EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Patient Health Protection

Assessment report for Octagam 5% and Octagam 10% medicinal products

International Non-proprietary Name: Human normal immunoglobulin

Procedure No. EMEA/H/A-107/1278

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

Rapid Alerts were circulated to CHMP, European Medicines Agency (EMA) and Commission by Germany and Sweden respectively on 16 September 2010 and 17 September 2010.

Germany informed (1) - of the suspension of the Marketing Authorisations of the lower formulation (5% and 50mg/ml) of Octagam and associated names on 15 September 2010, and (2) - of their intention to suspend the Marketing Authorisations of the higher formulation (10% and 100mg/ml) of Octagam and associated names, due to an increased risk of thromboembolic events (TEE) (see appendix 1).

Subsequently Sweden informed of the suspension of the Marketing Authorisations of both formulations in their Member State on 17 September 2010 due to the same safety concern (see appendix 1).

The CHMP agreed that the procedure described in Article 107 of Directive 2001/83/EC, as amended, applied.

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.

The Human Normal Immunoglobulin containing medicinal products, Octagam and associated names, are authorised and used in all EEA Member States except Ireland (see Annex I for the list of Octagam and associated names authorised in the EU).

On 16 September 2010 Germany informed the European Medicines Agency, pursuant to Article 107 of Directive 2001/83/EC as amended, (1) - of the suspension of the Marketing Authorisations of the lower formulation (5% and 50mg/ml) of Octagam and associated names, and (2) - of their intention to suspend the Marketing Authorisations of the higher formulation (10% and 100mg/ml) of Octagam and associated names, due to an increased risk of thromboembolic events (TEE).
In addition, on 17 September 2010, Sweden informed the European Medicines Agency, pursuant to Article 107 of Directive 2001/83/EC as amended, of the suspension of the Marketing Authorisations of both formulations in their Member State due to the same safety concern.

The CHMP considered the matter in accordance with Article 107(2) of Directive 2001/83/EC, as amended during the September 2010 CHMP plenary meeting.

Oral explanations were given by the Marketing Authorisation Holder on 20 September 2010.

Supplementary information was provided by the MAH on 21 September 2010. In addition a letter from the MAH including two proposals was provided on 22 September 2010.

2.2. Safety

TEE is a serious life threatening complication. According to the core SmPC for Human normal immunoglobulin for intravenous administration (CPMP/BPWG/574/99), the risk of thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses is known as a very rare adverse event, with a frequency of < 0.01% (below 1 out of 10 000 patients).

Since August 2010, 9 cases of TEE were reported to the German NCA leading to the withdrawal of the concerned batches of Octagam 5% by the Authorities and voluntary recall from the MAH. The German National Competent Authority (NCA), concerned by this unexpected high reporting of TEEs with Octagam 5%, investigated the issue with the MAH.

The documents provided by the MAH to the German NCA indicated that cases of TEE involving other batches had also been reported in other countries. The evaluation of spontaneous reports showed a steady increase of cases reported concerning TEE since 2008. The highest reporting rate is found for the 3rd quarter of 2010. Data from the MAH show that the adjusted world-wide reporting rate for TEE was as follows:

- one case per 1.49 million grams of Octagam 5% in 2005,
- one case per 1.53 million grams in 2006,
- and one case per 1.60 million grams in 2007.

On the other hand, the reporting rate since 2008 is;

- one case per 0.51 million grams in 2008,
- one case per 0.46 million grams in 2009,
- one case per 0.18 million grams of Octagam, for the period from January to July 2010.

The CHMP, in view of the above data, concluded that a steady increase in the reports of TEE during the administration of Octagam 5% since 2008 is confirmed.

The CHMP noted that, in the reported cases, TEEs were in timely relation to infusion and some patients experienced several TEEs. Beside venous also arterial TEEs were reported. In addition, some of the most serious TEEs events occurred in patients not having any concomitant disorders which could contribute to an increased risk of thromboembolic events. Overall, the CHMP is concerned by the unusual clinical picture of the TEEs (arterial, sometime multiple TEEs during or immediately after infusion).

During the Oral Explanations, the manufacturing process was explained by the MAH: for the manufacture of both final products three manufacturing sites, Stockholm (SE), Vienna (AT) and Lingolsheim (FR), exist. An additional site, Springe (DE), is authorized [redacted] Since 2008, the MAH has submitted two major variations concerning the manufacture of Octagam. On 23 June 2008 and 30 October 2008, for Octagam 5% and Octagam 10% respectively, the company 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 an alternative method at these three manufacturing sites. Since 27 November 2009 and 12 May 2010, 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].

Based on the increased world-wide reporting rate of TEE, the MAH in collaboration with the FDA developed a Thrombin generating Assay (TGA) to investigate the thrombogenicity of Octagam and to potentially determine the critical batches. The TGA used by the MAH refers to a test with which the endogenous thrombin potential can be identified in patients undergoing pro- or anti-coagulatory treatment. After defined activation (e.g. with tissue factor), the TGA measures the activation of the coagulation cascade and the amount of thrombin formation (one of the potential activator factor is the factor XIa). The test is primarily used to assess the final route of the coagulation cascade in patients with a sufficient prothrombin concentration in the plasma. The use of the assay for identifying an abnormal thrombogenic potential in plasma products in which thrombin depletion is to be effected has

not yet been validated, and is not part of the batch control testing requirements laid down in the European Pharmacopoeia Monograph "Human normal immunoglobulin for intravenous administration" (0918). The validation of the test is still ongoing by the MAH.

The MAH has deduced findings on possible thrombogenic effects of the concerned batches in particular from the results of the tests on individual batches using the TGA. Based on the batch test using the TGA and the evaluation of the test results using the limit values selected by the MAH [redacted] batches were recalled world-wide in the past few months. Furthermore the MAH did not release any batches which were not in accordance with the defined criteria. Thus, [redacted] batches manufactured with the licensed process were tested using the TGA at all three production sites during the production period of 2009 to July 2010, out of which [redacted] were rated as critical. [redacted] of the batches manufactured in Lingolsheim, [redacted] of those manufactured in Vienna, and [redacted] of those manufactured in Stockholm were not released internally, or were recalled. At the same time, a part of the [redacted] batches produced with the previous process [redacted] were also tested using the TGA, out of which [redacted] were rated as critical. Of the [redacted] tested [redacted] batches, critical values were found in [redacted] batches [redacted].

The CHMP is of the opinion that the cut-off limit proposed by the MAH is not acceptable since it is arbitrary and not validated. In several cases, batches were associated with TEEs while no critical values were measured using the TGA.

The MAH, during an oral explanation, presented their views as to the possible root cause of the manufacturing process leading to TEEs and presented some Risk Minimization Activities which are discussed below.

In view of the MAH's response, the CHMP comes to the conclusion that the causes for an increased thrombogenicity of a number of batches of Octagam 5% are still unknown. The increased content of factor XIa in some batches, as presented by the MAH, could be one of the causes but the root cause can not be restricted to it. The correlation of the assay results and the TEEs has not been established.

Furthermore, because the TGA test is not validated, results need to be interpreted with caution. The results of the analyses as well as the recall and rejection of batches indicates to CHMP that this problem is most likely related to the manufacturing steps which were introduced to the production process after 2007.
Likewise, the CHMP considers that the increased thrombogenicity is not limited to batches manufactured at the production sites of Vienna and Lingolsheim. Although fewer batches manufactured in Stockholm were associated with spontaneous TEE reports, the MAH could not provide any evidence which shows that site-specific differences using the same manufacturing procedure could result in final product with different thrombogenic potential. The differences in [redacted] adjustments at the sites of Lingolsheim and Vienna compared with Stockholm stated by the MAH were not convincing in this respect, since the [redacted] ranges overlap.
Therefore, the CHMP is of the opinion that no sufficient data were provided by the MAH to establish that the batches of Octagam 5% manufactured with intermediates from Stockholm involve less risk of thrombo-embolic events than those manufactured with intermediates from Vienna, Lingolsheim or Springe.

In addition, on the basis that the manufacturing process of Octagam 10 % is considered identical to the manufacturing process of Octagam 5% except for the final step of the formulation (i.e. identical intermediates for both strengths), the CHMP is of the opinion that Octagam 10 % has the same thrombogenic potential as Octagam 5 % and that Octagam 10 % poses an identical risk to patients. The absence of spontaneous reporting associated with the Octagam 10% is not accepted by the CHMP as a rationale to support its safety in view of the nature of spontaneous reporting as a signal generation tool which can not be used to confirm/determine the safety of a product.

Further to the oral explanation held on 20 September 2010, the MAH provided on 21 September 2010 (see appendices 3 and 4) the CHMP with further written information: the MAH considers that "incidence" of TEE reported by intermediate batches produced at Stockholm and Springe manufacturing sites is "1:30,300 doses in 2.5 years" and therefore, based on their TGA results, the MAH suggests that intermediates from Stockholm and Springe should continue to be used while the manufacturing at Lingolhsheim and Vienna could be subject to suspension. The CHMP reviewed these data and still considers that the root cause remains unknown. The CHMP acknowledges that the TEEs reporting rate (not the incidence) for batches produced from intermediates from Stockholm is lower compared to Lingolsheim, Vienna and Springe. However concluding that batches (intermediate)

produced in Stockholm are safer in contrast to intermediates produced in Vienna and Lingolsheim is not considered scientifically justified by CHMP. In general, spontaneous reporting of adverse reactions is an important tool for signal detection but not for hypothesis testing which has to be performed by other methods. In addition, taking into account the limitations of spontaneous reporting like underreporting, differences in reporting rates among Member States, changes of reporting frequency due to public awareness, lack of precise denominator data etc…, the CHMP considers that ADR reporting pattern of TEEs related to batches (intermediates) from different production sites need to be interpreted with caution. Therefore the CHMP is of the opinion that without certainty of the root cause and control of the manufacturing process, the product can not be administrated to patients safely considering this life-threatening event.

In the above letter, the MAH also states that they investigated the root cause for the TEE [redacted] The MAH also states that factor XIa is associated with TEEs. However, the CHMP still remains of the opinion that there is a poor correlation between FIXa and thrombin concentration indicating that other clotting activators may be present in the product.

The MAH also provided a letter on 22 September 2010, which included the two following proposals (see appendix 5):

1st proposal:

1. "We propose that Octagam will be continued to be manufactured for the EU market with the present process, subject to all batches being released with the TGA test criteria with a maximum value [redacted]. Products will only be produced in our Stockholm and Springe plants, which we have shown to you, have only TEE side effects below a normal level. Concerning our Vienna plant, no Octagam based on Vienna produced paste will be released for the EU until we by data acceptable to EMA where we are able to prove that this plant can produce and release Octagam of a similar quality as in Stockholm."

2nd proposal:

2. "Should EMA not be willing to accept our 1st proposal, we suggest that all four plants will immediately start to produce with the manufacturing process valid in 2007 (prior to the increase in reporting of TEEs). This means that we would release to the market a product with an impeccable safety record since the first introduction to the Portuguese market in 1995."

The CHMP carefully considered the 2 proposals:

1. in relation to the first one, the CHMP noted that the Thrombin Generation Assay (TGA) is not validated including, but not restricted to, the fact that the proposed cut-off [redacted] is arbitrary and the correlation of the assay results and the TEEs has not been established. In addition other impurities activating the coagulation cascade or activating platelets could be involved which would not be detected. The proposal to only use the Stockholm and Springe manufacturing sites was also not accepted by the CHMP as a single authorised manufacturing process [redacted] is used across all manufacturing sites. As the root cause(s) analysis of the problem within the licensed [redacted] manufacturing process leading to the increase of TEEs has not been identified yet, the Committee concluded that there is a risk of increased TEE independently of the manufacturing site and dose formulations. Therefore the above proposal is not acceptable.

2. in relation to the second proposal, the substitution to an alternative manufacturing process (even a previous authorised one) would require appropriate controls and reassurance in relation to TEEs. In addition, would the MAH decide to proceed with this proposal, a formal authorisation by the Regulatory Competent Authorities will be required. Meanwhile the current authorised manufacturing process is still the valid one and in view of the safety concerns already described the CHMP considered that a suspension is the appropriate measure.

2.3. Conclusion

Octagam is a Human normal immunoglobulin for intravenous administration indicated in replacement therapy, immunomodulation and allogeneic bone marrow transplantation.

In view of the above data, the CHMP concluded that there is an increased risk of thromboembolic events (TEE) in subjects treated with Octagam. TEE is a serious life threatening complication.

The cause of the increased reporting of TEEs is not elucidated to date; based on current knowledge this could be related to the presence of impurities which could act as clotting/coagulation factors in the product introduced during the manufacturing process. The Committee concluded there is a risk of increased TEE independently of the manufacturing site or dose formulations concerned.

Taking all these elements into account, the CHMP concluded that Octagam and associated names is harmful under the normal conditions of use and therefore recommended the suspension of the Marketing Authorisations.

2.4. Temporary measures

The CHMP, in view of the nature and unpredictability of this serious and life threatening adverse event, is of the opinion that the following temporary measures are taken immediately:

- all batches of Octagam and associated names from all manufacturing sites should be recalled from the distribution chain to pharmacy/hospital/patients level;
- all supply of Octagam and associated names should be prohibited;
- the Marketing Authorisations of Octagam and associated names should be suspended forthwith in all concerned EU Member States.

3. Overall conclusion

Whereas,

- The Committee considered the procedure under Article 107 of Directive 2001/83/EC, as amended, for the Human normal immunoglobulin containing medicinal products, Octagam and associated names (see Annex I).
- The Committee duly considered the information provided by the Member States, the information presented by the Marketing Authorisation Holder during the Oral Explanations as well as their latter proposals and the discussions within the Committee.
- The Committee concluded that the data showed 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. According to the core SmPC, the TEE frequency is below 1 out of 10 000 patients. At Member State levels, it was calculated that the reporting rate of TEEs is significantly higher compared to the frequency mentioned in the core SmPC. TEE is a serious and life threatening condition and the Committee noted that some of the most serious TEEs events occurred in patients not having any concomitant disorders which could contribute to an increased risk of thromboembolic events.
- The Committee considered that the cause of the increased reporting of TEEs is not sufficiently elucidated; based on current knowledge this could be related to the presence of impurities which could act as clotting/coagulation factors in the final product introduced during the manufacturing process; the MAH suggested the impurity factor XIa as potentially initiating TEE events. In the absence of root cause analysis, the contribution of other impurities and/or aspects of the manufacturing process to the occurrence of TEE could be involved.
- The single authorised harmonised manufacturing process [redacted] used to produce intermediates for the manufacture of the Octagam 5% and 10% strengths is common across all manufacturing sites. The root cause(s) analysis of the problem within the licensed [redacted] manufacturing process leading to the increase of TEEs has not been identified yet. Consequently the Committee concluded there is a risk of increased TEE independently of the manufacturing site or dose formulations concerned.

- The Committee considered that the risk minimisation measures proposed by the MAH will not adequately protect public health. In particular, the Thrombin Generation Assay (TGA) is not validated including, but not restricted to, the fact that the proposed cut-off is arbitrary and the correlation of the assay results and the TEEs has not been established. Although the MAH proposes factor XIa acting as activator of the coagulation cascade the root cause(s) leading to the increase of TEEs has not been yet identified. Other impurities activating the coagulation cascade or activating platelets could be involved.
- In view of the above, the Committee considered the Octagam medicinal product is harmful under the normal conditions of use and therefore recommended the suspension of the marketing authorisations for Octagam 5% and 10% medicinal products.

Therefore following the provisions under Article 107 of Directive 2001/83/EC, as amended, the Agency's Committee for Medicinal Products for Human Use (CHMP) adopted an opinion recommending the suspension of all Marketing Authorisations for both Octagam 5% and 10% medicinal products (see Annex I to the Opinion).
The CHMP, in view of the nature and unpredictability of this serious and life threatening adverse event, is of the opinion that the following temporary measures are taken immediately:

- all batches of Octagam and associated names from all manufacturing sites should be recalled from the distribution chain to pharmacy/hospital/patients level;
- all supply of Octagam and associated names should be prohibited;
- the Marketing Authorisations of Octagam and associated names should be suspended forthwith in all concerned EU Member States.

For the suspension to be lifted the Marketing Authorisation Holders would need to provide the National Competent Authorities with either the following:

A

A.1 - An overall root cause investigation report with supportive data that explains the observed TEEs and the appropriate corrective measures taken in the current [redacted] manufacturing process, and,
A.2 - Analytical data/method validation, and:
- 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 identified manufacturing sites (Stockholm, Springe, Lingolsheim and Vienna). Consideration should also be given on other clotting tests e.g. investigation of platelets activation factors or other factors contributing to the thrombogenicity of the product.
- the relevant documentation to support the validation of the TGA test and justification of the proposed cut-off level, and;
A.3 - a proposed protocol for a post-marketing study of TEEs following the improved manufacture of Octagam and associated names.

Alternatively,

B

B.1 - The substitution to an alternative manufacturing process for Octagam with appropriate controls and reassurance in relation to TEEs, and;
B.2 - a proposed protocol for a post-marketing study of TEEs following the improved manufacture of Octagam and associated names.