EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 January 2015
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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Active substance: ferumoxytol

Procedure no.: EMEA/H/C/002215/PSUV/0015

Period covered by the PSUR: 31 December 2013 – 30 June 2014

RMP version number: 3.3

PRAC Rapporteur:	Martin Huber

Status of this report and steps taken for the assessment				
	Procedure start date:			11 September 2014
☐	PRAC Rapporteur preliminary Assessment report (AR)	19 November 2014	Comments by:	10 December 2014
	Comments from the MAH received on:			19 December 2014
☐	Assessment report updated following comments:			23 December 2014
	An Oral explanation took place on:			07 January 2015
☒	Final PRAC assessment report adopted with recommendation on:			09 January 2015

Note

Variation 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

This is the assessment of the following PSUR submitted in accordance with the requirements set out in the list of Union reference dates (EURD list).

Centrally authorised Medicinal product: **For presentations: See Annex A**	**Marketing Authorisation Holder**
Rienso	Takeda Pharma A/S

An update to the RMP resulting from data presented in the PSUR was submitted.

2. Final assessment conclusions and actions

Rienso (Ferumoxytol) is an intravenous (IV) iron preparation, a superparamagnetic iron oxide particle consisting of an iron oxide core and a polyglucose sorbitol carboxymethylether (PSC) coating designed to minimize immunological reactivity. Ferumoxytol was authorised in the US on 30 June 2009 (under the name Feraheme) and in the EU on 30 June 2012 for the treatment of iron deficiency anaemia (IDA) in adult patients with chronic kidney disease (CKD). Rienso is currently marketed in 9 EU countries.

This is the 4th PSUR for Rienso covering the following period: 31 December 2013 - 30 June 2014.

Overall, 2,807 adult patients were exposed to ferumoxytol in one or more treatment courses in completed randomized or open-label IDA-CKD and all-cause IDA studies sponsored by in-license partner AMAG Pharmaceuticals, Inc. Additionally, 14 pediatric subjects and 230 adult subjects are enrolled in ongoing clinical trials also sponsored by AMAG.

Post-marketing exposure to ferumoxytol injection during the reporting period was estimated at 135,297 patient doses. This estimate includes 126,338 patient doses in the United States, 7,274 patient doses in Canada, 1,685 patient doses in Europe. There was no exposure to ferumoxytol in the Swiss market during the current report period. The cumulative worldwide exposure to ferumoxytol since IBD is estimated to be 1,046,721 patient-doses and 266,914 patient-years.

According to the current PSUR, the most cumulatively reported SOCs as SAEs in the clinical trials after ferumoxytol usage were infections and infestations (different PTs), cardiac disorders (mostly atrial fibrillation, congestive heart failure), gastrointestinal disorders (GIT pain, bleeding), respiratory disorder (pulmonary oedema, COPD), general disorders (chest pain), vascular disorder (hypotension) and renal disorders (acute/chronic renal failure).

In the post-marketing experience covered by this reporting period the most spontaneous reported SOCs as SAEs were:

- 16x Immune system disorder (6x anaphylactic reactions, 6x hypersensitivity, 3x anaphylctoid reactions, 1x anaphylactic shock).
- 10x Respiratory, thoracic and mediastinal disorders (7x dyspnoea, 1x respiratory arrest, 2x respiratory distress)
- 9x Nervous system disorder (3x unresponsive to stimuli, 1x burning sensation, 1x syncope, 1x clonus, 1x loss of consciousness, , 1x brain injury, 1x restless leg syndrome)

- 8x General disorders and administration site conditions (2x chest pain, 2x chest discomfort, 1x feeling hot, 1x malaise, 1x pain, 1x feeling abnormal)
- 8x Investigations (2x blood pressure decreased, 2x blood pressure increased, 1x heart rate increased, 1x pulse absent, 1x respiratory rate increased, 1x oxygen saturation decreased)
- 6x Cardiac disorder (1x cardiac arrest, 1x cardio-respiratory arrest, 1x Pulseless electrical activity, 1x myocardial infarction, 1x pericardial effusion, 1x cyanosis)
- 4x Gastrointestinal disorder (1x nausea, 2x vomiting, 1x dry mouth)
- 3x Skin and subcutaneous tissue disorders (1x swelling face, 1x pruritus, 1x pruritus generalised)
- 3x Musculoskeletal and connective tissue disorders (1x back pain, 1x flank pain, 1x pain in extremity).

Interference with Magnetic Resonance Imaging (MRI)

As part of RMP version 3.3 submitted with this PSUR, the MAH included "Misinterpretation of MRI" as a new important identified risk. The signal of "Interference in MRI interpretation" is actually not a new safety concern, as it was already included as warning into the SmPC of Rienso at the time of EU Marketing Authorisation in 2012. The addition of this risk into the RMP followed the recommendation of the PRAC from 2013 following publication of an article from a Canadian author (submitted for review in May 2013). This article describes a case report describing MRI of the liver performed 3 days following administration of ferumoxytol.

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, 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. The MAH acknowledges however 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. The MAH proposed therefore as part of this PSUR to amend the current warning in section 4.4 of the SmPC to extend the timeframe for interference which was agreed by the PRAC.

Hypersensitivity reactions and benefit/risk re-assessment

Following concerns about an increased reporting rate of hypersensitivity reactions including serious and fatal cases, after evaluation of data provided in the last PSUR, the PRAC and the CHMP concluded that the benefit-risk profile of Rienso remained positive with several amendments to the product information (new contraindication, new method of administration via 15 minutes infusion, strengthened warnings), the imposition of a PASS, circulation of a DHPC, and requests to the MAH to conduct further studies to further investigate this risk (adequately powered study to further investigate the risk of hypersensitivity in EU CKD patients comparing ferumoxytol with iron sucrose, study to investigate the mechanism of hypersensitivity associated with the exposure to ferumoxytol and study to measure the effectiveness of the new risk minimisation measures).

The MAH therefore provided within this PSUR an extensive discussion on this signal along with a 3 monthly cumulative review of all hypersensitivity case reports as requested by the PRAC in the previous PSUR.

Cumulatively 21 cases of hypersensitivity (8 serious, 13 non-serious) have been reported during clinical trials. Two new serious cases have been reported during this PSUR covering period.

Cumulatively, since the granting of the marketing authorisation up to the data lock-point of the current PSUR (i.e. 30/06/2014), 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). 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.

From IBD (30 June 2009) up to 30 June 2014, a total of 42 fatal cases have been reported, from which 29 cases (69%) were due to hypersensitivity. Countries of origin for the 29 fatal hypersensitivity cases were the United States (25), Canada (2), Finland (1), and Switzerland (1). Seventeen patients were male, 12 were female. Ages of the patients at event onset ranged from 47 to 98. Seven of the 29 patients were younger than 65, seven patients were in the age range 65 - < 70, six patients in the age category 70 - < 75, 5 between 75 - < 80 and four patients were older than 80 (83, 86, 90, and 98, respectively). Indications for use included iron deficiency anaemia in chronic kidney disease (17), anaemia due to chronic kidney disease and concurrent underlying malignancy (2), anaemia due to underlying malignancy (4), iron deficiency anaemia (2), and product used for unknown indication (4). Ten patients received one dose of ferumoxytol, 11 two doses, 3 three doses, and for 5 patients the number of doses received is unknown. Dosages of ferumoxytol administered were 1.5 ml (45 mg) (1), 3 ml (90 mg) (1), 4 ml (120 mg) (1), 7 ml (210 mg) (2), just over 8 ml (250 mg) (1), 17 ml (510 mg) (15 patients), or unknown (8).

The duration of ferumoxytol administration was as follows: less than one minute (8) patients), 1 minute (1), 3 minutes (1), 4 minutes (1), 5 minutes (5), 3-5 minutes (1), 6 minutes (1), 10 minutes (1), or unknown (10). Time to onset of the hypersensitivity reactions after administration was immediate (11 patients), 1 minute (3), 2-3 minutes (1), 4 minutes (1), 5 minutes (2), 7 minutes (1), 18 minutes (1), ± 30 minutes (2), within 24 hours (1), and unknown (6). Time to death after administration of ferumoxytol was 1 minute to 1 hour (8 patients), 1 hour to 1 day (12), 2 days (4), 5 days (2 [1-life-support was withdrawn and 1 patient expired under hospice care]), 9 days (1- hospital course was complicated by diagnosis of necrotic bowel with refusal for surgical intervention), or unknown (2). For 13 of the 29 patients (45%), drug hypersensitivity was reported in the medical history. In seven patients (24%) there was a history of multiple drug allergies. For the remaining 16 patients (55%), 5 (17%) were noted to have no known allergies, 1 (3.5%) was noted to have allergies to unspecified fruits and allergy information was unknown in 10 patients (34.5%). All 29 patients had an extensive medical history of varied morbidity with chronic renal failure and (congestive) cardiac failure being most prevalent. Nine patients suffered from malignant diseases.

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. The correlation between speed of administration and allergic reaction was extensively discussed in the last PSUR. With an infusion, in case of anaphylactic reaction, at least the rest volume of ferumoxytol can be stopped immediately. In line with the discussion in the last PSUR, the 6 fatal cases described above demonstrate that fatal hypersensitivity reactions can occur at each administration irrespective if previous administrations were uneventful and that administration of a minor part of the full dose may lead to fatal hypersensitivity reaction.

There were 23 serious post-marketing adjudicated non-fatal hypersensitivity cases received during the reporting interval. Cases were received from the United States (15), Canada (7) and Denmark (1). Ages ranged from 33-93 years in the 15 female and eight male patients. Event onset occurred coincident with the first dose in 6 patients, second dose in 8 patients, third dose in 3 patients, second or third dose in 1 patient and seventh dose in 1 patient (unknown in 4 patients). Outcome of the hypersensitivity events was fully recovered in 17 patients, recovering in 1 patient and unknown in 5 patients.

The MAH additionally provided with this PSUR submission as per PRAC's request, a 3 monthly cumulative review of hypersensitivity cases covering the period 01/07/2014 – 30/09/2014. Further 75,393 vials of ferumoxytol were sold, resulting in cumulative exposure of 280,529 patient years. A total of 20 cases (14 serious, 6 non-serious) met the search criteria for hypersensitivity. From 14 serious cases, 2 were fatal (already described above). All 20 of the reports originated from post-marketing. No cases were received from regulatory authorities, literature or clinical trials. Seven cases originated from Canada and 13 were from the United States. In terms of mode of administration, 5 of the 12 patients received ferumoxytol as IV push, whereas 2 received ferumoxytol as infusions. The method of administration was unknown in 5 patients.

Based on the cumulative number of hypersensitivity reactions including 35 fatal cases (28 of which occurred in patients > 65 years of age), the MAH was requested by the PRAC within this PSUR procedure to perform a re-evaluation of the benefit/risk balance of ferumoxytol. The MAH was also requested as part of the request for supplementary information to address a number of comments raised on the further studies requested from the MAH as part of the previous PSUR to investigate the risk of hypersensitivity.

The MAH was also requested in an oral explanation to justify a benefit/risk balance of ferumoxytol taking into account the 35 fatal cases reported and to discuss the effectiveness of the risk minimization measures implemented as part of the previous PSUR and to propose additional risk minimization measures.

With their responses to the supplementary information and at the oral explanation, the MAH highlighted that the DLP of the present PSUR is prior to the adoption of the PRAC recommendation and CHMP opinion from July 2014 on the previous PSUR and that therefore it is too early to judge the effectiveness of the risk minimisation measures implemented as part of the previous PSUR.

With regards to the 6 new fatal cases of hypersensitivity reactions, the MAH stressed that they all occurred in the US where the risk minimisation measures agreed in the EU as part of the previous PSUR have not been implemented.

To support a positive benefit/risk, the MAH discussed the results of a retrospective cohort study from the Chronic Disease Research Group (CDRG), a study to assess the crude incidence of hypersensitivity reactions, hypotension and mortality with IV iron administration using the US Medicare database. In phase I of this study (2010-2011), 640,344 patients were administered an IV iron preparation representing a total of 15,933,038 administrations. Two analyses were performed of event rates, one with the number of administrations as the denominator and one using the number of patients as the denominator.

The results show that in the administration based analysis in dialysis patients the ferumoxytol group was associated with higher event rates and mortality rates per administration than the other IV irons, however the patient-based analysis in this patient group showed the event rates and mortality rates were lowest in the ferumoxytol group compared to the other IV iron products. In the administration-based analysis in patients with non-dialysis dependent chronic kidney disease, the iron dextran group was associated with the highest event rates followed by the ferumoxytol group. The iron sucrose group was associated with the highest mortality rates and the ferumoxytol group with the lowest mortality rates. The

patient-based analysis in this patient group shows, however, that the hypersensitivity/hypotension event rates were highest in the iron dextran group and lowest in the ferumoxytol group and the all-cause mortality rates were highest in the iron sucrose and ferric gluconate groups and lowest in the ferumoxytol groups.

However this study did not stratify for seriousness of hypersensitivity or for death due to hypersensitivity reactions. In addition, as no adjustment for baseline characteristics of the respective IV iron user populations was done, it was not possible to assess the independent association between the IV iron use and hypersensitivity/hypotension/mortality. Comparisons between IV iron products in this study should therefore be interpreted with caution, particularly as the total number of injections required to administer the same amount of elemental iron differs between the iron containing medicinal products. For example to administer 2 grams of elemental iron requires a total of 4 injections with ferumoxytol and up to 20 with iron sucrose for dialysis patients.

A phase II of this CDRG study was initiated in December 2014 which will include one additional year of exposure (2012) and patient baseline characteristics, such as co-morbidities, concomitant medications and a history of allergic reactions to other medications across the various IV iron products. The MAH committed to provide the data, expected to be available in June 2015.

As additional risk minimisation measure, the MAH also proposed to include a new warning in the SmPC on the severity of hypersensitivity reactions in elderly patients with co-morbidities. The PRAC agreed to include a new warning under section 4.4 of the SmPC on the outcome of severe hypersensitivity reactions in elderly patients and patients with co-morbidities.

The MAH explained that the delay in the submission of the draft protocol of the mechanistic study which was requested as part of the previous PSUR by the PRAC was due to delays in convening a scientific advisory board on IV iron. The MAH provided timelines for the submission of the protocol and the final results of such mechanistic study (submission of the protocol: March 2015, submission of the final study report for Phase I: March 2016, for Phase II: August 2016 and for Phase III: October 2016) .

Considering that the mechanism of hypersensitivity reactions with ferumoxytol is still unknown and key to identify further measures to minimise this risk, the PRAC also agreed to include the submission of the mechanistic study already requested as part of the previous PSUR as a condition to the Marketing Authorisation for Rienso.

The MAH should also provide within the next PSUR a revised synopsis for the adequately powered study to further investigate the risk of hypersensitivity in EU CKD patients study with ferumoxytol using iron sucrose as comparator (and not iron carboxymaltose as proposed by the MAH) as requested by the PRAC already in the previous PSUR, 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 (using a retrospective chart review design), 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).

In addition, the MAH should submit three monthly and with each PSUR cumulative reviews of hypersensitivity case reports, all fatal cases and all pregnancy cases, together with usage data.

In conclusion, the high rate and severity of the reported hypersensitivity reactions cases with fatal outcome remains a major safety concern. However, limited new data has become available since the previous PSUR as this product is currently under a 6 monthly PSUR schedule. The exposure to ferumoxytol in the EU remains low compared to other territories such as the US. It should be also highlighted that the data lock-point for the present PSUR is 30/06/2014, before the conclusions were adopted by the PRAC and the CHMP on the previous PSUR. Therefore, the PRAC considered the evidence

provided so far too premature to carefully assess whether the risk minimisation measures implemented as part of the previous PSUR are effective. With regards to the 6 newly reported fatal cases of hypersensitivity reactions, they all occurred in the US where the risk minimisation measures agreed in the EU as part of the previous PSUR have not been implemented.

Finally, the PRAC noted that the safety profile of the reported adverse events other than hypersensitivity reaction in the current PSUR were comparable with the previous PSUR. Taking all these aspects into consideration the PRAC considered that the benefit/risk balance of ferumoxytol remains positive.

Scientific conclusions and grounds for variation to the terms of the marketing authorisations

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. The MAH acknowledges however 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. The MAH proposed therefore 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.

3. Final Recommendations

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.

The following changes to the product information of medicinal products containing ferumoxytol are recommended (new text = **bold underlined**; deleted text = ~~strikethrough~~):

Summary of Product Characteristics

- Section 4.4 Special warnings and precautions for use

A warning should be added as follows:

Hypersensitivity Reactions
Parenterally administered iron preparations can cause hypersensitivity reactions including serious and potentially fatal anaphylactic/anaphylactoid reactions. Hypersensitivity reactions have also been reported after previously uneventful doses of parenteral iron complexes.

The risk is enhanced for patients with known allergies including drug allergies, including patients with a history of severe asthma, eczema or other atopic allergy (see section 4.3).
There is also an increased risk of hypersensitivity reactions to parenteral iron complexes in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis).

Rienso should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available, in an environment where full resuscitation facilities can be assured. Patients should be carefully monitored for signs and symptoms of hypersensitivity reactions including monitoring of blood pressure and pulse during and for at least 30 minutes following each infusion of Rienso. In addition, patients should be placed in a reclining or semi-reclining position during infusion and for at least 30 minutes thereafter.

If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Facilities for cardio respiratory resuscitation and equipment for handling acute anaphylactic/anaphylactoid reactions should be available, including an injectable 1:1000 adrenaline solution. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

Fatal and life-threatening hypersensitivity reactions have been observed with Rienso in the post marketing setting. Clinical presentation has included anaphylactic type reactions presenting with cardiac arrest/cardiorespiratory arrest, clinically significant hypotension, syncope, and unresponsiveness (see section 4.8).

Elderly patients (> 65 years of age) or patients with multiple co-morbidities who experience a serious hypersensitivity reaction may have more severe outcomes.

[...]

Magnetic Resonance (MR) Imaging

Administration of Rienso may transiently affect the diagnostic ability of MR imaging.
Anticipated MR imaging studies should be conducted prior to the administration of Rienso.
The effect on vascular MR imaging lasts approximately 1-2 days while tissue diagnostic imaging may be affected for up to **6**~~2-3~~ months.
MR images are interpretable earlier by readers aware of the recent administration of Rienso or by the use of T1- or proton density-weighted MR pulse sequences.
Rienso will not interfere with X-ray, computed tomography (CT), positron emission tomography (PET), single photon emission computed tomography (SPECT), ultrasound or nuclear medicine imaging.

Package Leaflet

- Section 2 What you need to know before you receive Rienso

Warnings and precautions
Talk to your doctor, pharmacist or nurse before receiving Rienso:
- if you have a history of medicine allergy.
- if you have systemic lupus erythematosus.
- if you have rheumatoid arthritis.
- if you have severe asthma, eczema or other allergies.
- if you have a problem with your liver.
- if you have problems with your immune system.
- if you have any infections, including infections which have spread to your blood stream.
- if you are scheduled for magnetic resonance imaging (an MRI scan) ~~shortly after receiving Rienso~~, as this medicine may interfere with the interpretation of the scan. **For the same reason also talk to your doctor or radiographer if you have been given Rienso within the past 6 months and an MRI scan is subsequently arranged.**

Rienso can affect the interpretation of your blood iron test results.

- Section 4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects:
Tell your doctor or nurse immediately if you experience any of the following signs and symptoms indicating **serious side effects** during or shortly after treatment:
rash, itching, (sudden) dizziness, light-headedness, (increasing) swelling, difficulty breathing, wheezing or any other problems you may have.

In some patients these allergic reactions can become severe or life-threatening (known as anaphylactic reactions). These reactions can be associated with heart and circulation complications, loss of consciousness and may result in death**. If you are older than 65 years or have an underlying condition, such as liver or heart disease, the risk of having severe consequences including death may be higher after a serious allergic reaction.**

Doctors are aware of these possible side effects and will monitor you during the infusion and for at least 30 minutes after the infusion, and also have emergency treatment available if required.

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

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 provide the following within the next PSUR and the next update of the RMP as referred to into the above recommendation of the PRAC:

- Adequately powered study to further investigate the risk of hypersensitivity in 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 new 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 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 the severity classification according to Ring and Messmer classification.

4. PSUR frequency

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Attachments

Divergent Position

The undersigned members of PRAC did not agree with the PRAC'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 in EU CKD patients comparing ferumoxytol with iron sucrose as well as a proposal of a study (draft protocol) to measure the effectiveness of the new 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, 9 January 2015

PRAC Members expressing a divergent position:

A. Batz	9 January 2015	Signature: …….
M. Budny	9 January 2015	Signature: …….
J.M. Dogne	9 January 2015	Signature: …….
M. Guimaraes	9 January 2015	Signature: …….
M. Huber	9 January 2015	Signature: …….
B. Keller Stanislawski	9 January 2015	Signature: …….
H. Le Louet	9 January 2015	Signature: …….
C. Macchiarulo	9 January 2015	Signature: …….
D. Montero Corominas	9 January 2015	Signature: …….
V. Macolic Sarinic	9 January 2015	Signature: …….
T. Magalova	9 January 2015	Signature: …….
N. Petitpain	9 January 2015	Signature: …….
M. Radoha-Bergoc	9 January 2015	Signature: …….
L. Waldenlind	9 January 2015	Signature: …….