibrinolytic therapy, replacement of coagulation factors, and treatment of thrombotic thrombocytopenic purpura. A - (b)(4)- gel column, called -(b)(4)-, comprised of --- (b)(4) ----- will be used during the manufacture of OctaplasLG™, in an effort to reduce prions associated with Creutzfeldt-Jakob disease that may be present in human plasma.

To address any safety concerns associated with chemical or biological compounds that potentially leach from the -(b)(4) column into OctaplasLG™, the Applicant conducted toxicity and mutagenicity studies on --- (b)(4) --- column extract (report # 116-006-emd_Octaplas). These studies were designed to qualify the toxicity associated with --- (b)(4) --- or other impurities that might also leach from the (b)(4) matrix. The results

from repeat-dose studies in rats and from (b)(4) assays conducted with ---(b)(4)- extracts did not identify any significant toxicity. These results suggested that any leachable (b)(4) --- (b)(4)----- degradation products in OctaplasLG™ would not present a substantial risk to patients. However, these toxicology studies were conducted with --- (b)(4)---- extracts consisting ----- (b)(4)-- component and --- (b)(4)---- breakdown products, and ----- (b)(4)----- from the --- (b)(4)----- matrix material that comprises the (b)(4) column. Therefore, FDA sent an IR to the Applicant recommending a risk assessment be conducted based on results from analytical analyses to measure --- (b)(4)- impurities -- (b)(4)- extracted from the (b)(4) column matrix itself. It was also recommended that the mutagenic potential of the true extracts be determined by the (b)(4) assay to further ensure the safety of Octaplas LG™.

The Applicant responded to the IR by providing a report containing results from an extractables and leachables study again conducted on a --- (b)(4)-- matrix and by performing an abbreviated risk assessment based on a limited amount of analytical data. Herein are reviews of both studies provided by the Applicant in support of BL125416 for OctaplasLG™.

Review summary

----- (b)(4)-----, **Safety, Leachables and Extractables, compiled by ---- (b)(4)-- Head of Quality & Regulatory Affairs, July 5, 2012**

Purpose: To provide safety information of the leachables and extractables from the

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

Method: An unspecified ----- (b)(4)----- was extracted with an equal volume of ----- (b)(4)----- . The resulting suspension was filtered, and the filtrate was analyzed by (b)(4) under normal --- (b)(4)-- (b)(4) temperatures.

In a separate experiment, the --- (b)(4)- matrix was extracted with an unspecific amount of --- (b)(4)----- . The extraction performed at - (b)(4)- was considered a worst case scenario by the Applicant because --- (b)(4)--- procedures normally used on the column are performed at --- (b)(4)----- . The extract was then analyzed by --- (b)(4)-- to identify the chemical components.

Results: Following extraction of the --- (b)(4)----- column matrix with --- (b)(4)----- --- (b)(4)----- were identified by (b)(4). The results from the (b)(4) analysis are presented below in Table 1 and Figure 1 (abstracted from the Applicant's study report):

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

[(b)(4)]

The results from extraction study, presented in Table 2, performed with (b)(4) on the ---
(b)(4) matrix show the presence of a ---**(b)(4)**----- at concentrations of -
--**(b)(4)**-----, respectively. A small unidentifiable peak, presented in Figure 2, which
likely contained a mixture of ----**(b)(4)**----- was not considered a risk
by Applicant. The assumption that risk was acceptable was made by using the low
concentration of the unidentifiable peak to calculate a margin of safety --(b)(4) -orders of
magnitude above the expected level of this impurity in OctaplasLGTM.

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

[(b)(4)]

[(b)(4)]

The Applicant also provided results from toxicity studies conducted in animals administered -----(b)(4)----- in Appendix 1 of the report. However, the data provided (*i.e.* LD₅₀ and other standard toxicology results) were not adequate to calculate a permissible daily intake or the risk to patients exposed to leachates in OctaplasLG™ from the (b)(4) matrix.