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Assessment report for: Iron containing intravenous (IV) medicinal products

Procedure under Article 31 of Directive 2001/83/EC

Procedure number: EMEA/H/A-31/1322

Assessment Report as adopted by CHMP with all the information of a confidential nature deleted.

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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 7 December 2011, France triggered a referral under Article 31 of Directive 2001/83/EC. The CHMP was requested to give its opinion on whether the marketing authorisations for Iron containing intravenous medicinal products and associated names should be maintained, varied, suspended or withdrawn.

The procedure described in Article 32 of Directive 2001/83/EC, was applicable.

2. Scientific discussion

2.1. Introduction

France (ANSM) had concerns with regards to the hypersensitivity reactions of IV iron containing products indicated in iron deficiency situations when the oral route is insufficient or poorly tolerated especially in CKD patients (hemodialysis), but also in pre- or post-operative situations, or in case of intestinal absorption disorders.

In France, this risk was particularly of concern with low molecular-weight iron-dextran (LMWID) containing products, particularly in pregnant women for whom uterine hypertonia was observed. On 7 December 2011 France requested the CHMP under Article 31 of Directive 2001/83/EC to assess the above concerns regarding hypersensitivity and its impact on the benefit-risk balance for iron intravenous containing medicinal products, and to give its opinion on measures necessary to ensure the safe and effective use, and on whether the marketing authorisation for these products should be maintained, varied, suspended or withdrawn. The iron complexes involved in this procedure are iron gluconate (sodium ferric gluconate), iron sucrose, iron dextran, iron (ferric) carboxymaltose, and iron (III) isomaltoside 1000.

Products containing iron gluconate in low concentrations together with metal salts /or complexes for intravenous nutrition were initially identified. During the course of the procedure it was concluded that these products do not fulfil the scope of this referral procedure as their indication is different. Consequently they are not part of the Annex I of the CHMP opinion and the scientific conclusions of this referral are not applicable to these products.

In this CHMP report only a summary of the responses of mainly the innovator companies of these medicinal products is presented, and discussed due to the large amount of data received in the 4 rounds of assessment in this procedure. However, all submitted data have been assessed during the procedure.

During this referral procedure the CHMP requested the MAHs for data regarding preclinical and clinical studies, post-marketing reports and the published literature.

The MAHs were also requested to provide a detailed analysis classified according to Ring and Messmer classification[1] for the purpose of the review of risk of allergic reaction.

[1] Ring, J. and Messmer, K., Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* (1977), 466-469.

Table 1. The Ring and Messmer classification

Grade	Symptoms
I	Skin symptoms and or mild fever reaction
II	Measurable, but not life threatening Cardiovascular reaction (tachycardia, hypotension) Gastrointestinal disturbance (nausea) Respiratory
III	Shock, life threatening spams of smooth muscles (bronchi, uterus)
IV	Cardiac and or respiratory arrest

2.2. Non-clinical aspects

Pre-clinical studies

The safety of iron products is influenced by the stability of the iron complex. In fact, weakly bound iron may dissociate from the complex leading to the generation of reactive oxygen species (Agarwal, *et al* 2004). Furthermore, changes in the iron carbohydrate complex structure could affect the complex stability of IV iron preparation, which determines the extent of induced oxidative stress and tissue damage (MacDougall, 1999). These issues have been also raised by Toblli and colleagues (2006, 2009a and b) with respect to the safety of different iron preparations. An animal study has been conducted to evaluate the toxicological implications for oxidative stress in major tissues.

Iron can act as an oxidant and as such is capable of redox cycling. The impact and mechanism of iron sucrose and other iron preparations on oxidative stress is not very well understood. In literature there are more than 35 non-clinical studies reported on oxidative stress associated with treatment with iron preparations. Given the various experimental approaches to investigate the oxidative potential of the various iron preparations it is difficult to come to a final conclusion. In some publications it was concluded that pro-inflammatory and cytotoxic response to be generated most strongly by iron sucrose and sodium ferric gluconate.

Cytotoxicity of various iron complexes has been documented in the literature. Cytotoxicity is mediated throughout the formation of reactive oxygen species (ROS). This cytotoxicity is proper to any various iron complexes nevertheless the effect is related to the stability of the complex and therefore of the carbohydrate used for the coating.

Iron (III)-hydroxide dextran complex

Only a few preclinical studies with LMWID have been carried out and only studies with safety findings relevant to immunogenicity were referenced. Richter (1971) studied Hapten inhibition of passive systemic and cutaneous antidextran-dextran anaphylaxis by low MW fragments of dextran in guinea

pigs. Dextran fractions of varying MW were first tested for anaphylactogenicity. At different levels of sensitization, the largest dextran fragments with non-elicitor action had a MW of 990-10,500. At each level of sensitization, non-eliciting dextran fractions always exerted protection from anaphylaxis when given together with or prior to the anaphylactogenic dextran fraction upon challenge. When the molar ratio in a mixture of non-anaphylactogenic/anaphylactogenic fractions was about 7.6, protection was complete with reduction of mortality from 100 to 0 %. A molar ratio of 1.9, corresponding to a 13 % by weight admixture of non-anaphylactogenic dextran, still significantly reduced mortality from 100 to 50 % (82). Circulating dextran-reactive antibodies were raised in dogs by immunisation with Edestin-Dextran. A challenge by injection of 1 mL dextran-60 intravenously caused different degrees of dextran-induced ADRs, including anaphylactoid reactions characterised by a decrease in heart minute volume, arterial blood pressure, and in thrombocytes and leucocytes. Pre-injection of oligosaccharide (isomaltoside) significantly reduced the frequency and severity of dextran-induced ADRs.

The MAH's study had highlighted the inhibition of anaphylaxis throughout the use of low MW dextran. However, it is questionable how a parallel can be drawn to the related product since this study did not involve any chelated metal. Moreover, charge distribution over the dextran associated metal is supposed to be different from dextran on its own; therefore reactivity regarding the environment may be more variable and therefore the response given.

Due to the lack of data regarding the product on its own, it is not possible to ascertain a safety assessment on the preclinical data. Although, the non-clinical summary submitted did make a proper retrospective literature review of the iron complexes, cautious should be taken since specificity and formal identification of the product cannot be made.

Iron(III) isomaltoside 1000 complex

Only a few preclinical studies with iron(III) isomaltoside have been carried out. Reference is made to data from studies with other similar oligosaccharide preparations.

Iron gluconate (sodium ferric gluconate)

The MAH presented an overview of the toxicology program performed between 1970's and 1996 to support the registration of sodium ferric gluconate complex. The data do not show a risk of allergic reactions. However, animal data did not give important information regarding the safety of the products for the evaluation of the risk for allergic reactions. The CHMP concurred that evaluation must be based on clinical data.

Ferric Carboxymaltose

Intravenous iron preparations based on dextran or dextran derivatives carry the risk of inducing life-threatening dextran-induced anaphylactic reactions (DIAR). Dextran is composed of α(1→6)-linked polyglucose and is produced by bacteria, e.g. by caries-inducing and intestinal bacteria. Thus, a sensibilisation often results from naturally occurring dextran, and most people have dextran-reactive antibodies.

Immune reactions to dextran may therefore occur at the first clinical administration of dextran-containing products as well as after subsequent doses.

The *in vitro* reactivity of various marketed IV iron preparations towards antidextran antibodies was tested in a reverse single radial immunodiffusion assay. The results showed that the dextran-free preparations (iron sucrose, ferric carboxymaltose, sodium ferric gluconate) do not cross-react with antidextran antibodies. In contrast, the dextran-containing or dextran-based preparations, i.e., low molecular weight iron dextran, ferumoxytol, and iron isomaltoside 1000 reacted with the antibodies, as demonstrated by the formation of a precipitation ring in the assay.

In an animal study in guinea pigs that had been administered immune serum containing antidextran antibodies, a clear skin reaction after the administration of dextran was observed (positive control). However, no skin reactions were seen when ferric carboxymaltose was administered. This nonclinical study concluded that there was no cross-reactivity between ferric carboxymaltose and antidextran antibodies. As part of IV toxicity study over 26 weeks in rats, there was no clinical evidence of a hypersensitivity reaction following a challenge dose after the recovery phase, suggesting that ferric carboxymaltose does not have a sensitising potential.

Based on the specific carbohydrate component of ferric carboxymaltose and its easy degradation, the results of the *in vitro* and *in vivo* cross-reaction studies with antidextran antibodies, the toxicity study over 26 weeks in rats and the experience with other iron complexes containing glucose and gluconate, an immunogenic-allergic potential for ferric carboxymaltose is considered unlikely.

Ferric carboxymaltose does not react with antidextran antibodies. However, the use of antidextran antibodies is questionable since immunogenic response may happen regardless the activation or not of antidextran antibodies.

Regarding the reverse single radial immunodiffusion assay, this technique is known to be not highly sensitive and also this assay relies on aggregate formation and diffusion feasibility. Complex of low molecular weight will be less susceptible to precipitate even though they can respond to antibodies. As previously mentioned, the use of antidextran antibodies is not sufficient since for instance the product may react with other antibodies leading to any immunogenic reaction.

Iron intravenous products are injectable colloidal solutions; it has been shown that colloidal solution may generate complement activation and therefore in a mechanism wide away from the cross-reaction with antidextran antibodies and this point has not been discussed by the MAH.

In this context, the non-clinical data cannot answer to mechanism of the hypersensitivity reactions; therefore the conclusions should mainly rely on the clinical evaluation for the safety issue.

Iron sucrose

Parenterally administered sucrose is excreted unchanged in the urine. In a pharmacokinetics study of iron sucrose it was shown that it is quickly cleared from the serum with a terminal half-life of approximately 5−6 hours. Renal elimination of iron contributed very little to the overall elimination (in average <5%). In contrast, renal elimination of sucrose averaged about 68 ± 10% and 75 ± 11% of the administered dose after 4 and 24 hours, respectively.

In an animal study in guinea pigs that had been administered immune serum containing antidextran antibodies, no cross reactions of iron sucrose to anti-dextran antibodies were observed; however, a clear skin response after the administration of dextran was observed. These preclinical results specify a direct scientific relevance and prove that iron sucrose can be injected safely and without the risk of an anaphylactic reaction to dextran (due to the lack of its immunogenic-allergic potential) in patients who previously experienced an immunogenic-allergic reaction (commonly known as a hypersensitivity reaction) to iron dextran. However clinical data is essential in order to have firm conclusions.

Following the presentation of all the available pre-clinical data, the conclusions have to rely on the safety data from the clinical side and post-marketing reporting.

2.3. Clinical Safety

a. Clinical trials

Iron(III)-hydroxide dextran complex

Only two MAH studies have been conducted with low molecular weight iron(III)-hydroxide dextran (LMWID) complex.

A systematic review of the relevant published literature has been performed and randomised clinical studies and other study designs including uncontrolled retrospective and prospective studies have been included if they reported on adverse drug reactions (ADRs) associated with the use of LMWID complex.

A total of 33 publications reporting on the safety of LMWID were identified. The vast majority of these concerned treatment in patients undergoing chronic haemodialysis (HD). Other groups of patients included home total parenteral nutrition, those unable to tolerate or respond to oral iron, children with inflammatory bowel disease (IBD), patients with cancer, and pregnant women. Different regimens were employed from 100 mg maintenance doses in HD to high accelerated total dose infusions (TDIs). For several publications, various definitions of the terms “anaphylactoid” and “serious” were used. According to the MAH, the majority of studies were retrospective. As the studies are so heterogeneous in terms of design, patient groups, and definitions and methods of assessing adverse events (AEs) it is difficult to interpret and compare incidence of AEs data across studies. However, the majority of the reported ADRs were classified as Ring and Messmer grade I-II. Few serious adverse reactions (SARs) and no cases leading to fatal outcome were reported.

In the German LMWID post-authorisation observational registry, patients enrolled were aged of 63.4 ± 14.1 years and had diabetic nephropathy followed by chronic glomerulonephritis (86.4% of HD). A total of 65 patients (about 12%) experienced AEs and 90% of them (n=59) experienced serious AEs.

Among them, 20 had fatal outcome (NOS) and 11 experienced transplantation. A total of 9/59 (1.6%) were considered having a likely causality. No causality assessment has been provided in about 2/3 of patients with SAE in the first analysis.

A large majority of publications concerned patients in CKD and HD population (22 publications were identified): in most publications, the majority of anaphylactoid reactions reported with LMWID were classified as grade I-II of severity according to Ring and Messmer classification. Nevertheless, there was one grade IV (cardiac arrest) reported in Fishbane and al (1996) publication and a total of 15 hypersensitivity (7,3%) mainly grade II-III, reported in HD population (Haddad and al, 2009), all occurring during the test dose.

A higher incidence of total AE per patient and exposure within LMWID compared to iron sucrose group was identified but no difference between iron sucrose and iron gluconate (Ganguli and al 2008) in CKD population was observed.

In iron deficiency anaemia (NOS), there were three publications with no anaphylactoid reactions reported.

In IBD population, according to Khalil et al (2011), a total of 2/35 (6%) IBD patients experienced anaphylactoid reactions (Ring and Messmer grade I-II) to IV test dose (hypotension and dyspnoea following urticaria and one transient urticaria). In one patient, sensitivity to iron dextran was confirmed by intradermal allergy testing. According to Mamulla et al (2002), a total of 11 hypersensitivity

reactions (grade II) were observed (9% of total number of infusion) in IBD paediatric patients: transient hypotension developed in 3 children. None were life-threatening.

Iron(III) isomaltoside 1000

There are only three completed studies involving iron (III) isomaltoside 1000. The MAH has also provided a list of 11 on-going clinical studies. All studies have been performed applying a protocol not including a test dose.

Three patients experienced ADRs of potential allergic nature in completed studies. In two cases, the patients were re-exposed without re-occurrence of the reactions; however, the second patient received the second dose under treatment with cetirizine and has therefore also been included in the analysis of potential allergic reactions. Conclusively, two ADRs have been included in the analysis of allergic reactions according to the Ring and Messmer classification from the analysed or completed studies.

As of Data Lock Point, only two serious adverse reactions have been reported within the on-going clinical studies; one patient experienced a tonic-clonic seizure and one hypersensitivity reaction in an on-going study.

Thus, four cases of allergic reactions possibly related to iron (III) isomaltoside 1000 have been found in the trials. This is out of around 260 patients being included in clinical studies regarding iron (III) isomaltoside 1000 (studies that also assessed safety parameters).

In summary, there is only very limited data on safety from clinical studies.

Sodium ferric gluconate

One pivotal and one supportive controlled studies were conducted in adults in Canada and the United States to assess the efficacy and safety of sodium ferric gluconate as first line treatment for iron deficiency anaemia in renal haemodialysis patients on supplemental recombinant human erythropoietin.

In the pivotal controlled study a total of 88 patients received sodium ferric gluconate.

Three patients experienced allergic reactions leading to product discontinuation.

The most frequent AEs experienced by patients in all treatment groups were hypotension (48.7%), nausea (31.9%), vomiting (22.1%) and cramps. Of note, hypotension, nausea, vomiting and cramps are often symptoms associated with haemodialysis. Thirty-two of 88 patients experienced a reaction at injection site.

The MAH concludes, that a significant decrease in systolic blood pressure occurred in the treatment groups compared to control blood pressure (BP) in mm Hg: group 500 mg mean BP 144.5 ; group 1000 mg mean BP 155; control: mean BP [170 p = 0.001] while diastolic blood pressure was similar between the treatment groups. However, no clinically significant effects on vital signs were reported.

In the supportive controlled study a total of 63 patients were enrolled. Sodium ferric gluconate-treated patients were considered to have completed the study protocol, if they have received at least 8 doses of the study medication. Twelve (32%) received less than 8 doses and 32% had incomplete dosing information. Only 5 (13%) had completed the study. The maximum dose received was 1125 mg and the minimum was 62.5 mg.

The most frequent AE experienced by patients in the sodium ferric gluconate-treatment group was application site reaction (26.3%).

Published literature was also provided. Among all studies provided, only one life-threatening reaction was reported (Michael, *et al* 2002). This reaction occurred in a patient with a history of multiple drug

allergies including anaphylaxis to iron dextran. Furthermore, only three patients with serious adverse events, assessed as related to intravenous sodium ferric gluconate, have been described. One of these cases was an anaphylactoid reaction, and another was a probable serious allergic reaction. It might be of interest to note, that these patients had penicillin allergy and latex allergy, respectively. Altogether, this raises the question if patients with allergies (notably type 1-allergies) have an increased risk of serious allergic reactions to IV iron.

Among haemodialysis CKD adult patients, adverse reactions such as hypotension, nausea, vomiting, dizziness and malaise were common. These events could be reactions to haemodialysis, but they could also be symptoms of allergy. There are also some cases described of facial reddening, nausea and cramp; symptoms that also could be signs of allergy. Among non-dialysis CKD adult patients, there were also some patients who experienced hypotensive episodes.

Among paediatric CKD patients, many episodes of hypotension were reported, and it is impossible to assess if these were due to the haemodialysis or the intravenous iron given, especially since there were no control groups in these studies.

Data provided regarding safety in pregnancy and intestinal absorption disorder was very limited.

One study showed that slow administration of sodium ferric gluconate resulted in less allergic reactions than if this was done during a shorter period of time and another study indicated that sodium ferric gluconate gave rise to a less number of allergic reactions than iron dextran.

Due to the limitations of the studies provided the safety analysis is of not great value.

Ferric carboxymaltose

The MAH provided a summary list of all studies. According to the MAH, up to 31 December 2011, a total of 13,134 patients have been included in 29 MAH sponsored Phase 1 to 3 studies in different therapeutic areas (nephrology, gynaecology, gastroenterology, neurology, cardiology and iron deficiency anaemia), of which 6,608 have received ferric carboxymaltose.

Control patients were grouped into those receiving other IV irons (e.g., iron dextran, iron sucrose and other IV iron preparations; N=2,554), oral iron (ferrous sulphate; N=2,607) or placebo (0.9% saline infusion; N=1,365).

Approximately half of the patients receiving ferric carboxymaltose in clinical studies were treated with a protocol-defined maximum single dose of 750 mg (13 studies, 3255 patients, mean single dose = 636.5 mg, mean cumulative dose = 1410.8 mg). The other half of the patients was treated in protocols with a maximum single dose of 1,000 mg (16 studies, 3353 patients, mean single dose = 894.5 mg, mean cumulative dose = 1191.9 mg).

An overview of treatment emergent adverse events (TEAEs) and serious TEAEs was provided and concluded that related TEAEs to ferric carboxymaltose occurred in a frequency which is comparable to patients receiving comparator IV iron preparations and oral iron group.

The proportion of patients experiencing a related TEAE of severe intensity seems higher in the ferric carboxymaltose group compared to that of the comparator IV iron group. The MAH clarified that the difference is mainly explained by the incidence of hypophosphataemia seen with ferric carboxymaltose.

Serious AEs were reported less frequently in patients receiving ferric carboxymaltose than in those receiving other IV iron. The SAEs were related to ferric carboxymaltose in 8 cases (0.1%), less than other IV iron. These related SAEs included constipation, hypersensitivity, anaphylactoid reaction, arrhythmia, abnormal liver function test, supraventricular tachycardia, pulmonary embolism and systemic inflammatory response syndrome.

According to the MAH, TEAEs occurred at lower incidences in patients receiving placebo, regardless of their causality, severity or seriousness, possibly as a reflection of the much smaller sample size of this group.

Across all clinical trials, there were 33 (0.5%) fatal cases that occurred in patients receiving ferric carboxymaltose, versus 22 (0.9%) fatal cases in IV iron arm and 4 (0.4%) fatal cases in the placebo group.

According to the MAH, 5 cases were judged as unlikely related (myocardial infarction, chronic obstructive pulmonary disease, cerebrovascular accident, sepsis, 1 unspecified term) and 1 as possibly related (presumed cardiac arrhythmia one day after the second injection but among others, important cardiac medical history considered by the investigator as alternative contributory factors). A study (1VIT09030) was performed in a renal compromised population with significant cardiac co-morbidities in order to compare safety profile of ferric carboxymaltose and iron sucrose in this population. None of the deaths were related to either ferric carboxymaltose or iron sucrose.

The product was investigated in different indications namely nephrology, gynaecology, gastroenterology, restless leg syndrome, chronic heart failure, underlying diseases leading to iron deficiency anaemia. The safety profile was similar with no additional safety concerns. Only in iron deficiency anaemia in the paediatric population two patients (5.7%) reported AEs considered as related to ferric carboxymaltose (mild urticaria at first injection and mild oedema of the palms and fingers of both hands at first injection). Similar events were not recorded for the second administration for both patients.

In terms of the Ring & Messmer classification analysis, over all studies, 36 hypersensitivity events occurring in 35 patients were reported.

The MAH reported that 25 events were related to ferric carboxymaltose (20 grade I, 2 grade II, 2 grade III and 1 grade IV), 2 events were unlikely related to ferric carboxymaltose (1 grade II and 1 grade IV), 9 events were not related to ferric carboxymaltose (6 grade I, 1 grade II and 2 grade III). All patients recovered from the hypersensitivity event. For one patient, the event of hypersensitivity occurred after the first and the second injection. No dose response or relationship to method of administration (undiluted bolus injection versus diluted infusion) was observed for hypersensitivity events. More female patients suffered from hypersensitivity, which can be explained by the fact that most patients in the ferric carboxymaltose clinical trial program were female (N=5,230; 79.2%).

Iron sucrose complex

Twenty-two clinical studies were submitted. Over 8,000 patients have been included/treated across all arms in these clinical trials, of whom almost half (N=4,048) received iron sucrose either as the test product or as the reference (comparator) therapy. Other control patients have been grouped into those receiving other IV iron preparations (N=3,364), oral iron (N=887), placebo (N=256) or standard medical care [(SMC), N=159]. Some studies were iron sucrose only, some studies included a placebo or standard medical care arm, and some studies had another active substance as comparator.

According to the MAH, the majority of events were not related to study drug in either treatment arm. Most related TEAEs were of mild or moderate intensity and occurred with a similar incidence in both the iron sucrose and comparator groups.

A total of 36 patients (0.9%) in the iron sucrose group and 54 patients (1.6%) in the other IV iron preparations group discontinued due to related events.

The system organ class (SOC) with the most commonly (>2% of patients in any group) reported TEAEs for patients receiving iron sucrose were gastrointestinal Disorders (15.3%), General Disorders and Administration Site Conditions 12.5%, Infections and Infestations (11.7%), Vascular Disorders (10.4%) and Nervous System Disorders (10%). These frequencies were comparable with those in the other IV iron preparations group and generally lower than those in the other treatment arms.

The SOCs with the most frequent related SAEs reported for patients receiving iron sucrose were those of Respiratory, Thoracic and Mediastinal Disorders (0.1%), Immune System Disorders (0.1%), Vascular Disorders (0.1%) and Cardiovascular Disorders (0.05%). The vast majority of the related SAEs only occurred in one patient except for Hypersensitivity and Hypotension (4 and 3 patients, respectively). By comparison, in the other IV iron preparations group the Cardiac and Immune System Disorders SOCs recorded 2 patients each (0.1%) with none of the PTs throughout all SOCs having occurred in more than 1 patient.

A total of 57 patients (1.4%) receiving iron sucrose died during their study participation (no case was considered related to the drug administration). Death cases for 19 patients (0.56%) were recorded among patients exposed to other IV iron preparations with one case (0.03%) also judged related to the study drug administration. Two (0.22%) and 4 (1%) patients died in the oral iron and placebo/SMC groups, respectively, none of them considered treatment related.

According to the Ring and Messmer classification twenty patients recovered without sequelae and one case (Grade I, 1 patient) was ongoing at time of last follow-up. According to the Ring & Messmer algorithm, 15 non-serious cases were all coded as either Grade I or II cases. The 6 serious cases were reported as 1 Grade I case, 2 Grade III cases and 3 Grade IV cases.

The frequency of “hypersensitivity” related events reported with iron sucrose in the analysed clinical trials (0.27%) was considerably less than the hypersensitivity event risk for the respective background populations (1.2-16.8%).

b. Post-marketing reporting

Most of the information regarding the safety of these products comes from the post-marketing reporting.

Iron(III)-hydroxide dextran complex

Since the time of authorisation until 29 February 2012, the total number of 100 mg doses administered can be estimated to 19,600,000 doses excluding randomised patients in finalised and on-going post-authorisation studies (53,698 patients- days). As of DLP, a total of 587 case reports have been received yielding an ADR reporting rate of 0.003 % (which corresponds to 1093 case reports for 100,000 patients-days).

The majority of cases were reported as serious (366/587; 62%).

A total of 168 cases were reported with a primary event within the SOC of immune system disorders (28.6%) including 147 serious.

All cases within this SOC have been classified according to the Ring and Messmer classification.

The majority of cases were classified as grade III (53%) followed by grade II (32%).For reports classified as grade III, the most commonly reported term was “anaphylactic shock” and the outcome of these cases was either recovered, not recovered (1 case only) or unknown (8 cases). Six cases (4%) were classified as grade IV (2 reported anaphylactic shock leading to a fatal outcome and 4 anaphylactic shock leading to cardiac arrest (all patients made full recovery).

For some cases (108 out of 168) the time to onset of the reaction was reported. In approximately 90% of the cases in which the time to onset was reported the reaction occurred within the first 10 minutes of administration, and in about one third it occurred during the test dose. In only one case, the onset was reported as a late-occurring event (onset after one day). Anti-allergic treatment was reported for 94/168 cases.

For cases where gender was reported, the majority of cases were reported in women. The reported ADRs covered all age ranges. Three patients had previously reported similar reaction while treated with IV iron products. The dose range was 100-2,400mg. Data collection did not allow for a proper evaluation of the severity of the underlying disease, dose and duration of treatment, indication, concomitant medication, and concomitant/previous illness.

All serious cases reported with a primary event other than within the immune system disorders have been reviewed according to the common terminology criteria for adverse events (CTCAE) grade III-V in order not to oversee any severe potential allergic reactions (n=219 additional cases).

When classifying all cases that were not reported as immune reactions, according to CTCAE approximately 20% were classified as grade III. The far majority of cases could not be assessed as potential serious allergic reactions.

Six cases of allergic reactions were classified as grade V and all led to a fatal outcome due to cardiac arrest, hypotension, or circulatory failure. One case was received from Uzbekistan and it has been shown to concern a counterfeit product.

The time to onset was not reported in the majority of cases. In 21 cases, time to onset was > 1 hour. Nine serious and 12 non-serious were reported with the majority in women. There were 2 cases with primary event within the SOC of immune system disorders: one non serious generalised itching one day after treatment and one case of anaphylaxis and cardiac arrest in a 95-year-old man one day after treatment. Both patients recovered.

Four cases of late on-setting back pain, myalgia, and arthralgia were received, 3 non-serious and one serious, all reported as recovered. When reviewing the full data set, 17 of 587 cases were reported with a primary event within the SOC of musculoskeletal disorders which may include other late occurring events of myalgia and arthralgia.

Iron(III) isomaltoside 1000

As of 29 February 2012, a total of 26 case reports have been received yielding an ADR reporting rate of 0.02 %. The majority of cases were reported as serious and five cases were reported with a primary event within the immune system disorders. Of these, one was reported as non-serious and four as serious.

According to the Ring and Messmer classification, three cases were classified as grade II anaphylactoid reactions and one case as grade III. In two cases, no symptoms were reported and it was not reported whether treatment of the reaction was provided nor was the time to onset other than the day of the event reported, making it difficult to classify these events. All five patients made full recovery.

In conclusion, a total of 26 spontaneous reports have been reported with iron(III) isomaltoside 1000. Of these, 17 were considered serious, of which 5 within the immune system disorder. Of these, 3 were classified as anaphylactoid reactions. Interestingly, 2 of these 3 anaphylactoid reactions occurred in patients with Crohn´s disease.

Iron gluconate (sodium ferric gluconate)

The following analyses were performed on spontaneous or solicited cases, medically confirmed or not, recorded until 15 December 2011. Only the cases in which sodium ferric gluconate was given parenterally were taken into account. A total of 1649 cases including 546 serious and 1103 non-serious cases corresponding to 6179 ADRs were recorded.

Regarding allergic reactions, a total of 846 cases / 1524 ADRs/AEs were identified in the Sanofi global pharmacovigilance database. Among the 846 cases, approximately half cases were serious and half were non-serious.

Adverse reactions were reported more frequently in women (68%) than in male (11%) patients. The severity of reactions was independent of the gender. The epidemiology of iron deficiency anaemia may explain the imbalance observed (prevalence of iron deficiency anaemia is higher in women compared to men-30% versus 12%). Sodium ferric gluconate was mainly prescribed for the treatment of iron deficiency anaemia and rarely for the treatment of anaemia in pregnancy.

Among 20 patients who presented a reaction of grade IV, six (6) patients died. Out of these 6 patients, 5 patients died from a non-allergic reaction a few days after the last injection (e.g. complications of amputation, septic shock, bronchopulmonary disease complication, rhabdomyolysis and pulmonary embolism). One patient with previous allergies and severe complications NOS after administration of dextran, received an overdose of sodium ferric gluconate and died from an acute myocardial infarction the day of sodium ferric gluconate infusion.

The patients presenting grade IV reactions had about 3 medical histories while patients who experienced grade I or II reactions had a mean of less than one medical history. Among the 20 patients who presented a reaction of the SMQ “Anaphylactic reactions” grade IV, 35% (7/20) patients had a medical history of hypersensitivity reactions. This supports the conclusion that in patients with known allergies and with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis) the risk of hypersensitivity reactions is enhanced .

Patients with concomitant diseases might be specifically vulnerable to IV iron products.

In about one third of the cases (223/846), the patients recovered after drug withdrawal. In the 3% of cases where sodium ferric gluconate was re-administered, the patients experienced the same type of ADRs, mainly allergic reactions without aggravation of the symptoms. Only 1 patient experienced an aggravation of symptoms at the sodium ferric gluconate re-introduction: minor skin reaction at infusion site then hypotension, syncope, nausea and vomiting at the second administration. All these patients recovered after sodium ferric gluconate withdrawal.

Sodium ferric gluconate contains benzyl alcohol as a preservative (one of the excipients). Benzyl alcohol crosses the placental barrier into immature foetal tissues as readily as it crosses the blood-brain barrier. Young children cannot metabolise benzyl alcohol into hippuric acid using benzoic acid, which can result in an accumulation of chiefly benzoic acid. This excipient can cause serious adverse event and death when administered to neonates. It can also cause anaphylactoid reactions in infants and children up to 3 years. So it is recommended that attention is paid for patients who may exhibit allergic reaction due to this excipient.

A total of 17 children experienced at least one reaction of the SMQ “Anaphylactic Reactions”. Eight cases were reported in Italy, 5 in Germany and 4 in the United States. One child in the United States should not have received sodium ferric gluconate as it is contraindicated in children below 6 years as per the US prescribing information. Five children in Italy should not have received sodium ferric gluconate as it must not be administered below 3 years due to the presence of benzyl alcohol in the formulation as per the currently approved SmPC. Most of the cases were grade I or II (12/17). All the children recovered except 1 patient with multiple concomitant diseases who died 6 days after the

unique injection of sodium ferric gluconate. Despite a test-dose of sodium ferric gluconate, one of the children (4 years of age) experienced an anaphylactic reaction.

A total of 56 pregnancies have been reported. Among them, 19 pregnant women presented at least one AE of the SMQ Anaphylactic reaction. These 19 patients recovered at sodium ferric gluconate withdrawal with or without corrective treatment. Most of them received only one infusion. In about 80% of the cases, the outcome of pregnancy was unknown. However, due to very limited exposure *in utero* to sodium ferric gluconate the risk for neonates of developing any abnormality seems unlikely.

This product also has a recommendation of a test-dose. Among the 846 cases with allergic reaction, 55 patients (6.5%) received a dose-test of sodium ferric gluconate prior to the first i.v infusion. The test-dose does not seem to prevent the occurrence of severe reactions. The rate of grade III and IV reactions is below in the group of patients who received a test-dose compared to patients who have not received it. Grade III and IV cases are described below. In 4 of 7 grades III and IV cases, the patients had a previous allergy to dextran.

The test-dose does not seem to prevent the occurrence of severe reactions. This is illustrated e.g. by one case in United States where a pregnant woman had a test-dose of sodium ferric gluconate without complications one week before experiencing an anaphylactoid reaction after a unique infusion.

Further, a test-dose might give the prescriber a feeling of false assurance that an allergic reaction is unlikely to happen. A limited number of patients received test-dose and it does not seem to prevent the occurrence of anaphylactic reactions.

In conclusion, with sodium ferric gluconate a total of 846 cases / 1524 ADRs/AEs were identified in the brandleader pharmacovigilance database. Among the 846 cases, approximately half cases were serious and half were nonserious.

A very limited number of women received sodium ferric gluconate during their pregnancy and a few presented an allergic reaction. 19 pregnant women were reported presenting at least one AE of the SMQ Anaphylactic reaction. It is notable that this figure is higher than among chronically ill, dialysis patients. This might be because of the threshold for reporting adverse events among pregnant women being lower than for chronically ill patients.

Paediatric population and elderly did not present more severe allergic reactions than adult population.

Ferric carboxymaltose

The MAH provided a summary of 2,736 events as part of 1,466 cases received since the international birth date and up to data cut-off date of 31 October 2011.

AEs from SOCs General Disorders and Administration Site Conditions (899 AEs), Skin and Subcutaneous Disorders (592 AEs), Immune System Disorders (209 AEs) and GI Disorders (203 AEs) are the most frequently reported terms. The overall incidence of reported AEs from the market surveillance is 7.68 AE reports per 1,000 patient-years.

The SOC reporting the most of SAEs are Immune System Disorders (150 SAEs on 667 SAEs reported). Furthermore, most of AEs reported in the SOC Immune System Disorders are serious AEs (150 SAEs on 209 AEs).

From post-marketing spontaneous reports 191 cases of drug exposure during pregnancy with ferric carboxymaltose were reported. According to the MAH, no signal of adverse outcome or adverse event for mother and babies was detected.

One related fatal event reported from a post-marketing observational study.

Using a data cut-off date of 31 December 2011, a total of 236 hypersensitivity associated cases were identified, which occurred in a population of 393,160 patient-years. This corresponds to a hypersensitivity events frequency rate of 0.060%, which is lower than the frequency rate found in clinical trials.

An analysis on the severity of the hypersensitivity post marketing cases was provided (cut-off date 31 December 2011): 33 cases of the 178 serious cases required hospitalization, 31 cases of the 178 serious cases were of a life-threatening nature, from which 6 patients presented with a history of allergy. A fatal case notified on 21 September 2011 was reported. A 56 years old female patient experienced a cardiopulmonary arrest 5 minutes after the beginning of the first perfusion of ferric carboxymaltose. The patient also presented with a bronchospasm. The patient died.

The average age of the patients who had hypersensitivity associated AEs was 38.1 years old. The large majority was female.

The majority of hypersensitivity associated AEs (26.1%) occurred between 5 to 30 minutes after treatment with ferric carboxymaltose, closely followed by hypersensitivity associated AEs which occurred during the infusion/injection (15.9%).

There does not appear to be a consistent pattern or predictive dose or rate of infusion that relates to the chance of these events occurring and importantly the higher individual doses do not appear to be correlated with increased frequency or severity of events.

From the cases where an outcome was available (N=219) 78.5% with a Grade I or II classification recovered; all the cases classified as Grade III and IV made a full recovery.

In conclusion the post-marketing data are in accordance with the known safety profile of ferric carboxymaltose. A total of 236 cases of hypersensitivity reactions were reported (mainly grade I and II). A total of 34 grade III (14.4%) and 2 grade IV (0.8%) were reported. All recovered.

Iron sucrose

A total of 317 cases of hypersensitivity were identified from the MAH database, which occurred in 13,824,369 patient years (cut-off date 31 December 2011). The majority of patients were female.

The majority hypersensitivity reaction occurred within 30 minutes post dose (58.9%, N=112/190); however, for 40.1% (N=127/317) of cases the timing of the event was unknown.

In all cases with outcome data (72.6% of cases (N=230), 27.4% unknown outcome (N=87)) patients recovered without sequelae (94.8%).

This corresponds to a hypersensitivity events frequency rate of 0.0022%, which is lower than the frequency rate found in clinical trials. This is also significantly below the background incidence of hypersensitivity reactions, which can be as high as 1.2–15%.

No new safety concern emerges from the data provided: the post marketing data are consistent with clinical trial data regarding the risk of hypersensitivity.

Regarding the severity from the post-marketing dataset 73 cases (22.7%, 73/317) required hospitalisation, 51 cases (16.1%, 51/317) were deemed life-threatening, nine patients died due to these events (2.8%, 9/317) : of the 9 fatalities, 6 cases (1.9%, 6/317) were considered to be related; for the total treated patient population this is 0.00004% (N=9/13,824,369). Classification according Ring and Messmer of postmarketing cases was done. Grade I and grade II together account for 61.5% of all cases. Grade III and IV total together account for 23.1% of all cases and include hypersensitivity, anaphylactoid reaction and anaphylactoid shock.

Overall, 32 patients were treated with adrenaline of which 17 were reported as life-threatening cases (5.4%, 17/317 cases; 0.0001%, 17/13,824,369 patient years). Of these 17 life-threatening cases, 3 cases were graded as Grade IV.

In 8 cases of the total 51 life-threatening cases (15.7%; 8/51 cases, one graded as Grade IV), the patient presented with a history of allergy in general. Predisposition to an allergy or known asthma may result in a more severe reaction.

The dose immediately prior to events, in both clinical trial database and post marketing safety database varies widely. No consistent pattern or predictive dose appears and the higher individual doses do not appear to be correlated with increased frequency or severity of events.

During the post-marketing experience with iron sucrose, hypersensitivity events occurred at single doses ranging from 5-1,700 mg iron (single doses above 500 mg represent off-label use). The average single dose was <200 mg iron in 56.1% of patients, whilst 43.8% of the events occurred with a dose of 200 mg iron or above. In 56 patients (17.7%, 56/317) the dose was unknown.

There is no consistent pattern or predictive dose or administration relationship in relation with the occurrence of these events and importantly the higher individual doses do not appear to be correlated with increased frequency or severity of events.

In conclusion, regarding post-marketing data, 317 cases of hypersensitivity were reported (frequency rate 0.0022%). According to the Ring and Messmer algorithm, 56 cases were coded as grade I (17.7%), 139 as grade II (43.8%), 62 as grade III (19.9%) and 10 as grade IV (3.2%). There were 49 non gradable cases (15.5%) due to a lack of information. When outcome is known, most patients recovered without sequelae (94.8%). According to the MAH, of 9 fatal cases of hypersensitivity reactions reported, six (1.9%, 6/317) were considered to be related.

c. Pharmacoepidemiological studies

No pharmacoepidemiological studies concerning allergic reactions have been conducted with LMWID or with iron(III) isomaltoside 1000.

For Iron gluconate, no pharmacoepidemiological studies have been identified regarding anaphylactic risk and iron IV products. However, several epidemiological studies have been published which aim was to analyse the risk of mortality and the use of IV iron in haemodialysis patients. Epidemiologic studies examining the association of IV iron dose to morbidity and mortality have yielded conflicting results and results were not directly comparable as sources of data, exposure definition and statistical methodology differed across studies. However, when considering time-dependent modelling, these study results suggest no association between the risk of death and any level of IV iron administration.

Four non-interventional studies were completed with ferric carboxymaltose. According to the MAH, no new safety findings were identified, and the safety profile of ferric carboxymaltose in real-life situations could be confirmed.

All the pharmacoepidemiological studies mentioned with iron sucrose report the same trend with a higher risk for AEs with iron dextran therapy than with iron sucrose. Bailie and colleagues (2011) stated that the ADR rates of iron sucrose and ferric gluconate had a continued trend for lowest rates of AEs and are extremely low, respectively. No information on possible risk factors or the predictability of the ADRs could be retrieved from pharmacoepidemiologic literature

No specific pharmacoepidemiological studies were performed for most products.

d. Published literature.

Iron(III)-hydroxy dextran

Published reviews including meta-analysis of comparative and non-comparative studies as well as retrospective publications of data from safety surveillance databases confirm the low frequency of serious allergic reactions for parenteral iron in general.

Bailie and colleagues (2005) report a higher incidence of 29.2 SAEs per million dose of iron dextran compared to 4.2 for iron sucrose. However, there was no differentiation between HMWID and LMWID and therefore the value of this comparison is of limited value concerning LMWID.

A similar study (Bailie and al 2011) showed rates of spontaneously reported hypersensitivity reactions and SAEs for iron sucrose, iron gluconate, and iron dextran were comparable between Europe and North America. For North America, LMWID and HMWID were combined.

A systematic literature review to assess the frequency of ADRs associated with LMWID and iron sucrose was carried out by Critchley and Dundar (2007). As most of the larger studies were not comparative, it is difficult to state conclusively whether any parenteral iron product is safer than others.

Auerbach and Talib (2008) also compared safety profiles of available parenteral iron products in published literature. The authors concluded that if patients were in need of higher doses of iron than 2-300 mg then total dose infusion (TDI) of LMWID is preferred instead of treatment with iron sucrose or iron gluconate, which both are associated with high incidences of minor irritating, uncomfortable vasoactive reactions, even when the infusions are given slowly.

Overall, the MAH considered that the reported ADRs included unspecific hypersensitivity reactions seen with other iron compounds with symptoms such as rash, shortness of breath, tightness of chest, sensation of heat, flushing, nausea, itching, tachycardia, and hypotension. The relatively few studies available and report on commercial use suggest that serious or life-threatening ADRs are rare with LMWID.

Information on the risk of anaphylactoid reactions, including information that resuscitative medication and personnel trained to evaluate and handle anaphylactoid reactions should be available, is already included in the SmPC of iron(III)-hydroxide dextran complex. Furthermore, IV administration of LMWID by the TDI method is restricted to hospital use only and according to the SmPC, a test dose must be applied before the first dosing of iron (III)-hydroxide dextran complex. The risk of anaphylactoid reactions are listed as uncommon (≥1/1,000 to <1/100) which is in agreement with the above findings.

Iron(III) isomaltoside 1000

Only a limited number of studies of iron(III) isomaltoside 1000 and risk of allergic reactions have been published, as the results of the finalised clinical studies and an editorial of iron(III) isomaltoside 1000 have been published. Safety data from these publications have been reviewed and graded according to the Ring and Messmer classification above.

Iron gluconate (sodium ferric gluconate)

Published literature for iron gluconate has already been discussed (see clinical trials section).

Ferric carboxymaltose

For ferric carboxymaltose there is no published literature. Data are limited to the clinical trial database and spontaneous reports.

Iron sucrose complex

No difference in the safety of iron sucrose was observed for the use in children. Safety in children with CKD (age range 3 months to 17 years) has been investigated in detail by Anbu *et al.* 2005. Crary *et al.* 2011 reviewed retrospectively pharmacy records of children (≤ 18 years of age) who received iron sucrose at between January 2004 and June 2009. Patients who received iron sucrose for chronic renal disease were excluded from analysis. Among 38 children, who received a total of 510 doses of iron sucrose, there were only six adverse reactions.

Safety of intravenous iron in patients with rheumatoid arthritis

Administration of IV iron dextran to anaemic rheumatoid patients has been shown to cause an exacerbation of inflammatory synovitis in previously affected joints.

No spontaneously reported cases of rheumatoid arthritis have been reported. The risk of exacerbation of rheumatoid arthritis has been reported with the infusion of iron dextran, in the literature (Blake, *et al* 1985). Increased swelling, heat and pain in already affected joints occurred approximately 24 hours after infusion and can last for up to 2 weeks.

There are no published studies with iron(III) isomaltoside 1000 in patients with rheumatoid arthritis. As no data on the risk in patients with rheumatoid arthritis is currently available for iron(III) isomaltoside 1000, no firm conclusions can be drawn.

In conclusion and based on the literature, the evidence for a risk of exacerbation of joint inflammation in these patients is contradicting. If a risk exists it seems related to iron per se and must be considered a class effect. A warning in the SmPC for patients with inflammatory conditions was recommended by the CHMP.

Test dose

Some of the parenteral iron-containing products assessed here have a recommendation for a test dose to be administered prior to the final administration. As data from the post marketing reporting showed that a successful test dose may give false assurance to the professionals dealing with the product administration, no test dose should be applied. Instead caution should be exercised in each iron administration even in the cases or repeat administrations according to the CHMP recommendations.

Consultation with PRAC

The CHMP during the assessment of this referral procedure asked the PRAC for its input in two main questions.

Firstly the CHMP was concerned by the weak level of evidence related to the differences between the estimated rates of reported severe allergic reactions (including during pregnancy) among the different intravenous Iron containing medicinal products.

The PRAC acknowledged that the data from spontaneous reporting analysed during the referral were the only one available as there were no pharmacoepidemiological studies comparing neither the efficacy nor the safety of these products. The PRAC pointed out limitations of comparative analyses based on spontaneous reporting rates alone. Spontaneous reporting rates cannot be used to compare the benefit risk of products. The data has not been presented in a similar way for the different products and the exposure data are based on estimations. Further, there are differences in the time for which

different products have been on the market and it can be expected that reporting rates are higher for a new product compared to those which have been marketed for a longer time. Differences in geographical distributions of the consumption of the products may also add uncertainty to the reporting rates as it can be expected that routines for spontaneous adverse events reporting may vary in different countries. Thus, given the low total number of life-threatening and fatal events it is noted that the estimated rates are quite sensitive to even slight levels of under-reporting and differences in methodology for calculating these rates could also have an impact. However, it can be concluded that IV iron preparations can cause serious allergic reactions and the incidence is low. Additional data is needed to analyse the signal further.

In order to allow review of any new serious/fatal cases, the PRAC suggested that all MAHs should provide annual cumulative reviews of hypersensitivity case reports, all fatal cases and all pregnancy cases, together with usage data. These reports for all IV iron products should be assessed together in parallel (with the same timeframe).

Secondly the CHMP requested the PRAC to comment on which study, if any, could further explore the potential differences, especially between dextran and carboxymaltose iron compared to the other compounds.

In view of the limitations of the available comparative safety data (based largely on ADR reporting rates) for the IV iron products, the PRAC advised that consideration should be given to the feasibility of obtaining more data particularly regarding hypersensitivity reactions, for example in the form of a pharmacoepidemiolgical study.

The aim of further studies would be to further quantify the risk and to detect differences between specific products. Particular methodological challenges may be associated to the proposed data sources that can be assessed on their ability to handle specific issues raised by the study aim, e.g. to determine the extent of exposure: to identify specific products, and the duration and timing of the usage in relation to the adverse event. Issues related to confounding by indication may need to be considered. Furthermore, the ability of data sources /registries to reliably capture hypersensitivity events and to assess other risk factors for hypersensitivity (e.g. concomitant medication) should be taken into account.

The PRAC recommended that the MAHs should closely monitor cases of hypersensitivity with active follow-up of cases by targeted questionnaires.

In addition prospective data collection from national specialist centres e.g. renal centres could be considered, given the prevalence of renal disease / iron administration. The use of data already existing from renal registries in Europe such ERA-EDTA registry (European Registry collecting data on renal replacement therapy via the national and regional renal registries in Europe), QUEST initiative anaemia study could be explored.

2.4. Discussion

In 2011 the French medicines agency (ANSM) had concerns with regards to the risk of hypersensitivity reactions of intravenous iron containing products indicated in iron deficiency situations when the oral route is insufficient or poorly tolerated especially in chronic kidney disease (CKD) patients (haemodialysis), but also in pre- or post-operative situations, or in case of intestinal absorption disorders. This risk was particularly of concern with low molecular-weight iron-dextran (LMWID) containing products, particularly in pregnant women for whom uterine hypertonia was observed.

In view of the above, on 7 December 2011 France requested the CHMP under Article 31 of Directive 2001/83/EC to assess the above concerns regarding hypersensitivity and its impact on the benefit-risk balance for iron intravenous containing medicinal products, and to give its opinion on measures necessary to ensure the safe and effective use, and on whether the marketing authorisation for these products should be maintained, varied, suspended or withdrawn.

The iron complexes involved in this procedure are iron gluconate (sodium ferric gluconate), iron sucrose, iron dextran, ferric carboxymaltose, and iron (III) isomaltoside 1000.

Hypersensitivity (also called allergic reactions) refers to undesirable reactions produced by the normal immune system, including allergies and autoimmunity. These reactions may be damaging, uncomfortable, or occasionally fatal. One of the ways to classify the hypersensitivity reactions is according to Ring and Messmer (1977) definition. According to this definition Grade I show skin symptoms and or mild fever reaction; Grade II show measurable symptoms, but not life threatening, cardiovascular reaction (tachycardia, hypotension), gastrointestinal disturbance (nausea) and respiratory; Grade III symptoms show shock, life threatening spams of smooth muscles (bronchi, uterus); and Grade IV show cardiac and/or respiratory arrest.

The MAHs were requested by the CHMP to provide a detailed analysis classified according to Ring and Messmer for the purpose of the review of the risk of allergic reactions.

The CHMP reviewed all available data from pre-clinical and clinical studies, published literature and post-marketing experience on the hypersensitivity reactions of intravenous iron containing medicinal products.

Pre-clinical studies

Only a few preclinical studies with low molecular weight iron dextrans (LMWID), iron(III) isomaltoside 1000 have been carried out and only studies with safety findings relevant to immunogenicity were referenced in the data submission by the MAHs. For iron gluconate (sodium ferric gluconate) an overview of the toxicology program performed between 1970's and 1996 to support the registration of sodium ferric gluconate complex was submitted. For ferric carboxymaltose as well as iron sucrose in animal studies in guinea pigs that had been administered immune serum containing anti-dextran antibodies, a clear skin reaction after the administration of dextran was observed (positive control). However, no skin reactions were seen when ferric carboxymaltose or iron sucrose was administered. In addition *in vitro* reactivity of various marketed intravenous iron preparations towards anti-dextran antibodies was tested in a reverse radial immunodiffusion assays.

Cytotoxicity of various iron complexes has been documented in the literature. Cytotoxicity is mediated throughout the formation of reactive oxygen species (ROS). This cytotoxicity is proper to various iron complexes nevertheless the effect is related to the stability of the complex and therefore of the carbohydrate used for the coating. However the discussion of the existing preclinical data did not clear the immunogenic point, therefore the existing pre-clinical data do not allow for any firm conclusions; the CHMP conclusions were reached based on clinical and pharmacovigilance data.

Clinical Safety

Clinical studies

Iron (III)-hydroxide dextran complex

Only two MAH studies have been conducted with low molecular weight iron (III)-hydroxide dextran complex.

A systematic review of the relevant published literature has been performed and randomised clinical study and other study designs including uncontrolled retrospective and prospective studies have been included if they reported on ADRs associated with the use of low molecular weight iron dextran (LMWID) complex.

A total of 33 publications reporting on the safety of LMWID were identified. The vast majority of these concerned patients in chronic kidney disease (CKD) and treatment in patients undergoing chronic haemodialysis (HD). Other groups of patients included home total parenteral nutrition, those unable to tolerate or respond to oral iron, children with inflammatory bowel disease (IBD), patients with cancer, and pregnant women. Different regimens were employed from 100 mg maintenance doses in HD to high accelerated total dose infusions (TDIs). The majority of studies were retrospective.

In most publications the majority of anaphylactoid reactions reported with LMWID were classified as grade I-II of severity according to Ring and Messmer classification. Nevertheless, there was one grade IV (cardiac arrest) reported in Fishbane and colleagues (1996) publication and a total of fifteen hypersensitivity (7.3%) mainly grade II-III, reported in HD population (Haddad *et al*, 2009), all occurring during the test dose.

A higher incidence of total adverse events (AEs) per patient and exposure within LMWID compared to iron sucrose group was identified but no difference between iron sucrose and iron gluconate (Ganguli *et al* 2008) in CKD population was observed.

In iron deficiency anaemia there were three publications with no anaphylactoid reactions reported.

In inflammatory bowel disease population, according to Khalil *et al* (2011), 6% of IBD patients experienced anaphylactoid reactions (Ring and Messmer grade I-II).

Iron(III) isomaltoside 1000

There are only three completed studies involving iron (III) isomaltoside 1000 and eleven are still on-going. All studies have been performed applying a protocol not including a test dose.

Three patients experienced ADRs of potential allergic nature in completed studies. Two ADRs have been included in the analysis of allergic reactions according to the Ring and Messmer classification from the analysed or completed studies. Within the on-going clinical studies only two serious adverse reactions have been reported. Thus, four cases of allergic reactions possibly related to iron (III) isomaltoside 1000 have been found in the trials. This is out of around 260 patients being included in clinical studies regarding iron (III) isomaltoside 1000 (studies that also assessed safety parameters). In summary, there is only very limited data on safety from clinical studies. Therefore, no conclusions on safety can be drawn from these studies alone.

Sodium ferric gluconate

One pivotal and one supportive controlled studies were conducted in adults to assess the efficacy and safety of sodium ferric gluconate as first line treatment for iron deficiency anaemia in renal haemodialysis patients on supplemental recombinant human erythropoietin.

In the pivotal controlled study a total of 88 patients received sodium ferric gluconate. Three patients experienced allergic reactions leading to product discontinuation. The most frequent AEs experienced by patients in all treatment groups were hypotension (48.7%), nausea (31.9%), vomiting (22.1%) and cramps. Of note, hypotension, nausea, vomiting and cramps are often symptoms associated with haemodialysis. Thirty-two of 88 patients experienced a reaction at injection site.

Published literature was also provided. Among all studies provided, only one life-threatening reaction was reported (Michael, *et al* 2002). This reaction occurred in a patient with a history of multiple drug

allergies including anaphylaxis to iron dextran. Furthermore, only three patients with serious adverse events related to intravenous sodium ferric gluconate have been described. One of these cases was an anaphylactoid reaction, and another was a probable serious allergic reaction. It might be of interest to note, that these patients had penicillin allergy and latex allergy, respectively. The CHMP discussed the potential that patients with allergies (notably type 1-allergies) may have an increased risk of serious allergic reactions to intravenous iron.

Data provided regarding safety in pregnancy and intestinal absorption disorder was very limited. One study showed that slow administration of sodium ferric gluconate resulted in less allergic reactions than if this was done during a shorter period of time.

Ferric carboxymaltose

A total of 13,134 patients have been included in 29 MAH sponsored Phase 1 to 3 studies in different therapeutic areas (nephrology, gynaecology, gastroenterology, neurology, cardiology and iron deficiency anaemia), of which 6,608 have received ferric carboxymaltose and compared with those receiving other parenteral irons.

Over all studies, 36 hypersensitivity events occurring in 35 patients were reported.

The MAH reported that 25 events were related to ferric carboxymaltose (20 grade I, 2 grade II, 2 grade III and 1 grade IV), 2 events were unlikely related to ferric carboxymaltose (1 grade II and 1 grade IV), 9 events were not related to ferric carboxymaltose (6 grade I, 1 grade II and 2 grade III). All patients recovered from the hypersensitivity event. For one patient, the event of hypersensitivity occurred after the first and the second injection. No dose response or relationship to method of administration (undiluted bolus injection versus diluted infusion) was observed for hypersensitivity events.

Iron sucrose

Twenty-two clinical studies were submitted. Over 8,000 patients have been included/treated across all arms in these clinical trials, of whom almost half (N=4,048) received iron sucrose either as the test product or as the reference (comparator) therapy. Other control patients have been grouped into those receiving other IV iron preparations (N=3,364), oral iron (N=887), placebo (N=256) or standard medical care [(SMC), N=159]. Some studies were iron sucrose only, some studies included a placebo or standard medical care arm, and some studies had another active substance as comparator.

According to the Ring and Messmer classification reports twenty patients recovered without sequelae and one case (Grade I, 1 patient) was ongoing at time of last follow-up. According to the Ring & Messmer algorithm, 15 non-serious cases were all coded as either Grade I or II cases. The 6 serious cases were reported as 1 Grade I case, 2 Grade III cases and 3 Grade IV cases. The frequency of hypersensitivity related events reported with iron sucrose in the analysed clinical trials (0.27%) was considerably less than the hypersensitivity event risk for the respective background populations (1.2-16.8%).

Post marketing experience

The main safety data which were used in the CHMP assessment and conclusions were post-marketing data for all complexes.

Iron(III)-hydroxide dextran complex

Since the time of authorisation until 29 February 2012, a total of 587 case reports have been received yielding an ADR reporting rate of 0.003 % (which corresponds to 1093 case reports for 100,000 patients-days). The majority of cases were reported as serious (366/587; 62%).

A total of 168 cases were reported with a primary event within the System Organ Class (SOC) of immune system disorders (28.6%) including 147 serious. All cases within this SOC have been classified according to the Ring and Messmer classification.

The majority of cases were classified as grade III (53%) followed by grade II (32%). For reports classified as grade III, the most commonly reported term was “anaphylactic shock” and the outcome of these cases was either recovered, not recovered (1 case only) or unknown (8 cases). Six cases (4%) were classified as grade IV (2 reported anaphylactic shock leading to a fatal outcome and 4 anaphylactic shock leading to cardiac arrest (all patients made full recovery).

For some cases (108 out of 168) the time-to-onset of the reaction was reported. In approximately 90% of the cases in which the time to onset was reported the reaction occurred within the first 10 minutes of administration, and in about one third it occurred during the test dose. In only one case, the onset was reported as a late-occurring event (onset after one day). Anti-allergic treatment was reported for 94/168 cases.

All serious cases reported with a primary event other than within the immune system disorders has been reviewed according to the common terminology criteria for adverse events (CTCAE) grade III-V in order not to oversee any severe potential allergic reactions (n=219 additional cases).

When classifying all cases that were not reported as immune reactions, according to CTCAE approximately 20% were classified as grade III. The far majority of cases could not be assessed as potential serious allergic reactions.

Six cases were classified as grade V and all led to a fatal outcome due to cardiac arrest, hypotension, or circulatory failure.

Iron(III) isomaltoside 1000

As of 29 February 2012 a total of 26 case reports regarding hypersensitivity have been received yielding an ADR reporting rate of 0.02 %.

The majority of cases were reported as serious and five cases were reported with a primary event within the immune system disorders. Of these, one was reported as non-serious and four as serious.

According to the Ring and Messmer classification, three cases were classified as grade II anaphylactoid reactions and one case as grade III. In two cases, no symptoms were reported and it was not reported whether treatment of the reaction was provided nor was the time to onset other than the day of the event reported, making it difficult to classify these events. All five patients made full recovery.

In conclusion, a total of 26 spontaneous reports have been reported with iron(III) isomaltoside 1000. Of these, 17 were considered serious, of which five within the immune system disorder, as mentioned above. Of these, 3 were classified as anaphylactoid reactions. Two of these 3 anaphylactoid reactions occurred in patients with Crohn’s disease.

Iron gluconate (sodium ferric gluconate)

The following analyses were performed on spontaneous or solicited cases, medically confirmed or not, recorded until 15 December 2011. Only the cases in which sodium ferric gluconate was given parenterally were taken into account. A total of 1649 cases including 546 serious and 1103 non-serious cases corresponding to 6179 ADRs were recorded.

Regarding allergic reactions, a total of 846 cases / 1524 ADRs/AEs were identified of which approximately half cases were serious and half were non-serious.

Sodium ferric gluconate was mainly prescribed for the treatment of iron deficiency anaemia and rarely for the treatment of anaemia in pregnancy.

Among 20 patients who presented a reaction of grade IV, six (6) patients died. Out of these 6 patients, 5 patients died from a non-allergic reaction a few days after the last injection (e.g. complications of amputation, septic shock, bronchopulmonary disease complication, rhabdomyolysis and pulmonary embolism). One patient with previous allergies and severe complications NOS after administration of dextran, received an overdose of sodium ferric gluconate and died from an acute myocardial infarction the day of sodium ferric gluconate infusion.

Between the 20 patients who presented an anaphylactic reaction grade IV, 35% (7/20) patients had a medical history of hypersensitivity reactions. This supports the conclusion that in patients with known allergies and with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis) the risk of hypersensitivity reactions is enhanced.

In about one third of the total cases (223/846), the patients recovered after drug withdrawal. In the 3% of cases where sodium ferric gluconate was re-administered, the patients experienced the same type of ADRs, mainly allergic reactions without aggravation of the symptoms. Only 1 patient experienced an aggravation of symptoms at the sodium ferric gluconate re-introduction: minor skin reaction at infusion site then hypotension, syncope, nausea and vomiting at the 2nd administration. All these patients recovered after product withdrawal.

Pregnant women were among the cases with hypersensitivity reactions. 19 pregnant women presented at least one anaphylactic reaction. These 19 patients recovered at sodium ferric gluconate withdrawal with or without corrective treatment. Most of them received only one infusion. In about 80% of the cases, the outcome of pregnancy was unknown. However, due to very limited exposure *in utero* to sodium ferric gluconate the risk for neonates of developing any abnormality seems unlikely.

Among the 846 cases with allergic reaction, 55 patients (6.5%) received a dose-test of sodium ferric gluconate prior to the first IV infusion. The test-dose does not seem to prevent the occurrence of severe reactions. Further, a test-dose might give the prescriber a feeling of false assurance that an allergic reaction is unlikely to happen.

Ferric carboxymaltose

Until 31 December 2011, a total of 236 hypersensitivity associated cases were identified, for a total exposure of 393,160 patient-years. This corresponds to a hypersensitivity events frequency rate of 0.060%, which is lower than the frequency rate found in clinical trials.

Analysis on the severity of the hypersensitivity post marketing cases showed 33 cases of the 178 serious cases required hospitalization, 31 cases of the 178 serious cases were of a life-threatening nature, from which 6 patients presented with a history of allergy. A fatal case also reported.

The majority of hypersensitivity associated AEs (26.1%) occurred between 5 to 30 minutes after treatment with ferric carboxymaltose, closely followed by hypersensitivity associated AEs which occurred during the infusion/injection (15.9%).

There does not appear to be a consistent pattern or predictive dose or rate of infusion that relates to the chance of these events occurring and importantly the higher individual doses do not appear to be correlated with increased frequency or severity of events.

In conclusion the post-marketing data are in accordance with the known safety profile of ferric carboxymaltose. A total of 236 cases of hypersensitivity reactions were reported (mainly grade I and II). A total of 34 grade III (14.4%) and 2 grade IV (0.8%) were reported. Of these all patients recovered. A fatal case was also reported.

Iron sucrose

A total of 317 cases of hypersensitivity were identified from the MAH database, which occurred in 13,824,369 patient years (cut-off date 31 December 2011). The majority of patients were female.

In 8 cases of the total 51 life-threatening cases (15.7%; 8/51 cases, one graded as Grade IV), the patient presented with a history of allergy. Predisposition to an allergy or known asthma may result in a more severe reaction.

The dose immediately prior to events, in both clinical trial database and post marketing safety database varies widely. No consistent pattern or predictive dose appears and the higher individual doses do not appear to be correlated with increased frequency or severity of events.

There is no consistent pattern or predictive dose or administration relationship in relation with the occurrence of these events and importantly the higher individual doses do not appear to be correlated with increased frequency or severity of events.

The majority of hypersensitivity associated events (15.1%) occurred between 1 hour and 24 hours after treatment with iron sucrose, closely followed by hypersensitivity associated events which occurred between 5 and 30 minutes (13.9%)

In conclusion, regarding post-marketing data, 317 cases of hypersensitivity were reported (frequency rate 0.0022%). When outcome is known, most patients recovered without sequelae (94.8%). According to the MAH, of 9 fatal cases of hypersensitivity reactions reported, six (1.9%, 6/317) were considered to be related.

Test dose

Some of the assessed parenteral iron-containing products have a recommendation for a test dose to be administered prior to the final administration. As data from the post marketing reporting showed that a successful test dose may give false assurance to the professionals dealing with the product administration, no test dose should be applied. Instead caution should be exercised in each iron administration even in the cases of repeated administrations. In conclusion the CHMP recommended that no test dose is administered for any of the intravenous containing iron products.

2.5. Risk minimisation measures and other pharmacovigilance activities

As part of the risk minimisation measures the CHMP considered there was a need to ensure that all relevant information for the safe use of these products should be applied across authorised products and therefore agreed on the wording for all relevant sections dealing with the risk of hypersensitivity reactions including the sections on pregnancy.

The CHMP endorsed a Direct healthcare professional communication (DHPC), to communicate the outcome of the present review and to communicate to the healthcare professionals the updated method of administration for these products in an environment where trained staff and facilities for resuscitation exist and to highlight the risk of the hypersensitivity reactions.

In addition the CHMP requested the MAHs to submit annual cumulative reviews of hypersensitivity case reports, all fatal cases and all pregnancy cases, together with usage data yearly. This recommendation was also advised by the PRAC during the consultation requested by the CHMP.

The CHMP also agreed on the need of an updated risk management plan to be submitted for the products which have a risk management plan already; for the medicinal products which do not have an EU risk minimisation plan the CHMP is requesting the MAHs to submit one.

Furthermore the PRAC requested that the protocol of a post-authorisation safety study (PASS) should be submitted within the risk management plan submission, to better characterize the safety concerns for the hypersensitivity reactions. This recommendation was also advised by the PRAC during the consultation requested by the CHMP.

Finally educational material for prescribers as well for patients highlighting the risks and warnings of hypersensitivity reactions (by e.g. a checklist, to be implemented at national level) have been requested by the CHMP for submission within the risk management plan.

In accordance also with the Article 23 of Regulation (EC) No 726/2004 the products will be included in the list of products for additional monitoring. The relevant information as well as the pictogram (triangle) will be added in the product information of the products.

2.6. Overall benefit/risk assessment

The Committee reviewed all available data from pre-clinical, clinical studies, published literature, post-marketing experience on the safety of intravenous iron containing medicinal products with regards to hypersensitivity reactions.

As the conclusions of this assessment were mainly drawn from the post-marketing data, differentiation between these iron complexes in terms of hypersensitivity reactions could not be identified. So the CHMP conclusions are applicable to all the iron complexes assessed in this referral.

The CHMP concluded that the benefit-risk balance of intravenous iron containing medicinal products is favourable as the benefits continue to outweigh the risks in the treatment of iron deficiency when the oral route is insufficient or poorly tolerated. Furthermore the CHMP agreed on other changes to the product information, additional pharmacovigilance activities and risk minimisation measures to address the risk of hypersensitivity events to all patients including administration in pregnancy. For pregnancy specifically, as oral iron may be well tolerated in the first trimester of the pregnancy, the CHMP advised that the intravenous iron complexes are not given to pregnant women in the early stages. In later stages of pregnancy the intravenous iron preparations may be given but after careful consideration of the risks involved for the mother and foetus. Patients with known allergies and with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis) may enhance their risk when given these products as their condition may worsen unless it is deemed that the benefit outweighs the risks for these patients. All administrations of these iron complexes should be given in an environment with staff able to recognise and treat hypersensitivity reactions and where resuscitation facilities are available. Close monitoring for signs of hypersensitivity during and for at least 30 minutes after each administration of an intravenous iron product is also recommended.

The CHMP concluded that the information on test dose is not appropriate as it may give false reassurance to the healthcare professionals.

The CHMP endorsed a Dear healthcare professional communication (DHPC), to communicate the outcome of the present review.

The CHMP also agreed that the MAHs should submit annual cumulative reviews of hypersensitivity case reports, all fatal cases and all pregnancy cases, together with usage data, using same data lock point, same exposure definition, same event definition and the severity classification according to Ring and Messmer classification. The MAHs also should amend their risk management plan, provide a protocol of a PASS within the risk management plan submission to characterise the safety concerns on the hypersensitivity reactions and also provide educational material for prescribers and patients. The latter should also be included in the risk management plan, highlighting the risks and warnings of hypersensitivity reactions.

2.7. Communication plan

As part of this referral procedure, the MAHs and the CHMP agreed the wording of a 'Dear healthcare professional' communication designed to inform prescribers of the risk of hypersensitivity reactions associated with these iron IV containing medicinal products and the amendments to the Product information. This communication should be circulated within 30 days of the Commission decision of this referral procedure.

2.8. Changes to the product information

Summary of product characteristics

Section 4.2 Posology and method of administration

In this section the CHMP recommended that wording on careful monitoring of patients for signs and symptoms of hypersensitivity reactions during and following each administration should be included.

In addition the CHMP emphasised that the products 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 injection.

Furthermore the CHMP concluded that any reference to the test dose should be removed from this section.

Section 4.3. Contraindications

Contraindications for patients with known hypersensitivity to the active substance, to the product or any of its excipients listed was inserted. In addition the products are contraindicated for patients with known serious hypersensitivity to other parenteral iron products.

Section 4.4 Special warnings and precautions for use

As parenterally administered iron preparations can cause hypersensitivity reactions including serious and potentially fatal anaphylactic/anaphylactoid reactions caution should be excersiced during their administration.

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. 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).

Section 4.6 Fertility, pregnancy and lactation

The CHMP concluded that since there are no adequate and well-controlled trials of these products in pregnant women, careful risk/benefit evaluation is required before use during pregnancy and they should not be used during pregnancy unless clearly necessary.

Treatment with these products 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.

Section 4.8 Undesirable effects

The information on the way of reporting of adverse reactions was added in this section according to the latest template.

Package Leaflet

The corresponding sections of the package leaflet were amended accordingly.

3. Overall conclusion

Having considered the overall submitted data provided by the MAHs in writing, the CHMP concluded that the benefits of intravenous iron containing medicinal products continue to outweigh the risks in the treatment of iron deficiency situations when the oral route is insufficient or poorly tolerated.

The CHMP in addition stressed that the intravenous iron products should only be administered when staff trained to evaluate and manage anaphylactic/anaphylactoid reactions as well as resuscitation facilities are immediately available. Patients should be closely monitored for signs of hypersensitivity during and for at least 30 minutes after each administration of an intravenous iron product.

In addition the CHMP considered that the risk of hypersensitivity is increased in patients with known allergies (including drug allergies) and in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis) as well as in patients with a history of severe asthma, eczema or other atopic allergy. In these patients, intravenous iron products should only be used if the benefit is clearly judged to outweigh the potential risk.

Furthermore, the CHMP considered that in view of the currently available safety data in order to maintain a favourable benefit-risk balance, these intravenous iron containing medicinal products should be contraindicated in patients with history of hypersensitivity reactions to the active substance or any of the excipients of these products, as well as to patients who experienced allergic reactions to other parenteral iron containing products. In addition the CHMP stressed that these products should not be given to pregnant women in the first trimester of pregnancy; treatment should be confined to second or third trimester, if the benefit is clearly judged to outweigh the potential risks for both the mother and the foetus.

The Committee recommended further risk minimisation measures such as information to patients and healthcare professionals. Cumulative annual reporting of hypersensitivity reactions should be undertaken by all MAHs of these products. Furthermore the CHMP requested that a PASS will be conducted to further evaluate the safety concern of the hypersensitivity reactions, as well as adequate educational materials to be developed for patients and prescribers.

Therefore, the CHMP recommended the variation to the terms of the marketing authorisation for the medicinal products referred to in Annex I, for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III to the opinion.

The Committee as consequence concluded that the benefit-risk balance of intravenous iron containing medicinal products in the iron deficiency situations where the oral iron is not sufficient or tolerated remains positive under normal conditions of use, subject to the restrictions, warnings, changes to the product information, additional pharmacovigilance activities and risk minimisation measures agreed.

The conditions affecting the marketing authorisations are set out in Annex IV of the Opinion.

4. Annexes

The list of the names of the medicinal products, marketing authorisation holders, pharmaceutical forms, strengths and route of administration in the Member States are set out Annex I to the Opinion.