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CHMP assessment report

Review under Article 5(3) of **Regulation (EC) No 726/2004**

Octagam and associated names

Procedure no: EMEA/H/A-5(3)/1309

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Request for CHMP opinion

On 19 July 2011, the Paul-Ehrlich-Institut (PEI) requested the CHMP to draw up an opinion, in order to get a harmonised view on the reworking of specific Octagam batches.

With decision of the European Commission from 04 October 2010, the marketing authorisations of the medicinal products Octagam and associated names were suspended; the supply of the medicinal products concerned was prohibited and all batches of the medicinal products concerned were withdrawn from the market up to the level of pharmacies, hospitals, and patients.

In view of the above, the MAH has Octagam/intermediate on stock which the MAH intends to rework as it is a plasma derived product; these batches were not produced according to the revised process (as agreed during the Art. 31 referral procedure for which a Commission Decision was issued on 30 May 2011) and therefore do not meet the required quality standards according to the current dossier.

According to the Good Manufacturing Practice Guidelines (Eudralex Vol. 4, Part II: Basic Requirements for Active Substances used as Starting Materials), intermediates and active pharmaceutical ingredients (API) failing to meet established specifications should be identified as such and quarantined. These intermediates or APIs can be reprocessed or reworked, although these procedures should be exceptional. Batches that have been reworked should be subjected to appropriate evaluation, testing, stability testing if warranted, and documentation to show that the reworked product is of equivalent quality to that produced by the original process. Concurrent validation is often the appropriate validation approach for rework procedures. This allows a protocol to define the rework procedure, how it will be carried out, and the expected results. If there is only one batch to be reworked, then a report can be written and the batch released once it is found to be acceptable.

Based on the above and since the proposed re-processing procedure is complex and may represent a precedent for other immunoglobulin products, PEI was of the opinion that it was necessary to request the CHMP Opinion on this matter in order to get an harmonised view. This opinion was requested under Article 5(3) of Regulation 726/2004.

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 (PID) 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.

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

In September 2010, an increase in thromboembolic events (TEEs) was observed after administration of Octagam to patients. Certain batches were associated with increased TEEs, and Octapharma had to withdraw all Octagam batches from the EU and US markets. In Europe, the marketing authorisations (MA) were suspended in September 2010. This suspension was lifted in May 2011, after identification of the main biochemical and technical root causes and implementation of corrective and preventive measures, which included an adsorption step to minimize FXI/FXIa in the final product, as well as a routine release test for procoagulant activity.

Due to the suspension of the Marketing Authorisations, Octapharma has Octagam/intermediate on stock which Octapharma intends to rework. The Company intends to rework/reprocess this remaining material to manufacture new batches of Octagam finished product. The reworking/reprocessing will start from intermediate or final product. This reworked intermediate will be further processed to final container Octagam according the routine manufacturing process.

Octapharma intends to rework the Octagam final container and intermediate batches manufactured without adsorption as well as batches manufactured with insufficient adsorption to manufacture new batches of Octagam finished product.

Octapharma will only rework batches that are still within shelf life.

Octapharma is intending to perform rework from final container Octagam or intermediate to reworked intermediate on an approved manufacturing line at the facility in Springe, Germany, only. The further reprocessing of this reworked intermediate to the final product will be done at the other manufacturing sites in Lingolsheim, Vienna or Stockholm.

2.2. Reworking/Reprocessing

The guidance on reworking/reprocessing of rejected products is based on the Eudralex Volume 4 GMP guidelines (Part I Chapter 5 Production, Section 5.62):
"*The reprocessing of rejected products should be exceptional. It is only permitted if the quality of the final product is not affected, if the specifications are met and if it is done in accordance with a defined and authorised procedure after evaluation of the risks involved. Record should be kept of the reprocessing.*"

In addition, according to EudraLex Vol. 4 GMP guidelines, Part II (API) section 14.3, the reworking of an API is defined as follows:

"14.30 Before a decision is taken to rework batches that do not conform to established standards or specifications, an investigation into the reason for non-conformance should be performed.
14.31 Batches that have been reworked should be subjected to appropriate evaluation, testing, stability testing if warranted, and documentation to show that the reworked product is of equivalent quality to that produced by the original process. Concurrent validation is often the appropriate validation approach for rework procedures. This allows a protocol to define the rework procedure, how it will be carried out, and the expected results. If there is only one batch to be reworked, then a report can be written and the batch released once it is found to be acceptable.
14.32 Procedures should provide for comparing the impurity profile of each reworked batch against batches manufactured by the established process. Where routine analytical methods are inadequate to characterize the reworked batch, additional methods should be used."

Reprocessing is an exact repetition of one or more approved steps, whereas reworking is based on the inclusion of new steps in the manufacturing process.

2.3. Starting material

As mentioned above, the starting material is first processed to reworked intermediate. This intermediate is further processed to final container Octagam according the routine manufacturing process:

- Material for Rework A
  - Octagam 5% and 10% FC (No adsorption step) prior week 45 / 2010
  - Intermediate (No adsorption step) prior week 45 / 2010

- Material for Rework B
  - Octagam 5% and 10% FC (Adsorption step/revised process) after week 45 / 2010
  - Intermediate (Adsorption step/revised process) after week 45 / 2010

2.4. Quality - Rework on intermediate and Finished product

The rework/reprocessing as proposed by the MAH occurs at several manufacturing process steps: Rework of intermediate and rework of finished product into reworked intermediate, followed by reprocessing to finished product.
The repetition of the entire process is necessary in order to maximize the factor FXI and FXIa reduction. The rework part up to reworked intermediate is clearly different to the approved manufacturing process and adapted to the different starting material used (Final product or intermediate instead of plasma). In the provided development report the reworking process and the parameters were indicated and justified.

A list of all batches of the final container and intermediates (both within shelf life), that Octapharma intends to rework was provided to the CHMP.

For the process validation and investigation of reworked product Octagam final container batches were reworked to reworked intermediate and reprocessed to final product batches, furthermore intermediate batches were reworked to reworked intermediate and reprocessed to final product batches. Data provided demonstrate that the pro-coagulant activity was removed by the rework procedure. Also the Wessler Test and an investigation on platelet activation did not reveal any thrombogenic effect for the reworked batches. The data evaluation of the presented investigated parameters demonstrates that the planned rework strategy for both drug product and intermediate leads to a product quality that is not significantly different to a product produced with the approved manufacturing process.

The re-working procedure represents an entire repetition of the manufacturing process; therefore the CHMP considers that the impact on the stability of the final product from the re-worked and stored reworked intermediate is not known. It is acknowledged that the requested clinical data (see below) will impact the timelines before reprocessed product might be approved for marketing. Nevertheless potential uncertainties should be eliminated and the issue remains that the cumulative shelf life should be kept as short as feasible. The MAH revised the claimed shelf life and is currently proposing a shelf life of 12 months for reworked intermediate.

Real time stability data for re-worked intermediate should be submitted to the National Competent Authorities together with clinical data. The data package should also include stability data for the final container derived from reworked intermediate that has been stored for the maximum storage time of 12 months.

The applicant proposed the identical stability claim for the reworked batches as for the approved product (24 months shelf life). The CHMP is of the opinion that it is currently not possible to conclude on the behaviour of the reworked final product. Indeed, based on the limited data provided (2 data points), some degradation trends appears to occur for some quality attributes such as IgG content, HBs Ab, parvo B19 Ab and total protein. Based on the stability data provided (i.e. up to three month stability data), the extrapolation of the shelf life to 24 months can currently not be accepted by the CHMP but extrapolation will be considered according to ICH Q1E taking the real time and real temperature data into account as well as data from accelerated and stress conditions as supportive data.

The CHMP strongly recommended the establishment of an appropriate stability program in order to address the issues of shelf life of re-worked intermediate, shelf life of re-worked FC and also cumulative shelf life. In response to this recommendation, at the BWP oral clarification, the MAH proposed to add batches of re-worked FC manufactured from reworked intermediate stored for 6, 9 and 12 months to the stability programme. The aim will be to exclude an impact of storage period of reworked intermediate on the stability of the final product. The updated stability program is considered acceptable in order to address stability of intermediates and final product.

In conclusion, the stability protocols provided for both Octagam 5% and Octagam 10 % reworked from intermediate and final container are considered acceptable. The decision on the acceptable shelf life for reworked intermediate and reworked final product will be made by the relevant competent authority(ies) after evaluation of the actual data which will be submitted. Extrapolation may be considered according to ICH Q1E taking the real time and real temperature data into account as well as data from accelerated conditions as supportive data.

2.5. Clinical safety and efficacy

Preclinical data were provided to support comparability of reworked product with non-reworked product. However, no clinical data were provided.

The precise mechanisms by which IVIG act in autoimmune diseases have not been definitively established but is believed to involve the inhibitory Fc receptor. The actual primary target(s) of IVIG in autoimmune disease are still unclear. IVIG may work via a multi-step model where the injected IVIG first forms a type of immune complex in the patient. Additionally, IVIGs may bind directly to the auto antibody, stimulating its neutralisation. Alternatively, the massive quantity of antibody may stimulate the patient´s complement system, leading to enhanced removal of all antibodies. As many of the clinical features of IVIGs (both in the realm of efficacy and of safety) cannot be attributed to isolated parameters, it cannot be directly concluded from the characterisation studies that the clinical effects and the safety profile of the IVIG concentrates have not been impacted by the rework procedure.

According to the IVIG Guideline EMA/CHMP/BPWP/94033/2007 rev. 2, clinical data are needed to confirm safety and efficacy.

In this context, a PK study in Primary ImmunoDeficiency syndrome (PID) patients and an efficacy and safety study in Primary Immune Thrombocytopenia (ITP) patients, could give reassurance that the reworking would not impact the activity, the efficacy and the safety of the product.
Accordingly the Company has presented adequate study protocols.

The MAH has provided study protocols for a PK study in PID patients and a further study in ITP patients. Both studies will address efficacy and safety aspects and both generally adhere to the respective parts of the IVIG Guideline (EMA/CHMP/BPWP/94033/2007 rev. 2). The company intends to perform these studies from the reworked material of the final container, which would account for approximately 80% of the reworked material. This would most likely address the worst case scenario as this was the material involved in the occurrence of the TEEs. To achieve a prompt overview of the effects of the final container reworked material in patients and to deal with the stability time constraints of the reworked product, the MAH suggested submitting interim data in 10 patients each per study (PID and ITP). The MAH anticipates interim results of clinical studies to be available in 2013.The CHMP considers that this approach may be acceptable, depending on the quality and comparability of the submitted data. Seen in conjunction with the quality data, these clinical interim data would help address the issue of acute safety and clinical comparability of the reworked product; if the data show that point estimates are on target, this could be an argument in favour of the reworked product. In any case, if the resulting interim data should give rise to any untoward concerns, then a consideration to file will not be considered appropriate.

Concerning the safety of the reworked intermediate the MAH considers this to be sufficiently addressed by implementing pharmacovigilance measures. Their argumentation that the rework of intermediate will start from an intermediate which had never reached the state of final container and, thus, was never exposed to conditions that might impact the functionality of the immunoglobulin in the final formulation is acknowledged. Data from a more rigorous pharmacovigilance monitoring (the period of the PSUR will be reduced to 6-month periods for the 2 years following potential marketing of the reworked finish product) may be sufficient to monitor the safety of the reworked product.

The MAH outlined a clinical development plan (PK in PID and ITP studies). The CHMP considers that a specific Risk Management Plan is required: the MAH should describe which specific pharmacovigilance activities are planned including a description of the impact of the reworking on drug safety. The origin of the reworked product batches (finish product or intermediate) should be documented trough a specific monitoring.

3. Overall conclusion

The CHMP considered the procedure under Article 5(3) of Regulation (EC) No 726/2004 initiated by the PEI on the use of reworked Octagam.

The Committee considered that, in view of the data submitted in writing and during an oral clarification at the BWP by the MAH, that the presented investigated parameters demonstrate that the planned rework strategy leads to a product quality that is not significantly different to a product produced with the approved manufacturing process.

However, the Committee is of the opinion that the influence of cumulative stability due to storage of the reworked intermediate on the final product is not predictable and therefore the cumulative shelf life should be kept as short as feasible. Moreover, it cannot be directly concluded from the characterisation studies that the clinical effects and the safety profile of the IVIG concentrates have not been impacted by the rework procedure.

The Committee therefore concluded that real time stability data for re-worked intermediate would need to be submitted together with the required clinical data. A PK study in PID patients and a further study in ITP patients should be provided, adhering to the respective parts of the IVIG Guideline (EMA/CHMP/BPWP/94033/2007 rev. 2). Clinical interim data on 10 patients each in PID and ITP may be acceptable along with the stability data, depending on the quality and the comparability of the clinical results. Enhanced pharmacovigilance monitoring is expected further to any marketing of the reworked final product including a specific monitoring of batches origin (finished product or intermediate). The data package should also include stability data for the final container including batches derived from reworked intermediate stored for the maximum storage time of 12 months. Based on the stability data provided, extrapolation will be considered according to ICH Q1E taking the real time and real temperature data into account as well as data from accelerated and stress conditions as supportive data.

The Company's proposed stability program is considered acceptable in order to address stability of reworked intermediates and final product.

Overall while acknowledging that the quality of the reworked Octagam is satisfactory, the CHMP concluded that further stability and clinical data, as well as enhanced pharmacovigilance monitoring, are required at the time of consideration of the re-working/re-processing dossier by the Member States.