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Committee for Medicinal Products for Human Use (CHMP)

Rienso

Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation

International non-proprietary name: ferumoxytol

Procedure No. EMEA/H/C/002215/PSUV/0014

Period covered by the PSUR: 1 July 2013 – 30 December 2013

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Scientific conclusions and grounds recommending the variation to the terms of the Marketing Authorisation

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for Rienso, the scientific conclusions of PRAC are as follows:

Since the IBD (30 June 2009), there have been 491 cases of hypersensitivity (serious + non-serious, cumulative adjudicated results) reported; out of which 240 were classified as serious. There were 42 reports of fatal cases with ferumoxytol (excluding cases from Investigator Initiated Trials); in 22 of the 42 cases (19 in the US, 2 in Canada and 1 Switzerland) hypersensitivity was identified as the underlying cause. Since the IBD of ferumoxytol a total of 913,266 vials of ferumoxytol have been distributed/sold. The calculation of patient exposure in this PSUR is based on the amount of vials distributed/sold (single use vial containing 510 mg iron as ferumoxytol= single exposure). Considering 2000 mg iron per patient and per year, the total patient exposure is estimated as being 232883 patient-years [913,266 sold vials). There have been 491 cases of hypersensitivity reported (serious + non-serious, cumulative adjudicated results) of which 115 reports of serious hypersensitivity cases Grade III/IV. This corresponds to 210.83 overall hypersensitivity cases per 100 000 patient-years respective 49.38 serious (III/IV) hypersensitivity cases per 100 000 patient-years.

In addition to the 22 fatal hypersensitivity cases reported in the PSUR, it was clarified by the MAH within this PSUR procedure that an additional 7 fatal reported cases were related to hypersensitivity, which brings the total number of fatalities to 29 (the majority being reported in the US).

A total of 13 of the (initially confirmed) 22 patients (59%) with a fatal outcome had medical history of drug hypersensitivity and in 7 of these 13 patients (32% of all patients) there was a history of multiple drug allergies. For the remaining 9 patients, 3 were noted to have no known allergies, 1 was noted to have allergies to unspecified fruits, and allergy information was unknown in 5 patients. For 94 of the 218 patients (43%) with serious, non-fatal reports, drug hypersensitivity was reported in their medical history. In 49 of these 94 patients (22% of all patients), there was a history of allergy for multiple drugs. In 16 of the 218 patients, there was a history of previous allergy to IV iron products. For the remaining 124 patients, 59 were noted to have no known allergies, 2 had non drug allergies, and allergy information was unknown for 63 patients.

Therefore, in view of available data regarding hypersensitivity reactions, the PRAC considered that changes to the product information and to the conditions of the marketing authorisation were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds recommending the variation to the terms of the Marketing Authorisation

On the basis of the scientific conclusions for Rienso, the CHMP is of the opinion that the benefit-risk balance of the medicinal product containing the active substance ferumoxytol is favourable subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisation should be varied.

APPENDIX 1

CHMP detailed explanation of the scientific grounds for the differences with the PRAC recommendation

CHMP detailed explanation of the scientific grounds for the differences with the PRAC recommendation

Points of differences with the PRAC recommendation and scientific rationale of the CHMP position

Based on the PRAC review of data on safety and efficacy, the PRAC considers by majority decision that the risk-benefit balance of medicinal products containing the active substance ferumoxytol remains favourable subject to the additional risk minimisation measures and conditions imposed, as well as the undertakings to be provided within the next PSUR and Risk Management Plan as detailed below; in addition recommends that the terms of the marketing authorisation should be varied as follows:

Update of sections 1, 3, 4.2, 4.4, 6.4 and 6.6 of the SmPC to reflect that Rienso should only be administered as a 15 minutes infusion. Update of sections 4.2 and 4.4 of the SmPC to include a recommendation to carefully monitor patients for signs and symptoms of hypersensitivity (monitoring of blood pressure and pulse during and 30 minutes after administration) and that patients should be in a reclining/semi-reclining position during and after administration. Update of section 4.3 of the SmPC to include a new contraindication in patients with any known drug allergy. Update of sections 4.4 and 4.8 to include that fatal and life-threatening hypersensitivity reactions have been observed post-marketing. The Labelling and Package Leaflet are updated accordingly.

In addition the PRAC recommended that the prescribers are informed of these changes to the product information via a Dear Healthcare Provider Communication (DHPC).

The following changes to the conditions of the marketing authorisation of medicinal products containing the active substance ferumoxytol are recommended:

Annex II.D CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Obligation to conduct post-authorisation measures**

The MAHs shall conduct a PASS to further characterise the safety concerns on the hypersensitivity reactions. The study will also have to be reflected in the updated/new RMP submission. Final study report by:	31 July 2016

In addition, the MAH should also address the following issues in the next PSUR:

- The reference information should be updated in line with the outcome of the Article 31 referral.

In addition, the MAH should also provide the following within the next PSUR and the next update of the RMP as referred to into the above recommendation of the PRAC:

- A proposal of study (draft protocol) to investigate the mechanism of hypersensitivity with ferumoxytol.
- A synopsis for an adequately powered study to further investigate the risk of hypersensitivity in EU CKD patients comparing ferumoxytol with iron sucrose.
- A proposal of study (draft protocol) to measure the effectiveness of the new risk minimisation

measures agreed by the PRAC as part of the present PSUR.

- The MAH should submit within the PSUR cumulative reviews of hypersensitivity case reports, all fatal cases and all pregnancy cases, together with usage data. The review should follow the below principles:
  - exposure definition (expressed in 100,000 patients treated – daily dose of 100 mg equivalents)
  - event definition (Hypersensitivity SMQ (narrow scope), Asthma/bronchospasm SMQ (narrow scope), Anaphylactic reaction SMQ (algorithm), Hypotension Takeda MedDRA Query (TMQ), Angioedema SMQ (narrow scope))
  - and use the severity classification according to Ring and Messmer classification.
- Finally, the MAH should provide within the risk management a proposal for key elements of educational material for health care professionals and patients. These should highlight the risks and warnings on hypersensitivity reactions.

The updated RMP addressing the above should be submitted simultaneously to the next PSUR (DLP 30.06.2014).

Grounds for differences with the PRAC recommendation

Whereas, having taken into account the PRAC recommendation, the CHMP additionally considers:

- Based on the "Final Stability Report For Ferumoxytol Drug Product in Saline and Dextrose Solution", which was submitted by the MAH after the adoption of the final PRAC recommendation, it is proposed to add detailed in-use storage conditions in the SmPC and in the PL. Stability was tested only at 25°C and not at 2 – 8 °C. This has been amended in section 6.3 of the SmPC and in section 6 of the PIL. Additionally, the designation of "dextrose water" was changed to "glucose" as proposed by the MAH in sections 4.2, 6.4 and 6.6 of the SmPC and in section 6 of the PL. The designation of the concentration for sodium chloride was brought in line with the new QRD recommendations in sections 6.4 of the SmPC and in section 6 of the PIL. Furthermore the sterile nature of the used solvents was amended for reasons of consistency in sections 4.2 and 6.6 of the SmPC and in section 6 of the PL.
- A cross-reference to section 6.6 is proposed to be included in section 6.2 of the SmPC for clarification.
- The additional subheading "Description of selected adverse reactions" is proposed to be included in section 4.8 in line with the SmPC guideline.
- Besides, the CHMP noted the need to align Annex II.B Conditions or restrictions regarding supply and use with section 4.2 Posology and method of administration of the SmPC and therefore to change the prescription status from "Medicinal product subject to medical prescription" to "Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2)".

The CHMP, having considered the PRAC recommendation dated July 2014 and the totality of the information provided by the MAH, is of the opinion that the risk-benefit balance of medicinal products containing the active substance ferumoxytol remains favourable but recommends by majority decision that the terms of the marketing authorisation should be varied as follows:

Update of sections 1, 3, 4.2, 4.4, 6.2, 6.3, 6.4 and 6.6 of the SmPC to reflect that Rienso should only be

administered as a 15 minutes infusion. Update of sections 4.2 and 4.4 of the SmPC to include a recommendation to carefully monitor patients for signs and symptoms of hypersensitivity (monitoring of blood pressure and pulse during and 30 minutes after administration) and that patients should be in a reclining/semi-reclining position during and after administration. Update of section 4.3 of the SmPC to include a new contraindication in patients with any known drug allergy. Update of sections 4.4 and 4.8 to include that fatal and life-threatening hypersensitivity reactions have been observed post-marketing. The Labelling and Package Leaflet are updated accordingly.

The conditions imposed to the marketing authorisation are as follows:

Annex II.B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Annex II.D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Obligation to conduct post-authorisation measures**

The MAHs shall conduct a PASS to further characterise the safety concerns on the hypersensitivity reactions. The study will also have to be reflected in the updated/new RMP submission. Final study report by:	31 July 2016

APPENDIX 2

Divergent Position

Having considered the PRAC recommendation, the undersigned members of CHMP did not agree with the CHMP's opinion recommending that the Marketing Authorisation should be varied for Rienso.

The reasons for divergent opinion were as follows:

Whilst it is acknowledged that hypersensitivity reactions occur also with other intravenous iron containing products, the absolute number as well as the severity of hypersensitivity reactions associated with the administration of Rienso (ferumoxytol) are of major concern. Cumulatively, since the granting of the marketing authorisation of ferumoxytol a total of 482 post-marketing hypersensitivity cases have been reported and nearly 50% of these cases were serious (including life-threatening) allergic reactions (240 serious, 242 non-serious). There were in total 42 fatal cases and 29 of them were associated with hypersensitivity. Although there are well-known limitations of spontaneous reporting, these figures give raise to a serious safety concern impacting on the benefit risk balance of the product. Furthermore, the reason for the high number of cases with ferumoxytol currently remains unclear and the underlying mechanism is not fully understood.

The already existing routine risk minimisation measures included in SmPC and PL of Rienso did not seem to be sufficient. Therefore, to address the above mentioned concerns, further risk minimisation measures were proposed by the MAH and include a labelling update (inclusion of a new contraindication, reduction of the speed of administration), educational material as well as circulation of a further DHPC. However, there is uncertainty as to whether the risk minimisation strategy proposed would actually be able to mitigate the risk of hypersensitivity reactions and no reassurance could be given by the MAH in this regard. Any risk mitigation strategy needs to be sufficiently robust and evidence driven to prevent unnecessary harm, in particular in the context of a treatment for which there are therapeutic alternatives available to patients.

Taking all these aspects into account, the benefit risk balance of Rienso is considered negative. A suspension of the marketing authorisation is recommended considering the nature of the safety concern and the level of uncertainty to protect patient safety in an area where therapeutic alternatives are available. Suspension would remain until the marketing authorisation holder can provide convincing data to identify a group of patients in whom the benefits of the medicine outweigh its risks and adequate risk minimisation measures are proposed and implemented.

London, 24 July 2014

CHMP Members expressing a divergent position:

Agnes Gyurasics	24 July 2014	Signature: ……..
Bruno Sepodes	24 July 2014	Signature: ……..
Concepcion Prieto Yerro	24 July 2014	Signature: ……..
Daniel Brasseur	24 July 2014	Signature: ……..
Dimitrios Kouvelas	24 July 2014	Signature: ……..
Harald Enzmann	24 July 2014	Signature: ……..
Ivana Mikačić	24 July 2014	Signature: ……..
Jan Mueller Berghaus	24 July 2014	Signature: ……..
Jean-Louis Robert	24 July 2014	Signature: ……..
Nela Vilceanu	24 July 2014	Signature: ……..
Pierre Demolis	24 July 2014	Signature: ……..
Piotr Fiedor	24 July 2014	Signature: ……..
Stanislav Primozic	24 July 2014	Signature: ……..
Sol Ruiz	24 July 2014	Signature: ……..