



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 125416/0/22 (cross-reference, 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: OctaplasLG™, pooled (human) plasma, solvent detergent treated

Indication: Management of preoperative or bleeding patients who require replacement of multiple coagulation factors or substitution of intentionally removed plasma (*e.g.*, plasma exchange in patients with thrombotic thrombocytopenia purpura - TTP)

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

Date received: September 18, 2012

Executive summary

Octapharma (the Applicant) has developed OctaplasLG™, a solvent detergent treated plasma-derived product for the management of several indications including bleeding during fibrinolytic therapy, replacement of coagulation factors and for the treatment of TTP. To remove prions from this plasma-derived product, the Applicant uses a (b)(4) column comprised of ----(b)(4)------. Safety concerns regarding the levels of toxic ---(b)(4)----- that potentially migrate into OctaplasLG™ were initially addressed by a series of extraction and leachables (E/L) studies conducted by the Applicant. These studies were conducted using --(b)(4)----- as the solvents for extraction, and at temperatures that exceeded those employed in-process. These studies produced results that were not adequate to address the safety because a ---(b)(4)---- matrix, and not ---(b)(4)----- matrix, was used. A subsequent request was sent to the Applicant on June 19, 2012 seeking additional E/L information; however the response submitted by the Applicant on July 5, 2012 essentially reiterated the same information contained in the original BLA, and was deemed inadequate to address the

safety concern. On September 13, another information request was sent seeking information on the composition of the (b)(4) column, the identity of (b)(4) peaks obtained during an earlier extraction study, NOAEL values for column leachates previously identified, and a risk assessment for TTP patients repeatedly administered OctaplasLG™. The Applicant's response was received on September 18, 2012. This response is inadequate since it still does not identify all the potential leachates, still relies on results obtained using --(b)(4)-- matrix material, and does not provide all the requested NOAELs and margin of safety values requested. More important, the safety assessment performed by the Applicant, based on repeated exposures to ---(b)(4)--- leachates migrating from (b)(4) matrix, suggests the risk to TTP patients requiring 50 liter infusions of OctaplasLG™ more than once a year is not acceptable.

Recommendation

---(b)(4)----- from the (b)(4)column that potentially migrate into Octaplas LG™ present a risk that may not be acceptable to patients with TTP who undergo plasma exchange (requiring 50 liter infusions of product) more than once a year. Potential --(b)(4)--- exposure levels, based on the levels determined during E/L studies and the volume of OctaplasLG™ infused per course of treatment, and permissible levels of ---(b)(4)--- exposure determined using a threshold of toxicologic concern are compared in the following table:

[(b)(4)]

General comments (for internal FDA discussion only)

1. Regarding Applicant reply a)

- a) Provide a chemical equation (s), including a reaction mechanism(s), demonstrating the reaction of ----(b)(4)-----
----- (b)(4) -----
- b) Provide analytical data ----- (b)(4) -----

2. Regarding Applicant reply b)

- a) Provide a rationale for conducting a leachable and extractable study on ---(b)(4)----- when this material is considered an intermediate in the (b)(4)----- process during the---(b)(4)----- column.
- b) Provide data showing that the levels of ----(b)(4)----- used during -----(b)(4)----- column prior to applying partially processed OctaplasLG™.

3. Regarding Applicant reply c)

- a) Indicate the method used to distinguish -----(b)(4)----- (b)(4)----- present in OctaplasLG™ from each other, when their --(b)(4)--- -----(b)(4)-----are similar.

4. Regarding Applicant reply d)

- a) Justify calculating the margin of safety for column leachates using uncertainty factors equal to (b)4, when differences in routes of administration, species and species variability suggest that an uncertainty factor of (b)(4) is more appropriate.

5. Regarding Attachment 1

- a) You indicate that you were unable to locate a NOAEL or other toxicological information regarding -----(b)(4)----- --- (b)(4)----- in the published literature, so a margin of safety for this leachate was not calculated. Justify why the margin of safety was not calculated using data from ----(b)(4)----- or a compound that was structurally related to -----(b)(4)-----
- b) You state that the -----(b)(4)----- on page 1, and (b)(4) on page 2 of the Attachment. According to TOXNET, --- (b)(4)----- corresponds to -----(b)(4)----- and not (b)(4) Please rectify this discrepancy.

6. Regarding Attachment 2

- a) The calculation of intake used only includes the amount of one --(b)(4) ---- -----(b)(4)----- at concentrations of --(b)(4) and potentially several other unidentified (b)(4) peaks that may represent --- (b)(4)--- were observed during the extraction studies. Therefore, the residual intake under a worst-case TTP treatment scenario of (b)(4) ----- ----(b)(4)----- (b)(4)--- applied by the Applicant, should be used in any calculation of risk. Provide comment.

- b) In the risk calculation on page 2 of Attachment 2, you used a TDI of -(b)(4)------(b)(4)----- Please rectify this discrepancy.

The original FDA (IR) comments, below in red text, were sent to the Applicant on September 13, 2012. The Applicant responses, excerpted from their submission received on September 18, 2012, follow each FDA (IR) in red. The FDA follow up comments appear in italics.

FDA IR comment sent September 13, 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.

Applicant's response a) sent September 18, 2012

[(b)(4)]

FDA's follow up response to Applicant's reply a)

Although more detailed chemical information is provided, the Applicant's response to the IR is not adequate. The Applicant indicates ----(b)(4)----- is formed from the -----(b)(4)----- but provides no analytical data to support this claim.

Additional reviewer comments:

The Applicant will be asked to provide a chemical equation, (b)(4) results or some other analytical data to demonstrate -----(b)(4)-----.

The Applicant states the peak in ----(b)(4)- is "likely to be --(b)(4)----". The Applicant will be asked to provide peak mobility data for ---(b)(4)----- or other analytical data (e.g.,-- (b)(4)--) to support this statement.

FDA IR sent on September 13, 2013

- 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.

Applicant's response b) sent on September 18, 2012

Ad b)

The peaks observed in the extractable study are only present when the base matrix is subjected to (b)(4) (Conditions used in the Extractables Studies). As per data presented in the report (b)(4) dated 05 July, 2012) these compounds are not seen when the base matrix is subjected to conditions used to determine (b)(4)

Note that the data presented by the (b)(4) manufacturer in the report (b)(4) (b)(4) dated 05 July, 2012 relates to (b)(4).

(b)(4)

FDA's follow up response to Applicant's reply b)

The Applicant's response to this IR comment is not adequate. The Applicant should provide a rationale for conducting a leachable and extractable study on --(b)(4)----- when this material is considered an intermediate -----(b)(4)----- process or consider repeating the E/L study using the --(b)(4)----- matrix material.

*The Applicant should provide data showing levels of ---(b)(4)-----
------(b)(4)-----
(b)(4) to apply partially purified OctaplasLG™.*

FDA IR sent on September 13, 2013

- 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.

Applicant's reply c) sent on September 18, 2012

Ad c)

Information about extractables and leachables can be found in the following sections of the BLA:

Original BLA:

Module 3.2.P.5.5 Characterization of Impurities

Including:

Technical Memorandum: Leachate Analysis Results for Samples Supplied as part of Sample Analysis Proposal dated August 2011

Module 4.2.3.2 Repeat Dose Toxicity

Summary Report of Toxicological Studies on (b)(4) Leachates

(b)(4)

Including:

Appendix 1 – Study No. AFY 0017/074120

(b)(4)

(b)(4)

Appendix 2 – Study No 116-006:
maximum tolerated

(b)(4)

Toxicity at

FDA's follow up response for Applicant's reply c)

Results contained in both of these complete study reports are not adequate to assess the risk associated with ---(b)(4)----- leachates. However, --(b)(4)--- impurities are present at such low levels they may be below the limits of detection in a mixture as complex as OctaplasLG™.

As previously stated in Pharmacology/Toxicology discipline review memoranda, results presented in the study report entitled "Repeat dose toxicity" (Module 4.2.3.2) were generated with ----(b)(4)----- matrix material and cannot be used to adequately assess risk.

Continuation of Applicant's response "C", September 18, 2012

RESPONSE TO INFO REQUEST DATED AUGUST 15, 2012

Information in Amendments:Amendment #0004:

Module 1.2:

Attachment Q2_1: (b)(4) Leachables and Extractables, Report

(b)(4) 14.06.2012

Amendment #0009:

Module 1.2:

Attachment Q2_1: (b)(4)

Safety, Leachables and Extractables, Report M. (b)(4) 05.07.2012

FDA's follow up to Applicant's reply c), continued

Results presented in both amendments are inadequate to assess the risk of chemical leachates imparted by the (b)(4) column. Amendment #0004 contains erroneous literature references to toxicology studies and provides no additional information to assess the risk of potential --(b)(4)----- impurities in OctaplasLG™. As stated in earlier Pharmacology/Toxicology discipline memoranda, the results contained in Amendment #0009 were generated with --(b)(4)----- matrix material and cannot be used to assess the risk of (b)(4) column leachates present in OctaplasLG™.

FDA IR sent on September 13, 2012

- 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) ----- 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.

Applicant response d) sent on September 18, 2012

[(b)(4)]

FDA's follow up to Applicant's reply d)

The Applicant's response to this IR comment is not acceptable. The claimed margin of safety of ---(b)(4)----- is incorrect. Based on the Reviewer's calculation, including all uncertainty factors accounting for differences in routes of administration, species, and populations, a more accurate margin of safety based on the potential amount of ---(b)(4)----- present in OctaplasLG™ is approximately (b)(4).

The Applicant's claim that ---(b)(4)----- in OctaplasLG™ is not a safety concern is correct. The margin of safety of (b)(4) is consistent with results in the literature and supports the Applicant's safety claim.

FDA IR sent September 13, 2012

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 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.

Applicant's reply 3) sent on September 18, 2012

Ad e)

As mentioned in the response to Question 1d) the leachable/extractable components are not present under normal operating condition. Even assuming that the determined concentration levels could potentially be relevant in the thrombotic thrombocytopenia purpura (TTP) clinical setting and based on available acute toxicity data and NOAELs a

safety relevant or lifetime risk in case of both acute and chronic OctaplasLG dosing is not expected. The exposure level at each single treatment is (b)(4) under the calculated (b)(4) (for further details see Attachment 2 "Safety risk assessment").

The same applies to (b)(4) leachates as presented by (b)(4) (see summary of toxicological studies, document (b)(4) in section Module 4.2.3.2). The leachate level detected was estimated at (b)(4) under the doses level used in the described MTD (b)(4) study. In addition and as described above any residual traces are further reduced by the (b)(4) manufacture (b)(4) leachates exposure of patients treated with OctaplasLG should not be the case.

FDA's follow up to Applicant's reply e)

The Applicant's response to IR is not acceptable. As previously stated in FDA's response to part d, the margin of safety for -----(b)(4)----- claimed by the Applicant is incorrect.

Results presented in Study ----(b)(4)-----, referenced in the Applicant's response, were based on extractions and leaching studies conducted with --(b)(4)--- matrix material so are not relevant for assessing the risk of (b)(4) column leachates that may be present in OctaplasLG™.

Continuation of Applicant's response e) sent September 18, 2012

Enclosures:

Attachment 1: Non-clinical data in order to estimate the safety in patients who may be exposed to leachable/extractable components during OctaplasLG treatment, written by S. Wuschko September 2012

Attachment 2: Risk Assessment of the safety of repeated exposure to the leachable components during OctaplasLG treatment; written by S. Wuschko September 2012

Review of Attachment 1, “Non-clinical data in order to estimate the safety in patients who may be exposed to leachable/extractable components during OctaplasLG™ treatment” written by Silivo Wuschko, September 2012

In the second IR sent on September 13, 2013, FDA sought no observable adverse effect levels (NOAELs) for -----(b)(4)-----, and calculations of tolerable daily intake (TDI) and margins of safety for each leachate listed. The Applicant's response was presented in Attachment 1.

Reviewer comment

The Applicant was unable to locate NOAEL values or other toxicologic information regarding -----(b)(4)----- in the published literature so the margin of safety for this potential leachate in OctaplasLG™ was not calculated.

Reviewer comment:

A review of the literature identified a sub-chronic study where (b)(4) dogs were administered --- (b)(4) -----, considered a reasonable facsimile of --(b)(4)-----, at doses up to 400 ppm for 5 hr/day 5 days/week for 2 months by intravenous administration. The study did not produce any remarkable toxicity or histopathology.

In a separate study identified in the literature, hamsters administered --- (b)(4) ----- vapor at doses of 25, 100 and 400 ppm for 6 hr/5 days a week for 78 weeks did not result in any pathologic effects attributable to --- (b)(4) ----- . The results from both of these studies suggest ----(b)(4)----- in OctaplasLG™ may present a risk in TTP patients but the risk may be insignificant in subjects receiving single doses.

According to the Applicant's assessment in Amendment 1, the potential --(b)(4)--- --- (b)(4)----- levels in Octaplas LG™ may be --(b)(4)----- If a 70-kg patient is administered OctaplasLG™ at a dose of 15 ml/kg/day, the total (b)(4) dose received would be --- (b)(4)----- . Using the ----- (b)(4)----- a tolerated daily intake (TDI) of --(b)(4)----- is assumed by the Applicant. Therefore, the margin of safety for (b)(4) is then calculated by dividing --- (b)(4)----- (b)(4)-----

Reviewer comment:

A margin of safety for --(b)(4)----- is more appropriate and suggests potential (b)(4) levels in OctaplasLG™ might be a safety concern especially in TTP patients. The lower margin of safety compared with the Applicant's (b)(4) is calculated by using an uncertainty factor of (b)(4) for differences in oral and intravenous routes of administration multiplied a factor of (b)(4) for species differences between mice and humans and then multiplied by an additional factor of (b)(4) for differences in inter-

individuality plus quality of data and experimental design for a total uncertainty factor equal to (b)(4)

Based on uncertainty factors of (b)(4), instead of a (b)(4) used by the Applicant, the lower (b)(4) margin of safety is calculated by dividing the adjusted TDI of -----(b)(4)-----
------(b)(4)-----

The Sponsor calculated risk based on an expected OctaplasLG™ dose of 15 ml /kg/day. However, according to published reports (George (2000) *Blood*, 96:1223), TTP patients might receive OctaplasLG™ at doses as large as 50 ml/kg/day. This amount is calculated by assuming a 70-kg patient would exchange ~ 3700 ml of OctaplasLG™ or 1.5 volumes of plasma (i.e., 3700 ml/70 kg = ~50 ml/kg/day).

Reviewer comment:

The difference between the amount of ---(b)(4)----- potentially contained in OctaplasLG™ doses of ---(b)(4)----- is assumed to increase the risk in TTP patients.

A margin of safety was not calculated for -----(b)(4)----- --
(b)(4)---- because, according to the Applicant, no NOAEL or additional toxicologic data were available.

Reviewer comment

Based on a TOXNET search, mouse lymphoma cells exposed to ---(b)(4)----- a reasonable facsimile of --(b)(4)---, at concentrations ranging from --(b)(4)----- resulted in an increased frequency of mutations in these cells. Using the published results, (b)(4) will be considered a carcinogen for the purposes of this risk assessment. Therefore, the permissible levels of -----(b)(4)---- must remain below -----(b)(4)-----
------(b)(4)----- However, E/L data submitted by the Applicant suggests TTP patients may actually be exposed to ----(b)(4)----- which is a safety concern in this population.

During a worst case dosing regimen needed to treat TTP patients, a 70-kg patient would receive -----(b)(4)----- at a dose of ---(b)(4)----- during cycle 1 of treatment and then at doses of (b)(4)----- during cycles 2-4. The total potential ---(b)(4)----- dose that might be administered during this regimen is (b)(4). The level of exposure would increase substantially in these patients if the dosing regimen extends for more than 4 treatment cycles.

Assuming a TTP patient requires 1, 2, 3 or 4 treatments during a single year, the total (b)(4)----- exposure compared with the permissible levels are presented in the table that follows:

[(b)(4)]

Review of Attachment 2, “Risk assessment of the safety of repeated exposure to the leachable components during Octaplas LG™ treatment” written by S. Wuschko, September, 2012

In the second IR sent on September 13, 2012, FDA sought a risk assessment of the safety of repeated exposure to the leachable/extractable components of the (b)(4) column matrix in TTP patients. The Applicant response is contained in Attachment 2.

Based on results from extraction studies conducted on the base matrix, and not the (b)(4) column itself, the Applicant calculates an average 70-kg TTP patient administered OctaplasLG™ will intake residual -----(b)(4)-----

Reviewer comment

This calculation of intake only includes the amount of one -----(b)(4)----- identified at concentrations (b)(4)----- during the extraction studies. The results also contained several unidentified chromatographic peaks that may represent ---(b)(4)----- and increase the potential exposure in TTP patients even further. The residual intake of ---(b)(4)----- during cycle 1 and (b)(4)---(b)(4)--- during cycle 2 of the established TTP treatment regimen should be applied in any calculation of risk. These potential exposure levels are far larger than the maximum exposure of ---(b)(4)----- during cycle 1 and --(b)(4)----- during the second through fourth cycles used by the Applicant in their assessment of risk. Therefore, the Applicant’s assessment may under predict the risk in TTP patients administered OctaplasLG™.

The Applicant uses an -----(b)(4)----- and safety factor of (b)(4) to account for differences in species and routes of administration (intravenous compared with oral). The Applicant then uses these toxicologic data to calculate a (b)(4) - -----(b)(4)-----

Reviewer comment:

Based on the Reviewer's calculation, the margins of safety for -----(b)(4)-----
(b)(4)--- should be --(b)(4)--, for cycle 1 and 2 respectively, based on uncertainty factors
equal (b)(4). The low margins of safety imply that TTP patients are potentially exposed
to unacceptable levels of ---(b)(4)---- after just one plasma exchange with OctaplasLG™.

According to the Applicant, (b)(4) is metabolized rapidly and does not accumulate which
further suggests a low risk to TTP patients administered OctaplasLG™. However, the
(b)(4)----- suggests (b)(4) will accumulate in adipose and be released from
tissues over time thereby further exposing TTP patients to potentially mutagenic
--(b)(4). The potential for the accumulation and release of ---(b)(4)----- further
increases the risk to TTP patient populations administered OctaplasLG™ prepared using
the (b)(4) prion removal column.