EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

07 May 2012
EMA/289571/2012

Referral assessment report for Vivaglobin and associated names (human normal immunoglobulin solution for injection – subcutaneous use)

INN/active substance: Human normal immunglobulin

Procedure number: EMEA/H/A-36/1296

Referral under Article 36 of Directive 2001/83/EC

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

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 17 March 2011, Germany triggered a referral under Article 36 of Directive 2001/83/EC. The CHMP was requested to give its opinion on whether the marketing authorisations for medicinal products containing Human normal immunglobuline, Vivaglobin, and associated names should be maintained, varied, suspended or withdrawn.

The procedure described in Article 36 of Directive 2001/83/EC, as amended, was applicable.

2. Scientific discussion

2.1. Introduction

Vivaglobin is a Human normal immunoglobulin for subcutaneous administration (SCIg) with the following therapeutic indications:

- Replacement of antibodies in adults and children suffering from congenital (primary) immunodeficiency syndromes such as:
  - congenital absence of antibodies (agammaglobulinaemia) or antibody deficiency (hypogammaglobulinaemia);
  - common variable immunodeficiency;
  - severe combined immunodeficiency;
  - IgG subclass deficiencies with recurrent infections;

- Replacement of antibodies in:
  - cancer of bone marrow (myeloma);
  - malignant illness of white blood cells (chronic lymphatic leukaemia).

The Human Normal Immunoglobulin containing medicinal products, Vivaglobin and associated names, are authorised and used in all EEA Member States except, Bulgaria, Cyprus, Czech Republic, Estonia, Iceland, Ireland, Latvia, Lithuania, Malta, Romania, Slovakia, Slovenia and United Kingdom (see Annex I for the list of Vivaglobin and associated names authorised in the EU).

On 10 March 2011 the German National Competent Authority informed the Member States and the European Medicines Agency via a NUI (Non Urgent Information) about thromboembolic events (TEE) following administration of SCIg (Vivaglobin). Although thromboembolic events are known to occur with intravenous immunoglobulin medicines, they have not previously been linked with subcutaneous immunoglobulins.

Investigations performed by the MAH led to the conclusion that some of the materials used during the extraction of Vivaglobin from human blood activated substances in the blood were possibly triggering the formation of blood clots. The MAH proposed corrective actions accordingly by adapting the manufacturing process registered in the marketing authorisation dossier (for instance, a maximum of ATIII adsorption [redacted]) in order to ensure a low level of pro-coagulant activity.

The German Authority was of the opinion that the root cause of the thromboembolic potential of the product and the substitution to an alternative manufacturing process for Vivaglobin with appropriate controls to effectively reduce the thrombembolic contaminants in the product had to be further evaluated.

Therefore on 17 March 2011 Germany referred the matter to the CHMP so that the Committee could conduct an EU review of the root cause and evaluate the measures already introduced by the MAH to issue an opinion on whether the marketing authorisation of Vivaglobin should be maintained, varied, suspended or withdrawn.

TEE is a serious life threatening complication. Although, the total number of TEE reported with Vivaglobin is low, the evaluation of spontaneous reports indicated an increase of TEE reports since 2008.

The MAH received 19 reports of TEE reported worldwide after application of Vivaglobin during a period of 36 months (between 2008 and 2011). The MAH calculated approximately one TEE in 47,263 applications. On the basis of one application per week per patient it is estimated that there may be one TEE in 900 patients per year.

In most cases deep venous thrombosis were reported (8 cases of venous thrombosis, 5 cases of stroke and transient ischaemic attack (TIA), 3 cases of pulmonary embolism and 3 cases with unspecific symptoms, such as blood clot, loss of consciousness, amaurosis fugax). In the majority of the cases risk factors for thromboembolic events were identified such as cardiovascular disorders, prior thrombotic event, hyperlipoproteinemia, heterozygote for FV Leiden etc. A direct correlation between TEE and presence of prothrombotic factors in the product is not possible because the batch number was not documented in most case reports (12 of 19 cases).

2.1.1. Quality

The MAH provided investigation reports on the technical root cause analysis in order to explain the observed reporting of TEE associated with administration of the product.

Technical root cause

Manufacturing changes (within the approved process) were undertaken by CSL Behring in 2008, resulting in several lots shown to have procoagulant activity since that time. In vivo evaluation (Wessler model in rabbits) confirmed a prothrombotic effect of the affected batches after intravenous application, whereas no prothrombotic effect was seen after subcutaneous application. Due to the delayed resorption of subcutaneous immunoglobulin into the circulation, it is not clear whether thrombogenic activity will have the same impact than through IV infusion.

The MAH started investigations on the biochemical root cause of the thrombogenic potential of their product utilizing a Thrombin generation assay (TGA) and the determination of the non-activated prothrombin time (NaPTT) according to the Ph. Eur. monograph for FIX products. Furthermore the MAH focused the investigation on potential amidolytic activities in their product by determination of PKA activity within routine release testing of Vivaglobin and the recording of blank values within this assay which is a measure for kallikrein-like activity. This investigation supports the conclusion that FXIa is the main contributor to thrombogenic potential of Vivaglobin and kallikrein is a minor one.

Regarding the technical root cause several major changes were introduced into the manufacturing process since 2008. [redacted]

Corrective actions

Since 2008, the MAH has increased the optional adsorption rate of Prothrombin Complex and C1 Esterase Inhibitor. This is in line with the increased contamination of active clotting factor in batches produced since 2008. Addition of DEAE Sephadex resin to plasma (Prothrombin-adsorption) triggers contact activation. FXIIa activates Prekallikrein and FXI subsequently followed by Kallikrein and FXIa accumulation.

CSL Behring found an inverse correlation between levels of procoagulant activity and the level of Antithrombin III adsorption. 100 % AT III adsorption of Vivaglobin leads to a significant decrease in procoagulant activity, irrespective of the level of C1-adsorption. The MAH proposed corrective actions by adapting the manufacturing process (maximum of Anti-thrombin III adsorption [redacted]) in order to ensure a low level of kallikrein-like activity. The addition of [redacted] to plasma leads to enhanced Antithrombin activity followed by irreversible inactivation of Kallikrein/ FXIa.

The CHMP is of the opinion that the adsorption step [redacted] shall be mandatory.

The Nonactivated Partial Thromboplastin Time (NaPTT) is a suitable test for detecting activated clotting factors. NaPTT is included in the European Pharmacopoeia monograph for Human Prothrombin Complex and Human Coagulation Factor IX products. Although not validated for immunoglobulins, the MAH proposed the inclusion of an NAPTT test in the finished product specification with a requirement that the clotting time is not less than [redacted].

The CHMP is of the opinion that the specification does not need to be updated in that respect but requests that the results of NaPTT testing are provided within the documentation being submitted in support of the official control authority batch release procedure, covering all dilutions [redacted].

Finally, the addition of [redacted] to plasma (C1 Esterase Inhibitor adsorption) leads to exacerbation of procoagulant activity because natural inhibitor is removed. The optional adsorption of C1 Esterase Inhibitor step [redacted] was reviewed and the MAH demonstrated the effectiveness of the corrective action irrespective of the level of C1-adsorption. Nevertheless, a maximum of [redacted] adsorption for C1-inhibitor was defined on the basis of analytical results generated for 3 Vivaglobin batches.

Based on the data provided by the MAH, the CHMP therefore considers that a maximum of [redacted] adsorption for C1 Esterase Inhibitor on the [redacted] needs to be introduced into the manufacturing process of Vivaglobin through a variation to the marketing authorisation.

Inspections and inspections findings

A product or process specific inspection is not considered necessary as part of the Article 36 referral since there is no indication of non-compliance with GMP or with the dossier requirements.

The systematic implementation in the manufacturing process of the optional steps of ATIII adsorption [redacted] and adsorption for C1 Esterase Inhibitor with a maximum of [redacted] adsorption by the MAH was anyhow verified during a routine inspection of the manufacturing site (Marburg) in November 2011. In addition, the OMCL for Vivaglobin carried out testing for procoagulant activity (TGA and NAPTT) on batches submitted for Official Control Authority Batch Release along the procedure, confirming the quality standards of the released product.

2.2. Risk management plan

Vivaglobin was licensed in the EU without a Safety Risk Management Plan. A risk management Plan was requested by CHMP and submitted by the MAH accordingly.

The company presented a comprehensively RMP which included all relevant documents pertaining to the change in the manufacturing process and resulting in safety monitoring of thromboembolic events.

The CHMP, having considered the data submitted is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

The MAH should, as a condition to the marketing authorisation, submit a variation to the National Competent Authorities within one month after Commission Decision to amend the RMP. The revised version of the RMP should be amended for the important potential risk TEE detailing routine risk minimisation activities for TEE as *"Included in the precautions section of the SmPC (section 4.4), and included in the adverse effects section of the SmPC (section 4.8)."*

The CHMP noted that the MAH states in their responses package that independently from the current discussion on Vivaglobin, CSL Behring had planned a life cycle management strategy to phase out Vivaglobin and to replace it with the 20% SC Ig formulation Hizentra, and therefore by the end of the year 2012 all patients should have been switched.

The MAH states that its existing pharmacovigilance reporting processes will be sufficient for monitoring thromboembolic adverse events associated with the Vivaglobin therapy until the transition. The CHMP is not in agreement with the above and requires the MAH to perform an improved batch monitoring, as defined in the reviewed and agreed risk management plan, in order to monitor in particular the

incidence of TEEs with Vivaglobin and associated names following the improvement of the manufacturing process.

2.3. Overall benefit/risk assessment

There is evidence of an increased thrombogenic activity in batches produced since 2008.

The root cause of the thrombogenic potential of the product and the modification of the manufacturing process for Vivaglobin to effectively reduce the thrombogenic impurities in the product was evaluated during this procedure.

The root cause was the optional process for adsorption of Prothrombin Complex and possibly C1 Esterase Inhibitor, leading to procoagulant activity in the product determined to be mainly due to FXIa and Kallikrein-like activity.

The CHMP is of the opinion that the company should manufacture with a systematic adsorption step to diminish the amount of procoagulant activity (lots with 100% ATIII adsorption) and should limit the optional adsorption for C1 Esterase Inhibitor [redacted] to a maximum of [redacted]. In addition, the CHMP requests that the results of NaPTT testing are provided within the documentation being submitted in support of the official control authority batch release procedure, covering all dilutions [redacted].

The Committee is of the opinion that no recall of batches should be performed as quality of the product is ensured.

The CHMP noted that the MAH plans to phase out Vivaglobin and accelerate the transition to Hizentra 20% SC Ig formulation.

3. Overall conclusion

Whereas,

- The Committee considered the procedure under Article 36 of Directive 2001/83/EC, as amended, for the Human normal immunoglobulin containing medicinal products, Vivaglobin and associated names (see Annex I).
- The Committee considered the overall root cause investigation report, the analytical data and method validation, the final results on the investigation of NaPTT and the revised risk management plan.
- The Committee concludes that the MAH has performed a comprehensive investigation of the root cause within the licensed [redacted] process leading to the risk of thromboembolic events (TEE) in subjects treated with Vivaglobin under normal conditions of use since 2008. This investigation supports the conclusion that FXIa is the main contributor to thrombogenic potential of Vivaglobin and kallikrein is a minor one.
- The Committee considers that several critical process steps and parameters were identified in the current manufacturing process used to produce Vivaglobin and the appropriate corrective and preventive measures are now implemented. In this regards, the Committee notes that a systematic adsorption step [redacted] to diminish the amount of procoagulant activity was ensured, a further restriction of the manufacturing process concerning the optional adsorption for C1 Esterase Inhibitor [redacted] was applied, and that results of NaPTT testing will be provided within the documentation being submitted in support of the official control authority batch release procedure, covering all dilutions [redacted]
- Finally, the Committee requires the MAH(s) to perform an improved batch monitoring, as defined in the reviewed and agreed risk management plan, in order to monitor in particular the incidence of TEEs with Vivaglobin and associated names following the improvement of the manufacturing process.

In view of the above, the Committee considers the benefit risk balance of Vivaglobin and associated names is positive under normal conditions of use and therefore recommends the maintenance of the marketing authorisation with a variation to the marketing authorisations concerning changes to the manufacturing process and requirements with regards to the submission of NaPTT test results to the batch release documentation, subject to the following conditions, as set out in the annex III of the opinion:

National Competent Authorities shall ensure that the following conditions are fulfilled by the MAH(s):

Quality

The variation to the marketing authorisations concerning changes to the manufacturing process:

- a routine adsorption step [redacted] (as previously optional);
- Results of NaPTT testing to be provided within the documentation being submitted in support of the official control authority batch release procedure and will cover all dilutions [redacted]
- A maximum of [redacted] adsorption for C1 Esterase Inhibitor [redacted]

Pharmacovigilance

The MAH is requested to submit a revised RMP to the NCAs within one month following Commission Decision. The revised version of the RMP should be amended for the important potential risk of TEE detailing routine risk minimisation activities for TEE as *"Included in the precautions section of the SmPC (section 4.4), and included in the adverse effects section of the SmPC (section 4.8)."*

4. Annexes

The list of the names of the medicinal products, marketing authorisation holders, pharmaceutical forms, strengths and route of administration in the Member States are set out Annex I to the opinion.