EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Patient Health Protection

Assessment report for Octagam and associated names

International Non-proprietary Name: human normal immunoglobulin

Procedure No. EMEA/H/A-31/1281

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature redacted (under the format of a black box: [redacted]).

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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

The Human Normal Immunoglobulin containing medicinal products, Octagam and associated names, are authorised and used in all EEA Member States except Ireland.

On 16 September 2010 Germany informed the European Medicines Agency of the suspension of the Marketing Authorisations of the lower strength formulation (5% and 50mg/ml) of Octagam and associated names in its territory due to an increased risk of thromboembolic events (TEE). Germany also informed the European Medicines Agency about its consideration to suspend the Marketing Authorisations of Octagam 10 % in Germany. On 17 September 2010 Sweden informed the European Medicines Agency of the national suspension of the Marketing Authorisations of both formulations due to the same safety concern. The CHMP considered the matter in accordance with Article 107 of Directive 2001/83/EC as amended in its September 2010 CHMP plenary meeting, during which the CHMP adopted an opinion recommending the suspension of all Marketing Authorisations for Octagam (both strengths) and associated names medicinal products.

As per the Commission Decision of 4 October 2010, the Marketing Authorisation Holders were requested, for the suspension to be lifted, to provide additional supportive information as follows:

(A) an overall root cause investigation report, an analytical data/method validation and a proposed protocol for a post-marketing study of TEEs following the improved manufacture of Octagam and associated names
or alternatively,
(B) the substitution to an alternative manufacturing process for Octagam with appropriate controls and reassurance in relation to TEEs, and a proposed protocol for a post-marketing study of TEEs following the improved manufacture process.

At the request of Germany, an Article 31 referral procedure was triggered for Octagam during the October 2010 CHMP plenary meeting, so that the fulfilment of the above mentioned conditions could be assessed by CHMP.

2. Scientific discussion

2.1. Introduction

Octagam and associated names is a Human normal immunoglobulin for intravenous administration (IVIg) with the following therapeutic indications:

- Replacement therapy in:
  - Primary immunodeficiency syndromes such as:
    - congenital agammaglobulinaemia and hypogammaglobulinaemia
    - common variable immunodeficiency
    - severe combined immunodeficiency
    - Wiskott Aldrich syndrome
  - Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinemia and recurrent infections
  - Children with congenital AIDS and recurrent infections
- Immunomodulation:
  - Idiopathic thrombocytopenic purpura (ITP), in children or adults at high risk of bleeding or prior to
  - surgery to correct the platelet count
  - Guillain Barré Syndrome
  - Kawasaki disease
- Allogeneic bone marrow transplantation.

On 23rd September 2010, the Committee concluded on the existence of an increased risk of thromboembolic events (TEE) in subjects treated with Octagam under normal conditions of use since 2008 and an additional increase in the 2nd and 3rd quarter of 2010.

Since 2008, the MAH has submitted two major variations concerning the manufacture of Octagam. Both final products are manufactured at three manufacturing sites, Stockholm (SE), Vienna (AT) and Lingolsheim (FR). An additional site, Springe (DE), is authorized for the manufacture of the intermediates [redacted] only. Before 2008, the MAH manufactured Octagam 5% using the [redacted] method at these three manufacturing sites. In 2008, for Octagam 5% and Octagam 10% respectively, the company transferred the [redacted] method used at [redacted] the Springe site to the production sites of Vienna (AT), Lingolsheim (FR), and Stockholm (SE). Later on, the MAH harmonised the [redacted] manufacturing process for Octagam 5% and Octagam 10%, respectively, at all four production sites of the company for intermediates [redacted]. A single authorised manufacturing process [redacted] to produce intermediates for the manufacture of the Octagam 5% and 10% strengths is common across all manufacturing sites. The manufacturing of Octagam 5% and 10% [redacted] was intended to be identical for both strengths except the last formulation and filling step. However, differences were recognised by the MAH throughout the manufacturing process.

2.2. Quality

A list of question (LoQ) was addressed to the MAH by the CHMP in October 2010 and the related responses were provided by the MAH in December 2010. Due to a certain number of remaining issues, a list of outstanding issues (LoOI) and an inspection request were adopted at the February 2011 CHMP meeting, to which the MAH responded on 25 February 2011.

A product specific inspection, focused on the implementation of the new harmonised process and the root cause investigation, was conducted on the MAH Vienna site (OPG) in week 11 2011, and on MAH Lingolsheim site (OSA) the following week. Responses to issues raised during the inspection were addressed during the course of the inspections or in the following responses to the list of outstanding issues on 30 March 2011, 1 April 2011, 7 April 2011 and 8 April 2011.

Investigations of the biochemical and technical root cause

The data package provided by the MAH addressed the list of questions as well as corrective actions which were implemented. The MAH provided investigation reports on the biochemical and technical root cause analysis in order to explain the observed increased TEE reporting rate.

Biochemical root cause

A significant increase in the number of TEE cases reported was observed since 2008 for Octagam (as compared to the usual background level observed for the other IVIG preparations marketed). The highest reporting rate is found for the 3rd quarter of 2010.

Since 2008, the MAH has submitted two major variations concerning the manufacture of Octagam. On the 23 June 2008 and 30 October 2008 for Octagam 5% and Octagam 10% respectively, the MAH transferred the [redacted] method from the Springe site to the production sites of Vienna (AT), Lingolsheim (FR), and Stockholm (SE). Previously, the MAH manufactured Octagam 5% using [redacted] method at these three manufacturing sites. As per 27 November 2009 and 12 May 2010, the MAH harmonised the manufacturing process for Octagam 5% and Octagam 10%, respectively, at all four production sites for intermediates of the company [redacted].

TEE reports received since 2008 affected all three manufacturing procedures [redacted] 69 cases of TEE were associated with 56 batches. With regard to the origin of intermediate, batches associated with TEE from all four production sites are affected. Of altogether 56 batches affected, intermediate was manufactured in Lingolsheim in 29 cases, in Vienna in 12 cases, in Springe in 16 cases, and in Stockholm in 7 cases.

For products using [redacted] from Vienna origin, a drift of the product quality profile may have increased the thrombogenic potential through the different process versions; [redacted]

For products using intermediate from Lingolsheim origin, the shift observed by NATEM occurred earlier [redacted], with a significant variability in FXIa detected; for this paste, there was a significant level of TEE reported for the [redacted] process, which was further increased with the switch [redacted].

The review of the investigation data provided by the MAH revealed that FXIa is a major contributor in the increase in the incidence rate of TEE. A small amount of another compound was identified inducing coagulation at a delayed stage in the coagulation test (slight shift in coagulation parameter). This activity was entirely inhibited by addition of CTI (Corn Trypsin Inhibitor), an inhibitor of FXIIa, the initial trigger of the coagulation cascade. Thus the compound that causes this delayed coagulation induction could be kallikrein and/or FXIIa. It had been demonstrated that kallikrein is the most likely candidate for this reaction.

The investigation made by the MAH supports the conclusion that FXIa is the main contributor to thrombogenic potential of Octagam and kallikrein is a minor one. The CHMP is in agreement with the MAH's conclusions on the biochemical root cause.

Technical root cause

The technical root cause analysis of the entire manufacturing process with different optional steps (mass capture) was focussed on the reduction rates of factor XI and XIa (partitioning) and the thromboembolic potential (thrombin generation assay (TGA), NATEM).

The MAH considers that the increase of FXI in different intermediates is due to two major steps influencing the amount of factor XIa, the upstream mass capture step (adsorption of vitamin K dependent coagulation factors) and the amount of buffer [redacted] added before [redacted] precipitation. The CHMP is in agreement with the MAH's conclusions and therefore considered the below corrective actions appropriate to address the issues.

Corrective actions

After identification of the factor XIa as a major root cause, the MAH focused on their corrective actions to remove factor XIa (and kallikrein). Reasons were subsequently given in the responses to the list of outstanding issues to explain the activation of Factor XI into Factor XIa.

The MAH presented corrective actions to improve the manufacturing process (mandatory [redacted] chromatography and sedimentation step) and to implement additional controls (FXI:Ag in in-process controls and thrombin generation assay (TGA) in release specification) in order to reduce the thrombogenicity potential of the finished product:

1. The MAH determined that an optional [redacted] capturing step [redacted] already employed in the Stockholm manufacturing site is capable of sufficiently removing FXI and FXIa. As corrective action an additional adsorption step [redacted] has been implemented following the optional step "Adsorption of Vitamin K dependent Coagulation Factors". The suitability of each [redacted] batch will be confirmed by downscale runs prior to use in production in cooperation with the supplier. The specifications [redacted] were defined and agreed with the CHMP.

2. The amount of buffer [redacted] used in the resolubilisation of [redacted] was identified as another parameter influencing the amount of factor XIa. A constant amount of [redacted] buffer [redacted] was ensured and a sedimentation step [redacted] was introduced. The complete details of changes introduced at each site remained unclear [redacted] in the first responses provided by the MAH. The CHMP therefore requested that the production process for each site should be described in detail (including qualitative and quantitative details of the input materials, batch/intermediate size), controls, and conditions justifying the use of different options including detailed description of the corresponding equipment. The responses to the LoOI and the inspection revealed that the production process is now described, and includes details of relevant quality attributes and process parameters for each step. The method of preparation was updated and revised in sufficient details, including additional information on batch size, mass capturing per site, column characteristics and several critical additional process parameters.

3. The complete details of changes introduced at each site were provided and agreed with the CHMP.

4. Two Thrombin generation assays (TGA) have been developed by the MAH, one using normal human plasma as reference, and the other using FXI depleted plasma. This TGA test has been demonstrated to be a sensitive assay to show procoagulant potential, covering both the impact of FXIa and Kallikrein procoagulant activities. For the analytical validation of the TGA assay, the MAH decided to use FXIa for calibration.

   The data demonstrated that the assay performances are satisfactory in respect of specificity, linearity, accuracy, precision, limit of detection (LOD), limit of quantitation (LOQ), robustness and stability. The MAH defined acceptance criteria based on the validation of the TGA. Three result parameters (lag time, the time to peak and the peak thrombin concentration (PTC)) of this test are used as specification in order to detect batches with a too high procoagulant activity and mitigate the thrombogenic potential of the final product. The CHMP is of the opinion that the data provided by the MAH support the proposed final acceptance criteria [redacted]

   In addition, the CHMP is of the opinion that the TGA must be performed on two independent occasions using FXI depleted plasma and must be confirmed once in standard human plasma. The CHMP considers that the cut-off limits and acceptance criteria as defined by the MAH [redacted] are adequately justified and therefore considers that the proposed TGA should be included into the release specification.

   Regarding Phase 2 Official Control Authority Batch Release (OCABR) testing, the test(s) used by OMCLs must be in the Ph. Eur. monograph or Marketing Authorisation or be fully validated against one of those two and shown to be equivalent. As there is neither a method in the monograph nor an agreed common method across the OMCL laboratories, the transfer of the MAH's method(s) to OMCLs is ongoing. As a consequence of the inclusion of TGA in the release specification, the CHMP considers that Phase 2 OCABR testing for thrombogenic potential should be undertaken using the test and limits agreed in the product specification through this referral procedure.

5. Additionally to the Prekallikrein activator measurement according to the Ph. Eur., the Prekallikrein (PKA) blank values [redacted] were included in the specification. Higher blank values indicate proteolytic background activity in products in the absence of the prekallikrein substrate, suggesting that active proteases like kallikrein or related proteases are already present in these immunoglobulins. The current batch data indicate much lower values. The limit for the PKA-blank was tightened [redacted] by the MAH in the responses to the list of outstanding issues; the tightened limit is acceptable and based on actual batch data.

For intersite process validation a matrixing approach with a testing strategy (covering all optional steps and sites apart from the exceptions highlighted through the change management protocol) was used. This validation revealed appropriate clearance for all attributes tested. The CHMP is of the opinion that the FXIa is appropriately controlled and the revised process is capable of clearing the level of FXI:Ag to a sufficiently low level.

The batch data provided with this submission indicate that these batches produced with the revised manufacturing process comply with the approved and proposed specifications. All these validation batches were also tested by the French and German National Competent Authorities respectively (Afssaps and PEI) for procoagulation activity. This testing revealed that the thrombogenic potential of the new batches is very low and comparable to other marketed IVIGs.

The controls (TGA in release specification and FXI Ag as in process control) are implemented and the CHMP considers that these controls ensure the quality and therefore the safe use of Octagam and associated names.

Inspections and inspections outcomes

The currently valid GMP certificates for all four MAH manufacturing sites (OPG Vienna, OSA Lingolsheim, OAB Stockholm, OPG-D Springe) were provided by the MAH within the Article 31 procedure. However the CHMP considered that a product specific inspection of all 4 manufacturing sites was required and agreed on a stepwise inspection program to be conducted in 2 parts:

1. First, the inspection of the Vienna and Lingolsheim sites which took place before the CHMP opinion, both aiming to support the assessment of the MAH's investigations and to confirm that all proposed changes and corrective actions are adequately implemented in the routine manufacturing process.

These 2 sites were selected since they had a large number of TEE associated batches (the root cause analysis and identification of corrective/preventive actions were performed at the Vienna site and the higher number of major deviations and reprocessing occurred at the Lingolsheim site).

2. Then, the 2 other sites (Stockholm and Springe) will be inspected after the completion of the Article 31 procedure.

The CHMP considered the responses provided by the MAH along with the inspection findings of the Vienna and Lingolsheim sites. In addition to the above taken corrective actions, issues were raised during the course of the inspections to which the MAH responded during the course of the inspections and also via submissions of further data packages. In particular, the interchangeability of different intermediates between the Vienna, Stockholm and Lingolsheim sites was not covered by the intersite validation study. Thus, the CHMP recommends the restriction of the use of the combinations of manufacturing sites only to those already validated through the "intersite validation report".

The Committee reviewed and agreed the change management protocol provided by the MAH addressing how interchange of different intermediate fractions between sites not covered by the intersite validation study should be validated. The MAH submitted this protocol including the description of the conformance batches and tests that will be performed when the interchange of intermediate between sites will be done. According to the validation plan the first batch to be processed at each affected site will be validated [redacted]. The proposed acceptance criteria for the quality attributes as well as all critical parameters are considered acceptable by the CHMP. If the MAH intends to implement the interchange of intermediate between sites that is not covered by the intersite validation study, a variation supported by validation data according to the agreed change management protocol should be submitted by the MAH(s) to the national competent authorities.

On the basis of the harmonisation of the manufacturing process, the inspections findings at the Vienna and Lingolsheim sites and taking into account the nature of the inspection (multi-site/ joint/ product specific inspections), the CHMP is reassured that corrective actions have been implemented and will be subject of further monitoring. In view of this, the CHMP recommends the lifting of the suspension for the 4 manufacturing sites.

The CHMP requests that the inspection of the Stockholm and Springe sites will be performed by the end of October 2011, care being taken to ensure continuity with the inspections of the Lingolsheim and Vienna sites, and that the outcome of the inspection will be provided to National Competent Authorities.

2.3. Clinical safety

The MAH submitted protocols for non-interventional studies to collect information on occurrence of TEEs and demonstrate the safety of the improved manufacture process of Octagam and associated names.

Three different studies are planned to be conducted, which overall will allow to document at least 20,000 infusions within a 2-3 years period:

Table 1 Overview on Non-Interventional Studies Planned with Octagam

Study ID	Country of Conductance	Octagam Strength	Status	Plan
GAM10-05 ISRCTN58800347	Germany	10%	Ongoing (but currently on hold). Started in 2008.	To document at least a further 500 patients.
GAM5-28	US	5%	Planned. Submitted to FDA for review.	To document 250 patients for 1 year (subject to FDA approval).
GAM10-06* "GammaTrack"	Rest of world, including e.g.	5% and 10%**	Planned. Approved in	Minimum of 1000 patients.

	France, UK, Spain, Brazil, et al.		France. To be submitted in UK and other European (and non-European) countries.	

** Study ID may vary in case of country-specific submissions.*
*** To be amended (currently only 10% planned/submitted).*
The population will consist of about 2000 individual patients treated with Octagam in any indication, age group gender or treatment regimen.

The duration of observation for an individual patient will be as long as Octagam will be prescribed by the treating physician. For patients with primary immunodeficiency disorders the observation period will last a minimum of 10 months.

Under the assumption that the occurrence of TEEs follows a Poisson distribution with an underlying incidence rate of 2 from 10,000 infusions, a total number of 20,000 infusions was proposed which should be sufficient to allow the observation of at least 2 TEEs with a probability of 0.908422. Statistical analysis of all the parameters will be descriptive.

The design of these studies is considered appropriate to demonstrate safety of the improved manufacturing process, and the descriptive analyses are considered acceptable by the CHMP.

The adjusted world-wide reporting rate for TEE was one case per 0.51 million grams Octagam for 2008, one case per 0.46 million grams for 2009 and one case per 0.18 million grams for a period of seven months (January to July 2010). 0.18 million grams can be estimated to represent the annual dosage of approximately 640 adult patients (assuming 70 kg body weight and a single monthly dosage 0.4 g/kg body weight).

Assuming a TEE incidence of at least 1.5 in 1000 patients, 20,000 administrations in 2000 patients would represent a greater than 95% probability to observe at least 1 patient with a TEE. Anticipating independence between infusions and an underlying incidence of 1 TEE in 5000 infusions, the planned number of infusions would provide more than 90% probability to observe at least 2 TEE, which is considered acceptable. The plans for descriptive analyses are also considered acceptable.

In order to assess the precision of the results with regard to TEE, the results will need to include not only the point estimate, but also confidence intervals for the TEE-incidence.

In conclusion, the CHMP is of the opinion that the sample size and designs of the modified observational studies are sufficient to demonstrate safety of the improved manufacturing process.

In addition, in order to ensure the monitoring of TEEs of Octagam, the CHMP also requires that the MAH should submit Periodic Safety Update Reports to the National Competent Authorities on a 6 monthly basis for a period of two years.

2.4. Risk management plan

The MAH was requested to submit a Risk Management Plan (RMP). The MAH submitted a RMP that included "embolic and thrombotic events" as new safety issues identified from post-marketing use of Octagam 5% and 10% and considered thrombogenicity as an important identified risk for further evaluation. A protocol for a post-marketing study "plan for integrated safety analysis" was provided in appendix.

The CHMP considered it necessary to investigate the effectiveness of the implemented risk minimisation measures once the product will be re-introduced onto the market in EU Member States. Therefore a post-marketing study was required to monitor the safety of Octagam with regard to TEE after lifting the suspension. The MAH was requested to present a protocol for a postmarketing safety study to collect TEEs and to demonstrate the safety of the improved manufacture of Octagam and associated names.

The CHMP considered that the protocol for the postmarketing safety study submitted was acceptable (cf section 2.3) but that the rest of the RMP should be further improved.

In accordance to the RMP guideline EMEA/CHMP/96268/2005, the RMP should normally evaluate all important identified and potential risks for Octagam as well as all important missing information that could impact on the risk benefit balance of the product or have implication for public health. The MAH should update the Pharmacovigilance Specification with regard to the current experience and according to the core SPC guideline for intravenous immunoglobulins for human use with the next PSUR.

The information available on the identified risk of thrombogenicity should be more detailed and presented in accordance with the section "presentation of risk data" and " epidemiology " of the above mentioned guideline i.e. the expected background incidence rate of TEEs in the diverse populations in whom the products are indicated should be provided.

An evaluation of the need for risk minimisation activities and a risk minimisation plan should be included taking in account the risk minimisation measures that were considered necessary during this procedure to minimise the risk of thrombogenicity in order to re-introduce the products onto the market in EU Member States and describing the criteria to be used to verify the success of such measures.
In addition some general sections were missing and should be added such as: EU additional requirements, potential for medication errors, summary of the EU RMP, annexes. The RMP should be a stand alone document without any references to other parts of the dossier.

The MAH is therefore requested to submit to the National Competent Authorities, a revised risk management plan (RMP) that adequately describes all the important safety concerns, the pharmacovigilance activities and the interventions designed to identify, characterise, prevent or minimise the important risks with particular attention to the risk of thromboembolic events. This RMP shall follow the EU RMP template and shall include measures to assess the effectiveness of the interventions.

These points should be addressed in the next RMP update. As 6 monthly PSURs are required, the revised RMP should be presented with the next 6 monthly PSUR.

2.5. Overall benefit/risk assessment

The root cause investigation was appropriately performed by the MAH which considered all potential risk factors that could be identified. This investigation supports the conclusion that FXIa is the main contributor to thrombogenic potential of Octagam and Kallikrein is a minor one. The optional mass capture step and the amount of [redacted] buffer used for reconstitution of [redacted] were identified as the two main technical contributors to the increased level in FXIa activity, both related to the increase in FXI:Ag. Several other critical process steps and parameters that could influence the thrombogenic potential were also identified.

The CHMP considers the below corrective actions implemented by the MAH are appropriate to address the issues:

- an additional adsorption step [redacted] has been implemented following the optional step "Adsorption of Vitamin K dependent Coagulation Factors";
- a constant amount of [redacted] buffer [redacted] was ensured and a sedimentation step [redacted] was introduced;
- the identified critical parameters [redacted] are appropriately controlled;
- the TGA release test and specification as well as FXI Ag in process control are now implemented;
- the prekallikrein (PKA) blank values are now included in the specification.

The implementation of the above corrective actions were confirmed by the inspections at the Vienna and Lingolsheim sites and the inspection at the Stockholm and Springe sites will be performed by the end of October 2011.

The CHMP agreed with the proposals for the safety studies to collect information on occurrence of TEEs and demonstrate the safety of the improved manufacture process of Octagam and associated names.

In view of the above, the CHMP considered the benefit risk balance of Octagam medicinal product is positive under normal conditions of use and therefore has recommended the lifting of the suspensions of the Marketing Authorisations and the variation to the terms of the marketing authorisations concerning changes to the manufacturing process across the 4 sites and the addition of TGA release test and specification, subject to conditions.

3. Overall conclusion

Whereas

- The Committee considers the procedure under Article 31 of Directive 2001/83/EC, as amended, for the Human normal immunoglobulin containing medicinal products, Octagam and associated names.
- The Committee considers the overall root cause investigation report, the analytical data and method validation, the final results on the investigation of TGA, NaPTT, NATEM, FXIa for all batches and their intermediates at each step of the manufacturing process for the 4 manufacturing sites (Stockholm, Springe, Lingolsheim and Vienna) and the consideration given on other clotting tests e.g. investigation of platelets activation factors or other factors contributing to the thrombogenicity of the product, as well as the relevant documentation to support the validation of the TGA test and justification of the proposed cut-off level, and the proposed protocol for a post-marketing study of TEEs following the improved manufacture of Octagam and associated names.
- The Committee concludes that the MAH has performed a comprehensive investigation of the root cause within the licensed [redacted] manufacturing process [redacted] leading to the increased risk of thromboembolic events (TEE) in subjects treated with Octagam under normal conditions of use since 2008 and considered all potential risk factors that could be identified (including risk related to all the input materials). This investigation supports the conclusion that FXIa is the main contributor to thrombogenic potential of Octagam and kallikrein is a minor one.
- The Committee considers that several critical process steps and parameters were identified in the current [redacted] manufacturing process used to produce intermediates for the manufacture of the Octagam 5% and 10% strengths [redacted] and the appropriate corrective and preventive measures are now implemented. In this regards, the Committee notes that a constant amount of [redacted] buffer [redacted] was ensured and that an additional adsorption step [redacted], a sedimentation step [redacted] and the controls (TGA test in release specification and FXI Ag as in process control) are implemented.
- The Committee agrees with the inclusion of the added TGA release specification and the proposed cut-off level based on the TGA test validation data and batch analyses provided.
- The Committee requested a product-specific inspection to ensure the implementation of the proposed corrective and preventive actions and the harmonisation of the process. According to the stepwise inspection program agreed by the CHMP, Vienna and Lingolsheim sites were first inspected before the opinion, which gave reassurance that corrective actions have been implemented and the manufacturing process harmonised. In view of this and to continue the monitoring of the implementation of the corrective actions, the CHMP also requires that the 2 other manufacturing sites (Springe and Stockholm) should be inspected.
- The Committee notes that the interchangeability of different intermediates between the Vienna, Stockholm and Lingolsheim sites was not covered by the intersite validation study. Thus, the CHMP recommends the restriction of the use of the combinations of manufacturing sites only to those already validated through the "intersite validation report". The Committee reviewed and agreed a change management protocol addressing how interchange of different intermediate [redacted] between sites not covered by the intersite validation study should be validated.
- Finally, the Committee requires the MAH(s) to perform the observational post marketing safety studies, as defined in the reviewed and agreed protocols, in order to monitor in particular the incidence of TEEs with Octagam and related names following the improvement of the manufacturing process.

In view of the above, the Committee considers the benefit risk balance of Octagam medicinal product is positive under normal conditions of use and therefore recommends the lifting of the suspensions of the Marketing Authorisations and the variation to the terms of the marketing authorisations concerning changes to the manufacturing process across the 4 sites and the addition of TGA release test and specification, subject to the following conditions:

- **NATIONAL COMPETENT AUTHORITIES SHALL ENSURE THAT THE FOLLOWING CONDITIONS ARE FULFILLED BY THE MAH(S):**

Quality

1. The variation to the terms of the marketing authorisations concerning changes to the manufacturing process across the 4 sites:
   - an additional adsorption step [redacted]
   - a constant amount of [redacted] buffer [redacted] is ensured and a sedimentation step [redacted] is introduced;
   - the identified critical parameters [redacted] are appropriately controlled;
   - the TGA release test and specification as well as FXI Ag in process control is introduced;
   - the prekallikrein (PKA) blank values are included in the specification.

2. With regards to the validation of the column [redacted]: results should be provided to National Competent Authorities every 6 months for a 2-year period following Commission Decision.

3. Interchange of different intermediate fractions between sites not covered by the currently approved intersite validation study are required to be validated using the change management protocol agreed by the CHMP. If the MAH(s) intend(s) to do so, the validation data should be submitted and reviewed by National Competent Authorities through the relevant variation.

Clinical

1. The MAH(s) shall perform observational post marketing safety studies to collect TEEs and to demonstrate the safety of the improved manufacturing process. These studies should be initiated as soon as the product is reintroduced in the relevant market and at the latest within two months of the reintroduction. These studies shall document a total of at least 20,000 infusions including at least 2000 individual patients worldwide within 3 years. Results of the integrated interim analysis should be provided (to the National Competent Authorities) every 6 months and include the point estimate of the incidence of thromboembolic events with the confidence interval.
2. The MAH should submit Periodic Safety Update Reports to the National Competent Authorities on a 6 monthly basis for a period of two years
3. The MAH(s) shall submit to the National Competent Authorities, with the next Periodic Safety Update Report, a risk management plan (RMP) that adequately describes all the important safety concerns, the pharmacovigilance activities and the interventions designed to identify, characterize, prevent or minimize the important risks with particular attention to the risk of thromboembolic events. This RMP shall follow the EU RMP template and shall include measures to assess the effectiveness of the interventions.

- **THE FOLLOWING CONDITIONS HAVE TO BE IMPLEMENTED BY THE MEMBER STATES:**

1. Phase 2 Official Control Authority Batch Release (OCABR) testing for thrombogenic potential is undertaken using the test and limits agreed in the product specification through this referral procedure.
2. The inspection of the Stockholm and Springe sites should be performed by end of October 2011. Care should be taken to ensure continuity with the inspections of the Lingolsheim and Vienna sites. The outcome of the inspection should be provided to National Competent Authorities.