

Annex II

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

Scientific conclusions

Overall summary of the scientific evaluation of intravenous iron containing medicinal products (see Annex I)

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effective use, and on whether the marketing authorisation for these products should be maintained, varied, suspended or withdrawn.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, iron 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 Messmer¹ 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 spasms 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 iron-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

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

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.

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.

Overall conclusion

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.

Benefit –risk balance

The Committee 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.

Grounds for the variation to the terms of the marketing authorisation

Whereas

- The Committee considered the procedure under Article 31 of Directive 2001/83/EC for intravenous iron containing medicinal products.
- The Committee reviewed all available data from pre-clinical, clinical studies, pharmacoepidemiological studies, published literature, post-marketing experience on the safety of intravenous iron containing medicinal products with regards to hypersensitivity reactions.
- The Committee is of the opinion 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 Committee 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.
- The Committee 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.
- The Committee 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 concluded that there was need for 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.

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.