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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/0015

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Scientific conclusions

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

Hypersensitivity reactions

Cumulatively 21 cases of hypersensitivity (8 serious, 13 non-serious) have been reported during clinical trials. Cumulatively, since the granting of the marketing authorisation up to the data lock-point (DLP) of the current PSUR, a total of 527 reported post-marketing cases of hypersensitivity reactions of which more than 50 % were serious including life threatening allergic reactions (264 serious, 263 non-serious). In total 42 fatal cases have been reported cumulatively. 29 of them were associated with hypersensitivity reactions. Within the limitations inherent to post-marketing reporting, the following reporting rate can be calculated: As of 30 June 2014, the cumulative overall post-marketing reporting rate of hypersensitivity based on 2 g per person per year is: 527/266,914×100=0.20%. During this PSUR covering period, 45 new cases of hypersensitivity reactions have been reported: 24 serious including one fatal case already reported as part of the previous PSUR as late-breaking information and 21 non-serious cases.

After the DLP of the present PSUR, 6 additional fatal cases of hypersensitivity reactions with ferumoxytol have been reported. Two of these reports were included by the MAH as late breaking information into this PSUR. The additional four cases were reported after this PSUR was submitted for assessment. All six fatal hypersensitivity cases were reported in the US and involved elderly patients (> 65 years of age) with co-morbidities. One patient had a prior history of drug allergy. In 5 out of these 6 cases, ferumoxytol was administered via IV injection (either quick or slow IV push), for the remaining case the method of administration is unknown.

It should be noted that 28 out of the 35 fatal cases of hypersensitivity reactions occurred in elderly patients (> 65 years of age). There is no evidence that the risk of hypersensitivity reactions as such is increased in elderly patients, however, these patients have an increased risk of complications.

Considering the cumulative number of reported cases of hypersensitivity reactions (serious, non-serious) including 35 fatal cases, the PRAC considered new additional risk minimisation measures in addition to the ones already implemented as part of the previous PSUR, and recommended that a warning on the severity of the outcome of hypersensitivity reactions in patients over 65 or with co-morbidities should be added in section 4.4 of the SmPC.

Interference with Magnetic Resonance Imaging (MRI)

No spontaneous post-marketing reports of MRI interference have been received to date. Within this PSUR, a further literature review has been provided by the MAH identifying 9 relevant publications addressing ferumoxytol and MRI. Four case reports have been published describing the supraparamagnetic effects of ferumoxytol on MR imaging and emphasized the importance for the radiologists to be aware if a patient received ferumoxytol recently. Based on a limited number of case reports, the influence of ferumoxytol on the interpretation of MRIs appears to be primarily noted in the first few weeks after administration and, based on animal data, dissipated within 3 months. The MAH is of the opinion that the current EU SmPC accurately reflects the current literature and provides appropriate guidance to EU practitioners. However, the MAH acknowledges that Rostoker and Cohen recommend a minimum of 6 months between ferumoxytol's administration, which they base on the study with 6 healthy volunteers published by Storey et al. Therefore the MAH proposed as part of this

PSUR to amend the current warning in section 4.4 of the SmPC to reflect that interference with MRI can occur up to 6 months after administration of ferumoxytoll which was agreed by the PRAC.

Therefore, in view of available data regarding hypersensitivity reactions and interference with Magnetic Resonance Imaging (MRI), the PRAC considered that changes to the product information 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 within the PSUR, 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 the PRAC recommends that the terms of the marketing authorisation should be varied as follows:

Update of section 4.4 of the SmPC to add a warning on the outcome of severe hypersensitivity reactions in elderly patients or with co-morbidities. Update of section 4.4 of the SmPC to amend the warning on the interference with MRI. The Package leaflet is updated accordingly.

In addition, the PRAC recommended to include as a condition to the Marketing Authorisation the mechanistic study already requested as part of the previous PSUR (covering 01/07/2013 – 30/12/2013), to include the key elements of the educational materials already requested as part of the previous PSUR in Annex II. The PRAC also requested the MAH to provide within the next PSUR a revised synopsis for the adequately powered study to further investigate the risk of hypersensitivity with ferumoxytol using iron sucrose as comparator, a revised protocol for the study to measure the effectiveness of the risk minimisation measures agreed by the PRAC as part of the previous PSUR, an update on the progress with the mechanistic study, the final clinical study report of phase I (2010-2011) of the Chronic Disease Research Group along with the protocol for phase II (2012). Finally the PRAC requested the MAH to submit three monthly and with each PSUR cumulative reviews of hypersensitivity case reports, all fatal cases and all pregnancy cases, together with usage data.

Grounds for differences with the PRAC recommendation

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

- That for the adequately powered study to further investigate the risk of hypersensitivity reactions in EU CKD patients comparing ferumoxytol with iron sucrose, requested as part of the previous PSUR (covering 01/07/2013 – 30/12/2013), it should be clarified that such study should not be exclusively conducted in EU CKD patients but should include EU CKD patients. As the exposure of ferumoxytol in the EU is low and most of the exposure actually comes from the US, this study should be conducted in CKD patients including patients from the EU but also from other territories in order to be feasible.

The CHMP, having considered the PRAC recommendation 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 section 4.4 of the SmPC to add a warning on the outcome of severe hypersensitivity reactions in elderly patients or with co-morbidities. Update of section 4.4 of the SmPC to amend the warning on the interference with MRI. The Package leaflet is updated accordingly. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 9.0.

The conditions imposed to the marketing authorisation are as follows:

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

- **ADDITIONAL RISK MINIMISATION MEASURES**

Prior to the use of Rienso in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at highlighting the risks and warnings on hypersensitivity reactions and the monitoring of patients during and after administration.

The MAH shall ensure that in each Member State where Rienso is marketed, all healthcare professionals and patients/carers who are expected to use Rienso have access to/are provided with the following educational package:

- Healthcare professional checklist
- Patient alert card

The healthcare professional checklist shall contain the following messages:

- The checklist should include tick-boxes to check and document:
  - Confirmation on appropriate settings (emergency resuscitation equipment available) prior to administration of ferumoxytol
  - Patient's eligibility
  - Contraindications and warnings
  - Duration of administration
  - Semi-declined position during administration
  - Duration of monitoring of patients after administration.

The patient alert card shall contain the following key messages:

- Information regarding the increased risk of serious including fatal hypersensitivity reactions: contraindications, special patient populations (e.g. pregnant women, elderly), warnings, symptoms of hypersensitivity reactions, monitoring by health care professionals during 30 minutes after administration, warning on late onset of allergic reactions.

- **OBLIGATION TO CONDUCT POST-AUTHORISATION MEASURES**

The MAHs shall conduct a study to investigate the mechanism of hypersensitivity associated with the exposure to ferumoxytol, according to a protocol agreed by the CHMP. Final study report by:	31 October 2016

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

- Adequately powered study to further investigate the risk of hypersensitivity reactions in CDK patients, including EU CKD patients, comparing ferumoxytol with iron sucrose: the MAH should provide a revised synopsis using iron sucrose as comparator as requested by the PRAC.
- Study to measure the effectiveness of the risk minimisation measures agreed by the PRAC as part of the previous PSUR: the MAH should provide a revised protocol with as design a retrospective chart review as requested by the PRAC.
- Study to investigate the mechanism of hypersensitivity associated with the exposure to ferumoxytol: the MAH should provide an update on the progress.
- Phase I of the Chronic Disease Research Group (CDRG) study: the MAH should provide the full study report.
- Phase II of the Chronic Disease Research Group (CDRG)) study (additional year of exposure (2012)): the MAH should submit the protocol for this Phase II.
- The MAH should submit three monthly and within the PSURs 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 of the severity classification according to Ring and Messmer classification.

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 up to the data lock point of the current PSUR (June 2014) a total of 528 post-marketing hypersensitivity cases have been reported and more than 50% of these cases were serious (including life-threatening) allergic reactions (265 serious, 263 non-serious). In this period, there were in total 42 fatal cases and 29 of them were associated with hypersensitivity. After the data lock point of the current PSUR, 6 additional fatal hypersensitivity cases associated with ferumoxytol were notified by the Marketing Authorisation Holder (MAH), all involving elderly patients: 2 of these additional cases were included in the PSUR submission, 4 reported after the submission of the PSUR. 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 still not fully understood.

To address the above mentioned concerns, further risk minimisation measures were proposed by the MAH: These include a labelling update (inclusion of a wording to the "Warnings and Special precautions" section of the SmPC that elderly patients with multiple severe co-morbidities who experience a hypersensitivity reaction and/or hypotensive reaction in association with Rienso may have more severe outcomes) as well as amendments to the educational material.

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.

As outcome of the previous PSUR several additional pharmacovigilance activities have been requested by the PRAC, including a proposal of a 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 reactions in CKD patients, including EU CKD patients, comparing ferumoxytol with iron sucrose as well as a proposal of a study (draft protocol) to measure the effectiveness of the risk minimisation measures agreed by the PRAC as part of the previous PSUR. Until now, more progress could have been made and more efforts undertaken by the MAH with regard to these important studies. Therefore, it is currently unclear whether further characterisation of the risk that could inform any further risk minimisation measures will be possible within an acceptable timeframe.

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 should 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, 22 January 2015

CHMP Members expressing a divergent position:

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Concepcion Prieto Yerro	22 January 2015	Signature: ……..
Daniel Brasseur	22 January 2015	Signature: ……..
Daniela Melchiorri	22 January 2015	Signature: ……..
Harald Enzmann	22 January 2015	Signature: ……..
Ivana Mikacic	22 January 2015	Signature: ……..
Jan Mueller-Berghaus	22 January 2015	Signature: ……..
Nevenka Tršinar	22 January 2015	Signature: ……..
Pierre Demolis	22 January 2015	Signature: ……..
Sol Ruiz	22 January 2015	Signature: ……..