EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 July 2014
EMA/PRAC/404148/2014
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Active substance: ferumoxytol

Procedure no.: EMEA/H/C/002215/PSUV/0014

Period covered by the PSUR: 01 July 2013 – 30 December 2013

PRAC Rapporteur:	Martin Huber

Status of this report and steps taken for the assessment				
	Procedure start date:			13 March 2014
☐	PRAC Rapporteur preliminary Assessment report (AR)	02 May 2014	Comments by:	11 June 2014
	An Oral explanation took place on:			07 May 2014
	Comments from the MAH received on:			10 June 2014
☐	Assessment report updated following comments:			26 June 2014
	An Oral explanation took place on:			08 July 2014
☒	Final PRAC assessment report adopted with recommendation on:			10 July 2014

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 products **For presentations see Annex A**	**Marketing Authorisation Holder**
Rienso	Takeda Pharma A/S

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 3rd PSUR for Rienso covering the period from 01 July 2013 to 31 December 2013. Exposure to ferumoxytol during the reporting period is 33963 patient-years [133,187 sold vials= 67925 g iron), whereas total exposure worldwide since IBD is 232883 patient-years [913,266 sold vials= 465766 g iron). During this period an Article 31 referral concerning all IV iron-containing medicinal products authorised in the EU with the exception of Rienso (as Rienso was not authorised at the time of the start of the referral procedure) regarding the risk of hypersensitivity was completed on 13 September 2013. The referral concluded with the provision of introducing additional risk minimisation measures (update of product information and RMP, DHPC, educational material, cumulative annual reporting) and the imposition of a PASS). The MAH updated the product information of ferumoxytol in line with the outcome of the procedure on 17 January 2014.

The most cumulatively reported SOCs as SAEs in the clinical trials after ferumoxytol usage were cardiac disorders (mostly atrial fibrillation, congestive heart failure), infections and infestations (different PTs), gastrointestinal disorders (GIT pain, bleeding), 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 reported SOCs were 22 respiratory disorders (respiratory arrest (1), dyspnoea (6), respiratory distress (2), respiratory failure(1) stridor (1), aspiration (1), embolism (2), oedema (1), throat tightness (1), wheezing (1), choking/cough (3), orophyrangeal discomfort (1)), 17 Immune system disorders (anaphylactic reactions (13), anaphylactoid reactions (3), hypersensitivity (1)), 13 Cardiac disorders (cardiac arrest (3), cardio-respiratory arrest (4), atrial fibrillation (1), myocardial infarction (1)), Nervous system disorders (unresponsive to stimuli (5), syncope (3), cerebral infarction (1), convulsion (1), dizziness (1) paraesthesia (1), tremor (1)), 12 Vascular disorders (hypotension (7), flushing (3), DVT (1), hypertension (1), 10 Gastrointestinal disorders (vomiting/diarrhoea (5), GIT Pain (1), haemorrhage (1), swelling (1), swollen tongue (1)), 10 General disorders (chest discomfort/pain (5), chills (1), burning sensation (1) malaise (1) death (1)). Hypersensitivity comprises many symptoms, so that some SAEs reported in SOCs other than immune system disorder could have been based on allergic reactions (e.g. swollen tongue, flushing or hypotension).

Hypersensitivity reactions and Benefit – Risk re-assessment

The MAH presented with this PSUR an updated evaluation of hypersensitivity following a request from the PRAC in the previous PSUR. Based on the PRAC's request, the MAH conducted and presented standardized searches from its global safety database (for serious and non-serious post-marketing reports, and serious clinical trial reports) and also from its global clinical trial database (for non-serious reports) for Anaphylactic Reaction, Hypersensitivity, Hypotension, Angioedema and Asthma/Bronchospasm.

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 after the use of 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) and 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.

Based on the high rate of hypersensitivity reactions with fatal outcome reported in the PSUR, the MAH was requested by the PRAC within this PSUR procedure to perform a re-evaluation of the benefit risk of ferumoxytol taking into account the global age-standardized death rate for IDA (Lozano R et al. Lancet 2012;380(9859):2095-128) or IDA-CKD. The MAH was also requested as part of the request for supplementary information to provide additional information on the fatal hypersensitivity cases from post-marketing, to clarify a possible correlation between the speed of administration and the occurrence and severity of hypersensitivity reactions, to discuss possible mechanisms of the anaphylactic/anaphylactoid reactions and to propose additional risk minimization measures to mitigate the risk of hypersensitivity reactions. The MAH was also requested in an oral explanation to discuss the benefit/risk balance of ferumoxytol in the approved indication taking into account the high reporting rate of fatal and serious hypersensitivity reactions and to discuss possible risk minimization measures.

With their responses to the request for supplementary information, the MAH provided case details which reveal that further to the 22 fatal hypersensitivity cases 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, nonfatal 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 (of a total of 218), 59 were noted to have no known allergies, 2 had non drug allergies, and allergy information was unknown in 63 patients. Therefore the MAH proposed to add a contraindication for patients with a history of drug allergy as a way to mitigate the risk of hypersensitivity reactions.

A change in the method of administration (slower infusion over 15 minutes versus the currently recommended bolus injection in 17 seconds) was proposed by the MAH as a risk minimisation measure for the risk of hypersensitivity reactions. Infusion is a mode of administration that allows close observation of the patient during and after administration. A longer duration of administration allows for recognition of prodromal signs and symptoms of hypersensitivity including severe hypotension that would not be possible with an IV bolus injection. This mode of administration also allows for the cessation of drug delivery, if needed, and appropriate intervention by the treating physician. The MAH's proposal to administer Rienso via infusion over 15 minutes is comparable to the administration time of other IV iron containing medicinal products. One published study detailing infusion of 1g of ferumoxytol over 15 minutes in 60 patients with no SAEs of hypersensitivity is supportive of infusion as a mode of administration (Auerbach 2013). In addition the MAH provided exploratory PK simulations which evaluated the effect of decreasing the rate of infusion on Cmax and AUC. Simulations were performed using previously published ferumoxytol plasma PK parameters for a two-compartment open model with zero-order input and Michaelis-Mentel elimination (Pai et al. 2010). These simulations indicate that the newly proposed 15 minutes infusion duration would result in a minimal decrease in Cmax and AUC compared to a 1 minute infusion when the whole 510 mg is infused. In conclusion, these PK simulations support that the efficacy of ferumoxytol would most likely remain unchanged if the entire dose is administered as a bolus or over 15 minutes. A 15 minutes infusion would also allow the possibility to interrupt the dose if hypersensitivity occurred.

The MAH also proposed a strengthened clinical monitoring of patients (blood pressure and pulse monitoring during and after the administration) which is anticipated to contribute to mitigate the risk of hypersensitivity reactions.

Other possible risk minimisation measures were discussed by the MAH as part of their responses to the request for supplementary information and at the second Oral Explanation at the PRAC. These consist of more stringent monitoring in the clinical setting, proposal for additional studies, strengthening of the risk minimisation measures, implementation of educational material, and cumulative three monthly reporting.

The MAH provided an update on the status of the *"Feasibility Assessment of European Population Databases to Estimate the Risk of Severe Hypersensitivity Reactions among Users of Intravenous Iron Compounds"* (the PASS requested as part of the outcome of the article 31 referral procedure on intravenous iron containing products).The MAH also proposed to submit 3 monthly cumulative reviews on hypersensitivity reactions.

The MAH was also requested to investigate further measures, such as a study on the possible mechanism [IgE or non-IgE mediated] to elucidate the nature of anaphylactic/anaphylactoid reactions. Ongoing studies in the extended indication of all cause IDA discussed within the US which include hypersensitivity as a primary endpoint could add to the current information and the MAH proposed to submit these data when available.

The MAH also proposed new educational materials for patients, physicians and other healthcare professionals and to circulate a DHPC.

The PRAC agreed to contraindicate ferumoxyol in patients with any known history of drug allergy considering that in numerous reported cases patients had a history of allergic reactions. The PRAC also recommended updating the product information by removing the intravenous injection at a rate of 1 ml/sec (30 mg/sec) and introducing a 15 minutes infusion as the only recommended method of administration in order to mitigate the risk of hypersensitivity reactions as proposed by the MAH and based on the data provided by the MAH as described above. In addition the PRAC agreed, as proposed by the MAH, to include a warning in the product information that patients should be carefully monitored for signs and symptoms of hypersensitivity reactions including monitoring of blood pressure and pulse during and 30 minutes at least after administration to further mitigate the risk of hypersensitivity reactions. In addition, patients should be in a reclining or semi/reclining position during and after administration. Finally a statement that fatal and life-threatening hypersensitivity reactions have been observed post-marketing with ferumoxytol was also included in the product information.

The PRAC recommended that the prescribers are informed of the above changes to the product information implemented as part of this PSUR procedure via a Dear Healthcare Professional Communication (DHPC).

In line with the outcome of the Article 31 referral on IV iron containing medicinal products which concluded in June 2013 (CD issued in September 2013), the PRAC agreed to include as a condition to the Marketing Authorisation for Rienso that the MAH should conduct a Post Authorisation Safety Study (PASS) to further characterise the safety concerns on the hypersensitivity reactions.

Furthermore the PRAC recommended that the MAH further investigates the risk of hypersensitivity reactions with ferumoxytol by conducting additional studies. The MAH should provide within the next PSUR a proposal of study (draft protocol) to investigate the mechanism of hypersensitivity with ferumoxytol and a synopsis for an adequately powered study to further investigate the risk of hypersensitivity in EU CKD patients comparing ferumoxytol with iron sucrose.

In addition, the MAH should submit with each 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.

The MAH should also provide within the next PSUR 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.

Finally, the risk management plan (RMP) should be revised accordingly with the next PSUR and should also include a proposal of key elements for educational material for healthcare professionals and patients highlighting the risks and warnings on hypersensitivity reactions.

The baseline efficacy and benefit of ferumoxytol in the authorised indication (CKD-IDA) has not changed during this reporting period. However, the high rate of fatal outcomes due to hypersensitivity/allergic reactions after ferumoxytol usage is a point of concern that warrants the additional measures requested by the PRAC.

Based on the PRAC review of data on safety and efficacy, the changes to the product information and to the conditions of the Marketing Authorisation, the additional risk minimisation measures and undertaking to be provided by the MAH within the next PSUR as outlined above, the PRAC considers that the risk-benefit balance of ferumoxytol remains positive.

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

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) and 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.

Further to the 22 fatal hypersensitivity cases, 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, nonfatal 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 (of a total of 218), 59 were noted to have no known allergies, 2 had non drug allergies, and allergy information was unknown in 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.

3. Final Recommendations

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, 6.3, 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 amendments recommended to be introduced to the product information and conditions to the marketing authorisation are detailed in Annex 1.

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 infomation 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.

- Besides, 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).

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.

5. Annex 1: Recommended changes to the Product Information

RECOMMENDED CHANGES TO THE PRODUCT INFORMATION

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

Summary of Product Characteristics

- Section 1. Name of the medicinal product

Rienso 30 mg/ml solution for infusion~~injection~~

- Section 3. Pharmaceutical form

Solution for infusion~~injection. {Injection}~~

- Section 4.2 Posology and method of administration

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 (see section 4.4).
~~Monitor carefully patients for signs and symptoms of hypersensitivity reactions during and following each administration of Rienso.~~
~~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. The patient should be observed for adverse effects for at least 30 minutes following each Rienso injection (see section 4.4).~~

Posology

Treatment Course

The recommended course of Rienso is based on the patient's pre-treatment haemoglobin and body weight as provided in Table 1.

Each 510 mg dose is administered as an intravenous infusion for at least 15 minutes~~injection~~. For patients receiving two doses, the second 510 mg infusion~~intravenous injection~~ is to be administered 2 to 8 days later as per Table1.

Method of administration

Intravenous use by infusion.

Rienso should be administered as an infusion in 50-250 ml of 0.9% sodium chloride or 5% dextrose water for at least 15 minutes (see section 6.6).
~~Rienso is administered as an undiluted intravenous injection delivered at a rate of up to 1 ml/sec (30 mg/sec) resulting in at least 17 seconds for one vial.~~

~~Follow the administration with a slow flush of sodium chloride 9 mg/ml (0.9%) solution for injection to clear the line.~~

- Section 4.3 Contraindication

The use of Rienso is contraindicated in cases of:
- Hypersensitivity to the active substance, to Rienso or any of its excipients listed in section 6.1
- Patients with any known history of drug allergy including ~~Known serious~~ hypersensitivity to other parenteral iron products

- Section 4.4 Special warmings and precaustions for use

Hypersensitivity Reactions

[…]

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).

[…]

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. ~~Each patient should be observed for adverse effects for at least 30 minutes following each Rienso injection.~~ 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~~In the post-marketing experience with Rienso,~~ anaphylactic type reactions presenting with cardiac arrest/ cardiorespiratory arrest, clinically significant hypotension, syncope, and unresponsiveness ~~have been reported~~ (see section 4.8).

~~In patients with multiple substance allergies, the need for Rienso or alternative treatment options should be carefully considered.~~

- Section 4.8 Undesirable effects

Table 2: Adverse reactions observed during clinical studies and post-marketing experience

SYSTEM ORGAN CLASS	**COMMON (≥ 1/100 to < 1/10)**	**UNCOMMON (≥ 1/1,000 to < 1/100)**	**RARE (≥ 1/10,000 to < 1/1,000)**	**FREQUENCY NOT KNOWN (CANNOT BE ESTIMATED FROM AVAILABLE DATA)**
Blood and lymphatic system disorders			Eosinophilia	
Immune system disorders		Hypersensitivity including anaphylaxis*		Life-threatening Anaphylactic/Anaphylactoid reactions*

[…]

In clinical trials, adverse reactions leading to treatment discontinuation and occurring in ≥ 2 Rienso-treated patients included hypotension, infusion site swelling, increased serum ferritin levels, chest pain, diarrhoea, dizziness, ecchymosis, pruritis, chronic renal failure and urticaria.

*Fatal and life-threatening hypersensitivity reactions have been observed with Rienso in the post marketing setting (see sections 4.3 and 4.4).

- Section 6.4 Special precautions for storage

Rienso must only be mixed with sterile 0.9% m/V sodium chloride or sterile 5% dextrose water at concentration of 2-8 mg elemental iron per ml.

No other intravenous dilution solutions and therapeutic agents should be used. For dilution instructions, please see section 4.2.

- Section 6.6 Special precautions for disposal and other handling

Rienso Administration
The vials are for single use only.
The vials should be inspected visually to ensure the absence of particulate matter and damage prior to administration.

Rienso should be administered as an intravenous infusion~~injection~~ into a new or existing venous access site.

[…]

For all patients:
- Administer Rienso as an infusion as follows:
  - 510 mg (one vial) diluted in 50-250 ml of 0.9% sodium chloride or 5% dextrose water, administered for at least 15 minutes (concentration of 2-8 mg elemental iron per ml).
- 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 reclined or semi-reclined position during infusion and for at least 30 minutes thereafter.
- Administer a single vial as an infusion. A second vial of the medicine should be administered as an infusion two to eight days later if indicated
- Any unused product or waste material should be disposed of in accordance with local requirements.

~~Haemodialysis and Non-dialysis Patients:~~
- ~~Draw 17 ml of Rienso into a sterile syringe.~~
- ~~Administer Rienso as an intravenous injection of 17 ml at a rate not to exceed 1 ml/second (resulting in at least 17 seconds for one vial).~~
- ~~Monitor patients for signs and symptoms of hypotension and/or hypersensitivity for at least 30 minutes following each Rienso injection.~~
- ~~Follow the administration with a slow flush of sodium chloride 9 mg/ml (0.9%) solution for injection to clear the line.~~
- ~~Administer a single dose only. The second dose of the medicine should be administered in the same way two to eight days later.~~
- ~~Any unused product or waste material should be disposed of in accordance with local requirements.~~

Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton Label (1, 2, 6 or 10 vial pack)

1. NAME OF THE MEDICINAL PRODUCT

Rienso 30 mg/ml solution for infusion~~injection~~

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion~~injection~~

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial Label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Rienso 30 mg/ml infusion~~injection~~
Iron as ferumoxytol
For intravenous use only

Package Leaflet

- Section 1. What Rienso is and what it is used for

Rienso is an iron preparation, containing the active substance ferumoxytol, which is given by ~~injection~~infusion into a vein. It is used to treat iron deficiency anaemia resulting from a lack of stored iron, in adult patients with reduced kidney function.

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

You must not receive Rienso:
- if you are allergic (hypersensitive) to the product or any of the other ingredients of this medicine (listed in section 6).
- if you have a history of medicine allergy or ~~if you~~ have experienced serious allergic (hypersensitive) reactions to other injectable iron preparations .
- if you have iron overload (too much iron in your body).
- if your anaemia is not caused by iron deficiency.

- Section 3. How Rienso is given

Your doctor will decide how much Rienso to give you based on your weight and blood test results. The treatment you will receive can be 1 or 2 vials of Rienso (510 mg each) by infusion~~,~~ and each dose will be infused~~injected directly~~ into a~~the~~ vein. For patients receiving two vials, the second one will be infused~~given~~ two to eight days after the first infusion~~dose~~. Your doctor will decide if additional doses of Rienso are needed and for how long. He or she will also monitor your blood test results to avoid iron accumulation.

Your doctor or nurse will administer Rienso by infusion~~injection~~ into a vein. You will be lying down and your blood pressure and pulse will be monitored. Rienso will be administered in an environment where any allergic event can receive appropriate and prompt treatment.

You will be carefully observed during the infusion and for at least 30 minutes after each infusion~~administration~~ by your doctor or nurse. Please immediately tell the doctor or nurse if you start to feel unwell. They may decide to stop the infusion.

If you are on haemodialysis, you may receive Rienso via infusion over 15 minutes during a dialysis session.

If you receive more Rienso than you should

Overdose can cause accumulation of iron in your body~~storage sites~~. Your doctor will monitor iron levels to avoid iron accumulation.

- Section 4. Possible side effects

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, ~~and~~ difficulty breathing, ~~or~~ 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 ~~and~~ can be associated with heart and circulation complications, ~~and~~ loss of consciousness and may result in death.

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

Other side effects that you should tell your doctor, pharmacist or nurse about if they become serious:

Common side effects (may affect up to 1 in 10 people):

- bleeding, swelling, bruising, pain, rash, irritation or warmth at infusion/injection site

Side effects of unknown frequency (frequency cannot be estimated from the available data)
The following serious side effects have been reported shortly after receiving Rienso:

- life-threatening and fatal allergic reactions (anaphylactic/anaphylactoid hypersensitivity)

- Section 6. Content of the pack and other information

What Rienso contains

- The active substance is iron as ferumoxytol 30 mg/ml.
- 1 ml solution for infusion~~injection~~ contains 30 mg of iron as ferumoxytol.
- 17 ml solution for infusion~~injection~~ contains 510 mg of iron as ferumoxytol.

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 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 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, 10 July 2014

PRAC Members expressing a divergent position:

Carmela Macchiarulo	10 July 2014	Signature: ……..
Dolores Montero Corominas	10 July 2014	Signature: ……..
Eva Jirsova	10 July 2014	Signature: ……..
Isabelle Robine	10 July 2014	Signature: ……..
Jean-Michel Dogne	10 July 2014	Signature: ……..
Martin Huber	10 July 2014	Signature: ……..
Milena Radoha-Bergoc	10 July 2014	Signature: ……..
J. Neuhauser	10 July 2014	Signature: ……..
Roxana Stefania Stroe	10 July 2014	Signature: ……..
Tatiana Magalova	10 July 2014	Signature: ……..
Viola Macolic Sarinic	10 July 2014	Signature: ……..