ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Rienso 30 mg/ml solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 30 mg of iron as ferumoxytol.
Each vial of 17 ml solution contains 510 mg of iron as ferumoxytol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
Black to reddish brown solution
Osmolality: 270-330 mosm/kg
pH: 6.5 to 8.0

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rienso is indicated for the intravenous treatment of iron deficiency anaemia in adult patients with chronic kidney disease (CKD).

The diagnosis of iron deficiency must be based on appropriate laboratory tests (see section 4.2).

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).

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. For patients receiving two doses, the second 510 mg infusion is to be administered 2 to 8 days later as per Table1.

Table 1: Recommended Dosing Table for Rienso Administration

	Total Amount of Rienso to Administer mg of Iron (Number of vials)	
Haemoglobin	**≤ 50 kg Body Weight**	**> 50 kg Body Weight**
> 10-12 g/dl	510 mg iron (1 vial)	2 × 510 mg iron (2 vials)
≤ 10 g/dl	2 × 510 mg iron (2 vials)	2 × 510 mg iron (2 vials)

The maximum dose is 1020 mg (2 vials) and the two doses of Rienso must not be administered at the same time.

Rienso should not be given to patients if their haemoglobin is greater than 12 g/dl, serum Transferrin Saturation (TSAT) is greater than 50% or Ferritin is greater than 800 ng/ml (see section 4.4).

Patients should be re-assessed at least one month after the completion of a course of Rienso and this should include laboratory testing of haematologic and blood iron parameters.

Re-treatment

To maintain the target haemoglobin value, re-treatment with Rienso may be given after the patient has been re-assessed and confirmed to be iron deficient. For maintenance therapy and patient monitoring, the recommendations of current guidelines (e.g. Revised European Best Practice Guidelines) should be followed.

Paediatric population

The safety and efficacy of Rienso in children and adolescents below the age of 18 years has not been established. No data are available. Therefore Rienso should not be administered to children and adolescents below the age of 18 years (see section 5.1).

Special population – patients receiving haemodialysis

For patients receiving haemodialysis, Rienso should be administered once the blood pressure is stable and the patient has completed at least one hour of haemodialysis.

Hepatic Impairment

Rienso has not been specifically studied in patients with hepatic impairment; clinical experience is limited to 8 patients. In patients with liver dysfunction, parenteral iron should only be administered after careful risk/benefit assessment. No change in dosage is recommended from Table 1.

Method of administration

Intravenous use by infusion.

Rienso should be administered as an infusion in 50-250 ml of sterile 0.9% sodium chloride or sterile 5% glucose for at least 15 minutes (see sections 6.3 and 6.6).

4.3 Contraindications

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 hypersensitivity to other parenteral iron products
- Evidence of iron overload

- Anaemia not caused by iron deficiency

4.4 Special warnings and precautions for use

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.

Hypotension
Severe adverse reactions of clinically significant hypotension have been reported. Hypotension may follow Rienso administration with or without accompanying signs of hypersensitivity (see section 4.8).

Patients should be monitored for signs and symptoms of hypotension following each Rienso administration.

Iron Overload
Rienso should not be administered to patients with iron overload. Rienso must not be given to patients if their haemoglobin is greater than 12 g/dl, serum Transferrin Saturation (TSAT) is greater than 50% or ferritin is greater than 800 ng/ml (see section 4.2).

Immunologic Disease or Infection
Parenteral iron should be used with caution in cases of immunologic disease or acute or chronic infection. It is not recommended to administer Rienso to patients with ongoing bacteraemia.

Re-treatment / Long term use
Limited clinical study data is available regarding re-treatment with Rienso and no clinical study data is available for repeated long term use. For information on post-marketing experience see section 5.1.

Ethanol and sodium content
This medicinal product contains small amounts of ethanol (alcohol), less than 100 mg per 17 ml vial.
This medicinal product contains less than 23 mg sodium per 17 ml vial, i.e., is essentially "sodium free".

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 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.

Interference with Serological Testing
In the 24 hours following administration of Rienso, laboratory assays may overestimate serum iron and transferrin bound iron by also measuring the iron in the Rienso complex.

4.5 Interaction with other medicinal products and other forms of interaction

No drug-drug interaction studies have been performed. As with all parenteral iron preparations the absorption of oral iron is reduced when administered concomitantly.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential and pregnancy

There are no adequate and well-controlled trials of Rienso in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). A careful risk/benefit evaluation is therefore required before use during pregnancy and Rienso should not be used during pregnancy unless clearly necessary (see section 4.4).

Iron deficiency anaemia occurring in the first trimester of pregnancy can in many cases be treated with oral iron. Treatment with Rienso should be confined to second and third trimester if the benefit is judged to outweigh the potential risk for both the mother and the foetus.

Rienso is not recommended in women of childbearing potential not using adequate contraception.

Breastfeeding

It is unknown whether Rienso is excreted in human milk. Available pharmacokinetic data in animals have shown excretion of Rienso in milk (see section 5.3).

A risk to breastfeeding newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue Rienso therapy, taking into account the benefit of breast-feeding for the child and the benefit of the therapy for the mother.

Fertility

No adverse effects on fertility or general reproductive performance were noted in adult rats (see Section 5.3). In a prenatal and postnatal developmental study in rats adverse effects on sexual maturation and on the ability to produce a litter were noted in the F1-generation (see section 5.3).

4.7 Effects on ability to drive and use machines

Rienso may have a minor influence on the ability to drive and use machines. In the case of symptoms of dizziness, confusion or light headedness following the administration of Rienso, patients should not drive or use machinery until the symptoms have ceased.

No studies regarding effects on the ability to drive or operate machines have been performed.

4.8 Undesirable effects

Summary of the safety profile

In clinical trials involving 1562 subjects with CKD, adverse reactions were seen in 7.9% of patients who received Rienso, of which 0.2% were considered serious.

The most frequently reported adverse reactions were gastrointestinal symptoms (diarrhoea, constipation, nausea and vomiting), headache, dizziness and hypotension, all occurring in less than 2.5% of patients. Serious hypersensitivity or hypotensive reactions are uncommon (less than 1 case per 100 patients) and were reported in 0.2% (3/1562) of subjects with CKD who received Rienso during the clinical studies. One of these three cases was also characterized as an anaphylactoid reaction.

Tabulated list of adverse reactions

Table 2 presents all adverse experiences observed during the clinical studies in which 1562 subjects with CKD received two injections of 510 mg of Rienso separated by an interval of 2 to 8 days and post-marketing experience.

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*
Metabolism and nutrition disorders		Decreased appetite Increased appetite	Dehydration Gout Hyperkalaemia	
Nervous system disorders		Dizziness Dysgeusia Headache Somnolence Burning sensation	Paraesthesia	Syncope Unresponsiveness Loss of consciousness

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)
Eye disorders			Lacrimation increased Vision blurred	
Cardiac disorders				Tachycardia/Arrhythmia, Cardiac arrest Cardio-respiratory arrest Myocardial infarction Cyanosis Congestive heart failure
Vascular disorders		Hypotension (hypotension, blood pressure decreased) Flushing (flushing, hot flush) Hypertension (hypertension, accelerated hypertension)		Vasodilation
Respiratory, thoracic and mediastinal disorders		Dyspnoea	Epistaxis	Bronchospasm Cough Hyperventilation Hypoxia Laryngeal oedema Pharyngeal oedema Respiratory arrest Respiratory failure Throat irritation Throat tightness Wheezing
Gastrointestinal disorders		Diarrhoea Constipation Nausea Abdominal pain (Abdominal distension, abdominal pain upper, abdominal discomfort) Vomiting Faeces discoloured	Dry mouth Dyspepsia Glossodynia	Lip swelling Swollen tongue
Hepatobiliary disorders			Hepatic function abnormal	

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)
Skin & subcutaneous tissue disorders		Rash (rash, rash generalised, rash pruritic, urticaria) Pruritus (pruritus generalised) Ecchymosis Sweating (hyperhidrosis, night sweats) Skin hyperpigmentation Skin reaction		Angioedema
Musculoskeletal and connective tissue disorders		Muscle/joint pain or stiffness (arthralgia, myalgia, muscular weakness, musculoskeletal stiffness) Back pain Muscle spasms		
General disorders and administration site conditions	Injection site reactions (infusion/injection site bruising, pain, reaction, swelling, warmth, haemorrhage, irritation, rash)	Fatigue (asthenia, fatigue) Chest pain (chest discomfort, chest pain) Chills Fever (feeling hot, pyrexia)		Injection site discolouration Injection site pruritus
Investigations		Serum ferritin increased	Blood glucose decreased	Pulse absent Oxygen saturation decreased
Injury, poisoning and procedural complications		Contusion		

Description of selected adverse 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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions is an important way to gather more information to continuously monitor the benefit/risk balance of the medicinal product. Any suspected adverse reactions should be reported via the national reporting system listed in Appendix V.

4.9 Overdose

No data from clinical trials are available regarding overdose of Rienso in humans. During the post-marketing phase, several patients received an overdose of Rienso ranging from 1 g in 1 day to 2.5 g over 21 days. Only one case of minor rash was observed. Excessive administration of Rienso may lead to accumulation of iron in storage sites potentially leading to haemosiderosis.

Periodic monitoring of laboratory parameters of iron storage, such as serum ferritin and transferrin saturation, enables recognition of iron accumulation. However, caution should be exercised in interpreting serum iron levels in the 24 hours following administration of Rienso as laboratory assays may overestimate serum iron and transferrin bound iron by also measuring the iron in Rienso. Please see the iron overload section 4.4 and for dosing guidance, see section 4.2.

Overdose should be treated, if required, with an iron chelating agent.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Not yet assigned, ATC code: Not yet assigned

Mechanism of Action

Rienso is a colloidal iron-carbohydrate complex. It includes iron oxide particles with an iron oxide core surrounded by a polyglucose sorbitol-carboxymethylether shell. The shell isolates the bioactive iron from plasma components until the iron-carbohydrate complex enter reticuloendothelial system macrophages of the liver, spleen and bone marrow. The iron is then released intracellularly from the iron-carbohydrate complex within vesicles in macrophages. Iron then either enters the intracellular storage iron pool (e.g., ferritin) or is transferred to plasma transferrin for transport to erythroid precursor cells for incorporation into haemoglobin.

Clinical Efficacy and Safety

The safety and efficacy of Rienso (cumulative dose of 1.02 grams) for the treatment of iron deficiency in CKD patients with IDA were assessed in three randomized, open-label, controlled clinical studies (Studies 1, 2 and 3). The principal efficacy results at Day 35 from the controlled phase of each study are shown in Table 3. This includes the Baseline and mean change to Day 35 in haemoglobin (Hgb, g/dl), transferrin saturation (TSAT, %) and ferritin (ng/ml) as well as the proportion of subjects who were Hgb Responders at Day 35 (defined as proportion of subjects with an increase in Hgb of at least 1.0 g/dl) in each treatment group for Studies 1, 2, and 3.

Table 3: Summary of Efficacy Endpoints at Day 35 (Intent to Treat Population)

Endpoint	Study 1 Non-dialysis CKD		Study 2 Non-dialysis CKD		Study 3 CKD on Haemodialysis	
	Rienso n = 226	Oral Iron n = 77	Rienso n = 228	Oral Iron n = 76	Rienso n = 114	Oral Iron n = 116
Baseline Hgb (mean ± SD, g/dl)	**9.9** ± 0.8	**9.9** ± 0.7	**10.0** ± 0.7	**10.0** ± 0.8	**10.6** ± 0.7	**10.7** ± 0.6
Hgb change from Baseline at Day 35 (mean ± SD, g/dl)	**1.2*** ± 1.3	**0.5** ± 1.0	**0.8*** ± 1.2	**0.2** ± 1.0	**1.0*** ± 1.1	**0.5** ± 1.1
Proportion of Hgb Responders (%)	**51.8**	**19.5**	**39.0**	**18.4**	**49.1**	**25.0**
Baseline TSAT (mean ± SD, %)	**9.8** ± 5.4	**10.4** ± 5.2	**11.3** ± 6.1	**10.1** ± 5.5	**15.7** ± 7.2	**15.9** ± 6.3
TSAT change from Baseline at Day 35 (mean ± SD, %)	**9.2** ± 9.4	**0.3** ± 4.7	**9.8** ± 9.2	**1.3** ± 6.4	**6.4** ± 12.6	**0.6** ± 8.3
Baseline ferritin (mean ± SD, ng/ml)	**123.7** ± 125.4	**146.2** ± 136.3	**146.1** ± 173.6	**143.5** ± 144.9	**340.5** ± 159.1	**357.6** ± 171.7
Ferritin change from Baseline at Day 35 (mean ± SD, ng/ml)	**300.7** ± 214.9	**0.3** ± 82.0	**381.7** ± 278.6	**6.9** ± 60.1	**233.9** ± 207.0	**-59.2** ± 106.2

* $p \leq 0.001$ for main efficacy endpoint
Hgb = haemoglobin; TSAT = transferrin saturation; SD = standard deviation

In all three studies, patients with CKD and iron deficiency anaemia were randomized to treatment with Rienso or oral iron. Rienso was administered as two 510 mg intravenous injections (separated by 2 to 8 days) and oral iron (ferrous fumarate) was administered at a total daily dose of 200 mg elemental iron for 21 days. The major study outcomes assessed the change in haemoglobin from Baseline to Day 35. Studies 1 and 2 enrolled patients with non-dialysis dependent CKD and Study 3 enrolled patients who were undergoing haemodialysis.

In Study 1, the mean age of patients was 66 years (range, 23 to 95); 60% were female; 65% were Caucasian, 32% were Black, and 2% were other races. In the Rienso and oral iron groups, 42% and 44% of patients, respectively, were receiving erythropoiesis stimulating agents (ESAs) at Baseline.

In Study 2, the mean age of patients was 65 years (range, 31 to 96); 61% were female; 58% were Caucasian, 35% were Black, and 7% were other races. In the Rienso and oral iron groups, 36% and 43% of patients, respectively, were receiving ESAs at Baseline.

In Study 3, the mean age of patients was 60 years (range, 24 to 87); 43% were female; 34% were Caucasian, 59% were Black, and 7% were other races. All patients were receiving ESAs at Baseline.

Following completion of the controlled phase of each of the Phase 3 trials, patients who were iron deficient and anaemic could be optionally retreated and receive two additional 510 mg intravenous injections of Rienso for a total cumulative dose of 2.04 g. Overall, 69 patients received a total cumulative dose of 2.04 g. Adverse reactions following this repeat Rienso dosing were similar in character and frequency to those observed following the first two intravenous injections.

In a placebo-controlled, cross-over trial, 713 patients with CKD received a single 510 mg dose of Rienso and placebo. Adverse reactions reported in these patients were similar in character and frequency to those observed in the other clinical trials.

Post-Marketing Data from Dialysis Clinics in the United States

Retrospective observational data from three large haemodialysis clinics in the US over a 1 year period included the treatment of over 8,600 patients with more than 33,300 administered doses of Rienso; nearly 50% of patients received repeat dosing with 4 or more doses. Mean haemoglobin increased (0.5-0.9 g/dl) post-treatment and stabilised in the range of 11-11.7 g/dl over the 10 month post-dose period; no new safety signals were identified with repeat dosing.

Paediatric Population

The European Medicines Agency has deferred the obligation to submit the results of studies with Rienso in one or more subsets of the paediatric population in the treatment of iron deficiency anaemia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic Properties

The pharmacokinetic (PK) behaviour of Rienso has been examined in healthy subjects and in patients with CKD stage 5D on haemodialysis. Rienso exhibited dose-dependent, capacity-limited elimination from plasma with a half life of approximately 16 hours in humans. The clearance (CL) was decreased with increased doses of Rienso. Volume of distribution (Vd) was consistent with plasma volume, and the mean maximum observed plasma concentration (C_{max}) and terminal half-life ($t_{1/2}$) values increased with dose. The estimated values of CL and Vd following two 510 mg doses of Rienso administered intravenously within 24 hours were 69.1 ml/hr and 3.3 l, respectively. The C_{max} and time of maximum concentration (t_{max}) were 206 mcg/ml and 0.32 hr, respectively. Rate of infusion had no influence on Rienso PK parameters. No gender differences in Rienso PK parameters were observed. Rienso is not removed by haemodialysis.

5.3 Preclinical Safety Data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, local tolerance and immunotoxicity. In a 4 week repeated dose toxicity study in rats after a recovery of 26 weeks hepatic changes (focal or multifocal haemorrhage, hemorrhagic necrosis, chronic inflammation, and/or bile duct hyperplasia) were seen in the female animals (the cumulative HED of the dose groups compares to a safety multiple of 5.1 and 10.5 to the cumulative human therapeutic dose (2 x 510 mg Fe) in a 60 kg human). Such effects were not seen in the male animals of that study or in the 13 weeks repeated dose toxicity study in rats (without recovery). As seen from clinical data there is no evidence that these effects seen in female rats are relevant for humans.

No carcinogenicity studies were performed with Rienso.

No adverse effects on fertility or general reproductive performance were noted in rats given IV Rienso at doses up to 18 mg Fe/kg/day (Human Equivalent Dose of 2.9 mg Fe/kg/day).

Administration of Rienso during organogenesis in rats at maternally toxic doses of 100 mg Fe/kg/day caused a decrease in foetal weights.

In rabbits administration of Rienso during organogenesis induced decreased foetal weights and external and/or soft tissue malformations (malrotated or flexed fore- and malrotated hindlimbs, internal hydrocephaly, absent brains, cleft palate and microglossia) at the high dose of 45.3 mg Fe/kg/day (HED of 14.6 mg Fe/kg/day), a dose which induced only minimal maternal toxicity.

In a pre-natal and post-natal development study in rats sexual maturation was delayed in male pups in the high dose of 60 mg Fe/kg/day (HED of 9.7 mg Fe/kg/day). In female pups of the mid and high dose groups of 30 mg Fe/kg/day and 60 mg Fe/kg/day respectively (HED of 4.8 mg Fe/kg/day and

9.7 mg Fe/kg/day, respectively) sexual maturation was delayed and a disruption of the oestrus cycle was noted in some females. The ability to produce a litter (reproductive competence) was reduced in high dose males and in mid and high dose females, irrespective of whether F1 males were mated with F1 females or F1 males were mated with naive females and vice versa.

In a lactation study in rats, there was minimal excretion of Rienso or Rienso-derived radioactivity into milk following single IV administration of approximately 100 mg Fe/kg (HED of 16.1 mg Fe/kg, approximately 2 times the recommended 510 mg human dose on a mg/m^2 basis) of either the unlabelled, ^{59}Fe or ^{14}C-labelled product to lactating rats 10-11 days post-parturition, which peaked at 8 to 24 hours post-administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polyglucose-sorbitol carboxymethylether (PSC)
Mannitol
Water for Injections
Sodium hydroxide (for pH adjustment)
Hydrocholric acid (for pH adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products, except those mentioned in section 6.6.

6.3 Shelf life

48 months

Shelf-life after first opening and after dilution for infusion:
Chemical and physical in-use stability has been demonstrated for 96 hours at 25 °C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not be longer than 4 hours at 25 °C.

6.4 Special precautions for storage

Rienso must only be mixed with sterile sodium chloride 9 mg/ml (0.9%) or sterile 5% glucose up to a final concentration of 2-8 mg iron per ml.

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

Store in the original package in order to protect from light.
Do not freeze.

6.5 Nature and contents of container

17 ml of solution in a vial (type I glass) with a stopper (chlorobutyl rubber) and an aluminium crimp-on seal.

Available in packs sizes of 1, 2, 6 or 10 vials.

Not all pack sizes may be marketed.

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 into a new or existing venous access site.

Administration should be performed as follows:

Haemodialysis patients:
Dosing should begin when blood pressure is stable and the patient has completed at least one hour of haemodialysis.

For all patients:

- Administer Rienso as an infusion as follows:
    - 510 mg (one vial) diluted in 50-250 ml of sterile 0.9% sodium chloride or sterile 5% glucose, administered for at least 15 minutes (concentration of 2-8 mg 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 reclining or semi-reclining 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.

7. MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Dybendal Alle 10
2630 Taastrup
Denmark
P: +45 4677 1111
F: +45 4675 6640

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/774/001
EU/1/12/774/002
EU/1/12/774/003
EU/1/12/774/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 June 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release
Takeda Italia S.p.A.
Via Crosa 86
28065 Cerano (NO)
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product 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.

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

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **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-reclined 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 MAH shall complete, within the stated timeframe, the below measures:

Condition	**Date**
The MAH 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 RMP submission. Final study report by:	31 July 2016
The MAH 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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. 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
Iron as ferumoxytol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 30 mg of iron.
510 mg iron/17 ml

3. LIST OF EXCIPIENTS

Excipients:
Polyglucose-sorbitol carboxymethylether (PSC)
Mannitol
Water for injections
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
1 vial
2 vials
6 vials
10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Dybendal Alle 10
2630 Taastrup
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/774/001
EU/1/12/774/002
EU/1/12/774/003
EU/1/12/774/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille is accepted

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
Iron as ferumoxytol
For intravenous use only

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

510 mg/17 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Rienso 30 mg/ml solution for infusion
Iron as ferumoxytol

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rienso is and what it is used for

Rienso is an iron preparation, containing the active substance ferumoxytol, which is given by 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.

Iron is an essential element required to make haemoglobin, a molecule in red blood cells that enables oxygen to be carried around the body. When there is insufficient iron in the body, haemoglobin cannot be formed, resulting in anaemia (low levels of haemoglobin).

The aim of Rienso therapy is to replenish the body's iron stores.

2. What you need to know before you receive Rienso

Before you were prescribed Rienso, the doctor will have carried out a blood test to make sure that you have iron deficiency anaemia.

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 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.

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), 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 is subsequently arranged.

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

Children and adolescents
Rienso should not be given to children and adolescents under 18 years old.

Other medicines and Rienso
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

Pregnancy
Rienso has not been tested in pregnant women. Studies in animals have shown reproductive toxicity.
If you are pregnant, you should not receive Rienso.
It is important to tell your doctor if you are pregnant, think you may be pregnant, or are planning to have a baby.
If you are able to become pregnant, you must use birth control during treatment.
If you become pregnant during treatment, you must ask your doctor for advice.
Your doctor will decide whether or not you should be given this medicine.

Breast-feeding
It is not known whether the active substance in this medicine can pass into breast milk. If you are breast-feeding, ask your doctor for advice before you are given Rienso.

Driving and using machines
Some people may feel dizzy, confused or lightheaded after receiving treatment. If this happens to you, do not drive or use any tools or machinery.

Rienso contains ethanol and sodium
This medicine contains small amounts of ethanol (alcohol), less than 100 mg per 17 ml vial.
This medicine contains less than 23 mg sodium per 17 ml vial, i.e., it is essentially “sodium free”.

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 into a vein. For patients receiving two vials, the second one will be infused two to eight days after the first infusion. 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 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 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. Your doctor will monitor iron levels to avoid iron accumulation.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

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.

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

Uncommon side effects (may affect up to 1 in 100 people):
- dizziness
- low blood pressure
- feeling weak or tired
- feeling drowsy or sleepy
- flushing, hot flush
- feeling hot, fever
- sweating (including night sweats)
- chills
- high blood pressure (sudden increase in blood pressure)
- skin rash, itching, darkening of an area of skin or nails, bruising, hives
- burning sensation of skin
- shortness of breath
- diarrhoea
- constipation
- stomach pain/discomfort
- stomach distension or bloating
- nausea, vomiting

- discoloured stools
- changes in taste
- increased or decreased appetite
- muscle/joint pain, weakness or stiffness, muscle spasms
- headache
- chest pain/discomfort
- back pain
- changes in blood test results (e.g. iron parameters)
- allergic reaction including severe allergic reaction (see paragraph "serious side effects")

Rare side effects (may affect up to 1 in 1,000 people):
- burning, prickling, numbness or tingling sensation of skin
- dehydration
- upset stomach/indigestion
- nose bleed
- dry mouth
- burning or tingling sensation of tongue/mouth
- increased tearing
- blurred vision
- gout
- abnormal blood tests (decreased glucose, elevated potassium, abnormal liver function, elevated type of white blood cell i.e. eosinophilia)

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)
- cardiovascular complications (affecting the heart and blood vessels) including heart attack, congestive heart failure, palpitations, blood vessel dilation, changes in your pulse rate including weak/absent pulse, heart stops beating, heart and breathing stop, blue discolouration of skin and/or mucous membranes due to lack of oxygen in the blood (cyanosis)
- fainting/loss of consciousness/unresponsiveness
- sudden swelling up of skin or mucous membranes (angioedema), skin rash
- wheezing (bronchospasm), cough, upper airway swelling, difficulty breathing (change to breathing rate), inability to breathe
- throat irritation, throat tightness, lip swelling, tongue swelling
- injection site discolouration, injection site itching and discolouration

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report any side effects directly to the national reporting system via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rienso

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light.

Do not freeze.

Before administration, the vials will be inspected by the person administering the medicine for signs of damage or deterioration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

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 contains 30 mg of iron as ferumoxytol.
- 17 ml solution for infusion contains 510 mg of iron as ferumoxytol.
- The other ingredients are mannitol, Polyglucose-sorbitol carboxymethylether (PSC), Sodium hydroxide (for pH adjustment, Hydrochloric acid (for pH adjustment) and water for injections.

What Rienso looks like and contents of the pack

Rienso is a black to reddish-brown solution for infusion.
Rienso is supplied in glass vials containing 17 ml.
Rienso is available in packs sizes of 1, 2, 6 or 10 vials.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing authorisation holder:
Takeda Pharma A/S
Dybendal Alle 10
2630 Taastrup
Denmark
P: +45 4677 1111
F: +45 4675 6640

Manufacturer:
Takeda Italia S.p.A.
Via Crosa, 86
28065 Cerano (NO)
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Takeda Belgium
Tél/Tel: +32 2 464 06 11
takeda-belgium@takeda.com

България
Такеда България
Тел.: + 359 2 958 27 36; + 359 2 958 15 29

Lietuva
Takeda, UAB
Tel: +370 521 09 070
lt-info@takeda.com

Luxembourg/Luxemburg
Takeda Belgium
Tél./Tel: +32 2 464 06 11
takeda-belgium@takeda.com

Česká republika
Takeda Pharmaceuticals Czech Republic s.r.o.
Tel: +420 234 722 722

Danmark
Takeda Pharma A/S
Tlf: +45 46 77 11 11

Deutschland
Takeda GmbH
Tel: 0800 825 3325
medinfo@takeda.de

Eesti
Takeda Pharma AS
Tel: +372 6177 669

Ελλάδα
ΤΑΚΕDA ΕΛΛΑΣ Α.Ε
Τηλ: +30 210 6729570
gr.info@takeda.com

España
Takeda Farmacéutica España S.A.
Tel: +34 917 14 99 00
spain@takeda.com

France
Takeda France S.A.S
Tél: +33 1 46 25 16 16

Hrvatska
Takeda Pharmaceuticals Croatia d.o.o.
Tel: +385 1 377 88 96

Ireland
Takeda Products Ireland Limited
Tel: +353 (0) 1 6420021

Ísland
Vistor hf.
Sími: +354 535 7000
vistor@vistor.is

Italia
Takeda Italia S.p.A.
Tel: +39 06 502601

Κύπρος
Takeda Pharma A/S
Τηλ: +45 46 77 11 11

Magyarország
Takeda Pharma Kft.
Tel.: +361 2707030

Malta
Takeda Italia S.p.A.
Tel: +39 06 502601

Nederland
Takeda Nederland bv
Tel: +31 23 56 68 777
nl.medical.info@takeda.com

Norge
Takeda Nycomed AS
Tlf: + 47 6676 3030
infonorge@takeda.com

Österreich
Takeda Pharma Ges.m.b.H.
Tel: +43 (0) 800-20 80 50

Polska
Takeda Polska Sp. z o.o.
Tel.: +48 22 608 13 00

Portugal
Takeda - Farmacêuticos Portugal, Lda.
Tel: +351 21 120 1457

România
Takeda Pharmaceuticals SRL
Tel: +40 21 335 03 91

Slovenija
Takeda GmbH, Podružnica Slovenija
Tel: +386 (0) 59 082 480

Slovenská republika
Takeda Pharmaceuticals Slovakia s.r.o.
Tel.: +421 (2) 20 602 600

Suomi/Finland
Oy Leiras Takeda Pharmaceuticals Ab
Puh/Tel: +358 20 746 5000

Sverige
Takeda Pharma AB
Tel: + 46 8 731 28 00
infosweden@takeda.com

Latvija
Takeda Latvia SIA
Tel: +371 67840082

United Kingdom
Takeda UK Ltd
Tel: +44 (0)1628 537 900

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

The following information is intended for healthcare professionals only (see Section 3):

Rienso Administration

Rienso should only be administered when staff trained to evaluate and manage anaphylactic reactions are immediately available. Rienso should be administered as an intravenous infusion into a new or existing venous access site.
Administration should be performed as follows:

Haemodialysis patients:

Dosing should begin when blood pressure is stable and the patient has completed at least one hour of haemodialysis.

For all patients:

- Administer Rienso as an infusion as follows:
  - 510 mg (one vial) diluted in 50-250 ml of sterile 0.9% sodium chloride or sterile 5% glucose, administered for at least 15 minutes (concentration of 2-8 mg 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 reclining or semi-reclining 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 according to the SmPC.
- Any unused product or waste material should be disposed of in accordance with local requirements.

Incompatibilities

- Rienso must not be mixed with other medicinal products, with the exception of the infusion fluids mentioned below.
- Rienso must only be mixed with sterile sodium chloride 9 mg/ml (0.9%) or sterile 5% glucose up to a final concentration of 2-8 mg iron per ml.
- No other intravenous dilution solutions and therapeutic agents should be used.

Overdose

- Overdose should be treated, if required with an iron chelating agent. See SmPC Section 4.9 for further information.

Stability and Storage

- Shelf-Life – 48 months
- Shelf life after first opening and after dilution for infusion:
  Chemical and physical in-use stability has been demonstrated for 96 hours at 25 °C
- From a microbiological point of view, the product should be used immediately after first opening or immediately after dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not be longer than 4 hours at 25°C.
- Store in the original package in order to protect from light. Do not freeze.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS RECOMMENDING THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATIONS

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, due to its unique crystalline structure 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.