# RISK MANAGEMENT PLAN (EU)
# VENOFER®

| | |
|---|---|
| Active Substance: | Iron sucrose |
| Anatomical Therapeutic Code: | Anti-anaemic preparation. Iron trivalent, parenteral preparation (B03AC) |
| MAH or Applicant: | Vifor (International) Inc.<br>Rechenstrasse 37<br>9014 St. Gallen<br>Switzerland |
| Contact Person for this RMP: | [redacted] |
| Medicinal Product(s) to Which this RMP Refers: | Venofer |
| Products Concerned (Brand Name): | Venofer®/Idafer® 20 mg iron/mL, solution for injection or concentrate for solution for infusion |
| Data Lock Point for this RMP: | 1 January 2015 |
| Date of Final Sign-off: | 10 March 2015 |
| Version: | 2.1 |

# SIGNATURE PAGE

This Risk Management Plan (Version 2.1) for Venofer® for the period covered from international birth date to 1 January 2015 has been prepared and approved as follows:

Prepared by:

[redacted]

11. Jun 2015

Date (day month year)

Reviewed by:

[redacted]

11 Jun 2015

Date (day month year)

Approved by:

[redacted]

11 JUN 2015

Date (day month year)

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| | |
|---|---|
| CHF | Chronic heart failure |
| CKD | Chronic kidney disease |
| DLP | Data lock point |
| EEA | European Economic Area |
| EU | European Union |
| GI | Gastrointestinal |
| GLP | Good Laboratory Practice |
| Hb | Haemoglobin |
| IBD | Inflammatory bowel disease |
| ID | Iron deficiency |
| IDA | Iron deficiency anaemia |
| IV | Intravenous |
| MAH | Marketing Authorisation Holder |
| mcg | Micrograms |
| PASS | Post-authorisation safety study |
| PL | Package Leaflet |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PV | Pharmacovigilance |
| RMP | Risk Management Plan |
| RSI | Reference Safety Information |
| SmPC | Summary of Product Characteristics |
| TQ | Targeted Questionnaire |
| US | United States |

# PART I: PRODUCT OVERVIEW

## Administrative Information on the Risk Management Plan

| Part | Section/Annex | Date Last Updated for Submission (Sign-off Date) | Version No. of Risk Management Plan When Last Submitted |
|---|---|---|---|
| Part II Safety Specification | SI Epidemiology of the Indication and Target Population | 28 November 2013 | 1.0 |
| | SII Nonclinical Part of the Safety Specification | 22 April 2014 | 1.1 |
| | SIII Clinical Trial Exposure | 22 April 2014 | 1.1 |
| | SIV Populations not Studied in Clinical Trials | 22 April 2014 | 1.1 |
| | SV Post-authorisation Experience | 10 March 2015 | 2.0 |
| | SVI Additional EU Requirements for the Safety Specification | 11 June 2015 | 2.1 |
| | SVII Identified and Potential Risks | 11 June 2015 | 2.1 |
| | SVIII Summary of the Safety Concerns | 11 June 2015 | 2.1 |
| Part III Pharmacovigilance Plan | | 11 June 2015 | 2.1 |
| Part IV Plan for Post-authorisation Efficacy Studies | | 10 March 2015 | 2.0 |
| Part V Risk Minimisation Measures | | 11 June 2015 | 2.1 |
| Part VI Summary of RMP | | 10 March 2015 | 2.0 |
| Part VII Annexes | Annex 2 Current or Proposed SmPC/PL | 28 November 2013 | 1.0 |
| | Annex 3 Worldwide Marketing Status by Country | 10 March 2015 | 2.0 |
| | Annex 4 Synopsis of Clinical Trial Programme | 10 March 2015 | 2.0 |

| Part | Section/Annex | Date Last Updated for Submission (Sign-off Date) | Version No. of Risk Management Plan When Last Submitted |
|---|---|---|---|
| | Annex 5<br>Synopsis of Pharmacoepidemiological Study Programme | 28 November 2013 | 1.0 |
| | Annex 6<br>Protocols for Proposed and Ongoing Studies in Part III | 22 April 2014 | 1.1 |
| | Annex 7<br>Specific Adverse Event Follow-up Forms | 11 June 2015 | 2.1 |
| | Annex 8<br>Protocols for Studies in Part IV | 28 November 2013 | 1.0 |
| | Annex 9<br>Synopsis of Newly Available Study Reports in Parts III-IV | 10 March 2015 | 2.0 |
| | Annex 10<br>Details of Proposed Additional Risk Minimisation Activities | 10 March 2015 | 2.0 |
| | Annex 11<br>Mock-up Examples | 10 March 2015 | 2.0 |
| | Annex 12<br>Other Supporting Data | Not applicable | Not applicable |

## Overview of Versions

| | |
|---|---|
| Version number of last agreed RMP: | 1.1 |
| Agreed within: | UK/H/0313/001/II046 |

## Current RMP Versions Under Evaluation

| RMP Version Number | Submitted On | Submitted Within |
|---|---|---|
| 2.0 | 27 Mar 2015 – 03 Apr 2015 | UK/H/0313/001/IB/053<br>and 14 National Procedures |

| | |
|---|---|
| **Invented name in the EEA** | Venofer®/Idafer® 20 mg iron/mL, solution for injection or concentrate for solution for infusion[(1)]. |
| **Authorisation procedure** | Mutual Recognition<br>Austria, Belgium, Denmark, Finland, Greece, Ireland, Italy, Luxembourg, Spain, Sweden, United Kingdom<br>National<br>Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, France, Germany, Hungary, Iceland, Latvia, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia |
| **Brief description of the product including** | |
| Chemical class<br>Summary of mode of action<br>Important information about its composition | Venofer is a brown, sterile solution of iron sucrose containing 2% w/v iron (20 mg iron as iron(III)-hydroxide sucrose complex per mL) bound in a stable polynuclear, non-ionic sucrose complex, the core of which is structurally similar to that of the physiological iron storage protein ferritin. Iron sucrose belongs to the pharmacotherapeutic group of anti-anaemic preparations. |
| **Indication(s) in the EEA** | |
| Current | Venofer is indicated for the treatment of ID in the following indications[(2)]:<br>• Where there is a clinical need to deliver iron rapidly to iron stores<br>• In patients who cannot tolerate oral iron therapy or who are non-compliant<br>• In active IBD where oral iron preparations are ineffective<br>The diagnosis of ID must be based on appropriate laboratory tests (e.g., Hb, serum ferritin, serum iron, etc.). |
| Proposed | Not applicable |
| **Posology and route of administration in the EEA** | |
| Current | Normal posology: 100-200 mg iron 1-3 times a week[(3)].<br>Monitor carefully patients for signs and symptoms of hypersensitivity reactions during and following each administration of Venofer.<br>Venofer 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 Venofer injection (see Section 4.4 of the SmPC (Annex 2)).<br>Administration: Venofer must only be administered by the IV route. This may be by a slow IV injection or by an IV drip infusion.<br>Venofer must not be used for intramuscular injection.<br>Adults and the elderly: The total cumulative dose of Venofer, equivalent to the total iron deficit (mg), is determined by the Hb level and body weight. The dose for Venofer must be individually determined for each patient according to the total iron deficit calculated with the following formula:<br>Total iron deficit [mg]=body weight [kg] x (target Hb - actual Hb) [g/dL] x 2.4 + depot iron [mg]<br>• Below 35 kg body weight: target Hb=13 g/dL and depot iron=15 mg/kg body weight<br>• 35 kg body weight and above: target Hb=15 g/dL and depot iron=500 mg<br>• Factor 2.4=0.0034 x 0.07 x 1,000 x 10 (iron content of Hb=0.34%; blood volume=7% of body weight; Factor 1,000=conversion from g to mg; Factor 10=conversion from g/L to g/dL)<br>The total amount of Venofer required in mg is determined from the above calculation. |

Alternatively, the total amount of Venofer required in mL is determined from the following formula or dosage table.

$$\text{Total amount of Venofer required [mL]} = \frac{\text{Total iron deficit [mg]}}{20\ \text{mg/ml}}$$

**Table 1 Dosage Table Stating the Total Amount of Venofer in mL**

| Body Weight | Total Amount of Venofer to be Administered | | | |
|---|---|---|---|---|
| | Hb 6 g/dL | Hb 7.5 g/dL | Hb 9 g/dL | Hb 10.5 g/dL |
| 30 kg | 47.5 mL | 42.5 mL | 37.5 mL | 32.5 mL |
| 35 kg | 62.5 mL | 57.5 mL | 50 mL | 45 mL |
| 40 kg | 67.5 mL | 60 mL | 55 mL | 47.5 mL |
| 45 kg | 75 mL | 65 mL | 57.5 mL | 50 mL |
| 50 kg | 80 mL | 70 mL | 60 mL | 52.5 mL |
| 55 kg | 85 mL | 75 mL | 65 mL | 55 mL |
| 60 kg | 90 mL | 80 mL | 67.5 mL | 57.5 mL |
| 65 kg | 95 mL | 82.5 mL | 72.5 mL | 60 mL |
| 70 kg | 100 mL | 87.5 mL | 75 mL | 62.5 mL |
| 75 kg | 105 mL | 92.5 mL | 80 mL | 65 mL |
| 80 kg | 112.5 mL | 97.5 mL | 82.5 mL | 67.5 mL |
| 85 kg | 117.5 mL | 102.5 mL | 85 mL | 70 mL |
| 90 kg | 122.5 mL | 107.5 mL | 90 mL | 72.5 mL |

Notes: To convert Hb (mM) to Hb (g/dL), multiply the former by 1.61145.
Hb=Haemoglobin.

Example: For a patient of 60 kg body weight with an actual Hb of 6 g/dL, 90 mL should be administered. (Alternatively 18 ampoules/vials of 5 mL or 36 vials of 2.5 mL should be administered.)

Dosage: The total single dose must not exceed 200 mg of iron given not more than 3 times per week. If the total necessary dose exceeds the maximum allowed single dose, then the administration has to be split.

Children: The use of Venofer has not been adequately studied in children and, therefore, Venofer is not recommended for use in children.

IV drip infusion: Venofer must be diluted only in sterile 0.9% m/V sodium chloride solution:

2.5 mL Venofer (50 mg iron) in maximum 50 mL sterile 0.9% m/V sodium chloride solution

5 mL Venofer (100 mg iron) in maximum 100 mL sterile 0.9% m/V sodium chloride solution

10 mL Venofer (200 mg iron) in maximum 200 mL sterile 0.9% m/V sodium chloride solution

For stability reasons, dilutions to lower Venofer concentrations are not permissible.

Dilution must take place immediately prior to infusion and the solution should be administered as follows:

100 mg iron (5 mL Venofer) in at least 15 minutes

200 mg iron (10 mL Venofer) in at least 30 minutes

IV injection: Venofer may be administered by slow IV injection at a rate of 1 mL undiluted solution per minute and not exceeding 10 mL Venofer (200 mg iron) per injection.

Injection into dialyser: Venofer may be administered during a haemodialysis

| | |
|---|---|
| | session directly into the venous limb of the dialyser under the same procedures as those outlined for IV injection. |
| Proposed | Not applicable |
| **Pharmaceutical forms and strengths** | |
| Current | One mL of solution contains 20 mg of iron as iron sucrose (iron(III)-hydroxide sucrose complex).<br>Each 5 mL ampoule of Venofer contains 100 mg iron as iron sucrose (iron(III)-hydroxide sucrose complex).<br>Each 2.5 mL vial of Venofer contains 50 mg iron as iron sucrose (iron(III)-hydroxide sucrose complex).<br>Each 5 mL vial of Venofer contains 100 mg iron as iron sucrose (iron(III)-hydroxide sucrose complex).<br>For a full list of excipients, see Section 6.1 of the SmPC. |
| Proposed | Not applicable |

1 Within this RMP, Venofer refers to all medicinal products with the active ingredient iron sucrose, which are in the EU under the brand names Venofer and Idafer.
2 In single countries the indications differ from the indications listed above.
3 Posology and route of administration varies in France.
Notes: EEA=European Economic Area; Hb=Haemoglobin; IBD=Inflammatory bowel disease; ID=Iron deficiency; IV=Intravenous; RMP=Risk Management Plan; SmPC=Summary of Product Characteristics.

| | | |
|---|---|---|
| Country and date of first authorisation worldwide: | Switzerland | 6 December 1949 |
| Country and date of first launch worldwide: | Switzerland | 1950 |
| Country and date of first authorisation in the EEA: | Portugal | 1964 |
| Is the product subject to additional monitoring in EU? | Yes ☒ | No ☐ |

# PART II: SAFETY SPECIFICATION

# SI EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

Indication: Treatment of iron deficiency (ID) where there is a clinical need to deliver iron rapidly to iron stores, in patients who cannot tolerate oral iron therapy or who are non-compliant, in active inflammatory bowel disease (IBD) where oral iron preparations are ineffective.

Brand name: Venofer® 20 mg iron/mL, solution for injection or concentrate for solution for infusion.

## SI.1 Epidemiology of the Disease

### SI.1.1 Overview of the Disease

Anaemia is the result of a wide variety of causes that can exist isolated; however more often coexist. Globally, the most significant contributor to the onset of anaemia is ID so that iron deficiency anaemia (IDA) and anaemia are often used synonymously, and the prevalence of anaemia has often been used as a proxy for IDA. It is generally assumed that 50% of the cases of anaemia are due to ID [1]. In 2010, IDA was considered to be among the most important contributing factors to the global burden of disease affecting both developing and developed countries. Although prevalence varied substantially across communities, in 2010 IDA affected 14.9% of the world's population, all ages combined [2].

### SI.1.2 Definition and Diagnosis

The definition of anaemia varies by sex and age. The most commonly used definitions of anaemia come from the Centers for Disease Control and Prevention and the World Health Organization (Table 2).

**Table 2 Definition of Anaemia by Haemoglobin Value**

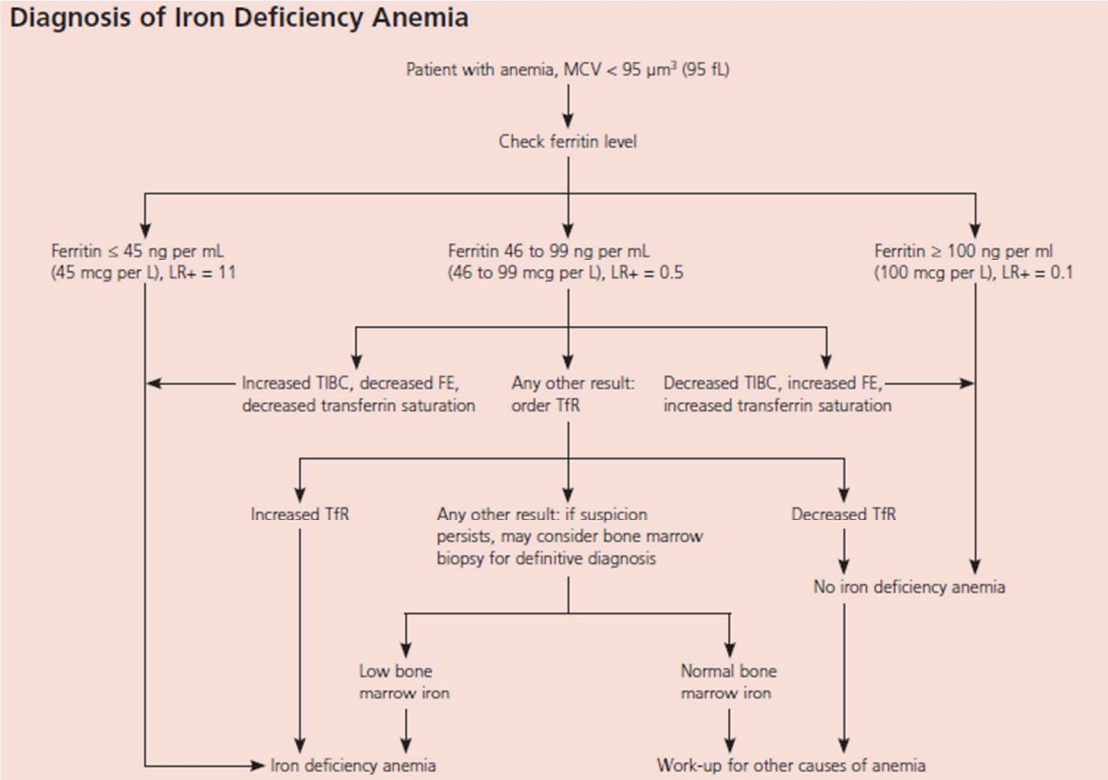
| | Haemoglobin Level | |
|---|---|---|
| | **WHO** | **CDC** |
| Infants 0.5 to 4.9 years | – | <11 g/dL |
| Children 5.0 to 11.9 years | – | <11.5 g/dL |
| Menstruating women | <12 g/dL | – |
| Pregnant women in first or third trimester | <11 g/dL | <11 g/dL |
| Pregnant women in second trimester | <11 g/dL | <10.5 g/dL |
| Men | <13 g/dL | – |

Notes: CDC=Centers for Disease Control and Prevention; WHO=World Health Organization.

The diagnosis of IDA requires that a patient be anaemic and show laboratory evidence of ID (Figure 1). Red blood cells in IDA are usually described as being microcytic

(i.e., mean corpuscular volume less than 80 $\mu m^3$ (80 fL)) and hypochromic, however the manifestation of ID occurs in several stages. The most accurate initial diagnostic test for IDA is the serum ferritin measurement. Serum ferritin values greater than 100 ng/mL (100 mcg/L) indicate adequate iron stores and a low likelihood of IDA [3]. Patients with a serum ferritin concentration less than 25 ng/mL have a very high probability of being iron deficient.

**Figure 1 Diagnostic Algorithm for Iron Deficiency Anaemia**

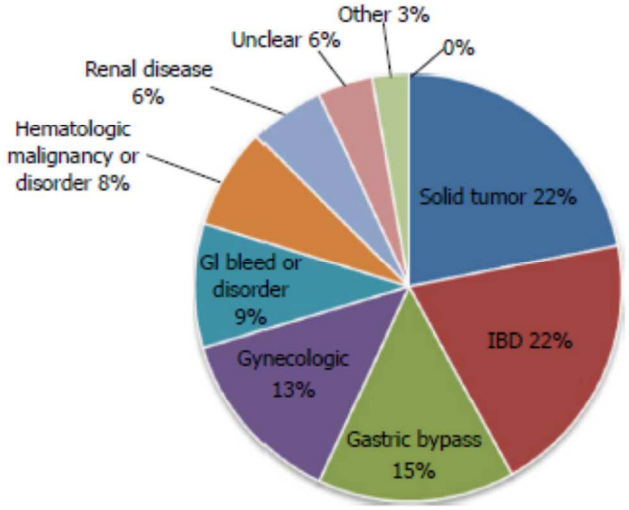



Notes: FE=Serum iron; LR+=Positive likelihood ratio; MCV=Mean corpuscular volume; TfR=Serum transferrin receptor; TIBC=Total iron-binding capacity [4].

Warsch and Byrnes [5] reported specific diagnoses associated with the administration of intravenous (IV) iron in 262 patients admitted at the Miami Hospital Clinic (US) from January 2007 to May 2012.

Several patients had multiple indications requiring treatment with IV iron. The most common indications for IV iron use were for issues related to cancer and its treatment (21.9%), IBD (20.1%), and gastric bypass (15.0%). Other indications included gynaecologic conditions (13%), a gastrointestinal (GI) bleed or disorder other than IBD (9%), and haematologic malignancies or disorders (8%) (Figure 2).

**Figure 2 Indications for Intravenous Iron**




Notes: GI=Gastrointestinal; IBD=Inflammatory bowel disease.

## SI.1.3 Aetiology and Risk Factors

The main risk factors for IDA include a low intake of iron, poor absorption of iron from diets high in phytate or phenolic compounds, and period of life when iron requirements are especially high (i.e., growth and pregnancy). Among the other causes of anaemia, heavy blood loss as a result of menstruation, or parasite infections such as hookworms, ascaris, and schistosomiasis can lower blood haemoglobin (Hb) concentrations. Acute and chronic infections, including malaria, cancer, tuberculosis, and HIV can also lower blood Hb concentrations. The presence of other micronutrient deficiencies, including Vitamins A and $B_{12}$, folate, riboflavin, and copper can increase the risk of anaemia. Furthermore, the impact of haemoglobinopathies on anaemia prevalence needs to be considered within some populations [6].

**Table 3 Epidemiology of Iron Deficiency**

| Epidemiology | Iron deficiency |
|---|---|
| Indication/target population | Venofer® is indicated for the treatment of ID in the following indications:<br>• Where there is a clinical need to deliver iron rapidly to iron stores<br>• In patients who cannot tolerate oral iron therapy or who are non-compliant<br>• In active IBD where oral iron preparations are ineffective<br>The diagnosis of ID must be based on appropriate laboratory tests (e.g., Hb, serum ferritin, serum iron, etc.).<br>The target population is the general population or populations with special needs such as patients with active IBD where oral preparations are ineffective.<br>Parenteral iron replacement is medically used:<br>• For patients needing iron replacement who are unable to tolerate compounds given orally.<br>• For patients losing iron (blood) at a rate too fast for oral intake to compensate for this iron loss. |

- For patients with a disorder of the GI tract, such as ulcerative colitis, in which symptoms of the disease may be aggravated by oral iron therapy.
- For patients who are unable to maintain the correct iron balance, e.g., on treatment with haemodialysis.

Incidence in target population

An accurate representation of incidence rates regarding ID in the target population is currently not available as most literature is focused on the prevalence of anaemia in the target population.

Prevalence in target population

Anaemia is a global public health problem affecting both developing and developed countries with major consequences for human health as well as social and economic development. It occurs at all stages of the life cycle, however is more prevalent in pregnant women and young children. In 2002, IDA was considered to be among the most important contributing factors to the global burden of disease [6].

The estimates presented are based on data from the World Health Organization Global Database on Anemia 1993-2005 [6,7].

Globally, anaemia affects 1.62 billion people (95% CI 1.50-1.74 billion), which corresponds to 24.8% of the worldwide population (95% CI 22.9-26.7%). Pregnant women and young children are at greatest risk. The highest proportion of individuals affected is in Africa and Asia: almost two-thirds of preschool-aged children living in Africa are anaemic.

**Table 4 Global Anaemia Prevalence and Number of Individuals Affected in 2006**

| Population Group | Prevalence of Anaemia | | Population Affected | |
|---|---|---|---|---|
| | Percent | 95% CI | Number (Million) | 95% CI |
| Preschool-age children | 47.4 | 45.7-49.1 | 293 | 283-303 |
| School-age children | 25.4 | 19.9-30.9 | 305 | 238-371 |
| Pregnant women | 41.8 | 39.9-43.8 | 56 | 54-59 |
| Non-pregnant women | 30.2 | 28.7-31.6 | 468 | 446-491 |
| Men | 12.7 | 8.6-16.9 | 260 | 175-345 |
| Elderly | 23.9 | 18.3-29.4 | 164 | 126-202 |
| Total population | 24.8 | 22.9-26.7 | 1,620 | 1,500-1,740 |

Note: CI=Confidence interval.

ID occurs in about 60-80% of patients with IBD [8], and anaemia manifests in approximately one-third of patients (the prevalence of IDA ranges from 36-76% [9]). Anaemia is the most common systemic manifestation of IBD.

Numbers and facts:

- IBD (in IDA): range from 36 to 90% [10,11]
  - Mean prevalence 68% [10,11]

Demographic profile of target population

WHO estimates 700 to 800 million people worldwide are suffering from IDA. Some patients are particularly at risk due to malabsorption of dietary iron (e.g., IBD, GI surgery) or increased utilisation or loss from the body (e.g., pregnant women, menstruating or lactating females, haemodialysis patients, patients undergoing surgery who might experience blood loss or trauma). ID adversely affects the cognitive performance, behaviour, and physical growth of children, immune status and morbidity from infections and the physical capacity and work performance of adolescents and adults of all age groups (WHO) [1].

Main treatment options

ID is a state of reduced body iron content where the physiological function of the blood and tissues, such as the brain and muscles, is impaired. Effective treatment of

| Epidemiology | Iron deficiency |
|---|---|
| | ID includes identifying and treating the underlying cause and initiating iron replacement therapy with either oral or IV iron.<br>Iron supplements intended for oral administration remains the most common treatment options. They contain bivalent ($Fe^{2+}$; ferrous sulphate, ferrous fumarate, ferrous gluconate) or trivalent ($Fe^{3+}$; ferric polymaltose complex) iron forms. Only bivalent iron is consequently resorbed from the GI tract. However, more than 90% of ingested iron remains unabsorbed [8]. Oral iron therapy is the treatment of choice for the majority of patients because of the ease of administration and the perceived effectiveness, safety and economy. Although appropriate for many patients, oral iron (in particular in the bivalent form) can cause dose-dependent, undesirable effects in up to 40% of patients [12].<br>Therapy of ID by IV administration may be initiated only in case if the oral preparations are ineffective or cannot be tolerated by the patient.<br>Severe IDA may require a blood transfusion, iron injections, or IV iron therapy.<br>Before iron supplementation, it has to be considered if anaemia is caused by Vitamin $B_{12}$ (cyanocobalamin) or folic acid deficiency. In case concomitant Vitamin $B_{12}$ or folic acid deficiency are diagnosed, these should be administered together with IV iron as they are crucial to ensure appropriate response to IV iron treatment as seen by increase of red blood cell counts to normal levels.<br>Other forms of anaemia may be a consequence of myelosuppression rather than ID and are commonly treated with erythropoietin, anabolic steroids, corticosteroids or blood transfusions. |
| Important comorbidities in target population | IBD, CHF, CKD, anaemia induced by cancer (oncology patients), HUB, postpartum anaemia, dysfunctional uterine bleeding and diabetes. |
| Risk factors for the disease | The main recognised risk factors for the onset of ID/IDA are as follows:<br>Increased iron loss:<br>• Gender (women, especially premenopausal or pregnant, are most likely to be affected by ID than men)<br>• Frequent blood donors<br>• Cancer patients suffering from intestinal cancers followed by occult intestinal bleeding<br>• Chronic and acute bleeding from the GI tract (e.g., peptic ulcer disease and gastritis)<br>• Patients with CKD undergoing haemo- or peritoneal dialysis.<br>Decreased iron uptake:<br>• Dietary factors such as vegetarianism or malnutrition (e.g., in elderly)<br>• Chronic GI diseases with decreased GI resorption (e.g., Crohn's disease, celiac disease)<br>• Chronic inflammatory status, e.g., CKD, CHF, rheumatoid arthritis<br>Increased iron need<br>• Age (children and adolescents are more frequently affected by ID)<br>• Excessive exercise<br>• Pregnancy and lactation |
| Mortality in target indication | The global age-standardised death rate for IDA was 1.0 per 100,000 (95% CI 0.8-1.2) in 2010 [13]. In terms of regional ranking of leading causes of years of life lost, IDA ranked 81-83 in high income North America and Western Europe, 89-90 in Eastern and Central Europe, 75 in South Asia, 44-54 in Southern and Eastern sub-Saharan Africa, 26-27 in Western and Central sub-Saharan Africa, and 15 in the Caribbean [14].<br>Higher mortality rates are observed in patients with anaemia in general. Anaemia is |

| Epidemiology | Iron deficiency |
|---|---|
| | associated with increased mortality in CKD, CHF and acute myocardial infarction patients [15].<br><br>• Anaemia alone: 16.6% [16]<br>• CHF + anaemia: 34.6% [16]<br>Klip et al, 2013 [17] investigated the predictive value of ID for mortality in CHF patients with or without anaemia in an international pooled analysis. ID but not anaemia remained an independent predictor for mortality (HR 1.42, 95% CI 1.14-1.77, p=0.002), even after adjustment for all univariate associated variables. No significant interaction was observed between ID and anaemia (p=0.841). ID remained an independent predictor of mortality in anaemic (HR 1.71, 95% CI 1.24-2.36, p=0.001) and nonanaemic patients (HR 1.44, 95% CI 1.11-1.87, p=0.006) [17].<br>• CKD + anaemia: 27.3% [16]<br>• CHF + CKD + anaemia: 45.6% [16] |
| Potential health risk | ID adversely affects the cognitive performance, behaviour, and physical growth of children, immune status and morbidity from infections and the physical capacity and work performance of adolescents and adults of all age groups. |

Notes: CHF=Chronic heart failure; CI=Confidence interval; CKD=Chronic kidney disease; GI=Gastrointestinal; Hb=Haemoglobin; HR=Hazard ratio; HUB=Heavy uterine bleeding; IBD=Inflammatory bowel disease; ID=Iron deficiency; IDA=Iron deficiency anaemia; IV=Intravenous; WHO=World Health Organization.

## SI.2 Medication(s) in the Target Population

Target population suffering from ID may be very broad including various oncology, gynaecology, nephrology (e.g., chronic kidney disease (CKD)) or GI conditions (e.g., IBD). Concomitant medication therefore, may include a large variety of both over-the-counter and prescription medicines.

However, there are some particular conditions which are more often associated with ID and IDA and represent important comorbidities of ID. These conditions are summarised in Table 3 and closely discussed in Table 5 in the following Section SI.3. Concomitant medication may include but is not limited to:

- IBD: aminosalicylates such as sulphasalazine and mesalazine, immunosuppressive medications such as azathioprine, corticosteroids; biological preparations such as infliximab, adalimumab
- Chronic heart failure (CHF): angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, digoxin, beta-blockers, diuretics, aldosterone antagonists
- CKD: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, low-dose aspirin, statins, Vitamin D supplements, phosphate binders
- Oncology: chemotherapeutics, corticosteroids, analgesics (including opioids), antiemetics.

## SI.3 Important Comorbidities Found in the Target Population

### Table 5 Important Comorbidities Found in Target Population

| **Comorbidity** | **IBD** |
|---|---|
| Incidence of condition | Incidence rates of IBD in ID patients are not available |
| Prevalence of condition | ID occurs in about 60-80% of patients with IBD and anaemia manifests in approximately one-third of patients [8]. Recently published review showed study data with the prevalence of anaemia in IBD patients ranging from 16-74%, with a mean value of 16% in outpatients and 68% in hospitalised patients [8].<br>Prevalence of ID in IBD adult outpatients:<br>• IBD - all: 35% [18]<br>• IBD - ulcerative colitis: 32% [18]<br>• IBD - Crohn's disease: 38% [18]<br>Goodhand et al, 2012 [19] demonstrated in a more recently published prospective trial that anaemia and IDA are particularly prevalent in children with IBD, the incidence of anaemia being 70% in children, 42% in adolescents, and 40% in adults with IBD. IBD was also found to occur more commonly in children (88%) and adolescents (83%) than in adults (55%) with IBD. |
| Mortality of condition | IBD patients suffering from anaemia have a higher mortality rates than patients without anaemia [20]. |
| **Comorbidity** | **CHF** |
| Incidence of condition | Incidence rates of CHF in ID patients are not available. |
| Prevalence of condition | Estimates of the prevalence of anaemia in patients with CHF and low ejection fraction range widely from 4% to 61% (median 18%), based on the different definitions of anaemia [21].<br>Estimates calculated within the last decade suggest a prevalence of CHF in general population of approximately 1–2% and >10% in the elderly population.<br>ID is present in 61.2% of anaemic patients with CHF [17].<br>It has been estimated that there are currently 6.5 million CHF patients in Europe and 5 million in the US [22]. |
| Mortality of condition | The long-term prognosis associated with CHF is poor.<br>Mortality rates:<br>• Anaemia alone: 16.6% [16]<br>• CHF: 26.1% [16]<br>• CHF + anaemia: 34.6% [16]<br>Klip et al, 2013 investigated the predictive value of ID for mortality in CHF patients with or without anaemia in an international pooled analysis. ID but not anaemia remained an independent predictor for mortality (HR 1.42, 95% CI 1.14-1.77, p=0.002), even after adjustment for all univariate associated variables.<br>No significant interaction was observed between ID and anaemia (p=0.841).<br>ID remained an independent predictor of mortality in anaemic (HR 1.71, 95% CI 1.24-2.36, p=0.001) and nonanaemic patients (HR 1.44, 95% CI 1.11-1.87, p=0.006) [17].<br>CKD is a common comorbidity of CHF [21]. |

| | |
|---|---|
| | Mortality rates:<br>• CHF and CKD: 38.4% [16]<br>• CHF, CKD and anaemia: 45.6% [16]<br>Please refer to Table 6 for more detailed information. |
| **Comorbidity** | **CKD** |
| Incidence of condition | Incidence rates of CKD in ID patients are not available.<br>The incidence and prevalence of CKD in the general population worldwide has risen markedly in the past decade.<br>In the National Health and Nutrition Examination Survey III, among older adults (age 65 and older) with anaemia, about 12% had renal insufficiency [23]. |
| Prevalence of condition | Anaemia was present in 47.7% of 5,222 pre-dialysis patients with CKD in performed cross-sectional survey [24]. Prevalence of anaemia increased as kidney function decreased. |
| Mortality of condition | The importance of the interaction between cardiovascular disease, CKD and anaemia has been discussed in a study conducted in a US Medicare sample of more than one million elderly patients [16,25]. Compared with patients who had no known comorbidity, patient with anaemia had a 100% increased risk of death. Patient with CKD had a 100% increased risk of death. For patient with anaemia and CKD, the relative mortality risk was even higher reaching 3.7. Mortality risk was further increased in patients who had multiple co morbidities with anaemia being a significant multiplier of mortality risk.<br>• CKD: 16.4% [16]<br>• CKD + anaemia: 27.3% [16]<br>Please refer to Table 6 for more detailed information. |
| **Comorbidity** | **Oncology – anaemia induced by chemotherapy** |
| Incidence of condition | The incidence of anaemia in cancer patients undergoing chemo- and/or radio-therapy was estimated to be 53.7%, calculated from a subpopulation of the survey that was not anaemic at enrolment and received their first cancer treatment during the survey period with a minimum of 2 cycles of chemotherapy or 2 follow-up data-points for radiotherapy. The patients who received chemotherapy had the highest incidence of anaemia, 62.7%, compared with concomitant chemo-radiotherapy, 41.9%, or radiotherapy, 19.5% [26]. |
| Prevalence of condition | European cancer patients were evaluated for up to 6 months. Prevalence of anaemia at enrolment was 39.3% and 67.0% during the survey (Hb <12.0 g/dL) [26].<br>The high prevalence of anaemia in patients with different cancer types (39% at enrolment and 68% becoming anaemic at least once during the 6-month survey period) has been already shown in the European Cancer Anaemia Survey. Conversely, published data on the prevalence of ID in cancer patients are scarce. Prevalence of ID was highest for colorectal cancer (60%, and 69% of those were also anaemic); probably, chronic blood loss may render patients with colorectal or GI cancers more prone to ID and anaemia. Nevertheless, reported prevalence of ID in different cancer population ranges from 32 to 60% and the prevalence of IDA ranges from 7 to 42% [27]. |

| | |
|---|---|
| Mortality of condition | A meta-analysis of 60 clinical studies found a 65% increase in the risk of death and a shortened survival time among patients with cancer treated by chemotherapy and anaemia compared with patients without anaemia [28]. |
| **Comorbidity** | **Dysfunctional uterine bleeding** |
| Incidence of condition | No data on the incidence of dysfunctional uterine bleeding among patients with ID/IDA were found. |
| Prevalence of condition | No data on the prevalence of dysfunctional uterine bleeding among patients with ID/IDA were found. |
| Mortality of condition | Dysfunctional uterine bleeding is not associated with a significant risk of mortality. |
| **Comorbidity** | **Diabetes** |
| Incidence of condition | No data on the incidence of diabetes among patients with ID/IDA were found. |
| Prevalence of condition | No data on the prevalence of diabetes among patients with ID/IDA were found. |
| Mortality of condition | Diabetes is a key risk factor for CKD, which is an important comorbidity of anaemia [29]. Evidence suggests that comorbid diabetes, CKD and anaemia places the patient at particular high risk of mortality [30]. Among patients with diabetes, anaemia as interaction term with CKD was associated with an 88% (HR 1.88, 95% CI 1.33-2.66) greater risk of all-cause mortality compared with patients without anaemia [30]. |

Notes: CHF=Chronic heart failure; CI=Confidence interval; CKD=Chronic kidney disease; GI=Gastrointestinal; Hb=Haemoglobin; HR=Hazard ratio; IBD=Inflammatory bowel disease; ID=Iron deficiency; IDA=Iron deficiency anaemia.

## Table 6 Mortality and Incidence in the Target Population

| Population | Mortality | Incidence of End-stage Renal Disease |
|---|---|---|
| No anaemia, CHF or CKD (background) | 7.7% | 0.1% |
| Anaemia | 16.6% | 0.2% |
| CHF | 26.1% | 0.2% |
| CHF + anaemia | 34.6% | 0.3% |
| CKD | 16.4% | 2.6% |
| CKD + anaemia | 27.3% | 5.4% |
| CHF and CKD | 38.4% | 3.5% |
| CHF, CKD and anaemia | 45.6% | 5.9% |

Notes: Data provided in the table were adapted from Silverberg et al, 2003 [16].
CHF=Chronic heart failure; CKD=Chronic kidney disease.

# SII NONCLINICAL PART OF THE SAFETY SPECIFICATION

There was no formal nonclinical development programme of iron sucrose at the time of the initial marketing authorisation which was approved in 1949, with no pharmacodynamic and pharmacokinetic studies (with the exception of two non-Good Laboratory Practice (GLP) rat absorption, distribution and excretion studies). Some safety pharmacology data are available from repeated-dose GLP-compliant toxicity studies, as well as a few publications on the effects of IV iron preparations in animals. A number of toxicology studies have been conducted over the last 20 years, in compliance with GLP, that address the single and repeated-dose toxicity, genotoxicity, reproductive toxicity and local tolerance of iron sucrose.

A full programme of reproductive toxicity studies was conducted, including a fertility study in rats, embryo-foetal toxicity studies in rats and rabbits, and a pre- and postnatal toxicity study in rats.

In addition, an antigenicity study was conducted to demonstrate that iron sucrose does not cross-react with dextran antibodies, such that iron sucrose could be administered safely to patients who may have been sensitised to iron dextran.

The programme of toxicity studies conducted on iron sucrose comprises a fairly comprehensive toxicological evaluation of the product that would meet the toxicology requirements for a novel pharmaceutical product as laid out in the International Conference on Harmonisation Guideline M3 (R2) [31].

All the pivotal nonclinical toxicology studies were conducted in accordance with GLP regulations.

The nonclinical data are considered adequate and acceptable for the purposes of conducting a meaningful human risk assessment for iron sucrose and there is no need for additional nonclinical data.

**Table 7 Key Nonclinical Safety Findings**

| Key Safety Findings (From Nonclinical Studies) | Relevance to Human Usage |
|---|---|
| **Toxicity** | |
| **Repeat-dose Toxicity** | |
| Data from the repeated-dose toxicity studies using high iron doses showed the expected pattern of changes associated with iron overload.<br>Toxic effects were observed only at cumulative doses of >117 mg Fe/kg in rats and dogs. | Data from repeated-dose toxicity studies are not relevant for the assessment of the risk of haemosiderosis in humans, since iron replete animals were administered with high doses of iron, up to 1,170 mg Fe/kg body weight. |
| **Genotoxicity** | |
| A battery of genotoxicity tests showed no evidence of mutagenic or clastogenic potential for iron sucrose. | Based on the results, iron sucrose is considered as non-genotoxic substance. |

| Key Safety Findings (From Nonclinical Studies) | Relevance to Human Usage |
|---|---|
| **Carcinogenicity** | |
| Carcinogenicity studies have not been performed. | The genetic toxicity data, the knowledge of the nature of the product, its use as a replacement therapy for correction of ID/IDA, and the lack of any findings indicative of pre-neoplastic lesions in the chronic toxicity studies all together suggest a low potential for carcinogenic effects of the product. |
| **Reproductive/Developmental Toxicity** | |
| In reproductive toxicology studies using iron replete animals, iron sucrose was associated with minor skeletal abnormalities in the foetus, but only at dosages that caused maternal toxicity. | Preclinical data showed no special hazards based on conventional studies of toxicity to reproduction. |
| **Local Tolerance** | |
| Following a single intra-arterial injection in rabbits, histopathological examination revealed minimal dermal haemorrhage and trace haemorrhage in the arterial wall, indicating only a slight risk of irritant potential by this route.<br>In the perivenous study, a greater degree of irritancy was observed compared with the saline control with dermal oedema, haemorrhage, inflammation, ulceration and increased scab formation. | The results of the repeated-dose toxicity studies in the rat and dog together with clinical experience indicate that IV injection is well tolerated but the local tolerance results showed that irritancy can be expected following inadvertent perivenous injection or leakage. |
| **General Safety Pharmacology** | |
| **Cardiovascular (Including Potential for QT Interval Prolongation)** | |
| No dedicated safety pharmacology studies have been conducted. Data on the effects of iron sucrose on cardiovascular and respiratory systems were obtained as a part of the 13 week toxicity studies in dogs. No effect of iron sucrose at dosages up to 30 mg Fe/kg (administered over either 1 or 4 hours as an IV infusion) was observed on ECG, blood pressure or respiration rate in these studies. | N/A |
| **Mechanisms for Drug Interactions** | |
| Specific drug interactions for Venofer® have not been identified during the nonclinical development programme. | There have not been identified any specific drug interactions during the clinical development programme. The current SmPC considers a known class effect of interaction with oral iron:<br>"As with all parenteral iron preparations, iron sucrose should not be administered concomitantly with oral iron preparations since the absorption of oral iron is reduced." |
| **Other Toxicity-related Information or Data** | |
| **Cross-reactivity to Anti-dextran Antibodies** | |
| Iron sucrose showed no cross-reactivity with anti-dextran antibodies. | These findings indicate that it would be safe to administer iron sucrose to patients that had previously shown a reaction to iron dextran, without fear of hypersensitivity reactions occurring. |

Notes: ECG=Electrocardiogram; ID=Iron deficiency; IDA=Iron deficiency anaemia; IV=Intravenous; N/A=Not applicable; SmPC=Summary of Product Characteristics.

There is no need for any additional nonclinical data.

## SII.1 Conclusions on Nonclinical Data

**Table 8 Summary of Safety Concerns Resulting from Section SII**

| Safety Concerns | |
|---|---|
| Important identified risks (confirmed by clinical data) | Injection/infusion site reactions |
| Important potential risks (not refuted by clinical data or which are of unknown significance) | Haemosiderosis |
| Missing information | None |

# SIII CLINICAL TRIAL EXPOSURE

Based on the Good Pharmacovigilance (PV) Practices Module V – Risk Management Systems, Section V.C.3.1.f., Section SIII may be omitted for the Risk Management Plan (RMP) of medicinal products that have been marketed in the EU for 10 or more years. Venofer has been marketed in Portugal and Germany since 1995.

# SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Based on the Good PV Practices Module V – Risk Management Systems, Section V.C.3.1.f., Section SIV may be omitted for the RMPs of medicinal products that have been marketed in the EU for 10 or more years. Venofer has been marketed in Portugal and Germany since 1995.

# SV POST-AUTHORISATION EXPERIENCE

The first marketing authorisation for Venofer was received on 6 December 1949 in Switzerland, where the product was first launched in 1950. Venofer was then approved in Portugal (November 1964) and Germany (November 1969) but it was not marketed in these countries until 1995.

Up until the data lock point (DLP) of this RMP, Venofer had received marketing authorisation in a total of 89 countries worldwide and in all of them is currently marketed.

## SV.1 Action Taken by Regulatory Authorities and/or MAHs for Safety Reasons

All EU registered IV iron medicinal products, including Venofer, were evaluated as part of an Article 31 referral procedure (EMEA/H/A-31/1322) by the EMA, whereby the risk of serious allergic reactions with the use of these products was investigated. The CHMP adopted an opinion on 27 June 2013, which was endorsed by the European Commission decision on 13 September 2013.

The conclusion was that the benefit/risk balance of IV iron-containing medicinal products for the treatment of ID in situations where 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 PV activities and risk minimisation measures agreed.

The conditions affecting the marketing authorisation are set out in Table 9.

**Table 9 Conditions Affecting the Marketing Authorisation**

| Conditions | Due Date | Status |
|---|---|---|
| The MAHs should circulate the agreed DHPC in coordination with the NCAs according to the action plan agreed by CHMP. | Within 30 days following EC decision | DHPC distribution completed in October/ November 2013 |
| The MAHs should update the RMP for products with an existing RMP to include the additional risk minimisation measures and the additional pharmacovigilance activities agreed as part of this procedure. | Within 3 months following EC decision | RMP Version 1.0 submitted on 6 December 2013 - 23 December 2013, approved in 22 of 29 countries, partly with modifications |
| The MAHs shall conduct a PASS to further characterise the safety concerns on the hypersensitivity reactions. The study will also have to be reflected in the updated/new RMP submission. Final study report by: | 31 July 2016 | PASS feasibility report submitted on 19 December 2014 |
| The MAHs should submit annual cumulative reviews of hypersensitivity case reports, all fatal cases and all pregnancy cases, together with usage data. | 31 March 2014 and annually thereafter | Annual Review No. 01 submitted on 27 March 2014 - 1 April 2014, version No. 2 currently in preparation and to be submitted by 31 March 2015 |
| The MAHs should implement risk minimisation measures in the context of an RMP in the form of educational materials for prescribers and patients. These materials will highlight the risks and warnings on hypersensitivity reactions (by e.g., a checklist, to be implemented at national level). | Within 3 months following EC decision | RMP Version 1.0 submitted on 6 December 2013 - 23 December 2013, approved in 22 of 29 countries, partly with modifications. Translated HCP and patient educational materials are currently in review by NCAs or have already been approved by NCAs. In countries where the educational materials have been approved the distribution is completed or ongoing. |

Notes: EC=European Commission; DHPC=Direct Healthcare Professional Communication; HCP=Healthcare professional; MAH=Marketing Authorisation Holder; NCA=National Competent Authority; PASS=Post-authorisation safety study; RMP=Risk Management Plan.

As a further commitment following the outcome of the referral procedure, the product information of all EU registered IV irons was revised to include a class label on the risks of hypersensitivity with the use of these products. This class label also included an inverted black triangle symbol indicating that all EU registered IV irons are being particularly closely monitored by EU regulatory authorities.

All actions taken by the Marketing Authorisation Holder (MAH) for safety reasons during the reporting interval are related to the conditions affecting the marketing authorisations of iron-containing parenteral medicinal products and are summarised in Table 10.

## Table 10 Detailed Description of Actions Taken Since the Last Update to This Section

| **Hypersensitivity/Anaphylactoid Reaction and Use in Pregnant or Lactating Women** | |
|---|---|
| Background to issue | The conclusion of the EMA referral procedure (please refer to Table 11) |
| Evidence source | Article 31 EMA referral procedure EMEA/H/A-31/1322 |
| Countries affected | EU/EEA |

| | **Actions Taken** | **Date(s) of Action** |
|---|---|---|
| 1 | Implementation of class label on the risks of hypersensitivity with the use of iron-containing parenteral medicinal products | Implemented in September 2013 (Type $IA_{IN}$ variation submitted on 01-Oct-2013 to 14-Oct-2013) |
| 2 | Distribution of a DHPC | Distribution completed in Oct-Nov-2013 |
| 3 | Submission of an updated RMP | RMP Version 1.0 submitted on 06-Dec-2013 to 23-Dec-2013, approved in 22 of 29 countries, partly with modifications |
| 4 | Submission of annual cumulative review of hypersensitivity case reports, all fatal cases and all pregnancy cases | Annual Review No. 01 submitted on 27-Mar-2014 to 01-Apr-2014 |
| 5 | Submission of PASS feasibility report | PASS feasibility report submitted on 19-Dec-2014 (refer also to Annex 9) |
| 6 | Distribution of healthcare professional and patient educational materials | RMP Version 1.0 submitted on 06-Dec-2013 to 23-Dec-2013, approved in 22 of 29 countries, partly with modifications. The healthcare professional and patient educational material have been approved by the large majority of NCAs; a few approvals are still ongoing. Distribution had taken place in most countries by the end of 2014. For more details, refer also to Annex 10. |

Notes: DHPC=Direct Healthcare Professional Communication; NCA=National Competent Authority; PASS=Post-authorisation safety study; RMP=Risk Management Plan.

**Table 11 Cumulative List**

| Hypersensitivity/Anaphylactoid Reaction and Use in Pregnant or Lactating Women | | | |
|---|---|---|---|
| **Countries** | **Action Taken** | **Comment** | **Date(s)** |
| EU | EC decision on the Article 31 referral procedure EMEA/H/A-31/1322 initiated in Dec-2011. The CHMP opinion, which was endorsed by the EC, concluded that the benefit/risk balance of IV iron-containing medicinal products for treatment of ID in situations where 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 | On 07-Dec-2011 EMA requested the CHMP under Article 31 of Directive 2001/83/EC to assess concerns regarding hypersensitivity and its impact on the benefit/risk balance for all IV iron-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 | 7-Dec-2011 (start of the procedure)<br>27-Jun-2013 (CHMP opinion)<br>13-Sep-2013 (EC decision) |
| EEA | Implementation of class label on the risks of hypersensitivity with the use of iron-containing parenteral medicinal products | Commitment or condition of the marketing authorisation of iron-containing parenteral medicinal products from EC decision C(2013)5970 on the Article 31 referral procedure EMEA/H/A-31/1322 | Sep-2013 |
| | DHPC distribution | As per above | Oct-Nov-2013 |
| | Introduction of a Risk Management Plan | As per above | 06-Dec-2013 to 23-Dec-2013, follow-up submissions in single countries ongoing |
| | Submission of annual cumulative review (2014) of hypersensitivity case reports, all fatal cases and all pregnancy cases | As per above | 27-Mar-2014 to 01-Apr-2014 |
| | Submission of PASS feasibility report to NCAs | As per above | 19-Dec-2014 |
| | Distribution of healthcare professional and patient educational materials | As per above | Ongoing (refer also to Annex 10) |

Notes: DHPC=Direct Healthcare Professional Communication; EC=European Commission; ID=Iron deficiency; IV=Intravenous; NCA=National Competent Authority; PASS=Post-authorisation safety study.

# SV.2 Non-study Post-authorisation Exposure

## SV.2.1 Method Used to Calculate Exposure

The exact numbers of patients exposed to Venofer are not available. The exposure to Venofer was calculated from the number of vials sold, expressed in 100 mg equivalents (1 mL of solution in each vial contains 20 mg of iron). Post-marketing data are available only since 1997.

The patient years are calculated based on an estimated annual cumulative dose of iron given as Venofer which is 2,000 mg.

### SV.2.2 Exposure

Up to the DLP of this RMP (1 January 2015), the cumulative exposure is estimated to be 19,334,271 patient years based on the method of calculation described above, representing 386,685,422 sold 100 mg iron equivalents. Exposure data sorted by region are presented in Table 12. Post-marketing data for Venofer are only available since 1997.

Details on age, gender or race/ethnic origin in exposed patients are not available.

**Table 12 Cumulative Exposure from Marketing Experience from 1997 Until 31 December 2014**

| Region (from January 2012) | Exposure (Units) | |
|---|---|---|
| | Patient Years | Number of 100 mg Iron Equivalents |
| North America | 1,873,791 | 37,475,815 |
| Latin America | 586,880 | 11,737,590 |
| Europe | 992,502 | 19,850,033 |
| Africa | 72,502 | 1,450,040 |
| Middle East | 536,623 | 10,732,455 |
| Asia Pacific | 452,981 | 9,059,610 |
| Global exposure between 1997-2011[(1)] | 14,818,994 | 296,379,879 |
| **Total** | **19,334,271** | **386,685,422** |

1 Detailed exposure data for the different territories is not available for the period between 1997-2011.

## SV.3 Post-authorisation Use in Populations Not Studied in Clinical Trials

Information about the use in populations not included in the clinical studies is not available. The only data regarding the exposure could be derived from post-marketing adverse drug reaction reporting.

## SV.4 Post-authorisation Off-label Use

**Table 13 EU Off-label Use**

| Off-label Category | Country | Source of Information | Comment |
|---|---|---|---|
| Medication errors | 1 case from France | Spontaneous reports | Subcutaneous route of administration. |
| | 6 cases from UK | Spontaneous reports | EpiPen® administration. |
| | 1 case from France | Spontaneous reports | Intentional dilution error. |

**Table 13 EU Off-label Use (Cont'd)**

| Off-label Category | Country | Source of Information | Comment |
|---|---|---|---|
| Drug exposure during pregnancy in the first trimester | 1 case from France | Spontaneous reports | As per the RSI this is not contraindication, only warning and as such not considered off-label use. |
| Prescription error | 1 case from UK | Spontaneous reports | Prescribed by the general practitioner. |
| Paediatric use | 2 cases from Spain<br>1 case from France(1) | Spontaneous reports | As per the RSI this is not contraindication, only warning and as such not considered off-label use. |
| | 1 case from France | Spontaneous reports | Premature baby. |
| Patient blood management | 1 case from France(1)<br>4 cases from Spain | Spontaneous reports | As per the RSI this is not considered off-label use. |
| Other indications | 1 case from France | Spontaneous reports | Oncology (possible administration). |
| | 4 case from France | | Unknown indication. |
| | 1 case from Sweden | | For thrombocyte dysfunction. |
| | 1 case from France | Spontaneous reports | Venofer® administered at home. |

1 The same case is presented twice in 2 different categories (i.e., this was a child case and a patient blood management case).
Note: RSI=Reference Safety Information.

Potential off-label use cases, sorted by country of origin are presented in Table 14 below.

**Table 14 Number of Off-label Use Case Reports Reported Sorted by Country**

| Country | Number of Reported Cases |
|---|---|
| France | 10 |
| United Kingdom | 7 |
| Spain | 6 |
| Sweden | 1 |
| **Total** | **24** |

## SV.5 Epidemiology Study Exposure

Not applicable.

# SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATIONS

## SVI.1 Potential for Harm from Overdose

There were no reports of overdose in clinical trials with Venofer.

The individual iron need is calculated using the Ganzoni formula, taking into account patient's baseline Hb, target Hb and weight. Calculation errors can lead to administration of high doses of iron, which can have acute and chronic toxic effect on patient.

If IV iron is given at a dose which is higher than the allowed single dose (200 mg per infusion, 3 times weekly or 500 mg per infusion once a week in most countries), signs of acute iron toxicity can occur as a consequence of the labile iron complex releasing too much labile iron into the blood stream. Symptoms of acute iron toxicity include nausea, dizziness, flush and metallic taste. If overdose caused by single dose occurs, symptoms begin during the infusion and are most commonly self-limiting and of short duration.

If the cumulative iron dose is inappropriately high, and exposure to IV iron is prolonged and continued, iron may accumulate in organs such as the liver or spleen, as no excretion mechanism for iron exists. In haematology laboratory tests, iron overload is diagnosed with transferrin saturation >50% and unphysiologically high serum ferritin values over a prolonged time. If this situation is not recognised and iron infusions continue, haemosiderosis can be the result.

Overdose should be treated, if required, with an iron chelating agent or according to standard medical practice.

## SVI.2 Potential for Transmission of Infectious Agents

The continuous control of the Venofer production process compliant with Good Manufacturing Practice as well as the lack of any cases indicative of possible transmission of infectious agents supports the safety of Venofer. Venofer does not contain any materials of biologic origin.

The potential for transmission of infectious agents is considered remote and hypothetical.

## SVI.3 Potential for Misuse for Illegal Purposes

Venofer has no illicit effect and therefore, the potential for illegal misuse is considered negligible. Risk of drug abuse is low as Venofer is administered by and under the direct supervision of healthcare professionals as an IV administration.

## SVI.4 Potential for Medication Errors

Venofer has a certain potential for medication errors:

- Wrong cumulative dose calculation
- Wrong single dose application (too high, too low)
- Both of the above in children
- Wrong injection/infusion speed
- Wrong dilution (wrong concentration, wrong solution in which it has been dissolved)
- Wrong placement of cannula (resulting in paravenous administration)
- Administration in conjunction with another IV drug (via y-connector given at the same time)
- Mix of different drugs in the same infusion bag

Medication error represents an important identified risk of Venofer and it is discussed further in the RMP.

### SVI.4.1 Preventive Measures for the Final Product(s) Being Marketed

The potential for medication errors caused by suboptimal labelling has been assessed in the pre-authorisation phase. Venofer is a prescription only medicine administered exclusively by healthcare professionals.

### SVI.4.2 Effect of Device Failure

Not applicable.

### SVI.4.3 Description of Medication Errors During the Clinical Trial Programme

There were no case reports of medication error in the clinical development programme with Venofer.

### SVI.4.4 Reports of Medication Errors with the Marketed Product(s)

Cumulatively until 1 January 2015, 488 (serious 154, 31.5%) spontaneous post-marketing medication error cases related to Venofer were reported. Out of the 1,974 adverse events reported with the 488 cases, less than 20% (318, 16.1%) of them were unlisted events.

Of the 154 serious cases, 9 had a fatal outcome, 1 case was lost to follow-up, 3 had not recovered/not resolved, 47 recovered/resolved without sequelae, 1 recovered with sequelae, 1 was recovering/resolving, 29 had unknown outcome, and the outcome from

63 cases cannot be retrieved from the safety database (older cases with different data entry conventions). Of the 334 non-serious cases, 5 were lost to follow-up, 2 had no available outcome, 12 had not recovered/not resolved, 117 recovered/resolved without sequelae, 8 were recovering, 76 had unknown outcome, and for 114 cases the outcome cannot be retrieved from the safety database (older cases with different data entry conventions). The most common medication error types are presented in Table 15 below. Venofer product information is constantly being improved to ensure the appropriate use of the product.

**Table 15 Summary Tabulation of Medication Errors (Preferred Term Counts ≥5) with Venofer®**

| Description of Error | No. of Occurrences | Analysis of Cause | Steps Taken to Prevent | Comment |
|---|---|---|---|---|
| Wrong technique in drug usage process | 139 | Not applicable. The product information is continuously being improved for greater clarity on the proper use of Venofer. | | |
| Incorrect drug administration rate | 97 | | | |
| Overdose | 63 | | | |
| Incorrect route of drug administration | 50 | | | |
| Incorrect dose administered | 20 | | | |
| Drug administration error | 20 | | | |
| Incorrect drug administration duration | 12 | | | |
| Medication error | 12 | | | |
| Drug prescribing error | 10 | | | |
| Drug administered at inappropriate site | 10 | | | |
| Inappropriate schedule of drug administration | 8 | | | |
| Accidental overdose | 6 | | | |
| Drug dispensing error | 5 | | | |

## SVI.5 Potential for Off-label Use

As with any other medicinal product, the possibility for off-label use may exist. Venofer may possibly be administered to patients suffering from anaemia not caused by ID, such as thalassaemia or other forms of microcytic anaemia, e.g., in a myelodysplastic syndrome or in myelodepression. Therefore, the Reference Safety Information (RSI) clearly states that the use of Venofer is contraindicated in patients of which it is known that their anaemia is not caused by ID. To further strengthen this warning, it is also stated that the diagnosis must be confirmed by appropriate investigations.

## SVI.6 Specific Paediatric Issues

### SVI.6.1 Issues Identified in Paediatric Investigation Plan

No Paediatric Investigation Plan has been developed for Venofer.

### SVI.6.2 Potential for Paediatric Off-label Use

The approval for the use of Venofer in children varies in the EEA countries. In 15 EEA countries (Bulgaria, Croatia, Cyprus, Czech Republic, France, Germany, Hungary, Latvia, Lithuania, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia), Venofer is approved for use in children, i.e., Section 4.2 of the Summary of Product Characteristics (SmPC) contain dosing instructions for children in case of clinical need. In 14 EEA countries (Mutual Recognition Procedure countries (Austria, Belgium, Denmark, Finland, Greece, Ireland, Italy, Luxembourg, Spain, Sweden, United Kingdom) as well as Estonia, Iceland, and Norway) Venofer is not recommended for use in children.

There is a moderate amount of data in children under study conditions, and the paediatric population is generally not excluded from the target population of Venofer. Therefore, the use of Venofer in the paediatric population is not considered off-label use. If there is a clinical need for IV iron treatment in children, Venofer can be given. Specific paediatric posology is provided in Section 4.2 of the national labels of those countries where this was approved (in the 15 EEA countries listed above). The paediatric posology is as follows: “If there is a clinical need in children, it is recommended not to exceed 0.15 ml of Venofer (3 mg iron) per kg body weight not more than three times per week.”

## SVI.7 Conclusions

**Table 16 Safety Concerns As Result of Section SVI**

| Safety Concern | Comment |
|---|---|
| Medication error | No medication error-specific adverse drug reactions except for injection site discolouration and pain associated with extravasation were detected for Venofer®. |

# SVII IDENTIFIED AND POTENTIAL RISKS

## SVII.1 Newly Identified Safety Concerns (Since This Section was Last Submitted)

This is the second version of the RMP for Venofer. There have been no new safety concerns identified by the MAH since the submission of the previous version of the RMP.

The completed Article 31 referral procedure EMEA/H/A-31/1322 (for further details, refer to Section SV.1) had an impact on the PV activities and risk minimisation measures of 'Hypersensitivity/anaphylactoid reaction' and 'Use in pregnant or lactating women' safety concerns which will be further discussed in PART III and PART V of this RMP.

## SVII.2 Recent Study Reports with Implications for Safety Concerns

Not applicable.

## SVII.3 Details of Important Identified and Potential Risks from Clinical Development and Post-authorisation Experience (Including Newly Identified)

**Table 17 Important Identified Risk of Hypersensitivity/Anaphylactoid Reaction**

| **Identified Risk** | **Hypersensitivity/anaphylactoid reaction** |
|---|---|
| Frequency with 95% CI | **Related Clinical Trial Population** |

| **Number of Venofer® Related Cases(1)** | **Number of Subjects Exposed** | **Frequency per 10,000 Patients (95% CI)** |
|---|---|---|
| 162 (non-serious)<br>7 (serious)<br>169 (total) | 4,064 | 399 (341.5, 464.6)<br>17 (7.5, 37.2)<br>416 (357.5, 483.0) |

**Post-marketing Experience**

| **Number of Cases** | **Exposure Since International Birth Date to DLP** | **Frequency per 100,000 Patients Years** |
|---|---|---|
| 802 (non-serious)<br>842 (serious)<br>1,644 (total) | 19,334,271<br>patient years | 4.15<br>4.35<br>8.5 |

1 Based on the interim outcomes of now completed referral procedure EMEA/H/A-31/1322, the MAH has proactively broadened the search criteria string for the 'Hypersensitivity' case reports to include SMQ 'Anaphylactic reactions' and 'Angioedema' together with PT 'Hypersensitivity'. This broadened search string has been used retrospectively for all the searches within the safety databases since the international birth date. Therefore, the number of respective case reports has significantly increased. This increase is not caused by the changing trend in 'Hypersensitivity' case reporting frequency.

**From Completed Clinical Trials: in 4,064 patients:**

7 serious related cases

**From Post-marketing Experience: in 18,339,646 patient years:**

842 serious cases

| Identified Risk | Hypersensitivity/anaphylactoid reaction |
|---|---|
| Severity and nature of risk | Hypersensitivity reactions in general may be life-threatening conditions with fatal outcome.<br>Subsequent information reviewed in the PSUR does not change the overall assessment of this important identified risk. |
| Background incidence/ prevalence | A general safety concern with regard to all parenteral iron preparations is potential hypersensitivity reactions, based on historical experience with dextran containing iron products. However, iron sucrose is a non-dextran IV iron.<br>Hypersensitivity drug reactions are responsible for significant morbidity, mortality and socioeconomic costs that are often underestimated. Current epidemiological data have to be regarded carefully as different studies used different populations (either adult or paediatric populations or both, inpatients or outpatients), different definitions of hypersensitivity reactions, different methodologies and methods of data analyses. It should also be kept in mind that the assessment of severity, preventability and drug imputability of reactions relies mostly on clinical history, which can sometimes be ambiguous [33].<br>**Hospital-based Population**<br>Currently not many studies have studied the hospital-based population with regards to hypersensitivity reactions. A review performed by Lazarou [referenced in 33] showed in a meta-analysis of 33 prospective studies from the US between 1966 and 1996, that 15.1% of hospitalised patients suffered an ADR (6.7% severe) and that the incidence of drug-related hospital admissions ranged from 3.1 to 6.2% [33].<br>In Singapore, a 2-year prospective study by Thong [referenced in 33], using a network based electronic notification system for which each case was verified by a trained allergist, detected 366 cases of reported drug allergy from a total of 90,910 inpatients. After review, 210 were classified as drug allergy. Cutaneous manifestations were the most common clinical presentation (95.7%); systemic manifestations occurred in 30% of the cases and serious adverse reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis and general exfoliative dermatitis occurred in 11 patients (5.2%). Antibiotics and anti-epileptic drugs accounted for 75% of the reactions. They concluded that the frequency of drug allergy in hospitalised patients was 4.2 per 1,000 hospitalisations and mortality attributable to drug allergy was 0.09 per 1,000 hospitalisations [33].<br>**General Population**<br>Until recently, studies have been limited by small sample size or samples that may not represent the general population. Neugut et al, 2001 [34] suggested that the better approach to estimating risk would be to “use estimates specifically calculated from epidemiologic studies measuring anaphylaxis in the general population.” Despite the obvious difficulties in estimating the overall incidence of anaphylaxis, the authors addressed this issue via a review of the literature of what they termed were the “four major subtypes of anaphylaxis (food, drugs, latex, and insect stings)” [34]. They calculated an overall estimate of the risk of anaphylaxis using data derived from the incidence of episodes to these specific agents. Then, based on a 1999 US population of 272 million, they attempted to estimate the population at risk; their calculations yielded between 3.3 million and 43 million Americans. They also estimated that a total of 1,443 to 1,503 were at risk for a fatal event attributable to food, medications, latex, and insect stings. Thus, they concluded that the reported frequency of anaphylaxis was not as rare as previously believed and estimated that 1.2% to 15% of the total US |

| Identified Risk | Hypersensitivity/anaphylactoid reaction |
|---|---|
| | population may experience an anaphylactic reaction and that 0.002% of these might experience a fatal event [34].<br>Overall, there is few epidemiological data on hypersensitivity drug reactions, which account for about 33% of all ADRs. They affect 10-20% of hospitalised patients and up to 7% of outpatients. The available information based predominantly on the epidemiology of ADRs, requires cautious interpretation as these reactions are rarely accurately classified or proven. Both under-diagnosis because of underreporting and over-diagnosis due to the common use of the term 'allergy' have also to be considered. |
| Risk groups or risk factors | Although several risk factors have been identified, their clinical importance has not been fully understood. Future progress in immunogenetics and pharmacogenetics may help identify populations at risk for hypersensitivity reactions. |
| Potential mechanisms | Nonclinical studies with Venofer® did not show any cross-reactivity with iron dextran antibodies.<br>There appear to be 2 types of reactions to IV iron, a Type I hypersensitivity reaction (anaphylactic) and an anaphylactoid reaction [35].<br>Anaphylaxis is defined for the purposes of this document as a condition caused by an IgE-mediated reaction. Anaphylactoid reactions are defined as those reactions that produce the same clinical picture as anaphylaxis but are not IgE-mediated. Where both IgE-mediated and non–IgE-mediated mechanisms are a possible cause, the term ''anaphylactic'' has been used to describe the reaction. Anaphylactic reactions are often life-threatening and almost always unanticipated. Even when there are mild symptoms initially, the potential for progression to a severe and even irreversible outcome must be recognised. Any delay in the recognition of the initial signs and symptoms of anaphylaxis can result in a fatal outcome either because of airway obstruction or vascular collapse. Symptoms of an anaphylactic reaction consist for 90% of cutaneous symptoms followed by respiratory (40-60%) and vascular symptoms (30-35%) and less often abdominal complaints occur (20-25%) [36]. |
| Preventability | Drug-related hypersensitivity reactions occur in approximately 33% of all hypersensitivity reactions, with 10-20% occurring in an inpatient setting. This number can be significantly reduced by carefully recording each patient's medical history, especially allergic medical history/other atopy. Careful medical monitoring with regards to early detection of hypersensitivity symptoms could result in prompt medical interventions and subsequently decrease serious hypersensitivity reactions. |
| Impact on individual patient | Hypersensitivity reactions are uncommon, and in most cases mild to moderate in severity, self-limiting and of short duration. However, severe cases of hypersensitivity may require medical intervention as the outcomes of these cases may be fatal. |
| Potential public health impact of safety concern | The potential public health impact is probably not high, as hypersensitivity reactions are uncommon, and fatalities occur in 0.002-1% only (figure based on the US population [34]) and depends widely on the comorbidities of the affected patient and the setting in which the hypersensitivity reaction occurs. Post-marketing data showed an overall occurrence of 0.08% (figure based on EU and US populations) with no fatalities reported. When the severity of the cases is taken into account only 0.06% was serious of which only 0.01% was of a life-threatening nature, which is significantly below the background incidence of anaphylaxis, which can be as high as 1.2-15%. |

| Identified Risk | Hypersensitivity/anaphylactoid reaction |
|---|---|
| Evidence source | The Vifor Pharma Clinical Trial Database and Safety Database, literature [33-36] |
| MedDRA terms | MedDRA SMQ Anaphylactic reaction<br>MedDRA SMQ Angioedema<br>MedDRA PT Hypersensitivity |

Notes: ADR=Adverse drug reaction; CI=Confidence interval; DLP=Data lock point; IgE=Immunoglobulin; IV=Intravenous; MAH=Marketing Authorisation Holder; MedDRA=Medical Dictionary for Regulatory Activities; PSUR=Periodic Safety Update Report; PT=Preferred term; SMQ=Standardised MedDRA query.

## Table 18 Important Identified Risk of Medication Error

**Identified Risk:** Medication error

**Frequency with 95% CI**

**Related Clinical Trial Population**

| Number of Venofer® Related Cases | Number of Subjects Exposed | Frequency per 10,000 Patients (95% CI) |
|---|---|---|
| 0 | 4,064 | 0.0 |

**Post-marketing Experience**

| Number of Cases | Exposure Since International Birth Date to DLP | Frequency per 100,000 Patient Years |
|---|---|---|
| 334 (non-serious)<br>154 (serious)<br>488 (total) | 19,334,271<br>patient years | 1.73<br>0.79<br>2.52 |

**Seriousness/outcomes**

**From Completed Clinical Trials: in 4,064 patients:**

No serious related cases

**From Post-marketing Experience: in 19,334,271patient years:**

154 serious cases

**Severity and nature of risk**

In the post-marketing setting it is not always possible to determine the severity of an event due to lack of sufficient information or severity not being reported as such.

**Background incidence/ prevalence**

The most common occurring medication errors will be discussed according to medical guidelines from the World Health Organization [37], National Coordinating Counsel of Medication Error Reporting and Prevention [38], the Medicines and Healthcare products Regulatory Agency [39] and the United Nations Office on Drugs and Crime [40] and relevant literature articles.

**Medication Error**

Short definition: “An unintended act (either of omission or commission) or one that does not achieve its intended outcomes” [37].

Extended definition: “A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing; order communication; product labelling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use” [38].

| Identified Risk | Medication error |
|---|---|
| | Drug Administration Error: "A drug administration error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to an error in administration of the wrong drug, dosage, dilution, dilution medium, route of drug delivery, scheduling plan, etc."<br>Off-label Use: This is a prescription by a doctor of a medicine when there are no alternatives or where access to effective alternatives is restricted; also the import of a medicine that has been licensed outside Europe on what is known as a named patient basis or "unlicensed" use [39].<br>Wrong Technique in Drug Usage Process: This MedDRA PT term is used to classify medication errors that may consist of medication errors due to incorrect infusion rate of a prescribed drug, a drug being inappropriately diluted or a drug given by whatever means in a dosage which causes an overdose. Each of these 3 common medication errors, which are due to a wrong technique in drug usage process, will be discussed here:<br>1. Infusion Rate Incorrect: "A drug which is infused at a speed (mL/min) which is either too fast or too slow resulting in an inappropriate administration or dilution of a predetermined mixture of a drug that should only be administered at such a rate that the drug is infused into the patient without causing harm. "<br>2. Inappropriate Dilution: "A dilution of a medication which can be diluted, which results in an alteration of the stability of the medication which has been diluted. This inappropriate dilution results in an altered drug composition, which may change the pharmacodynamic and pharmacokinetic properties of that medication. These changes in medication composition may result in harm to the patient."<br>3. Overdose: "A dose is considered that quantity of a drug which is required to elicit the desired response in the individual, both in medicine and for abuse purposes. The use of any drug in such an amount (inappropriate dose) that acute adverse physical or mental effects are produced is determined an overdose" [40].<br>4. Other medication errors relevant to Venofer® may include:<br>– Wrong cumulative dose calculation<br>– Wrong single dose application (too high, too low)<br>– Both of the above in children<br>– Wrong injection/infusion speed<br>– Wrong dilution (wrong concentration, wrong solution in which it has been dissolved)<br>– Wrong placement of cannula (resulting in paravenous application)<br>– Application in conjunction with another IV drug (via y-connector given the same time)<br>– Mix of different drugs in the same infusion bag<br>Incidence rates of ADRs vary from 2 per 100 admissions to 7 per 100 admissions among the hospitals that have conducted ADR studies [41]. Some ADRs are preventable, while others are not. Preventable ADRs are a leading cause of injury in the US [41]. A study done by Bates et al, 1995 found that 20% of ADRs were associated with |

| Identified Risk | Medication error |
|---|---|
| | medication errors and are by definition preventable [42]. Medication errors can occur at any stage of the medication process: drug ordering, transcribing, dispensing, administering or monitoring [41]. Errors at the medication administration stage, while accounting for 26% of overall serious medication errors, occur in large numbers. One study found that 11.5% of the doses administered had an administration error, and 3.1% of the administrations had errors that could potentially harm patients [41]. Another study performed in 36 hospitals showed that 19% of medication administrations contained an error and have found that 7% of administration errors have the potential to cause patient harm and were considered potential ADRs [41]. These numbers are significant because medication administration errors are seldom intercepted by nurses or anyone else. Because so many medication doses are administered, the potential for harm cannot be underestimated; for example, a 300-bed facility (that administers 3,000 doses per day) may experience 40 potential ADRs per day, while that number at a 735-bed tertiary academic medical centre (that administers 16,200 doses per day) is estimated at 98 per day. ADRs manifest in a number of ways, ranging from mild allergic reactions to anaphylaxis or even death [41].<br>The rate of serious and life-threatening potential ADRs resulting in actual patient harm or ADRs stands at 7.5% (95% CI 6.98 to 8.01) [41]. In addition, 3% (95% CI 2.12 to 3.6) of serious and life-threatening potential ADRs led to serious or life-threatening ADRs [41]. Given previous estimates of serious or life-threatening potential ADR(s) of 1.33 per 100 medication doses administered, we estimate that in the study hospital where 6 million doses are administered per year, more than 4,200 preventable ADRs attributable to medication administration errors occur annually [41].<br>The rate of preventable ADEs and potential ADEs in ICUs was 19 events per 1,000 patient days, nearly twice that rate of non-ICUs ($p<0.01$) [43]. The medical ICU rate (25 events per 1,000 patient days) was significantly ($p<0.05$) higher than the surgical ICU rate (14 events per 1,000 patient days) [43]. When adjusted for the number of drugs used in the previous 24 hours or ordered since admission, there were no differences in rates between ICUs and non-ICUs. ICU acuity, length of stay, and severity of the ADE were greater in ICUs than non-ICUs, but there were no differences between medical ICU and surgical ICU patients [43]. |
| Risk groups or risk factors | **Risk Groups**<br>Any patient under the care of medical staff in any facility, being in a hospital or in a non-hospital setting, e.g., general practitioner's office, is susceptible to the potential of a medication error of any form, when drugs are prescribed and administered.<br>**Risk Factors**<br>The hospital care system can lead to errors and result in failure to detect these errors. Reason et al [referenced in 43] discussed in detail the relationship between higher error rates and overwork, fatigue, stress, work environment, poor systems of care, and many other factors beyond an individual's control. These factors increase the probability for an individual to make an error and decrease the probability that another person will discover the error [43]. See potential mechanisms section below as well.<br>Of importance for the administration of Venofer are the use of an inappropriate dilution, followed by overdose and wrong technique in drug usage process. Among the other medication errors most were |

| Identified Risk | Medication error |
|---|---|
| | reported as incorrect infusion rate reported as an infusion rate too fast. The remaining medication errors could be classified as isolated events. |
| Potential mechanisms | Medication administration errors warrant attention as they are typically not intercepted; 84% of these errors go unintercepted according to a study by Leape et al, 1995 [44]. Medication administration is carried out by nurses, who are mostly alone at the time of medication administration. Nurses at the point-of-care also face a variety of cognitive and system challenges as they complete many medication-related and non-medication-related tasks in a compressed time window.<br>The likelihood of an error rises with increasing complexity of the work environment and with building work pressure. Nursing human factors studies have suggested that a high nursing workload leads to medication errors [41]. While interventions like no interruptions during medication passes, quiet medication preparation rooms or 2-nurse medication administration can work to improve human level performance, well-targeted systems improvements and safety technology implemented at the point-of-care may reduce errors, protect the healthcare worker and patient from harm, and save costs to the system [41].<br>Structured interviews to analyse the risk and occurrence of medication administration errors indicated almost no differences between ICUs and non-ICUs for many characteristics of the patient, patient care team, systems, and individual caregivers.<br>The rate of preventable and potential ADEs was twice as high in ICUs compared with non-ICUs. However, when adjusted for the number of drugs ordered, there was no greater likelihood for preventable ADEs and potential ADEs to occur in ICUs than in non-ICUs. Preventable ADEs and potential ADEs occurred in units that functioned normally and involved caregivers who were working under reasonably normal circumstances, not at the extremes of workload, stress, or a difficult environment [43]. |
| Preventability | As was described before, dispensing medication without interruptions during medication passes, quiet medication preparation rooms or 2-nurse medication administration can work to improve human level performance, well-targeted systems improvements and safety technology implemented at the point-of-care may reduce errors, protect the healthcare worker and patient from harm, and save costs to the system [41].<br>Bar code medication verification technology reduced the rate of non-timing potential ADEs by 50.8% [41]. These findings suggest that ADEs are associated with a small number of drug classes and, therefore, computerised warnings during administration of high risk drug classes such as insulin, opiates, potassium chloride and anticoagulants may be of value. This strategy is supported by Leape et al, 1995 [44] who previously pointed out that improved dissemination and display of drug and patient data should make errors in the use of drugs less likely. Other promising interventions that have been studied in this area include the use of radio frequency identification. High reliability technologies are effective at reducing error rates although they are expensive to acquire and deploy; given the costs of ADEs, the investments seem well worthwhile [41]. |
| Impact on individual patient | To date, medication errors were accompanied by reports in case of overdose which may present with nausea, dizziness, headache etc.<br>Adverse events reported so far were similar to adverse events observed even without medication error. The impact of this risk on individual |

| Identified Risk | Medication error |
|---|---|
| | patient remains unknown. |
| Potential public health impact of safety concern | Medical treatment is estimated to accidentally injure 1.3 million people each year in the US. Although many of these injuries are not preventable, as many as two-thirds may be secondary to errors in management [43]. In order to reduce this injury rate, it is essential to determine how errors occur and how they may be prevented. The Harvard Medical Practice Study found that the most common cause of AEs (i.e., injuries related to medical care) was medications [43].<br>These results can to some part also be extrapolated to the European continent, and have far reaching consequences for the patients involved, most ADEs occurring as a result of medication error are believed to be preventable. The rate of serious and life-threatening potential ADEs resulting in actual patient harm or ADEs stands at 7.5% (95% CI 6.98 to 8.01) [41]. In addition, 3% (95% CI 2.12 to 3.6) of serious and life-threatening potential ADEs led to serious or life-threatening ADEs [41]. Given previous estimates of serious or life-threatening potential ADEs of 1.33 per 100 medication doses administered, we estimate that in the study hospital where 6 million doses are administered per year, more than 4,200 preventable ADEs attributable to medication administration errors occur annually. There are several studies that attempt to calculate the cost of an ADE, with the cost ranging from $4,700 to $8,700 per ADE depending on the considerations and methodology used to make these estimations [42]. Given these estimates, the cost of patient harm from medication administration errors could range anywhere between $25 and $33 million in a 700-bed teaching hospital annually. The high incidence and cost implications for ADEs due to medication administration errors justify the need to target interventions to prevent these errors in a hospital setting. |
| Evidence source | Vifor Pharma Clinical Trial Database and Safety Database; literature search [37-44] |
| MedDRA terms | MedDRA HLGT Medication error<br>MedDRA PT Intentional overdose<br>MedDRA PT Substance abuse<br>MedDRA PT Intentional drug misuse<br>MedDRA PT Multiple drug overdose<br>MedDRA PT Drug toxicity<br>MedDRA PT Therapeutic agent toxicity<br>MedDRA PT Overdose<br>MedDRA PT Accidental overdose<br>MedDRA PT Drug abuse<br>MedDRA PT Drug dependence<br>MedDRA PT Drug level increased<br>MedDRA LLT Chronic overdose<br>MedDRA LLT Polysubstance abuse<br>MedDRA LLT Overdose NOS<br>MedDRA LLT Drug overdose<br>MedDRA LLT Overdose accidental<br>MedDRA LLT Overdose effect |

Notes: ADE=Adverse drug event; ADR=Adverse drug reaction; AE=Adverse event; CI=Confidence interval; DLP=Data lock point; HLGT=High level group term; ICU=Intensive care unit; IV=Intravenous; LLT=Lowest level term; MedDRA=Medical Dictionary for Regulatory Activities; NOS=Not otherwise specified; PT=Preferred term.

## Table 19 Important Identified Risk of Injection/infusion Site Reactions

| Identified Risk | Injection/infusion site reactions |
|---|---|
| Frequency with 95% CI | **Related Clinical Trial Population** |

| Number of Venofer® Related Cases | Number of Subjects Exposed | Frequency per 10,000 Patients (95% CI) |
|---|---|---|
| 94 (non-serious)<br>0 (serious)<br>94 (total) | 4,064 | 231 (188.3; 283.6)<br>–<br>231 (188.3; 283.6) |

**Post-marketing Experience**

| Number of Cases | Exposure Since International Birth Date to DLP | Frequency per 100,000 Patient Years |
|---|---|---|
| 515 (non-serious)<br>99 (serious)<br>614 (total) | 19,334,271<br>patient years | 2.66<br>0.51<br>3.17 |

| | |
|---|---|
| Seriousness/outcomes | **From Completed Clinical Trials: in 4,064 patients:**<br>No serious related cases.<br>**From Post-marketing Experience: in 19,334,271 patient years:**<br>98 serious related cases. |
| Severity and nature of risk | In the post-marketing setting it is not always possible to determine the severity of an event due to lack of sufficient information or severity not being reported as such.<br>Subsequent information reviewed in the PSUR does not change the overall assessment of this important identified risk. |
| Background incidence/ prevalence | Extravasation, the inadvertent leakage of IV medication from the vein into the surrounding tissue, is an iatrogenic cause of patient injury. Extravasation has been reported to occur in 0.1% to 6.5% of hospital inpatients, the true incidence is likely higher because of inconsistent documentation and reporting. The incidence may be higher among children because they have multiple risk factors, including small and fragile veins, decreased peripheral circulation, capillary leakage, and flexible subcutaneous tissue [45].<br>In a medical centre for infants and children over a time period of 5 years IV infiltration injuries were found to have occurred in 10% to 30% of paediatric patients receiving IV infusions and in 55% in neonates [46]. |
| Risk groups or risk factors | **Risk Groups**<br>Children, elderly, patients with vein abnormalities, such as small and fragile veins, decreased peripheral circulation, capillary leakage, and flexible subcutaneous tissue [45].<br>The most common sites for extravasation injuries are the dorsum of the hand, the forearm, the cubital fossa and the dorsum of the foot, which are all areas where the skin and subcutaneous tissue are thinnest; also making them the most commonly used sites for IV access [47].<br>**Risk Factors**<br>Identified risk factors in patients of all ages include insertion of the cannula and administration of the medication by inexperienced staff; venipuncture and cannula placement in small, fragile veins in the vicinity of joints (particularly in elderly patients and children); multiple venipuncture attempts at a given site because the number of easily |

| Identified Risk | Injection/infusion site reactions |
|---|---|
| | visualised peripheral veins is limited; and presence of decreased perfusion. Children commonly have multiple risk factors, which increases the likelihood of IV extravasation injuries. Although children of all ages receiving IV therapy are at greater risk of extravasation injury than adults, neonates have additional factors that may increase the severity of injury, such as poor venous integrity, capillary leakage, decreased peripheral circulation, and more flexible subcutaneous tissue, which can expand quickly with infiltration of fluid. An additional risk for children is that a small volume of extravasated IV fluid has the potential to cause substantial tissue damage secondary to local pressure effects and compartment syndromes [45].<br>The risk of a serious extravasation injury depends on drug characteristics, including osmolarity, pH, cytotoxicity, and vasoactivity (vasoconstrictors, such as norepinephrine, have a higher potential for causing injury than vasodilators) [48]. |
| Potential mechanisms | Extravasation is the accidental (non-intentional) administration of IV infused medicinal drugs into the surrounding tissue, either by leakage (e.g., because of brittle veins in very elderly patients), or direct exposure (e.g., because the needle has punctured the vein and the infusion goes directly into the surrounding tissue). Extravasation of medicinal drugs during IV therapy is an administration error that can and should be avoided. Occurrence is possible with all IV drugs; however is a larger problem with cytotoxic drugs for the treatment of cancer (i.e., during chemotherapy). The percentage of all patients affected by extravasation may be as high as 10% [48,49]. However, the actual percentage is unknown, since extravasation is often unnoticed and/or undocumented, especially if not severe [48,49].<br>Extravasation injury usually refers to the damage caused by leakage of solutions from the vein to the surrounding tissue spaces during IV administration. Once an extravasation has occurred, the effects when untreated could be extensive. Therefore, treatment should not be delayed. Five percent of patients who received a course of cytotoxic injections experienced extravasations [48,49].<br>In mild cases, extravasation can cause pain, reddening, or irritation of the arm in which the infusion needle was placed. Medicinal drugs that cause only slight damage to the tissue of the arm after extravasation occurred are called irritants, and medicinal drugs that cause more extensive damage (ultimately leading to tissue necrosis (see part with cytotoxic drugs)) if extravasated are called vesicants.<br>Extravasation should be suspected in the following situations:<br>• Erythema, swelling, or leakage is observed at the injection site.<br>• An IV infusion does not flow freely or the rate is reduced.<br>• Resistance is felt during administration of IV push medications.<br>• No blood return occurs with aspiration.<br>Notably, blood return does not exclude extravasation, and ruling out infiltration because of blood return has been implicated in a number of serious extravasation injuries [48]. |
| Preventability | The best “treatment” of extravasation is prevention. If a substance known to cause an extravasation injury is to be used, it is important to ensure that the cannula is in an adequate vein and that this area is monitored regularly. Multiple puncture holes in the vein and obstructed venous systems should be avoided. It remains paramount that all IV sites be watched and monitored very carefully [47].<br>While there is no real treatment per se, there are some techniques that |

| Identified Risk | Injection/infusion site reactions |
|---|---|
| | can be applied in case extravasation occurs with certain toxic medications (e.g., chemotherapy), though their efficacy is modest. In certain cases extravasation of these toxic medications may lead to tissue necrosis, in this case surgical reconstruction may be helpful.<br>**Treatments and Techniques**<br>• Stop infusion immediately. Put on sterile gloves.<br>• Replace infusion line with a disposable syringe. While doing this, do not exert pressure on the extravasation area.<br>• Slowly aspirate blood back from the arm, preferably with as much of the infusion solution as possible.<br>• Remove the original cannula or other IV access carefully from the arm (removal of the original cannula is not advised by all healthcare institutions, as access to the original cannula by surgeons can be used to help clean extravasated tissue).<br>• Elevate arm and rest in elevated position. If there are blisters on the arm, aspirate content of blisters with a new thin needle.<br>• If, for the extravasated medicinal drug, substance-specific measures apply, carry them out.<br>• Early treatment may include the injection or application of medication (e.g., hyaluronidase, phentolamine, or nitroglycerin ointment) and appropriate dressings [46].<br>**Prevention of Extravasation in Hospitals**<br>• Venipuncture and placement of the cannula (or other IV access) should be performed by experienced personnel, especially for patients prone to extravasation (e.g., patients with hardly visible veins, very obese patients, very elderly patients, young children, etc.). Multiple venipunctures in the same area should be avoided.<br>• Choose a large, intact vein with good blood flow for the venipuncture and placement of the cannula. Do not choose inadvertently "dislodgeable" veins (e.g., dorsum of hand or vicinity of joints) if an alternative vein is available.<br>• Use thin cannulas with high gauges. Check the position of the cannula by aspirating blood, as well as the patency of the vein by flushing with the carrier solution (e.g., 0.9% NaCl solution), before beginning the IV infusion. Although other studies state that extravasation may occur independently of the injection rates (high or low) and regardless of small or large size cannulas used [50].<br>• Observe infusion at least for the first 10 minutes.<br>• The IV infusion should be freely flowing. The arm with the infusion should not develop oedema, erythema or increased local temperature, and the patient should not notice any irritation or pain on the arm. If this occurs, stop infusion immediately.<br>• The infusion should consist of a suitable carrier solution with an appropriately diluted medicinal drug inside.<br>After the IV infusion has finished, flush the vein "clean" with only the carrier solution. |
| Impact on individual patient | Injection/infusion site reactions are usually painful incidents which could have some impact of patients' quality of life. |
| Potential public health impact of safety concern | The public health impact is determined by the conditions under which the extravasation occurs, to note the injection site location and the type of drug that is extravasated (see above). Extravasation injuries initially present as local swelling, erythema, blistering, and pain. These injuries |

| Identified Risk | Injection/infusion site reactions |
|---|---|
| | can lead to severe and progressive destruction of the tissue, including tissue necrosis, and can ultimately interfere with the function of the affected extremity or result in amputation. Therefore, injuries resulting from extravasation are considered to constitute a medical emergency and necessitate immediate treatment [45].<br>The impact of injection/infusion site reactions can potentially be long lasting and of significant medical impact, e.g., when injection/infusion site discolouration occurs (potentially long lasting) or tissue necrosis with limb movement impairment is involved (significant medical impact). |
| Evidence source | Vifor Pharma Clinical Trial Database and Safety Database; literature search [45-50] |
| MedDRA terms | MedDRA HLT Infusion site reaction<br>MedDRA HLT Injection site reaction<br>MedDRA HLT Administration site reactions NEC<br>MedDRA PT Infusion related reaction |

Notes: CI=Confidence interval; DLP=Data lock point; HLT=High level term; IV=Intravenous; MedDRA=Medical Dictionary for Regulatory Activities; NEC=Not elsewhere classified; PSUR=Periodic Safety Update Report; PT=Preferred term.

## Table 20 Important Potential Risk of Haemosiderosis

| Potential Risk | Haemosiderosis |
|---|---|
| Frequency with 95% CI | **Related Clinical Trial Population** |

| Number of Venofer® Related Cases | Number of Subjects Exposed | Frequency per 10,000 Patients |
|---|---|---|
| 3 (non-serious)<br>0 (serious)<br>3 (total) | 4,064 | 7 (1.91, 23.5)<br>–<br>7 (1.91, 23.5) |

**Post-marketing Experience**

| Number of Cases | Exposure Since International Birth Date to DLP | Frequency per 100,000 Patients Years |
|---|---|---|
| 2 (non-serious)<br>5 (serious)<br>7 (total) | 19,334,271<br>patient years | 0.01<br>0.03<br>0.04 |

| | |
|---|---|
| Seriousness/outcomes | **From Completed Clinical Trials: in 4,064 patients:**<br>Non-serious cases: 3 cases of iron overload. The outcome of all 3 cases is recovered. The diagnosis was made on the basis of transient slight increase of either TSAT over 50% or serum ferritin over 300 ng/mL. For all 3 patients the outcome was recovered.<br>Serious cases: No serious case was reported<br>**From Post-marketing Experience: in 19,334,271 patient years:**<br>Non-serious cases: 2 cases from a literature article [51] reported 2 adolescent CKD patients with iron overload as evidenced by TSAT ≥50% and/or serum ferritin ≥800 ng/mL. The outcome was not reported.<br>Serious cases: 1 out of 5 serious cases was reported as related to Venofer by the reporter and the rest were not assessed. The reported terms were haemosiderosis (3 cases), iron overload (1 case) and iron toxicity (1 case, coded as iron overload). The first case does not have laboratory |

| Potential Risk | Haemosiderosis |
|---|---|
| | measurements or investigations to support the diagnosis (consumer case, with the reported term of iron toxicity). The second case was supported only by an MRI investigation that was reported by the investigator as false positive as it was performed shortly after the Venofer administration. The third case was supported by high ferritin values (750 ng/mL). The iron overload case was supported by MRI examination revealing iron deposition in the liver and spleen, without other laboratory data, dates of examination or Venofer administration. The iron toxicity was supported by liver biopsy and high ferritin values (1,000 ng/mL) in a haemodialysis patient that was administered 8 g of Venofer over the course of 8 months (overdose). Outcome: 2 cases were reported as "not recovered/not resolved", and 3 cases were reported as "unknown". |
| Severity and nature of risk | In the post-marketing setting it is not always possible to determine the severity of an event due to lack of sufficient information or severity not being reported as such.<br>Subsequent information reviewed in the PSUR does not change the overall assessment of this important potential risk. |
| Background incidence/ prevalence | Under physiological conditions, iron transport is highly conserved and is controlled via negative feedback regulatory mechanisms involving transferrin and its receptors as well as other iron transporters. In several clinical conditions, including primary haemochromatosis and secondary iron overload, iron metabolism is perturbed, which, in combination with modifying environmental factors, leads to chronic iron overload and its associated morbidity and mortality. Iron overload conditions are rapidly increasing in worldwide prevalence due to reductions in childhood mortality and increased use of blood transfusions.<br>Iron-mediated cellular damage plays a key pathophysiological role in multiple disorders, including acute iron toxicosis, iron overload cardiomyopathy, Friedreich's ataxia associated cardiomyopathy, and myocardial ischemia-reperfusion injury in the setting of iron overload.<br>Primary haemochromatosis (hereditary or idiopathic) is a common inherited disorder and presents as distinct subtypes. In this condition, excessive iron accumulation results primarily from increased GI absorption of iron coupled with abnormal iron metabolism in other tissues and cell types.<br>Type 1 primary haemochromatosis (classic hereditary haemochromatosis) is an autosomal recessive disorder linked to mutations of the HFE gene, which is involved in controlling GI absorption of iron. The distribution of the 2 mutations differ with the C282Y mutation being limited to those of northern European ancestry and has an allele frequency of about 10%, whereas the H63D mutation occurs at allele frequencies >5% in Mediterranean/Middle East regions and the Indian subcontinent. In addition to the classical (Type 1) haemochromatosis, there are several other types of primary haemochromatosis (Types 2, 3, and 4) that have been linked to mutations in various proteins involved in iron metabolism.<br>Unlike primary haemochromatosis, secondary iron overload occurs primarily in patients with hereditary anaemias including α-thalassaemia, β-thalassaemia, and sickle cell anaemia. In these patients, excessive iron exposure and secondary iron overload ensues primarily because of repeated blood transfusions as well as increased GI iron absorption in the setting of ineffective erythropoiesis. A reduction in childhood mortality from infection and malnutrition coupled with increased use of chronic blood transfusions have led to a growing incidence of iron overload in patients with thalassaemia and sickle cell disease. Thalassaemia |

| Potential Risk | Haemosiderosis |
|---|---|
| | originates mainly from the Mediterranean region, Africa, Middle East, Indian subcontinent, and Southeast Asia, where the estimates of gene frequencies range from 3% to 10% in some areas, but can reach frequencies as high as 30% to 40% within certain subpopulations. Sickle cell anaemia is the most common and severe form of sickle cell disease caused by the homozygous presence of sickle Hb and occurs most commonly in individuals of African ancestry. In the US, 9% of African Americans carry the sickle cell trait and 1 in 600 has sickle cell anaemia.<br>Approximately 60% to 80% of patients with myelodysplastic syndrome will develop anaemia at some point in their disease and 80% to 90% will need blood transfusions, which has been linked to the development of iron overload cardiomyopathy and HF. In addition to thalassaemia, sickle cell disease, and myelodysplastic syndrome, several other clinical disorders are associated with secondary iron overload including sideroblastic anaemia, acute myeloid leukaemia, congenital dyserythropoietic anaemia, and chronic renal failure (secondary to IV iron supplementation). |
| Risk groups or risk factors | In several clinical conditions, including primary haemochromatosis and secondary iron overload, iron metabolism is perturbed, which, in combination with modifying environmental factors, leads to chronic iron overload and its associated morbidity and mortality. Iron overload conditions are rapidly increasing in worldwide prevalence due to reductions in childhood mortality and increased use of blood transfusions.<br>Unlike primary haemochromatosis, secondary iron overload occurs primarily in patients with hereditary anaemias including α-thalassaemia, β-thalassaemia, and sickle cell anaemia. In these patients, excessive iron exposure and secondary iron overload ensues primarily because of repeated blood transfusions as well as increased GI iron absorption in the setting of ineffective erythropoiesis. A reduction in childhood mortality from infection and malnutrition coupled with increased use of chronic blood transfusions have led to a growing incidence of iron overload in patients with thalassaemia and sickle cell disease.<br>Risk groups: Patients with relevant hepatic comorbidity (damage of major storage organ) pose a special risk for iron overload leading to haemosiderosis.<br>**Risk Groups**<br>1. Primary haemochromatosis<br>a) Classical (Type 1) due to mutations in the HFE gene resulting in a cysteine-to-tyrosine substitution at amino acid 282 (C282Y) or an aspartate-to-histidine substitution at amino acid 63 (H63D) inherited as an autosomal recessive condition<br>b) Nonclassical Type 2 (also known as juvenile haemochromatosis) resulting from mutations in iron-regulatory protein, haemojuvelin (HJV gene) inherited as an autosomal recessive condition<br>c) Nonclassical Type 3 resulting from mutations in the transferrin receptor (TfR2gene) inherited as an autosomal recessive condition<br>d) Nonclassical Type 4 resulting from mutations in the iron exporter, ferroportin (SLC40A1 gene) inherited as an autosomal dominant condition<br>2. Secondary iron overload<br>a) Alpha and beta thalassaemia |

| Potential Risk | Haemosiderosis |
|---|---|
| | b) Sickle cell anaemia<br>c) Myelodysplastic syndrome<br>d) Aplastic anaemia<br>e) IV iron supplementation in patients with end-stage renal disease<br>f) Friedreich's ataxia (mitochondrial iron overload)<br>**Risk Factors**<br>1. Iron overload, due to excessive iron exposure (as a result of cause 2)<br>2. Increased use of blood transfusions<br>Increased GI iron absorption in the setting of ineffective erythropoiesis.<br>One of the potential mechanisms for all parenteral iron preparations is the overload of iron after multiple administration of parenteral iron (long-term use). Ongoing supplementation of more iron than needed by the body may result in accumulation of iron in iron storage sites leading to haemosiderosis. Data from nonclinical trials concerning repeat-dose toxicity studies, using high iron doses showed the expected pattern of changes associated with iron overload. There is uptake and retention of iron in the cells of RES in the major storage organs. |
| Preventability | To prevent the possibility of iron overload it is important to only supplement the amount of iron needed. The treatment of any cause of anaemia should be instituted in a clinical setting and it is advised to monitor patients at all times. |
| Impact on individual patient | So far, it is not possible to estimate the impact on individual patient, without further characterisation. |
| Potential public health impact of safety concern | **Iron Overload and Hepatic Dysfunction**<br>Parenteral iron administration should be avoided in patients with hepatic dysfunction where iron overload is a precipitating factor, in particular PCT. Careful monitoring of iron status is recommended to avoid iron overload.<br>**Iron Overload and PH Syndromes**<br>The prognosis for the PH syndromes as a group is difficult to determine because of the infrequency of the diagnosis and the variability among cases and aetiologies. Furthermore, no national database monitors children with PH.<br>When focusing on IPH, the clinical course varies greatly; however, the prognosis has always been regarded as poor, with a mean survival of 2.5-3 years after diagnosis. Death can occur acutely from massive haemorrhage or after progressive pulmonary insufficiency and right HF. The available therapeutic modalities are not associated with a better outcome.<br>One study of 30 children with IPH listed the following prognostic criteria:<br>• The severity of the disease at its onset does not correlate with the survival.<br>• Females survive longer than males.<br>• Young age at the onset of disease seems to carry a less favourable prognosis.<br>• Common therapeutic modalities have not improved outcome.<br>Another retrospective study of 15 children with IPH found that the presence of antineutrophil cytoplasm antibodies or other auto-antibodies signal poor prognosis.<br>**Iron Overload/Haemosiderosis and CVD** |

| Potential Risk | Haemosiderosis |
|---|---|
| | IV iron and recombinant human EPO, like all other medications, are associated with the risk of AEs. Historically, the primary concern with iron therapy has been the possibility of iron overload, which exposes the individual to the effects associated with non-transferrin-bound iron. Experience with EPO use has demonstrated an association with hypertension and with the up-regulation of a number of markers of inflammation. The impact of these potential adverse effects merits careful analysis, given that both IV iron and EPO are designed for long-term use in a patient population at high risk for infection and CVD. However, the incidence of iron overload and the risks associated with non-transferrin-bound iron have dramatically been reduced since the introduction of EPO therapy, and no data exist that demonstrate a definitive association between IV iron and an increased risk of morbidity related to infection or CVD.<br>On the other hand, EPO use is associated with hypertension, endothelial dysfunction, and prothrombotic and inflammatory states in haemodialysis patients. Risks associated with hypertension can be minimised by using the lowest effective EPO dose, which may be achieved through the regular use of IV iron. Judicious use of both IV iron and EPO may optimise cardiovascular outcomes [52].<br>**Iron Overload and Cardiomyopathy**<br>Iron overload cardiomyopathy is an important and potentially reversible cause of HF at an international scale and involves diastolic dysfunction, increased susceptibility to arrhythmias and a late-stage dilated cardiomyopathy. Iron studies, cardiac magnetic resonance imaging with T2 measurement, echocardiographic assessment, and plasma brain natriuretic peptide levels are all important diagnostic and prognostic tools to evaluate patients with iron overload cardiomyopathy. Iron overload-induced cardiomyopathy is reversible if therapy is introduced before the onset of overt HF and effective therapy exists including phlebotomy and iron chelation for primary haemochromatosis and secondary iron overload, respectively [53]. |
| Evidence source | Study and post-marketing information retrieved from the Vifor Pharma Clinical Trial Database and Safety Database and literature sources used [51,53]. |
| MedDRA terms | MedDRA PT Haemosiderosis<br>MedDRA PT Haematochromatosis<br>MedDRA PT Iron overload<br>MedDRA PT Hepatic siderosis<br>MedDRA PT Cardiac siderosis<br>MedDRA PT Pulmonary haemosiderosis<br>MedDRA PT Superficial siderosis of central nervous system |

Notes: AE=Adverse event; CI=Confidence interval; CKD=Chronic kidney disease; CVD=Cardiovascular disease; DLP=Data lock point; EPO=Erythropoietin; GI=Gastrointestinal; Hb=Haemoglobin; HF=Heart failure; IPH=Idiopathic pulmonary haemosiderosis; IV=Intravenous; MedDRA=Medical Dictionary for Regulatory Activities; MRI=Magnetic resonance imaging; PCT=Porphyria cutanea tarda; PH=Pulmonary haemosiderosis; PSUR=Periodic Safety Update Report; PT=Preferred term; RES=Reticuloendothelial system; TSAT=Transferrin saturation.

# SVII.4 Identified and Potential Interactions

## SVII.4.1 Overview of Potential for Interactions

As with all parenteral iron preparations, iron sucrose should not be administered concomitantly with oral iron preparations since the absorption of oral iron is reduced.

Therefore, oral iron therapy should be discontinued 24 hours prior to the first injection of iron sucrose and should not be started within 5 days after the last injection of iron sucrose.

### SVII.4.2 Important Identified and Potential Interactions

Not applicable.

## SVII.5 Pharmacological Class Effects

### SVII.5.1 Pharmacological Class Risks Already Included as Important Identified or Potential Risks

A general safety concern in all parenteral preparations is the potential for hypersensitivity reactions (see Section SVII.3).

A safety concern for all parenteral iron preparations is the potential of iron overload after long-term use. Supplementation of more iron than needed by the body may result in accumulation of iron in iron storage sites leading to haemosiderosis (see Section SVII.3).

**Table 21 Pharmacological Class Effects Included as Important Identified/Potential Risks**

| Risk | Frequency in Clinical Trials of Medicinal Product | Frequency Seen with Other Products in Same Pharmacological Class | Comment |
|---|---|---|---|
| Hypersensitivity/ anaphylactoid reaction | The frequency of hypersensitivity/anaphylactoid reaction in clinical trials with Venofer® was 416 (95% CI 357.5, 483.0) per 10,000 patients. Of 169 reported cases in 4,064 study subjects exposed to Venofer, only 7 cases included serious events. | 256 of 7,268 patients (352 per 10,000) treated with Ferinject® (ferric carboxymaltose) experienced a non-serious hypersensitivity events in clinical trials, which was considered related to ferric carboxymaltose.<br>Two of 7,268 patients (3.0 per 10,000) treated with Ferinject experienced a serious hypersensitivity events in clinical trials, which was related to ferric carboxymaltose.<br>Based on the published literature, hypersensitivity reactions are very rare events also for iron gluconate [54]. | Iron sucrose did not show any cross-reactivity with anti-dextran antibodies. Nonetheless Venofer must not be administered to patients with known serious hypersensitivity to any parenteral iron preparation. |

**Table 21 Pharmacological Class Effects Included as Important Identified/Potential Risks (Cont'd)**

| Risk | Frequency in Clinical Trials of Medicinal Product | Frequency Seen with Other Products in Same Pharmacological Class | Comment |
|---|---|---|---|
| Haemosiderosis | The frequency of haemosiderosis reaction in clinical trials with Venofer® was 7 cases (95% CI 1.91, 23.5) per 10,000 patients. All 3 cases reported in 4,064 study subjects were non-serious. | Three of 7,268 patients (4 per 10,000) treated with Ferinject (ferric carboxymaltose) experienced a non-serious event of iron overload in clinical trials, which was considered related to ferric carboxymaltose. No serious iron overload/ haemosiderosis case was reported in clinical trials. Cases of haemosiderosis were received through the PV system for Ferinject (ferric carboxymaltose), a parenteral pharmaceutical similar to Venofer. | For all 3 Venofer cases the reported term was iron overload, and the diagnosis was made on the basis of transient slight increase of either TSAT over 50% or serum ferritin over 300 ng/mL. For all 3 patients the outcome was recovered. |

Notes: CI=Confidence interval; PV=Pharmacovigilance; TSAT=Transferrin saturation.

## SVII.5.2 Important Pharmacological Class Effects not Discussed Above

Not applicable.

# SVIII SUMMARY OF THE SAFETY CONCERNS

**Table 22 Summary of Safety Concerns**

| | |
|---|---|
| Important identified risks | Hypersensitivity/anaphylactoid reaction<br>Medication error<br>Injection/infusion site reactions |
| Important potential risks | Haemosiderosis |
| Missing information | Use in paediatric population<br>Use in elderly patients<br>Use in patients with infectious diseases<br>Use in pregnant or lactating women |

# PART III: PHARMACOVIGILANCE PLAN

## III.1 Safety Concerns and Overview of Planned PV Activities

### Table 23 Overview of PV Activities for Hypersensitivity/Anaphylactoid Reaction

| Areas Requiring Confirmation or Further Investigation | Proposed Routine and Additional PV Activities | Objectives |
|---|---|---|
| Changes in the profile and frequency of the event | Routine PV:<br>• All cases with hypersensitivity/ anaphylactoid events will be carefully followed up and a thorough assessment will be made.<br>• A follow-up TQ specific for hypersensitivity reactions has been incorporated into routine follow-up.<br>Additional PV:<br>• Cumulative annual review of hypersensitivity reactions. | To monitor any increase in frequency and severity of hypersensitivity/ anaphylactoid reactions. |
| Safety of Venofer® administration with respect to this safety concern | • Joint PASS feasibility report was submitted to EU/EEA NCAs on 19 December 2014. | • Feasibility phase: To evaluate the feasibility of conducting a European multi-country PASS on the utilisation and the risk of severe hypersensitivity among users of IV iron products (see synopsis in annex)<br>• PASS: To estimate the utilisation and the risk of severe hypersensitivity among users of IV iron products |

Notes: IV=Intravenous; NCA=National Competent Authority; PASS=Post-authorisation safety study; PV=Pharmacovigilance; TQ=Targeted Questionnaire.

### Table 24 Overview of PV Activities for Medication Error

| Areas Requiring Confirmation or Further Investigation | Proposed Routine and Additional PV Activities | Objectives |
|---|---|---|
| Changes in the profile and frequency of the event | Routine PV:<br>• All cases where any form of medication error is reported will be carefully followed up and a thorough assessment will be made. In all ongoing clinical trials medication error is already an area of special interest. | To monitor and analyse any type of medication error. |

Note: PV=Pharmacovigilance.

## Table 25 Overview of PV Activities for Injection/Infusion Site Reactions

| Areas Requiring Confirmation or Further Investigation | Proposed Routine and Additional PV Activities | Objectives |
|---|---|---|
| Changes in the profile and frequency of the event | Routine PV:<br>• All cases where any form of injection/infusion site reaction is reported will be carefully followed up and a thorough assessment will be made.<br>• In all ongoing clinical trials injection/infusion site reaction is already an area of special interest.<br>• A follow-up TQ specific for injection/infusion site reactions has been incorporated into routine follow-up. | To monitor and analyse any type of injection/infusion site reaction. |

Note: PV=Pharmacovigilance; TQ=Targeted Questionnaire.

## Table 26 Overview of PV Activities for Haemosiderosis

| Areas Requiring Confirmation or Further Investigation | Proposed Routine and Additional PV Activities | Objectives |
|---|---|---|
| The relevance of this risk to Venofer® therapy | Routine PV:<br>• All cases with patients suffering from haemosiderosis will be carefully followed up and a thorough assessment will be made. | To monitor and analyse any events on haemosiderosis.<br>To better characterise the event for more precise causality assessment. |

Note: PV=Pharmacovigilance.

## Table 27 Overview of PV Activities for Use in Paediatric Population

| Areas Requiring Confirmation or Further Investigation | Proposed Routine and Additional PV Activities | Objectives |
|---|---|---|
| Efficacy and safety in paediatric population | Routine PV:<br>• All paediatric cases will be carefully followed up and a thorough assessment will be made with regards to the possibility of paediatric use. | To monitor any increase in frequency and severity of use in children, occurring from spontaneous reporting. |

Note: PV=Pharmacovigilance.

## Table 28 Overview of PV Activities for Use in Elderly Population

| Areas Requiring Confirmation or Further Investigation | Proposed Routine and Additional PV Activities | Objectives |
|---|---|---|
| Efficacy and safety of iron sucrose therapy in elderly patients | Routine PV:<br>• All cases with hepatic impaired patients will be carefully followed up and a thorough assessment will be made. | To monitor any increase in frequency and severity of cases concerning hepatic dysfunction, occurring from spontaneous reporting or in clinical trials. |

Note: PV=Pharmacovigilance.

## Table 29 Overview of PV Activities for Use in Patients with Infectious Diseases

| Areas Requiring Confirmation or Further Investigation | Proposed Routine and Additional PV Activities | Objectives |
|---|---|---|
| Efficacy and safety of iron sucrose therapy in patients with underlying infectious infection | Routine PV:<br>• All cases with patients with known infections will be carefully followed up and a thorough assessment will be made.<br>• A follow-up TQ specific for injection site reactions has been incorporated into routine follow-up(1). | To monitor any increase in frequency and severity of cases concerning an infectious disease, occurring from spontaneous reporting or in clinical trials. |

1 The MAH has been using a specific TQ for collecting supplementary information on Venofer use in patients with infections since July 2011. Following a comprehensive analysis of responses and their quality to the TQs that were sent out until 31 July 2014, Vifor Pharma retired the TQ and address the questions related to infectious diseases during the regular follow-up activity on 27 November 2014, since no response was received for any of the 14 TQs that were sent during follow-up. The MAH decided to re-instate the TQ as of 1 June 2015, following the preliminary assessment report of the RMP Version 2.0 on the procedure number UK/H/0313/001/IB/053.

Note: MAH=Marketing Authorisation Holder; PV=Pharmacovigilance; RMP=Risk Management Plan; TQ=Targeted Questionnaire.

## Table 30 Overview of PV Activities for Use in Pregnant or Lactating Women

| Areas Requiring Confirmation or Further Investigation | Proposed Routine and Additional PV Activities | Objectives |
|---|---|---|
| Safety of iron sucrose therapy during pregnancy or lactation. | Routine PV:<br>• All pregnancy and lactation cases will be carefully followed up, including the outcome of birth (using specific follow-up forms).<br>Additional PV:<br>• Cumulative annual reporting of drug exposure during pregnancy. | To monitor any increase in frequency and severity of use in pregnant women, occurring from spontaneous reporting or in clinical trials. |

Note: PV=Pharmacovigilance.

## III.2 Additional PV Activities to Assess Effectiveness of Risk Minimisation Measures

Risk minimisation measures will be assessed via routine PV activities only.

## III.3 Studies and Other Activities Completed Since Last Update of PV Plan

Not applicable.

## III.4 Details of Outstanding Additional PV Activities

All EU registered IV iron medicinal products, including Ferinject®, were evaluated by the EMA as part of an Article 31 referral procedure (EMEA/H/A-31/1322) whereby the risk of serious allergic reactions with the use of these products was investigated (see Section SV.1). The CHMP adopted an opinion on 27 June 2013, which was endorsed by the EC decision on 13 September 2013.

The conditions affecting the marketing authorisation included a request that the IV iron MAHs should conduct a post-authorisation safety study (PASS) to further characterise the safety concerns of hypersensitivity reactions.

The CHMP also recommended exploring the existing databases, e.g., European Renal Association-European Dialysis and Transplant Association and QUEST. These databases were explored and following discussions and correspondence with the responsible staff, it was concluded that they do not provide IV iron data needed for hypersensitivity analysis.

The companies joining the consortium of MAHs further explored the European Network of Drug Allergies and also the databases of the EU (EUCLID) and US dialysis clinics, but these are unfortunately also not suitable tools with regard to safety data that are required for the PASS.

The MAHs are aware of the Mini-Sentinel Center for Drug Evaluation and Research Assessment Protocol on Parenteral Iron and Anaphylactoid Reactions and will follow this study closely.

Based on the information mentioned above, the MAH is presenting (Table 32 and Table 33) details about planned additional PV activities to further characterise the safety concerns of hypersensitivity reactions. The PASS feasibility study has been submitted to the National Competent Authorities and the Pharmacovigilance Risk Assessment Committee (PRAC) on 19 December 2014.

The feasibility study was conducted and executed by RTI Health Solutions and evaluated 10 well-known European databases in 9 different countries. Based on the feasibility study results and several consultations with external experts, the iron consortium concludes that there are important limitations in all evaluated databases. The main ones are:

- Limited data availability for all IV iron medicinal products in all databases in relation to the endpoint of interest (risk of anaphylaxis/hypersensitivity reactions), of which the frequency is known to be low

- Only a few databases cover a relatively high number of patients exposed to IV iron medicinal products, but these databases have also several of the other mentioned limitations

- Several databases only contain prescription data of the primary care, while in the majority of evaluated countries IV iron medicinal products are mainly used in the hospital setting

- Relevant endpoints are not available in the majority of the evaluated databases

- Validation of endpoints of the evaluated databases, except for Denmark, is not available

- Privacy laws in some countries prevent linkage of relevant data sources

Consequently a PASS, as originally envisioned covering all IV iron medicinal products used in Europe with source record validation of potential cases, is not feasible. Data on relevant endpoints are very limited. This can also partly be explained by the low absolute number of events related to IV iron medicinal products. In a recent article [55], 4,141 cases of anaphylaxis were evaluated (Germany, Austria and Switzerland). Of these, 15% were induced by medicines. Painkillers, antibiotics were the main contributors. IV iron medicinal products were not specifically mentioned, but could have been included in the miscellaneous group that accounted for 6.7% of the medicine induced anaphylaxis cases.

Based on the low frequency of the event and the limitations in precision and validation of the evaluated databases, the iron consortium members conclude that there are too many uncertainties around the data quantity and quality.

Such a database study would not lead to the result ‘to further characterize the safety concerns on hypersensitivity reactions’ of IV iron medicinal products and therefore should not be conducted.

The iron consortium members are awaiting PRAC assessment.

### III.4.1 Imposed Mandatory Additional PV Activity (Key to Benefit/Risk)

**Table 31 Imposed Additional PV Activities**

| Action | Description of Activity (or study title if known) | Milestone(s) | Due/Actual Date(s) |
|---|---|---|---|
| 1 | Joint PASS to further characterise the safety concern on hypersensitivity reactions | PASS feasibility report was submitted to EU/EEA NCAs on 19-Dec-2014 (refer to Annex 9) | 19-Dec-2014 |

Note: NCA=National Competent Authority; PASS=Post-authorisation safety study; PV=Pharmacovigilance.

### III.4.2 Mandatory Additional PV Activity (Being a Specific Obligation)

Not applicable.

### III.4.3 Required Additional PV Activities to Address Specific Safety Concerns or To Measure Effectiveness of Risk Minimisation Measures

Not applicable.

### III.4.4 Stated Additional PV Activities

Not applicable.

## III.5 Summary of the PV Plan

### III.5.1 Ongoing and Planned Additional PV Studies/Activities in the PV Plan

**Table 32 Overview of Ongoing and Planned PV Studies or Activities**

| Study/Activity Type, Title and Category (1-3) | Objectives | Safety Concerns Addressed | Status (Planned/ Started) | Date for Submission of Interim or Final Reports (Planned or Actual) |
|---|---|---|---|---|
| Joint PASS (Category 1) | • Feasibility phase: To evaluate the feasibility of conducting a European multi-country PASS on the utilisation and the risk of severe hypersensitivity among users of IV irons products (see feasibility report in Annex 9).<br>• PASS: To estimate the utilisation and the risk of severe hypersensitivity among users of IV irons products. | Hypersensitivity/ anaphylactoid reaction | Completed | PASS feasibility report was submitted to EU/EEA NCAs on 19-Dec-2014<br>PASS: final report by 31-Jul-2016 |

Notes: IV=Intravenous; NCA=National Competent Authority; PASS=Post-authorisation safety study; PV=Pharmacovigilance.

### III.5.2 Completed Studies/Activities

Not applicable.

# PART IV: PLAN FOR POST-AUTHORISATION EFFICACY STUDIES

## IV.1 Applicability of Efficacy to All Patients in the Target Population

Venofer has been shown to be effective in the treatment of ID in appropriately controlled clinical trials in several therapeutic areas, including CKD in both non-dialysis and haemodialysis-dependent patients, GI disorders, obstetrics and gynaecology (including pregnant and postpartum women, ID/IDA but otherwise healthy premenopausal women), oncology, blood management prior to surgery, and chronic heart disease.

Studies in paediatric patients have also been conducted in both CKD and non-renal conditions. However, there is only limited data on child use under study conditions.

The MAH is supporting an Investigator-initiated post-authorisation efficacy study (see Annex 8). The MAH does not plan to conduct any additional post-authorisation efficacy studies.

## IV.2 Tables of Post-authorisation Efficacy Studies

There are no proposed post-authorisation efficacy studies; therefore, this section is not applicable.

## IV.3 Summary of Post-authorisation Efficacy Development Plan

Not applicable.

## IV.4 Summary of Completed Post-authorisation Efficacy Studies

Not applicable.

# PART V: RISK MINIMISATION MEASURES

## V.1 Risk Minimisation Measures by Safety Concern

### Table 33 Risk Minimisation Measure for Hypersensitivity/Anaphylactoid Reaction

| **Hypersensitivity/Anaphylactoid Reaction** | |
|---|---|
| Objective(s) of the risk minimisation measures | To inform about this risk and associated risk factors using routine risk minimisation activities. |
| Routine risk minimisation measures | **Text in Summary of Product Characteristics**<br>Section 4.2 – Posology<br>Monitor carefully patients for signs and symptoms of hypersensitivity reactions during and following each administration of Venofer®.<br>Venofer 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 Venofer injection (see Section 4.4).<br>Section 4.3 – Contraindications<br>The use of Venofer is contraindicated in cases of:<br>• hypersensitivity to the active substance, to Venofer or any of its excipients listed in section 6.1<br>• known serious hypersensitivity to other parenteral iron products<br>Section 4.4 – Special warnings and precautions<br>Parenterally administered iron preparations can cause hypersensitivity reactions including serious and potentially fatal anaphylactic/ anaphylactoid reactions. Hypersensitivity reactions have also been reported after previously uneventful doses of parenteral iron complexes.<br>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.<br>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).<br>Venofer 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. Each patient should be observed for adverse effects for at least 30 minutes following each Venofer injection. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Facilities for cardio respiratory resuscitation and equipment for handling acute anaphylactic/anaphylactoid reactions should be available, including an injectable 1:1000 adrenaline solution.<br>Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.<br>Allergic reactions, sometimes involving arthralgia, have been more commonly observed when the recommended dose is exceeded.<br>**Comment**<br>Local product information may differ in the wording but the context of the information provided remains identical.<br>**Other routine risk minimisation measures**<br>Prescription only medicine. |

| Hypersensitivity/Anaphylactoid Reaction | |
|---|---|
| Additional risk minimisation measure(s) | **Objective and justification of why needed**<br>To inform healthcare professionals and patients about the outcomes of completed EMA referral procedure and its impact on the IV therapy and about the strengthened recommendations for use.<br>The objective is to minimise the risk of serious hypersensitivity reactions based on class label.<br>**Proposed actions/components and rationale**<br>Dissemination of DHPC about the risks of IV iron associated with hypersensitivity reactions. All healthcare professionals should follow the recommendations presented in the DHPC (distribution performed October-November 2013). Dissemination of Educational Materials to healthcare professionals and patients (ongoing; please refer to: Annex 10A for detailed information about the Educational Materials; Annex 10B for the distribution tracker and Annex 11 for the mocks ups). |
| **Effectiveness of Risk Minimisation Measures** | |
| How effectiveness of risk minimisation measures for safety concern will be measured | Effectiveness will be measured by means of routine PV activities, including signal detection, follow-up requests and review of received case reports relevant to this safety concern. |
| Criteria for judging the success of the proposed risk minimisation measures | The success of the proposed risk minimisation measures will be based on a reporting rate (comparison of product information versus case reports received). |
| Planned dates for assessment | Assessment will be performed during medical review of case reports and during signal detection evaluation meetings. |
| Results of effectiveness measurement | Results will be presented regularly in PSUR and RMP updates. |
| Impact of risk minimisation | Not applicable. |
| Comment | None. |

Notes: DHPC=Direct Healthcare Professional Communication; EMA=European Medicines Agency; IV=Intravenous; PSUR=Periodic Safety Update Report; PV=Pharmacovigilance; RMP=Risk Management Plan.

## Table 34 Risk Minimisation Measure for Medication Error

| Medication Error | |
|---|---|
| Objective(s) of the risk minimisation measures | To inform about this risk and associated risk factors using routine risk minimisation activities. |
| Routine risk minimisation measures | Text in Summary of Product Characteristics<br>Section 4.1 – Indications<br>The diagnosis of iron deficiency must be based on appropriate laboratory tests (e.g. Hb, serum ferritin, serum iron, etc.).<br>Section 4.2 – Posology<br>Posology and method of administration includes cumulative iron dose determination for accurate posology and information about the proper administration technique.<br>Section 4.4 – Special warnings and precautions<br>Paravenous leakage must be avoided because leakage of Venofer at the injection site may lead to pain, inflammation, tissue necrosis and brown discolouration of the skin. |

| Medication Error | |
|---|---|
| | Section 4.9 – Overdose<br>Overdosage can cause acute iron overloading which may manifest itself as haemosiderosis. Overdosage should be treated, if required, with an iron chelating agent.<br>**Comment**<br>Local product information may differ in the wording but the context of the information provided remains identical.<br>**Other routine risk minimisation measures**<br>Prescription only medicine. |
| Additional risk minimisation measure(s) | **Objective and justification of why needed**<br>Not applicable.<br>**Proposed actions/components and rationale**<br>None proposed. |
| **Effectiveness of Risk Minimisation Measures** | |
| How effectiveness of risk minimisation measures for safety concern will be measured | Effectiveness will be measured by means of routine PV activities, including signal detection, follow-up requests and review of received case reports relevant to this safety concern. |
| Criteria for judging the success of the proposed risk minimisation measures | The success of the proposed risk minimisation measures will be based on a reporting rate (comparison of product information versus case reports received). |
| Planned dates for assessment | Assessment will be performed during medical review of case reports and during signal detection evaluation meetings. |
| Results of effectiveness measurement | Results will be presented regularly in PSUR and RMP updates. |
| Impact of risk minimisation | Not applicable. |
| Comment | None. |

Notes: Hb=Haemoglobin; PSUR=Periodic Safety Update Report; PV=Pharmacovigilance; RMP=Risk Management Plan.

## Table 35 Risk Minimisation Measure for Injection/infusion Site Reactions

| **Injection/infusion Site Reactions** | |
|---|---|
| Objective(s) of the risk minimisation measures | To inform about this risk and associated risk factors using routine risk minimisation activities. |
| Routine risk minimisation measures | **Text in Summary of Product Characteristics**<br>Section 4.2 – Posology<br>Posology and method of administration includes cumulative iron dose determination for accurate posology and information about the proper administration technique.<br>Section 4.4 – Special warnings and precautions<br>Paravenous leakage must be avoided because leakage of Venofer at the injection site may lead to pain, inflammation, tissue necrosis and brown discolouration of the skin.<br>**Comment**<br>Local product information may differ in the wording but the context of the information provided remains identical.<br>**Other routine risk minimisation measures**<br>Prescription only medicine. |
| Additional risk minimisation measure(s) | **Objective and justification of why needed**<br>Not applicable.<br>**Proposed actions/components and rationale**<br>None proposed. |
| **Effectiveness of Risk Minimisation Measures** | |
| How effectiveness of risk minimisation measures for safety concern will be measured | Effectiveness will be measured by means of routine PV activities, including signal detection, follow-up requests and review of received case reports relevant to this safety concern. |
| Criteria for judging the success of the proposed risk minimisation measures | The success of the proposed risk minimisation measures will be based on a reporting rate (comparison of product information versus case reports received). |
| Planned dates for assessment | Assessment will be performed during medical review of case reports and during signal detection evaluation meetings. |
| Results of effectiveness measurement | Results will be presented regularly in PSUR and RMP updates. |
| Impact of risk minimisation | Not applicable. |
| Comment | None. |

Notes: PSUR=Periodic Safety Update Report; PV=Pharmacovigilance; RMP=Risk Management Plan.

## Table 36 Risk Minimisation Measure for Haemosiderosis

| **Haemosiderosis** | |
|---|---|
| Objective(s) of the risk minimisation measures | To inform about this risk and associated risk factors using routine risk minimisation activities. |
| Routine risk minimisation measures | **Text in Summary of Product Characteristics**<br>Section 4.1 – Therapeutic indication<br>The diagnosis of iron deficiency must be based on appropriate laboratory tests (e.g. Hb, serum ferritin, serum iron, etc.).<br>Section 4.3 – Contraindications<br>The use of Venofer is contraindicated in cases of:<br>iron overload or disturbances in utilisation of iron<br>Section 4.4 – Special warnings and precautions<br>In patients with liver dysfunction, parenteral iron should only be administered after careful risk/benefit assessment. Parenteral iron administration should be avoided in patients with hepatic dysfunction where iron overload is a precipitating factor, in particular PCT. Careful monitoring of iron status is recommended to avoid iron overload.<br>Section 4.9 – Overdose<br>Overdosage can cause acute iron overloading which may manifest itself as haemosiderosis. Overdosage should be treated, if required, with an iron chelating agent.<br>**Comment**<br>Local product information may differ in the wording but the context of the information provided remains identical.<br>**Other routine risk minimisation measures**<br>Prescription only medicine. |
| Additional risk minimisation measure(s) | **Objective and justification of why needed**<br>Not applicable.<br>**Proposed actions/components and rationale**<br>None proposed. |
| **Effectiveness of Risk Minimisation Measures** | |
| How effectiveness of risk minimisation measures for safety concern will be measured | Effectiveness will be measured by means of routine PV activities, including signal detection, follow-up requests and review of received case reports relevant to this safety concern. |
| Criteria for judging the success of the proposed risk minimisation measures | The success of the proposed risk minimisation measures will be based on a reporting rate (comparison of product information versus case reports received). |
| Planned dates for assessment | Assessment will be performed during medical review of case reports and during signal detection evaluation meetings. |
| Results of effectiveness measurement | Results will be presented regularly in PSUR and RMP updates. |
| Impact of risk minimisation | Not applicable. |
| Comment | None. |

Notes: Hb=Haemoglobin; PCT=Porphyria cutanea tarda; PSUR=Periodic Safety Update Report; PV=Pharmacovigilance; RMP=Risk Management Plan.

## Table 37 Risk Minimisation Measure for Use in Paediatric Population

| **Use in Paediatric Population** | |
|---|---|
| Objective(s) of the risk minimisation measures | To acknowledge the limitation of knowledge in this special population. |
| Routine risk minimisation measures | **Text in Summary of Product Characteristics**<br>Section 4.2 – Posology<br>Children: The use of Venofer has not been adequately studied in children and, therefore, Venofer is not recommended for use in children.<br>**Comment**<br>Local product information may differ in the wording but the context of the information provided remains identical.<br>**Other routine risk minimisation measures**<br>Prescription only medicine. |
| Additional risk minimisation measure(s) | **Objective and justification of why needed**<br>Not applicable.<br>**Proposed actions/components and rationale**<br>None proposed. |
| **Effectiveness of Risk Minimisation Measures** | |
| How effectiveness of risk minimisation measures for safety concern will be measured | Effectiveness will be measured by means of routine PV activities, including signal detection, follow-up requests and review of received case reports relevant to this safety concern. |
| Criteria for judging the success of the proposed risk minimisation measures | The success of the proposed risk minimisation measures will be based on a reporting rate (comparison of product information versus case reports received). |
| Planned dates for assessment | Assessment will be performed during medical review of case reports and during signal detection evaluation meetings. |
| Results of effectiveness measurement | Results will be presented regularly in PSUR and RMP updates. |
| Impact of risk minimisation | Not applicable. |
| Comment | None. |

Notes: PSUR=Periodic Safety Update Report; PV=Pharmacovigilance; RMP=Risk Management Plan.

## Table 38 Risk Minimisation Measure for Use in Elderly Patients

| **Use in Elderly Patients** | |
|---|---|
| Objective(s) of the risk minimisation measures | To acknowledge the limitation of knowledge in this special population. |
| Routine risk minimisation measures | **Text in Summary of Product Characteristics**<br>Section 4.2 – Posology<br>Posology and method of administration to elderly patients includes cumulative iron dose determination for accurate posology.<br>**Comment**<br>Local product information may differ in the wording but the context of the information provided remains identical.<br>**Other routine risk minimisation measures**<br>Prescription only medicine. |
| Additional risk minimisation measure(s) | **Objective and justification of why needed**<br>Not applicable.<br>**Proposed actions/components and rationale**<br>None proposed. |
| **Effectiveness of Risk Minimisation Measures** | |
| How effectiveness of risk minimisation measures for safety concern will be measured | Effectiveness will be measured by means of routine PV activities, including signal detection, follow-up requests and review of received case reports relevant to this safety concern. |
| Criteria for judging the success of the proposed risk minimisation measures | The success of the proposed risk minimisation measures will be based on a reporting rate (comparison of product information versus case reports received). |
| Planned dates for assessment | Assessment will be performed during medical review of case reports and during signal detection evaluation meetings. |
| Results of effectiveness measurement | Results will be presented regularly in PSUR and RMP updates. |
| Impact of risk minimisation | Not applicable. |
| Comment | None. |

Notes: PSUR=Periodic Safety Update Report; PV=Pharmacovigilance; RMP=Risk Management Plan.

## Table 39 Risk Minimisation Measure for Use in Patients with Infectious Diseases

| **Use in Patients with Infectious Diseases** | |
|---|---|
| Objective(s) of the risk minimisation measures | To acknowledge the limitation of knowledge in this special population. |
| Routine risk minimisation measures | **Text in Summary of Product Characteristics**<br>Section 4.4 – Special warnings and precautions<br>Parenteral iron must be used with caution in case of acute or chronic infection. It is recommended that the administration of iron sucrose is stopped in patients with ongoing bacteraemia. In patients with chronic infection a risk/benefit evaluation has to be performed, taking into account the suppression of erythropoiesis.<br>**Comment**<br>Local product information may differ in the wording but the context of the information provided remains identical.<br>**Other routine risk minimisation measures**<br>Prescription only medicine. |
| Additional risk minimisation measure(s) | **Objective and justification of why needed**<br>Not applicable.<br>**Proposed actions/components and rationale**<br>None proposed. |
| **Effectiveness of Risk Minimisation Measures** | |
| How effectiveness of risk minimisation measures for safety concern will be measured | Effectiveness will be measured by means of routine PV activities, including signal detection, follow-up requests and review of received case reports relevant to this safety concern. |
| Criteria for judging the success of the proposed risk minimisation measures | The success of the proposed risk minimisation measures will be based on a reporting rate (comparison of product information versus case reports received). |
| Planned dates for assessment | Assessment will be performed during medical review of case reports and during signal detection evaluation meetings. |
| Results of effectiveness measurement | Results will be presented regularly in PSUR and RMP updates. |
| Impact of risk minimisation | Not applicable. |
| Comment | None. |

Notes: PSUR=Periodic Safety Update Report; PV=Pharmacovigilance; RMP=Risk Management Plan.

## Table 40 Risk Minimisation Measure for Use in Pregnant or Lactating Women

| **Use in Pregnant or Lactating Women** | |
|---|---|
| Objective(s) of the risk minimisation measures | To acknowledge the limitation of knowledge in this special population. |
| Routine risk minimisation measures | **Text in Summary of Product Characteristics**<br>Section 4.6 – Pregnancy and lactation<br>There are no adequate and well-controlled trials of Venofer in pregnant women. A careful risk/benefit evaluation is therefore required before use during pregnancy and Venofer should not be used during pregnancy unless clearly necessary (see section 4.4). |

| Use in Pregnant or Lactating Women | |
|---|---|
| | IDA occurring in the first trimester of pregnancy can in many cases be treated with oral iron. Treatment with Venofer 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.<br>Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Data on a limited number of exposed human pregnancies indicated no adverse effects of Venofer on pregnancy or on the health of the foetus/newborn child.<br>Non metabolised Venofer is unlikely to pass into the mother's milk. No well-controlled clinical studies are available to date. Animal studies do not indicate direct or indirect harmful effects to the nursing child.<br>**Comment**<br>Local product information may differ in the wording but the context of the information provided remains identical.<br>**Other routine risk minimisation measures**<br>Prescription only medicine |
| Additional risk minimisation measure(s) | **Objective and justification of why needed**<br>To inform the healthcare professionals about the outcomes of completed EMA referral procedure and its impact on the IV therapy and about the strengthened recommendations for use.<br>The objective is to minimise the risk of serious hypersensitivity reactions based on class label.<br>**Proposed actions/components and rationale**<br>Dissemination of DHPC about the risks of IV iron associated with hypersensitivity reactions. All healthcare professionals should follow the recommendations presented in the DHPC (distribution performed October-November 2013). Dissemination of Educational Materials to healthcare professionals and patients (ongoing; please refer to: Annex 10A for detailed information about the Educational Materials; Annex 10B for the distribution tracker and Annex 11 for the mocks ups). |
| **Effectiveness of Risk Minimisation Measures** | |
| How effectiveness of risk minimisation measures for safety concern will be measured | Effectiveness will be measured by means of routine PV activities, including signal detection, follow-up requests and review of received case reports relevant to this safety concern. |
| Criteria for judging the success of the proposed risk minimisation measures | The success of the proposed risk minimisation measures will be based on a reporting rate (comparison of product information versus case reports received). |
| Planned dates for assessment | Assessment will be performed during medical review of case reports and during signal detection evaluation meetings. |
| Results of effectiveness measurement | Results will be presented regularly in PSUR and RMP updates. |
| Impact of risk minimisation | Not applicable. |
| Comment | None. |

Notes: DHPC=Direct Healthcare Professional Communication; IDA=Iron deficiency anaemia; IV=Intravenous; PSUR=Periodic Safety Update Report; PV=Pharmacovigilance; RMP=Risk Management Plan.

## V.2 Risk Minimisation Measure Failure

### V.2.1 Analysis of Risk Minimisation Measure(s) Failure

Not applicable for the initial submission of the RMP.

### V.2.2 Revised Proposal for Risk Minimisation

Not applicable for the initial submission of the RMP.

## V.3 Summary Table of Risk Minimisation Measures

**Table 41 Summary Table of Risk Minimisation Measures**

| Safety Concern | Routine Risk Minimisation Measures | Additional Risk Minimisation Measures |
|---|---|---|
| Hypersensitivity/ anaphylactoid reaction | Warning about the need for patient monitoring during and following administration as well as need for appropriately trained staff and full resuscitation facilities are stated in Section 4.2 of the SmPC.<br>Appropriate contraindications are listed in Section 4.3: in cases of hypersensitivity to Venofer components or serious hypersensitivity to other parenteral iron products.<br>Special warnings and precautions relevant to this risk are present in Section 4.4. This includes a warning regarding hypersensitivity and serious anaphylactic/anaphylactoid reactions, a warning regarding patients with enhanced risk, the requirement for the presence of appropriately trained staff and resuscitation facilities , the need for an observation period of 30 minutes after each injection as well as instructions in case hypersensitivity reactions occur.<br>Prescription only medicine. | DHPC and Educational Materials for prescribers and patients |
| Medication error | Section 4.1 states the need for laboratory investigations before initiation of therapy.<br>Correct posology, including route of administration is included in Section 4.2.<br>Section 4.4 summarises warnings and precautions relevant to this risk, such as the use with caution and personalised dosing to be used in patients with hepatic impairment of infections or that care should be taken not to administer too fast or paravenously.<br>Symptoms associated with overdose are discussed in Section 4.9 and the recommendation of treatment using iron chelating agents if required..<br>Prescription only medicine. | Not applicable |
| Injection/infusion site reactions | Correct posology is included in Section 4.2.<br>Special warnings and precautions associated with this risk are included in Section 4.4, such as the need to avoid paravenous leakage as it can cause local reactions.<br>Prescription only medicine. | Not applicable |

| | | |
|---|---|---|
| Haemosiderosis | Indication provided in Section 4.1 states the need for laboratory tests-confirmed ID before the initiation of therapy.<br>Appropriate contraindication is listed in Section 4.3: use in patients with anaemias not attributable to iron deficiency, iron overload or disturbances in utilisation of iron.<br>Symptoms associated with overdose and iron overload are discussed in Section 4.9 and the treatment with iron chelating agents is recommended, if required.<br>Prescription only medicine. | Not applicable |
| Use in paediatric population | Section 4.2 includes information relevant to this special population: the use of Venofer has not been adequately studied in children and, therefore, Venofer is not recommended for use in children.<br>Prescription only medicine. | Not applicable |
| Use in elderly patients | Section 4.2 includes information relevant to this special population: for elderly as well as for adults the dosage of Venofer must be individually determined.<br>Prescription only medicine. | Not applicable |
| Use in patients with infectious diseases | Section 4.4 includes the following warning relevant to patients with infectious diseases: “Parenteral iron must be used with caution in case of acute or chronic infection. It is recommended that the administration of iron sucrose is stopped in patients with ongoing bacteraemia. In patients with chronic infection a risk/benefit evaluation has to be performed, taking into account the suppression of erythropoiesis”.<br>Prescription only medicine. | Not applicable |
| Use in pregnant or lactating women | All information relevant to pregnancy and lactation is presented in Section 4.6 of the SmPC, such as the usage to be confined to second and third trimester, and only if the benefit is judged to outweigh the potential risk for both the mother and the foetus.<br>Prescription only medicine. | DHPC and Educational Materials for prescribers and patients |

Notes: DHPC=Direct Healthcare Professional Communication; ID=Iron deficiency; SmPC=Summary of Product Characteristics.

# PART VI: SUMMARY OF ACTIVITIES IN THE RMP BY PRODUCT

## VI.1 Elements for Summary Tables in the European Public Assessment Report

### VI.1.1 Summary Table of Safety Concerns

**Table 42 Summary of Safety Concerns**

| | |
|---|---|
| Important identified risks | Hypersensitivity/anaphylactoid reaction<br>Medication error<br>Injection/infusion site reactions |
| Important potential risks | Haemosiderosis |
| Missing information | Use in paediatric population<br>Use in elderly patients<br>Use in patients with infectious diseases<br>Use in pregnant or lactating women |

### VI.1.2 Ongoing and Planned Additional PV Studies/Activities in the PV Plan

**Table 43 Overview of Ongoing and Planned PV Studies or Activities**

| Study/Activity Type, Title and Category (1-3) | Objectives | Safety Concerns Addressed | Status (Planned/ Started) | Date for Submission of Interim or Final Reports (Planned or Actual) |
|---|---|---|---|---|
| Joint PASS | • Feasibility phase: To evaluate the feasibility of conducting a European multi-country PASS on the utilisation and the risk of severe hypersensitivity among users of IV irons products (see synopsis in Annex 9). | Hypersensitivity/ anaphylactoid reaction | Completed | PASS feasibility report submitted to EU/EEA NCAs on 19-Dec-2014. |
| | • PASS: To estimate the utilisation and the risk of severe hypersensitivity among users of IV irons products. | | | PASS: final report by 31-Jul-2016 |

Notes: IV=Intravenous; NCA=National Competent Authority; PASS=Post-authorisation safety study; PV=Pharmacovigilance.

## VI.1.3 Summary of Post-authorisation Efficacy Development Plan

Not applicable.

## VI.1.4 Summary Table of Risk Minimisation Measures

### Table 44 Summary Table of Risk Minimisation Measures

| Safety Concern | Routine Risk Minimisation Measures | Additional Risk Minimisation Measures |
|---|---|---|
| Hypersensitivity/ anaphylactoid reaction | Warning about the need for patient monitoring during administration is stated in Section 4.2 of the SmPC.<br>Appropriate contraindication is listed in Section 4.3.<br>Special warnings and precautions relevant to this risk are present in Section 4.4.<br>Prescription only medicine. | DHPC and Educational Materials for prescribers and patients |
| Medication error | Section 4.1 states the need for laboratory investigations before initiation of therapy.<br>Correct posology, including route of administration is included in Section 4.2.<br>Section 4.4 summarises warnings and precautions relevant to this risk.<br>Symptoms associated with overdose are discussed in Section 4.9.<br>Prescription only medicine. | Not applicable |
| Injection/infusion site reactions | Correct posology is included in Section 4.2.<br>Special warnings and precautions associated with this risk are included in Section 4.4.<br>Prescription only medicine. | Not applicable |
| Haemosiderosis | Indication provided in Section 4.1 states the need for laboratory tests-confirmed ID before the initiation of therapy.<br>Appropriate contraindication is listed in Section 4.3.<br>Symptoms associated with overdose and iron overload are discussed in Section 4.9.<br>Prescription only medicine. | Not applicable |
| Use in paediatric population | Section 4.2 includes information relevant to this special population.<br>Prescription only medicine. | Not applicable |
| Use in elderly patients | Section 4.2 includes information relevant to this special population.<br>Prescription only medicine. | Not applicable |
| Use in patients with infectious diseases | Section 4.4 includes the warning relevant to patient with infectious diseases.<br>Prescription only medicine. | Not applicable |
| Use in pregnant or lactating women | All information relevant to pregnancy and lactation is presented in Section 4.6 of the SmPC.<br>Prescription only medicine. | DHPC and Educational Materials for prescribers and patients |

Notes: DHPC=Direct Healthcare Professional Communication; ID=Iron deficiency; SmPC=Summary of Product Characteristics.

## VI.2 Elements for a Public Summary

### VI.2.1 Overview of Disease Epidemiology

Venofer® is a preparation containing iron given through a vein to patients who do not have enough iron in their body, a condition known as iron deficiency (ID).

Anaemia, a condition where there is a decreased number of red blood cells, often occurs as a result of ID and is a public health problem around the world. Anaemia can cause major health problems and increase the cost of healthcare. One-half of all anaemia happens due to ID [1].

Iron deficiency and iron deficiency anaemia (IDA) are particularly frequent in pregnant women and young children.

The number of patients with newly diagnosed ID each year is not known since most reports only contain information on the number of patients who currently have ID/IDA.

The risk of death each year due to anaemia is different depending on the cause of ID and the other conditions or diseases the patient has. Patients suffering from anaemia only have a 16.6% higher risk of death than the general population [12]. In patients with ID who also have chronic heart failure (CHF) or chronic kidney disease (CKD) or both, the risk of death increases by 34.6% for CHF, 27.3% for CKD or 45.6% for both [12].

### VI.2.2 Summary of Treatment Benefits

Intravenous (IV, given through the vein) iron therapy is helpful in treating ID and IDA especially when there is: 1) not enough iron being absorbed from the patient's diet or from iron therapy taken by mouth; 2) loss of blood due to bleeding or other causes; 3) problems with not being able to take all of the oral iron as directed; or 4) stomach upset or other unpleasant effects from oral iron therapy. The use of IV iron preparations is also recommended when erythropoiesis stimulating agents are used to treat IDA, especially in patients with CKD.

In many clinical studies and in over 60 years of experience in giving Venofer to patients (equal to over 17 million patient years of experience) Venofer has been shown to be effective with few side effects for the treatment of ID and IDA in several different diseases and clinical conditions. Venofer has been shown to be a good choice when oral iron does not work or when the patient cannot take oral iron. This has been demonstrated in several therapeutic areas, including CKD in both patients who are and who are not haemodialysis-dependent, disorders of the stomach and guts, pregnant women and women who have recently given birth or otherwise healthy premenopausal women with ID, cancer patients, patients who might need blood prior to surgery, and patients with chronic heart disease.

## VI.2.3 Unknowns Relating to Treatment Benefits

Venofer was shown to be effective in the treatment of ID in adults of different age and ethnic origin in appropriately controlled clinical studies. These studies included a representative sample of patients known from general practice. Experience in children is limited.

## VI.2.4 Summary of Safety Concerns

### Table 45 Important Identified Risks

| Risk | What Is Known | Preventability |
|---|---|---|
| Allergic reactions (hypersensitivity/ anaphylactoid reaction) | Allergic reactions that may include rash, hives, fever, difficulty breathing, and low blood pressure have been reported in association with injectable iron preparations, including Venofer®. Although usually reversible with treatment, they can be severe, life-threatening or even cause death. | Unknown.<br>Patients with known serious hypersensitivity to IV iron preparation should not take Venofer.<br>Careful medical monitoring could help to identify the risk of serious hypersensitivity reactions earlier and decrease the risk of such reactions. |
| Unintentional errors in the prescribing, dispensing or administration of a medicinal product (medication error) | As with any medicine, the administration of Venofer may be associated with unintentional errors. Incorrect dosing or administration may result in iron overload or reactions at or near the site of administration. | The recommendations for proper administration of Venofer should be carefully followed per the approved label. |
| Adverse reactions at the site of injection (injection/infusion site reactions) | The IV administration of Venofer may be associated with reactions at or near the site of administration. | The recommendations for proper administration of Venofer should be carefully followed per the approved label. |

Note: IV=Intravenous.

### Table 46 Important Potential Risks

| Risk | What Is Known |
|---|---|
| Iron overload disorder (haemosiderosis) | Administration of iron preparations beyond what is needed by the body to replace iron stores or make red blood cells may be associated with an increase in iron stores in the body leading to possible iron deposits in tissues and other organs or an iron overload disease called haemosiderosis. Careful monitoring of iron parameters and appropriate use of Venofer should be done. |

**Table 47 Missing Information**

| Risk | What Is Known |
|---|---|
| Use in children | Children and adolescents were excluded from the formal clinical development programme of Venofer®. However, there is limited information in the published literature about the efficacy and safety of Venofer use in children and adolescents. |
| Use in elderly patients | Elderly patients were under-represented in the clinical development programme of Venofer. Therefore, the knowledge about efficacy and safety of Venofer in this population is scarce. |
| Use in patients with infectious diseases | Patients with acute infection or known infectious disease (e.g., hepatitis B, C or HIV) were excluded from the clinical development programme. Therefore, the knowledge about efficacy and safety of Venofer in these patients is limited and the administration of Venofer in patients with an active infection is not recommended. |
| Use in pregnant or lactating women | There is no or only a limited amount of data (less than 300 pregnancy outcomes) from the use of iron sucrose in pregnant women in the first trimester. A moderate amount of data (between 300-1,000 pregnancy outcomes) from the use of Venofer in pregnant women in the second and third trimester showed no safety concerns for the mother or newborn. It cannot be excluded that newborns/infants may be exposed to iron derived from Venofer via the mother's milk. Therefore, the benefit/risk should be assessed before Venofer is prescribed to a pregnant or nursing woman. |

## VI.2.5 Summary of Risk Minimisation Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with information on the risks associated with the medicine and recommendations on the appropriate use of the medicine to ensure an acceptable benefit/risk. An abbreviated version of the SmPC in easy to understand language is provided in the form of the Package Leaflet (PL). The recommendations in these documents are considered routine risk minimisation measures.

The SmPC and the PL for Venofer can be found on the web pages of the national Competent Authorities in the EU.

Like all medicines, Venofer has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). How these conditions and restrictions for safe and effective use are implemented for Venofer in each country will depend upon agreement between the Marketing Authorisation Holder and the national authorities.

These additional risk minimisation measures are for the following risks.

## Table 48 Allergic Reactions (Hypersensitivity/Anaphylactoid Reaction)

| **Risk Minimisation Measure(s) – DHPC and Educational Materials for Healthcare Professionals (in the Form of a Checklist)** |
|---|
| Objective and rationale:<br>HCPs to better understand the risk of hypersensitivity and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity.<br>Summary description of main additional risk minimisation measure<br>DHPC<br>HCP and patient educational materials to be provided to prescribing physicians including advice on:<br>• Information to be provided to patients before administration of the IV iron<br>• Importance of adherence to the recommendations to avoid use of IV iron in patients with an increased risk of experiencing an allergic reaction<br>• Need to have trained staff administering the product to the patient, and adequate facilities and equipment for handling acute allergic reactions<br>• Need to observe the patient 30 minutes after each administration of IV iron<br>Objective and rationale:<br>• HCPs to better understand the risk of hypersensitivity and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity<br>• Summary description of main additional risk minimisation measure |

Notes: DHPC=Direct Healthcare Professional Communication; HCP=Healthcare professional; IV=Intravenous.

## Table 49 Use in Pregnant or Lactating Women

| **DHPC and Educational Materials for Healthcare Professionals (in the Form of a Checklist)** |
|---|
| Objective and rationale:<br>HCPs to better understand the risk of hypersensitivity in pregnancy and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity.<br>Summary description of main additional risk minimisation measures<br>DHPC<br>HCP and patient educational materials to be provided to prescribing physicians including advice on:<br>• Information to be provided to patients before administration of the IV iron<br>• Importance of adherence to the recommendations for use only if necessary, when the benefits are judged to outweigh the potential risks for the mother and the foetus<br>• Use of the IV iron only in 2nd and 3rd trimester of pregnancy<br>Objective and rationale:<br>• HCPs to better understand the risk of hypersensitivity in pregnancy and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity |

Notes: DHPC=Direct Healthcare Professional Communication; HCP=Healthcare professional; IV=Intravenous.

## VI.2.6 Planned Post-authorisation Development Plan

### Table 50 Summary of Post-authorisation Development Plan

| Study/Activity | Objectives | Safety Concerns/ Efficacy Issue Addressed | Status | Planned Date for Submission of Interim and Final Results |
|---|---|---|---|---|
| **Pharmacovigilance Plan** | | | | |
| Joint PASS | • Feasibility phase: To evaluate the feasibility of conducting a European multi-country PASS on the utilisation and the risk of severe hypersensitivity among users of IV irons products (see synopsis in Annex 6). | Hypersensitivity/ anaphylactoid reaction | Completed | Feasibility report submitted to EU/EEA NCAs on 19-Dec-2014 (see Annex 9). |
| | • PASS: To estimate the utilisation and the risk of severe hypersensitivity among users of IV irons products | | | Not applicable. |

Notes: IV=Intravenous; NCA=National Competent Authority; PASS=Post-authorisation safety study.

### Studies Which Are a Condition of the Marketing Authorisation

A PASS is a condition of the marketing authorisation.

## VI.2.7 Summary of Changes to the RMP Over Time

### Table 51 Major Changes to the RMP Over Time

| Version | Date | Safety Concerns | Comment |
|---|---|---|---|
| 1.0 | 28-Nov-2013 | Important identified risks:<br>• Hypersensitivity/anaphylactoid reaction<br>• Medication error<br>• Injection/infusion site reactions<br>Important potential risks:<br>• Haemosiderosis<br>Missing information:<br>• Use in paediatric population<br>• Use in elderly patients<br>• Use in pregnant or lactating women<br>• Use in patients with infectious diseases | Initial RMP for Venofer® |
| 2.0 | 10-Mar-2015 | – | Feasibility report for the PASS study<br>Status of additional risk minimisation measures (distribution of educational material) |

Notes: PASS=Post-authorisation safety study; RMP=Risk Management Plan.

# PART VII: ANNEXES

# LIST OF REFERENCES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## Annex 1 EudraVigilance Interface

Interface is available in electronic format only.

## Annex 2 SmPC and Package Leaflet

| | | | |
|---|---|---|---|
| Vifor (International) Inc. | Page 1/9 | Date: 25.04.2008 | Translation: DWL |
| Translation of Original Document SPC- YA539/YV004/YV003/ EU/E03 T UK02 | | Date: | Approval: |
| Verteiler: | | | |

**Summary of Product Characteristics** **Vifor (International) Inc.**

Regulatory Affairs

| | | |
|---|---|---|
| Document No:<br>SPC-YA539/YV004/ YV003/EU/E03 | **VENOFER**<br>**5 ml Ampoules**<br>**2.5 ml Vials**<br>**5 ml Vials** | Research & Development |
| Page 1/9 | | Int. Product Management |
| Valid from: | | Drug Safety |
| Replaces document:<br>SPC-YA539/YV004/ YV003/EU/E02 | Regulatory Affairs | Quality Assurance |
| **Distribution:** | | |

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

## 1. NAME OF THE MEDICINAL PRODUCT

Venofer 20 mg iron / ml, solution for injection or concentrate for solution for infusion.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One millilitre of solution contains 20 mg of iron as iron sucrose (iron(III)-hydroxide sucrose complex).

Each 5 ml ampoule of Venofer contains 100 mg iron as iron sucrose (iron(III)-hydroxide sucrose complex).

Each 2.5 ml vial of Venofer contains 50 mg iron as iron sucrose (iron(III)-hydroxide sucrose complex).

Each 5 ml vial of Venofer contains 100 mg iron as iron sucrose (iron(III)-hydroxide sucrose complex).

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection or concentrate for solution for infusion.
Venofer is a dark brown, non transparent, aqueous solution.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic Indications

Venofer is indicated for the treatment of iron deficiency in the following indications:

- where there is a clinical need to deliver iron rapidly to iron stores,
- in patients who cannot tolerate oral iron therapy or who are non-compliant,
- in active inflammatory bowel disease where oral iron preparations are ineffective.

The diagnosis of iron deficiency must be based on appropriate laboratory tests (e.g. Hb, serum ferritin, serum iron, etc.).

## 4.2. Posology and Method of Administration

Monitor carefully patients for signs and symptoms of hypersensitivity reactions during and following each administration of Venofer.

Venofer 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 Venofer injection (see section 4.4).

**Administration:** Venofer must only be administered by the intravenous route. This may be by a slow intravenous injection or by an intravenous drip infusion.
Venofer must not be used for intramuscular injection.

**Adults and the elderly:** The total cumulative dose of Venofer, equivalent to the total iron deficit (mg), is determined by the haemoglobin level and body weight. The dose for Venofer must be individually determined for each patient according to the total iron deficit calculated with the following formula:

Total iron deficit [mg] = body weight [kg] x (target Hb - actual Hb) [g/l] x 0.24* + depot iron [mg]

- Below 35 kg body weight: target Hb = 130 g/l and depot iron = 15 mg/kg body weight
- 35 kg body weight and above: target Hb = 150 g/l and depot iron = 500 mg

*Factor 0.24 = 0.0034 x 0.07 x 1000 (Iron content of haemoglobin ≅ 0.34%; Blood volume ≅ 7% of body weight; Factor 1000 = conversion from g to mg)

The total amount of Venofer required in mg is determined from above calculation.
Alternatively, the total amount of Venofer required in ml is determined from the following formula or dosage table.

$$\text{Total amount of Venofer required [ml]} = \frac{\text{Total iron deficit [mg]}}{20\ \text{mg/ml}}$$

**Dosage table stating the total amount of Venofer in ml :**

| Body Weight | Total amount of Venofer to be administered | | | |
|---|---|---|---|---|
| | Hb 60 g/l | Hb 75 g/l | Hb 90 g/l | Hb 105 g/l |
| 30 kg | 47.5 ml | 42.5 ml | 37.5 ml | 32.5 ml |
| 35 kg | 62.5 ml | 57.5 ml | 50 ml | 45 ml |
| 40 kg | 67.5 ml | 60 ml | 55 ml | 47.5 ml |
| 45 kg | 75 ml | 65 ml | 57.5 ml | 50 ml |
| 50 kg | 80 ml | 70 ml | 60 ml | 52.5 ml |
| 55 kg | 85 ml | 75 ml | 65 ml | 55 ml |
| 60 kg | 90 ml | 80 ml | 67.5 ml | 57.5 ml |
| 65 kg | 95 ml | 82.5 ml | 72.5 ml | 60 ml |
| 70 kg | 100 ml | 87.5 ml | 75 ml | 62.5 ml |
| 75 kg | 105 ml | 92.5 ml | 80 ml | 65 ml |
| 80 kg | 112.5 ml | 97.5 ml | 82.5 ml | 67.5 ml |
| 85 kg | 117.5 ml | 102.5 ml | 85 ml | 70 ml |
| 90 kg | 122.5 ml | 107.5 ml | 90 ml | 72.5 ml |

To convert Hb (mM) to Hb (g/l), multiply the former by 16.1145.

Example: For a patient of 60 kg body weight with an actual Hb of 60 g/l 90 ml should be administered. *(Alternatively 18 ampoules/vials of 5 ml or 36 vials of 2.5 ml should be administered.)*

**Dosage:** The total single dose must not exceed 200 mg of iron given not more than three times per week. If the total necessary dose exceeds the maximum allowed single dose, then the administration has to be split.

**Children:** The use of Venofer has not been adequately studied in children and, therefore, Venofer is not recommended for use in children.

**Intravenous drip infusion:** Venofer must be diluted only in sterile 0.9% m/V sodium chloride solution:

- 2.5 ml Venofer (50 mg iron)
  in max. 50 ml sterile 0.9% m/V sodium chloride solution
- 5 ml Venofer (100 mg iron)
  in max. 100 ml sterile 0.9% m/V sodium chloride solution
- 10 ml Venofer (200 mg iron)
  in max. 200 ml sterile 0.9% m/V sodium chloride solution

For stability reasons, dilutions to lower Venofer concentrations are not permissible.

Dilution must take place immediately prior to infusion and the solution should be administered as follows:

- 100 mg iron (5 ml Venofer) in at least 15 minutes
- 200 mg iron (10 ml Venofer) in at least 30 minutes

**Intravenous injection:** Venofer may be administered by slow intravenous injection at a rate of 1 ml undiluted solution per minute and not exceeding 10 ml Venofer (200 mg iron) per injection.

**Injection into dialyser:** Venofer may be administered during a haemodialysis session directly into the venous limb of the dialyser under the same procedures as those outlined for intravenous injection.

## 4.3. Contraindications

The use of Venofer is contraindicated in cases of:

- hypersensitivity to the active substance, to Venofer or any of its excipients listed in section 6.1
- known serious hypersensitivity to other parenteral iron products
- anaemias not attributable to iron deficiency
- iron overload or disturbances in utilisation of iron.

## 4.4. Special Warnings and Precautions for Use

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

The risk is enhanced for patients with known allergies including drug allergies, including patients with a history of severe asthma, eczema or other atopic allergy.
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).

Venofer 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. Each patient should be observed for adverse effects for at least 30 minutes following each Venofer injection. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Facilities for cardio respiratory resuscitation and equipment for handling

acute anaphylactic/anaphylactoid reactions should be available, including an injectable 1:1000 adrenaline solution. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

In patients with liver dysfunction, parenteral iron should only be administered after careful risk/benefit assessment. Parenteral iron administration should be avoided in patients with hepatic dysfunction where iron overload is a precipitating factor, in particular Porphyria Cutanea Tarda (PCT). Careful monitoring of iron status is recommended to avoid iron overload.

Parenteral iron must be used with caution in case of acute or chronic infection. It is recommended that the administration of iron sucrose is stopped in patients with ongoing bacteraemia. In patients with chronic infection a risk/benefit evaluation has to be performed, taking into account the suppression of erythropoiesis.
Hypotensive episodes may occur if the injection is administered too rapidly. Allergic reactions, sometimes involving arthralgia, have been more commonly observed when the recommended dose is exceeded.

Paravenous leakage must be avoided because leakage of Venofer at the injection site may lead to pain, inflammation, tissue necrosis and brown discoloration of the skin.

## 4.5. Interactions with other Medicinal Products and other forms of Interaction

As with all parenteral iron preparations, Venofer should not be administered concomitantly with oral iron preparations since the absorption of oral iron is reduced. Therefore, oral iron therapy should be started at least 5 days after the last injection of Venofer.

## 4.6. Pregnancy and Lactation

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

Iron deficiency anaemia occurring in the first trimester of pregnancy can in many cases be treated with oral iron. Treatment with Venofer 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.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Data on a limited number of exposed human pregnancies indicated no adverse effects of Venofer on pregnancy or on the health of the foetus/newborn child.

Non metabolised Venofer is unlikely to pass into the mother's milk. No well-controlled clinical studies are available to date. Animal studies do not indicate direct or indirect harmful effects to the nursing child.

## 4.7. Effects on Ability to Drive and Use Machines

In the case of symptoms of dizziness, confusion or light headedness following the administration of Venofer, patients should not drive or use machinery until the symptoms have ceased.

## 4.8. Undesirable Effects

The most frequently reported adverse drug reactions (ADRs) of Venofer in clinical trials were transient taste perversion, hypotension, fever and shivering, injection site reactions and nausea, occurring in 0.5 to 1.5% of the patients. Non-serious anaphylactoid reactions occurred rarely.

In general anaphylactoid reactions are potentially the most serious adverse reactions (see "Special warnings and Precautions for Use" section 4.4).

In clinical trials, the following adverse drug reactions have been reported in temporal relationship with the administration of Venofer, with at least a possible causal relationship:

***Nervous system disorders***
*Common (≥ 1/100, < 1/10):* transient taste perversions (in particular metallic taste).
*Uncommon (≥ 1/1000, < 1/100):* headache, dizziness.
*Rare (≥ 1/10000, < 1/1000):* paraesthesia, syncope, loss of consciousness, burning sensation.

***Cardio-vascular disorders***
*Uncommon (≥ 1/1000, < 1/100):* hypotension and collapse, tachycardia and palpitations.
*Rare (≥ 1/10000, < 1/1000): hypertension.*

***Respiratory, thoracic and mediastinal disorders***
*Uncommon (≥ 1/1000, < 1/100):* bronchospasm, dyspnoea.

***Gastrointestinal disorders***
*Uncommon (≥ 1/1000, < 1/100):* nausea; vomiting, abdominal pain, diarrhoea.

***Skin and subcutaneous tissue disorders***
*Uncommon (≥ 1/1000, < 1/100):* pruritus, urticaria, rash, exanthema, erythema.

***Musculoskeletal, connective tissue and bone disorders***
*Uncommon (≥ 1/1000, < 1/100):* muscle cramps, myalgia.

***General disorders and administration site disorders***
*Uncommon (≥ 1/1000, < 1/100):* fever, shivering, flushing, chest pain and tightness. Injection site disorders such as superficial phlebitis, burning, swelling.
*Rare (≥ 1/10000, < 1/1000):* arthralgia, peripheral oedema, fatigue, asthenia, malaise, feeling hot, oedema.

***Immune system disorders***
*Rare (≥ 1/10000, < 1/1000):* anaphylactoid reactions.

Moreover, in spontaneous reports the following adverse reactions have been reported:
*Isolated cases:* reduced level of consciousness, light-headed feeling, confusion, angio-oedema, swelling of joints, hyperhidrosis, back pain, bradycardia, chromaturia.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

## 4.9. Overdose

Overdosage can cause acute iron overloading which may manifest itself as haemosiderosis. Overdosage should be treated, if required, with an iron chelating agent.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1. Pharmacodynamic Properties

The ferrokinetics of Venofer labelled with $^{59}Fe$ and $^{52}Fe$ were assessed in 5 patients with anaemia and chronic renal failure. Plasma clearance of $^{52}Fe$ was in the range of 60 to 100 minutes. $^{52}Fe$ was distributed to the liver, spleen and bone marrow. At two weeks after administration, the maximum red blood cell utilisation of $^{59}Fe$ ranged from 62% to 97%.

## 5.2. Pharmacokinetic Properties

Following intravenous injection of a single dose of Venofer containing 100 mg iron in healthy volunteers, maximum iron levels, averaging 538 µmol/l, were obtained 10 minutes after injection. The volume of distribution of the central compartment corresponded well to the volume of plasma (approximately 3 litres).

The iron injected was rapidly cleared from the plasma, the terminal half-life being approx. 6 h. The volume of distribution at steady state was about 8 litres, indicating a low iron distribution in the body fluid. Due to the lower stability of iron sucrose in comparison to transferrin, a competitive exchange of iron to transferrin was observed. This resulted in iron transport of approx. 31 mg iron/24 h.

Renal elimination of iron, occurring in the first 4 h after injection, corresponds to less than 5% of the total body clearance. After 24 h the plasma levels of iron were reduced to the pre-dose iron level and about 75% of the dosage of sucrose was excreted.

### 5.3. Preclinical Safety Data

There are no preclinical data of relevance to the prescriber that are additional to information already in other sections of the SPC.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of Excipients

Water for injections
Sodium hydroxide

### 6.2. Incompatibilities

Venofer must only be mixed with sterile 0.9% m/V sodium chloride solution. No other solutions and therapeutic agents should be used as there is the potential for precipitation and/or interaction. The compatibility with containers other than glass, polyethylene and PVC is not known.

### 6.3. Shelf Life

**Shelf life of the product as packaged for sale:**

3 years.

**Shelf life after first opening of the container:**

From a microbiological point of view, the product should be used immediately.

**Shelf life after dilution with sterile 0.9% m/V sodium chloride solution:**

From a microbiological point of view, the product should be used immediately after dilution with sterile 0.9% m/V sodium chloride solution.

### 6.4. Special Precautions for Storage

Store in original carton. Do not store above 25°C. Do not freeze.

**6.5. Nature and Contents of Container**

5 ml solution in one ampoule (type I glass) in pack sizes of 5.
2.5 ml solution in one vial (type I glass) in pack sizes of 5.
5 ml solution in one vial (type I glass) in pack sizes of 5.

Not all pack-sizes may be marketed.

**6.6. Special precautions for disposal and other handling**

Ampoules or vials should be visually inspected for sediment and damage before use. Only those with sediment free and homogenous solution must be used.
The diluted solution must appear as brown and clear.
See also 6.3 shelf-life.
Each ampoule or vial of Venofer is intended for single use only. Discard any remaining contents after first use.

**7. MARKETING AUTHORISATION HOLDER**

Vifor France SA
7-13, Bd Paul Emile Victor
92200 Neuilly-sur-Seine
France
Tel. +33 (0)1 41 06 58 90
Fax +33 (0)1 41 06 58 99

**8. MARKETING AUTHORISATION NUMBER(S)**

UK: PL 15240/0001

**9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION**

UK: 08.06.1998 / 20.05.2008

**10. DATE OF REVISION OF THE TEXT**

09/2013

**Patient Information Leaflet** **Vifor (International) Inc.**

Regulatory Affairs

| | | |
|---|---|---|
| Document No:<br>PIL-YA539/YV004/YV003/ EUN/E03 | **VENOFER**<br>**5 ml Ampoules**<br>**2.5 ml Vials**<br>**5 ml Vials** | Research & Development |
| Page 1/7 | | Drug Safety |
| Valid from: | | Int. Product Management |
| Replaces document:<br>PIL-YA539/YV004/YV003/ EUN/E02 | Regulatory Affairs | Quality Assurance |
| **Distribution:** | | |

**PACKAGE LEAFLET: INFORMATION FOR THE USER**
**Venofer 20 mg iron /ml**
**Solution for injection or concentrate for solution for infusion**
**Iron Sucrose**

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

**Read all of this leaflet carefully before you are given this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor.
- If any of the side effects becomes serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

**In this leaflet:**


## 1. WHAT VENOFER IS AND WHAT IT IS USED FOR

Venofer is a medicine that contains iron.

Medicines that contain iron are used when you do not have enough iron in your body. This is called “iron deficiency”.

Venofer is given when:
- You cannot take iron by mouth - such as when iron tablets make you feel ill.
- You have taken iron by mouth - and it has not worked.

## 2. BEFORE VENOFER IS GIVEN TO YOU

**You must not receive Venofer if:**

- You are allergic (hypersensitive) to the product or any of the other ingredients of this medicine (listed in section 6).
- You have experienced serious allergic (hypersensitive) reactions to other injectable iron preparations.
- You have anaemia which is not caused by a shortage of iron.
- You have too much iron in your body or a problem in the way your body uses iron.

You must not be given Venofer if any of the above apply to you. If you are not sure, talk to your doctor before having Venofer.

**Warnings and precautions**
Talk to your doctor or nurse before receiving Venofer if:
- You have a history of medicine allergy.
- You have systemic lupus erythematosus.
- You have rheumatoid arthritis.
- You have severe asthma, eczema or other allergies.
- You have any infections.
- You have liver problems.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before you are given Venofer.

**Taking other medicines**

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription, including herbal medicines.

This is because Venofer can affect the way some other medicines work. Also some other medicines can affect the way Venofer works.

In particular tell your doctor or pharmacist if you are taking:
- Medicines that contain iron which you take by mouth. These may not work if they are taken at the same time that Venofer is given to you. When you have finished treatment with Venofer, wait 5 days before taking iron by mouth.

**Pregnancy and breast-feeding**

Venofer has not been tested in pregnant women. It is important to tell your doctor if you are pregnant, think you may be pregnant, or are planning to have a baby.
If you become pregnant during treatment, you must ask your doctor for advice.
Your doctor will decide whether or not you should be given this medicine.

If you are breast-feeding, ask your doctor for advice before you are given Venofer.

Ask your doctor or pharmacist for advice before taking any medicine, if you are pregnant or breast-feeding.

**Driving and using machines**

You may feel dizzy, confused or light-headed after being given Venofer. If this happens, do not drive or use any tool or machines. Ask your doctor if you are not sure.

## 3. HOW VENOFER IS GIVEN

Your doctor will decide how much Venofer to give you. He or she will also decide how often you need it and for how long. Your doctor will do a blood test to help work out the dose.

**How Venofer is given**
Your doctor or nurse will administer Venofer in one of the following ways:
- Slow injection into your vein – 1 to 3 times per week.
- As an infusion (drip) into your vein – 1 to 3 times per week.
- During dialysis – it will be put into the venous limb of the dialyser.

Venofer will be administered in a structure where immunoallergic events can receive appropriate and prompt treatment.
You will be observed for at least 30 minutes by your doctor or nurse after each administration.

Venofer is a brown liquid and so the injection or infusion will look brown.

**Children**
Venofer is not recommended for use in children.

## 4. POSSIBLE SIDE EFFECTS

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

**Allergic reactions** (affects less than 1 in 1,000 people)
If you have an allergic reaction, tell your doctor or nurse straight away. The signs may include:
- Low blood pressure (feeling dizzy, light-headed or faint).
- Swelling of your face.
- Difficulty breathing.

Tell your doctor or nurse straight away if you think you are having an allergic reaction.

**Other side effects include:**

**Common** (affects less than 1 in 10 people)
- Changes in your taste such as a metallic taste. This does not usually last very long.

**Uncommon** (affects less than 1 in 100 people)
- Fast pulse rate.
- Headache or feeling dizzy.
- Low blood pressure and collapse.
- Pounding heart beat (palpitations).
- Stomach pain or diarrhoea.
- Feeling sick (nausea) or being sick (vomiting).
- Wheezing, difficulty in breathing.
- Itching, hives, rash or skin redness.
- Muscle cramps or muscle pain.
- Flushing.
- Fever or shivering.
- Chest pain and chest tightness.
- Reactions around the site of injection such as inflammation, a feeling of burning and swelling.

**Rare** (affects less than 1 in 1,000 people)
- Fainting.
- Loss of consciousness.
- Tingling or ”pins and needles”.
- A feeling of burning.
- High blood pressure.
- Feeling hot.

- Swelling (dropsy).
- Pain in your joints.
- Swelling of hands and feet.
- Tiredness, weakness or general feeling of illness.

Other side effects include: feeling less alert, light-headed or confused; swelling of your joints, face and tongue; increased sweating; back pain; low pulse rate; changes to the colour of your urine.

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

## 5. HOW TO STORE VENOFER

Keep out of the reach and sight of children.
Do not use Venofer after the expiry date which is stated on the label.
Do not store above 25°C. Do not freeze. Keep the ampoules or vials in the outer carton.

Once the Venofer ampoules or Venofer vials have been opened, they should be used immediately. After dilution with sodium chloride solution, the diluted solution should be used immediately.
Venofer will normally be stored for you by your doctor or the hospital.

## 6. FURTHER INFORMATION

**What Venofer contains**

- The active substance is iron (as iron sucrose). Each millilitre contains 20 mg iron.
- The other ingredients are water for injections and sodium hydroxide.

**What Venofer looks like and contents of the pack**

Venofer is a dark brown, non transparent, aqueous solution.
Venofer comes in following pack-sizes:

- 5 Glass ampoules of 5 ml. Each ampoule of 5 ml corresponds to 100 mg of iron.
- 5 Glass vials of 2.5 ml. Each vial of 2.5 ml corresponds to 50 mg of iron.
- 5 Glass vials of 5 ml. Each vial of 5 ml corresponds to 100 mg of iron.

Not all pack-sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

Vifor France SA
7-13, Bd Paul Emile Victor
92200 Neuilly-sur-Seine
France
Tél. +33 (0)1 41 06 58 90
Fax +33 (0)1 41 06 58 99

**This leaflet was last revised in 09/2013.**

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

Vifor Pharma UK Limited
The Old Stables, Bagshot Park
Bagshot
Surrey
GU19 5PJ
United Kingdom
Tel: +44 1276 853600
Fax : +44 1276 452341

## The following information is intended for medical or healthcare professionals only:

**Administration**
Monitor carefully patients for signs and symptoms of hypersensitivity reactions during and following each administration of Venofer.

Venofer 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 Venofer injection.

*Mode of Administration:*
Venofer must only be administered as a slow intravenous injection or as an intravenous drip infusion. Venofer must not be used for intramuscular injection.

Paravenous leakage must be avoided because leakage of Venofer at the injection site may lead to pain, inflammation, tissue necrosis and brown discoloration of the skin.

*Intravenous drip infusion:*
Venofer must be diluted only in sterile 0.9% m/V sodium chloride solution:

- 2.5 ml Venofer (50 mg iron) in max. 50 ml sterile 0.9% m/V sodium chloride solution
- 5 ml Venofer (100 mg iron) in max. 100 ml sterile 0.9% m/V sodium chloride solution
- 10 ml Venofer (200 mg iron) in max. 200 ml sterile 0.9% m/V sodium chloride solution

For stability reasons, dilutions to lower Venofer concentrations are not permissible.

Dilution must take place immediately prior to infusion and the solution should be administered as follows:

- 100 mg iron (5 ml Venofer) over at least 15 minutes
- 200 mg iron (10 ml Venofer) over at least 30 minutes

*Intravenous injection:*
Venofer may be administered by slow intravenous injection at a rate of 1 ml undiluted solution per minute and not exceeding 10 ml Venofer (200 mg iron) per injection.

*Injection into the dialyser*:
Venofer may be administered during a haemodialysis session directly into the venous limb of the dialyser under the same procedures as those outlined for intravenous injection.

**Incompatibilities**

Venofer must only be mixed with sterile 0.9% m/V sodium chloride solution. No other solutions and therapeutic agents should be used, as there is the potential for precipitation and/or interaction. The compatibility with containers other than glass, polyethylene and PVC is not known.

**Stability**

The product must not be used after the expiry date which is stated on the label and on the outer carton.
From a microbiological point of view, the product should be used immediately after first opening or immediately after dilution with sterile 0.9% m/V sodium chloride.

**Instruction for use and handling**

Ampoules/Vials should be visually inspected for sediment and damage before use. Only those with sediment free and homogenous solution must be used. The dilution solution must appear as brown and clear.
Any unused product or waste material should be disposed of in accordance with local requirements.

## Annex 3 Worldwide Market Authorisation Status by Country (Including EEA)

## Table 1 Worldwide Market Authorisation Status for EU/EEA Countries

| Country[1] | Action - Date | Launch Date | Trade Name(s) | Comments[2] |
|---|---|---|---|---|
| Portugal | A - 11/64<br>AR - pending | 1995 | Venofer® | Indications vary[3]. |
| Germany | A - 11/69<br>AR - 11/05 | 1995 | Venofer | Indications vary[4]. |
| Poland | A - 06/79<br>AR - 07/13 | 1998 | Venofer | – |
| Slovakia | A - 12/92<br>AR - 06/07 | 1998 | Venofer | Indications vary[5]. |
| Romania | A - 03/93<br>AR - pending | 1998 | Venofer | – |
| Netherlands | A - 10/97<br>AR - 10/12 | 1999 | Venofer | Indications vary[6]. |
| Latvia | A - 04/98<br>AR - 06/08 | 2002 | Venofer | – |
| UK | A - 06/98<br>AR - 05/08 | 1999 | Venofer | Exclusion of children; dose varies; indications vary[5]. |
| Hungary | A - 06/98<br>AR - 03/09 | 2008 | Venofer | Indications vary[7]. |
| France | A - 12/98<br>AR - pending | 1999 | Venofer | Administration only in diluted form as an infusion; dose varies; indications vary[8] |
| Ireland | A - 03/00<br>AR - 05/08 | 1999 | Venofer | Exclusion of children; dose varies; indications vary[5] |
| Sweden | A - 02/00<br>AR - 05/08 | 2002 | Venofer | Exclusion of children; dose varies; indications vary[5] |
| Belgium | A - 08/00<br>AR - 05/08 | 2001 | Venofer | Exclusion of children; dose varies; indications vary[5] |
| Denmark | A - 08/00<br>AR - 05/08 | 2002 | Venofer | Exclusion of children; dose varies; indications vary[5] |
| Austria | A - 08/00<br>AR - 05/08 | 2000 | Venofer | Exclusion of children; dose varies; indications vary[5] |
| Greece | A - 09/00<br>AR - 05/08 | 1997 | Venofer | Exclusion of children; dose varies; indications vary[5] |
| Finland | A - 01/01<br>AR - 05/08 | 2002 | Venofer | Exclusion of children; dose varies; indications vary[5] |
| Spain | A - 06/01<br>AR - 05/08 | 2001 | Venofer | Exclusion of children; dose varies; indications vary[5] |
| Luxembourg | A - 07/01<br>AR - 05/08 | 2001 | Venofer | Exclusion of children; dose varies; indications vary[5] |
| Iceland | A - 09/01<br>AR - 10/08 | 2002 | Venofer | Exclusion of children; dose varies; indications vary[5] |
| Norway | A - 01/02<br>AR - 03/09 | 2002 | Venofer | Exclusion of children; dose varies; indications vary[5] |
| Lithuania | A - 04/04<br>AR - 04/13 | 2002 | Venofer | Indications vary[9] |

| Country[1] | Action - Date | Launch Date | Trade Name(s) | Comments[2] |
|---|---|---|---|---|
| Czech Republic | A - 03/04<br>AR - 04/12 | 2009 | Venofer | – |
| Estonia | A - 10/04<br>AR - 09/14 | 2002 | Venofer | Exclusion of children; dose varies; indications vary[10] |
| Italy | A - 11/04<br>AR - 05/08 | 2005 | Venofer | Exclusion of children; dose varies; indications vary[5] |

1 Countries in which Vifor (International) Inc. or a Vifor Pharma company are Marketing Authorisation Holder. Marketing authorisations held by other companies in: Bulgaria, Croatia, Cyprus, and Slovenia.

2 The following indications are according to the Company Core Data Sheet. Countries with a different indication are listed.

Venofer is indicated for the treatment of iron deficiency in the following indications:

- where there is a clinical need for a rapid iron supply;
- in patients who cannot tolerate oral iron therapy or who are non-compliant;
- where oral iron preparations are ineffective (e.g., in active inflammatory bowel disease).

3 Approved indications in Portugal:

Venofer is indicated for the treatment of:

- functional iron deficiency during erythropoietin therapy;
- iron deficiency, or all cases requiring rapid and safe replacement of iron. These include the following: prior to and after surgery in patients who require rapid replenishment of iron (autologous blood donation); final stages of pregnancy; patients who do not tolerate or respond to oral iron; patients with malabsorption or who are non-compliant with oral iron therapy;
- iron deficiency in patients with rheumatoid arthritis.

4 Approved indications in Germany:

- Intravenous treatment of iron deficiency, if oral treatment is not possible or is not effective.

5 Approved indications in the MRP countries (Austria, Belgium, Denmark, Finland, Greece, Ireland, Italy, Luxembourg, Spain, Sweden, United Kingdom) as well as in Iceland, Norway, Slovakia:

Venofer is indicated for the treatment of iron deficiency in the following indications:

- where there is a clinical need to deliver iron rapidly to iron stores;
- in patients who cannot tolerate oral iron therapy or who are non-compliant;
- in active inflammatory bowel disease where oral iron preparations are ineffective.

6 Approved indications in the Netherlands:

- in patients who do not tolerate oral iron therapy;
- in patients with malabsorption (such as inflammatory bowel disease);
- in patients in whom the iron loss is greater than can be compensated by oral ingestion (such as in chronic haemodialysis).

7 Approved indications in Hungary:

- Iron deficiency in patients in whom oral iron therapy is not sufficiently effective, is ineffective or cannot be used, such as in cases of oral iron intolerance, inflammatory gastrointestinal diseases/e.g., ulcerative colitis/which may be caused by oral iron therapy, or iron deficiency conditions refractory to treatment, where it is suspected that iron preparations are not being taken consistently.

8 Approved indications in France:

- treatment of anaemia in chronic renal failure patients undergoing haemodialysis, pre-dialysis or peritoneal dialysis, when treatment by oral iron has proved to be insufficient or poorly tolerated;
- preoperatively: in patients included in an autologous blood donation programme in combination with erythropoietin, on the condition that they have moderate anaemia (Hb between 9 and 11 g/100 mL), and their initial blood ferritin level is less than 150 µg/l;
- treatment of acute anaemia in the immediate postoperative period in patients unable to tolerate oral feeding;
- treatment of acute anaemia in the immediate postoperative period in patients unable to tolerate oral feeding.

9 Approved indications in Lithuania:

Indicated for the treatment of iron deficiency in the following indications:

- in patients who cannot tolerate oral iron therapy or who are non-compliant;
- in patients where insufficient efficacy of oral iron therapy is proven;
- in patients where there is a clinical need to deliver iron rapidly to iron stores.

10 Approved indications in Estonia:

- Treatment of iron deficiency anaemia where oral iron preparations are ineffective or not tolerated.

Notes: A=Authorised; AR=Authorisation renewal.

**Table 2 Worldwide Market Authorisation Status for non-EU/EEA Countries**

| Country[1] | Action - Date | Launch Date | Trade Name(s) | Comments[2] |
|---|---|---|---|---|
| Switzerland | A - 12/49<br>AR – 07/14 | 1950 | Venofer® | Indications vary[3] |
| Venezuela | A – 11/73<br>AR – 07/09 | 2001 | Venofer | – |
| Guatemala | A - 02/86<br>AR - 10/11 | 2000 | Venofer | Indications vary[4] |
| Ecuador | A - 02/88<br>AR – 07/13 | 1992 | Venofer | – |
| Panama | A - 03/94<br>AR - pending | 1994 | Venofer | Indications vary[4] |
| Peru | A - 01/96<br>AR - 01/11 | 1997 | Venofer | Indications vary[4] |
| Tunisia | A - 09/96<br>AR - 07/11 | 2000 | Venofer | Indications vary[4] |
| Lebanon | A - 08/96 | 1996 | Venofer | Indications vary[4] |
| Russia | A - 09/97<br>AR - 08/08 | 2001 | Venofer | Indications vary[4] |
| Colombia | A - 09/97<br>AR - 10/07 | 1997 | Venofer | Indications vary[4] |
| Iraq | A - 10/98<br>AR - pending | 2010 | Venofer | Indications vary[4] |
| Syria | A - 01/99<br>AR – 09/12 | 1999 | Venofer | Indications vary[4] |
| Pakistan | A – 06/99<br>AR – 09/14 | 1999 | Venofer | Indications vary[4] |
| Singapore | A - 07/00<br>AR - 06/11 | 2000 | Venofer | Indications vary[4] |
| El Salvador | A - 07/00<br>AR - pending | 2000 | Venofer | – |
| Haiti | A - 10/00<br>AR - 04/13 | 2000 | Venofer | Indications vary[4] |
| Jordan | A - 04/01<br>AR - pending | 2001 | Venofer | Indications vary[3] |
| Uzbekistan | A - 11/00<br>AR - 03/14 | 2001 | Venofer | Indications vary[4] |
| Honduras | A - 12/01<br>AR - 11/11 | 2001 | Venofer | – |
| Ukraine | A - 07/02<br>AR - 07/13 | 2003 | Venofer | Indications vary[4] |
| China | A - 03/03<br>AR - 09/13 | 2005 | Venofer | Indications vary[5] |
| Trinidad and Tobago | A - 06/03 | 2003 | Venofer | Indications vary[4] |
| Georgia | A - 08/04<br>AR – pending | 2004 | Venofer | Indications vary[4] |
| Australia | A - 05/04 | 2004 | Venofer | Indications vary[6] |

| Country[1] | Action - Date | Launch Date | Trade Name(s) | Comments[2] |
|---|---|---|---|---|
| India | A – 04/06<br>AR – 01/12 | 1999 | Iron Sucrose V814 | Indications vary[7] |
| Jamaica | A - 06/07 | 2006 (due to special permit for import) | Venofer | Indications vary[4] |
| Algeria | A – 11/07<br>AR – 10/14 | 2008 | Venofer | Indications vary[3] |
| Azerbaijan | A - 01/08<br>AR – 11/13 | 2008 | Venofer | Indications vary[4] |
| Libya | A - 01/09 | 2009 | Venofer | – |
| Kazakhstan | A - 11/09<br>AR – 10/14 | 2012 | Venofer | Exclusion of children; Indications vary[4] |
| Iran | A - 08/11 | 2011 | Venofer | Indications vary[7] |
| Bolivia | A – 01/14 | 2014 | Venofer | – |

1 Countries in which Vifor (International) Inc. or a Vifor Pharma company are marketing authorisation holder. Marketing authorisations held by other companies in: Argentina, Bosnia and Herzegovina, Botswana, Brazil, Brunei, Canada, Chile, Hong Kong, Indonesia, Israel, Kenya, Kosovo, Macao, Macedonia, Malaysia, Mexico, Morocco, Namibia, New Zealand, Philippines, Saudi Arabia, South Africa, South Korea, Sri Lanka, Thailand, Turkey, United States, and Vietnam.

2 The following indications are according to the Company Core Data Sheet. Countries with a different indication are listed:

Venofer is indicated for the treatment of iron deficiency in the following indications:

- where there is a clinical need for a rapid iron supply;
- in patients who cannot tolerate oral iron therapy or who are non-compliant;
- where oral iron preparations are ineffective (e.g., in active inflammatory bowel disease).

3 Approved indications in Switzerland, Jordan and Algeria:

Iron deficiency in patients in whom oral iron therapy is not sufficiently effective or not feasible, such as:

- Intolerance to oral iron preparations;
- Inflammatory gastrointestinal disorders (e.g., ulcerative colitis) which may be aggravated by oral iron therapy;
- Treatment-refractory iron deficiency states where unreliability in taking oral iron preparations is suspected.

4 Approved indications in Azerbaijan, Colombia, Georgia, Guatemala, Haiti, Iraq, Jamaica, Kazakhstan, Lebanon, Pakistan, Panama, Peru, Russia, Singapore, Syria, Tunisia, Trinidad/Tobago, Ukraine, Uzbekistan, Venezuela:

Venofer is indicated for the treatment of iron deficiency in the following indications:

- where there is a clinical need to deliver iron rapidly to iron stores;
- in patients who cannot tolerate oral iron therapy or who are non-compliant;
- in active inflammatory bowel disease where oral iron preparations are ineffective.

5 Approved indications in China:

This product is indicated in patients in whom the results following oral administration of iron preparations are not good and who require intravenous iron therapy, such as:

- patients who cannot tolerate oral iron therapy;
- patients for whom absorption of orally administered iron is not adequate.

6 Approved indications in Australia:

- treatment of iron deficiency anaemia in patients undergoing chronic haemodialysis and who are receiving supplemental erythropoietin therapy.

7 Approved indications in India, Iran:

Venofer is indicated for the treatment of iron deficiency anaemia in the following indications:

- where there is a clinical need for a rapid iron supply;
- in patients who cannot tolerate oral iron therapy or who are non-compliant;
- in active inflammatory bowel disease where oral iron preparations are ineffective.

Notes: A=Authorised; AR=Authorisation renewal.

## Annex 4 Synopsis of Ongoing and Completed Clinical Trial Programme

| Study | Description | Study Design | Planned/Actual No. of Patients | Duration of Follow-up | Estimated/ Actual Completion Date |
|---|---|---|---|---|---|
| **Phase 4 Studies** | | | | | |
| 1VIT13032 | A study to evaluate the utility of serum hepcidin levels to predict response to oral or intravenous iron and compare the safety, effect on quality of life and resource utilisation, of Injectafer® vs. intravenous iron standard of care for the treatment of iron deficiency anaemia in an infusion centre setting | Multicentre, randomised, open-label study | Planned ,1000 (FCM 500)<br>Enrolled 831 | N/A | Recruitment ongoing<br>CSR expected Q2 2016 |

Notes: CSR=Clinical Study Report; FCM=Ferric carboxymaltose.

## Annex 5 Synopsis of Ongoing and Completed Pharmacoepidemiological Study Programme

| Study | Research Question | Population & Study Size | Duration of Follow-up | Milestones & Dates | Status |
|---|---|---|---|---|---|
| Not applicable | - | - | - | - | - |

## Annex 6 Protocols for Proposed and Ongoing Studies in Categories 1-3 of the Section "Summary Table of Additional Pharmacovigilance Activities" in RMP Part III

### Table 1 Overview of Included Protocols

| Study Title | Protocol Status | Version of Protocol | Date of Protocol |
|---|---|---|---|
| Not applicable | – | – | – |

## Annex 7 Specific Adverse Event Follow-up Forms

Vifor Pharma

FOR GDS 171: PREGNANCY REPORT V01

### REPORT ON EXPOSURE TO MEDICINES DURING PREGNANCY Part 1

**Name of Vifor Drug** (Trade name / IMP): _____

Clinical Trial Protocol Identifier (if applicable): _____

Patients Initials / No: _____ Country: _____ Local Reference No: _____

### Details of Mother and Pregnancy

Date / Year of Birth: / / (dd/mmm/yyyy) Age: Occupation:

**Previous Pregnancy**

Yes ☐ No ☐ Total no. of pregnancies: _____ Normal Deliveries: _____

Abortions (Spontaneous ): _____ Abortions (performed): _____

**Relevant Medical History**:
(including pregnancy risk factors, Pre-eclampsia, eclampsia, smoking, alcohol, environmental & occupational exposures etc.)

**Relevant Family History**:
(hereditary diseases e.g. hypertension, diabetes)

### Current Pregnancy

First day of Last Menstruation: / / (dd/mmm/yyyy) Expected Delivery Date: / / (dd/mmm/yyyy)

Gestational age of foetus (specify at time of exposure / time of reporting) : _____

Ultrasound performed? Yes ☐ No ☐ If yes, findings if any: _____

Any complications, infections or illnesses during pregnancy? Yes ☐ No ☐

If yes, elaborate: _____

### Drug Exposure during Pregnancy

| Mother /Father Exposure | Suspect Drug/ Concomitant medication | Product Name (Trade / IMP) Batch no. | Total Daily Dose (Units) | Therapy Start date | Therapy Stop date | Indication for use | Route of application (oral, infusion, injection) |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |

_____ _____

**Place, Date** (dd/mmm/yyyy) **Name/ Signature/Stamp of Reporter**

**REPORT ON EXPOSURE TO MEDICINES DURING PREGNANCY Part 2**

**Information on Outcome of Pregnancy**

**Name of Vifor Drug** (Trade name/IMP)**:** _____

Clinical Trial Protocol Identifier (if applicable): _____

Patients Initials / No: _____ Country: _____ Local Reference No: _____

**Outcome of Pregnancy**

☐ Full Term — Normal delivery or Caesarean: _____

☐ Premature Birth — If premature birth, gestational age: _____ weeks

☐ Spontaneous Miscarriage

☐ Elective termination — Medical Reason? ☐ Yes ☐ No

If yes, specify: _____

Details / Comments (if any): _____

☐ Healthy Baby ☐ Multiple Births

☐ Sick Baby (e.g. Birth trauma, infection etc.) ☐ Congenital anomaly or Birth defect ☐ Still Birth

Date of Birth ___/___/_____ (dd/mmm/yyyy) Sex ☐ Male ☐ Female

Size: _____ Weight: _____ APGAR scores, if provided (Birth/5/10 mins.) _____

Details / Comments (if any): _____

Please comment on any abnormal condition or occurrence regarding outcome of pregnancy and/or birth/delivery.

**Is there a suspicion that adverse outcome of pregnancy is related to exposure to Product?**

☐ Yes ☐ No

Please elaborate: _____

_____ _____

**Place, Date** (dd/mmm/yyyy) **Name/ Signature/Stamp of Reporter**

**Please always send both Part I and Part II of the form to safety.VIT@viforpharma.com or fax to: +0041 58851 8659**

## 1. Patient details:

Initials (First name / family name): ..... Date of Birth: ..... Age: .....

Gender: M ☐ F ☐ Weight (in kg): ..... Height (in cm): .....

Seriousness criteria No ☐ Yes ☐ If yes specify:

☐ Patient died

☐ Involved or prolonged patient hospitalization

☐ Involved persistence of significant disability

☐ Life-threatening

☐ Congenital anomaly

Was the patient treated in the office No ☐ Yes ☐ Unknown ☐

Did the patient go the Emergency room No ☐ Yes ☐ Unknown ☐

Was the subject hospitalized No ☐ Yes ☐ Unknown ☐

Start of the AE (date): ..... Clearing of the AE (date): .....

## 2. Eliciting medication:

Indication: .....

**Iron preparation:**

| Brand name / generic name | Administered dose | Route of application | Start date | End date | Duration |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |

**Pre-medication:** no ☐ yes ☐ unknown ☐ If yes, please specify:

| Substance | Brand name / generic name | Administered dose (mg) | Route of application | Date | Time |
|---|---|---|---|---|---|
| Antihistamines | | | | | |
| Corticosteroids | | | | | |
| Other substance | | | | | |
| | | | | | |
| | | | | | |

**Other medication (ACE inhibitors, beta blockers etc.):**

| Brand name / generic name | Administered dose | Route of application | Start date | End date | Duration |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | |

**3. Chronology:**

3.1 Time to onset (Interval between drug start and first symptoms): ☐ minutes: ..... ☐ hours: ……☐ days: .....

3.2 Time to recovery (Duration until symptoms subsided): ☐ minutes: ..... ☐ hours:…….☐ days: .....

3.3 Previous exposure with same iron medication: no ☐ yes ☐ Unknown ☐ If yes, please specify:

- Date: ..... Adverse reaction: no ☐ yes ☐ Unknown ☐ .....

3.4 Previous exposure with other iron medication: no ☐ yes ☐ Unknown ☐ If yes, please specify:

- Date: ..... Adverse reaction: no ☐ yes ☐ Unknown ☐ .....

3.5 Later exposure with the same iron medication: no ☐ yes ☐ Unknown ☐ If yes, please specify:

- Date: ..... Adverse reaction: no ☐ yes ☐ Unknown ☐ .....

3.6 Later exposure with other iron medication: no ☐ yes ☐ Unknown ☐ If yes, please specify:

- Date: ..... Adverse reaction: no ☐ yes ☐ Unknown ☐ .....

## 4. Clinical reaction:

4.1 Skin / mucosa:

- Pruritus (itch): no ☐ yes ☐ Unknown ☐ If yes: local ☐ generalized ☐
- Flush face / upper chest: no ☐ yes ☐ Unknown ☐
- Flush generalized: no ☐ yes ☐ Unknown ☐
- Angioedema skin: no ☐ yes ☐ Unknown ☐ Location: .....
- Urticaria: no ☐ yes ☐ Unknown ☐ Location: .....
- Angioedema lips / eyelids: no ☐ yes ☐ Unknown ☐
- Angioedema oral mucosa: no ☐ yes ☐ Unknown ☐
- Angioedema tongue: no ☐ yes ☐ Unknown ☐
- Other skin lesions, e.g. macules, papules, purpuric lesions, vesicles / bullae (blisters), pustules (please specify type, location): .....

4.2 Respiratory symptoms:

- Cough: no ☐ yes ☐ Unknown ☐
- Dyspnea: no ☐ yes ☐ Unknown ☐
- Hyperventilation: no ☐ yes ☐ Unknown ☐
- Wheezing / bronchospasm: no ☐ yes ☐ Unknown ☐ PEFR or FEV1 (if known): ..... l/s
- Respiratory distress: no ☐ yes ☐ Unknown ☐
- Respiratory arrest: no ☐ yes ☐ Unknown ☐
- Rhinitis: no ☐ yes ☐ Unknown ☐
- Conjunctivitis: no ☐ yes ☐ Unknown ☐
- Other (please specify): .....

4.3 Gastrointestinal symptoms:

- Nausea / emesis: no ☐ yes ☐ Unknown ☐
- Abdominal pain / colics: no ☐ yes ☐ Unknown ☐
- Diarrhea: no ☐ yes ☐ Unknown ☐
- Stool incontinence: no ☐ yes ☐ Unknown ☐
- Other (please specify): .....

4.4 Cardiovascular symptoms:

- Tachycardia: no ☐ yes ☐ Unknown ☐ Beats per minute: .....
- Arrhythmia: no ☐ yes ☐ Unknown ☐
- Hypotension: no ☐ yes ☐ Unknown ☐ BP (systolic/diastolic): ..... mmHg
- Collapse: no ☐ yes ☐ Unknown ☐
- Loss of consciousness: no ☐ yes ☐ Unknown ☐
- Cardiovascular arrest: no ☐ yes ☐ Unknown ☐
- Other (please specify): .....

4.5 Other / general symptoms:

- Feeling of impending doom: no ☐ yes ☐ Unknown ☐
- Metallic taste: no ☐ yes ☐ Unknown ☐
- Urine incontinence: no ☐ yes ☐ Unknown ☐
- Lower back pain: no ☐ yes ☐ Unknown ☐
- Headache: no ☐ yes ☐ Unknown ☐
- Fever: no ☐ yes ☐ Unknown ☐ Temperature: ..... °C
- Lymph node swelling: no ☐ yes ☐ Unknown ☐ Localization: .....
- Arthralgia: no ☐ yes ☐ Unknown ☐ Localization: .....
- Arthritis: no ☐ yes ☐ Unknown ☐ Localization: .....
- Myalgia: no ☐ yes ☐ Unknown ☐ Localization: .....

## 5. Prior history / underlying disorders:

5.1 Co-factors / risk factors:

- Concurrent infection: no ☐ yes ☐ Unknown ☐ If yes, please specify: (e.g. viral, bacterial, other): .....
- Exercises / effort / stress: no ☐ yes ☐ Unknown ☐ If yes, please specify: .....
- Pregnancy: no ☐ yes ☐ Unknown ☐ If yes, week of gestation: .....
- Alcohol: no ☐ yes ☐ Unknown ☐
- Smoking: no ☐ yes ☐ Unknown ☐
- Mastocytosis: no ☐ yes ☐ Unknown Mast cell tryptase level baseline: ..... ng/ml
- Other conditions: no ☐ yes ☐ Unknown ☐ If yes, please specify: .....

5.2 Allergic disorders: Allergen:

- Atopic allergy (hay fever): no ☐ yes ☐ Unknown ☐ If yes, please specify: .....
- Asthma, allergic: no ☐ yes ☐ Unknown ☐ If yes, please specify: .....
- Food hypersensitivity: no ☐ yes ☐ Unknown ☐ If yes, please specify: .....
- Hymenoptera venom allergy: no ☐ yes ☐ Unknown ☐ If yes, please specify: .....
- Drug hypersensitivity: no ☐ yes ☐ Unknown ☐ If yes, please specify: .....
- Recurrent / chronic urticaria, angioedema: no ☐ yes ☐ Unknown ☐ If yes, please specify: .....
- Recurrent / eczematous exanthemas: no ☐ yes ☐ Unknown ☐ If yes, please specify: .....

5.3 Underlying disorders:

- Cardiovascular disease: no ☐ yes ☐ Unknown ☐ If yes, please specify: .....
- Respiratory disease: no ☐ yes ☐ Unknown ☐ If yes, please specify: .....
- Kidney disease: no ☐ yes ☐ Unknown ☐ If yes, please specify: .....
- Hematological disease: no ☐ yes ☐ Unknown ☐ If yes, please specify: .....
- Malignancy: no ☐ yes ☐ Unknown ☐ If yes, please specify: .....
- Autoimmune disorder: no ☐ yes ☐ Unknown ☐ If yes, please specify: .....
- Psychological condition: no ☐ yes ☐ Unknown ☐ If yes, please specify: .....

**6. Diagnosis based on:**

- Clinical manifestation / chronology: no ☐ yes ☐
- Photography of skin lesions: no ☐ yes ☐
- Laboratory analysis:
  - Mast cell tryptase: no ☐ yes ☐ Date / time: ..... Level: ..... ng/ml
  - Hematology: no ☐ yes ☐ Date / time: .....
  - Chemistry: no ☐ yes ☐ Date / time: .....
- Skin test
  - Prick test ..... Negative ☐ Positive ☐ Unknown ☐
  - Intradermal test ..... Negative ☐ Positive ☐ Unknown ☐
  - Lymphocyte Transformation Test Negative ☐ Positive ☐ Unknown ☐
- Other (please specify): .....

**7. Management of AE:**

- Stop of infusion: no ☐ yes ☐ Unknown ☐ After, time: ..... minutes
- Emergency treatment: no ☐ yes ☐ Unknown ☐ If yes, please specify:

| Substance | Brand name / generic name | Dose | Route of application | Date | Time |
|---|---|---|---|---|---|
| Antihistamines | | | | | |
| Epinephrine/adrenaline | | | | | |
| Corticosteroids | | | | | |
| Bronchodilatator | | | | | |
| Schock treatment (plasma expander, IV fluids) | | | | | |

- Other emergency treatment (e.g. infusion, oxygen etc.): no ☐ yes ☐ Unknown ☐ If yes, please specify:

  .....

  .....

  .....
- Response to emergency treatment (e.g. infusion, oxygen etc.): no ☐ yes ☐ Unknown ☐

  If no, please specify: .....

  .....

  If yes, please specify (response): .....

  .....

  In: ☐ minutes: ..... ☐ hours: ..... ☐ days: .....

**8. Outcome:** **Date end** **Time end**

- Complete recovery: no ☐ yes ☐ ..... .....
- Surveillance: no ☐ yes ☐ ..... .....
- Hospitalization: no ☐ yes ☐ ..... .....
- Temporary sequelae: no ☐ yes ☐ ..... .....
- Permanent sequelae: no ☐ yes ☐ ..... .....

- Death: no ☐ yes ☐ ..... .....
- Unknown ☐

**9. Reporting Physician:**

Name: ..... E-mail: ..... Phone no. .....

Address: ..... Fax no. .....

Date: ..... Signature: .....

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## Targeted Questionnaire for Evaluating an Adverse Event of Extravasation/Skin Discolouration Events

Enter the Vifor Coding Number for this Questionnaire:

Please check the following sections to include in the Targeted Questionnaire:

1. **Patient Demography** ☐
2. **Previous Exposure to any Iron Product** ☐
3. **Information on Suspect Iron Product** ☐
4. **Adverse Event Information – Extravasation/Paravasation** ☐
5. **Adverse Event Information – Skin Discolouration** ☐
6. **Reporter Details** *(Required)* ☑

Generate Questionnaire

**NOTE**: Macros must be enabled in order to create Questionnaires using this template.

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**Targeted Questionnaire for Evaluating an Adverse Event of Extravasation/Skin Discolouration Events**

**Vifor Coding Number:**

**1. Patient Demography**

Gender: ☐ Male ☐ Female Age: Year of Birth:

**Patient Skin Colour** (according to US Environmental Protection Agency (EPA) Categories):

☐ Pale or milky white (alabaster)
☐ Very light brown, sometimes freckles
☐ Light tan; Brown or olives (distinctly pigmented)
☐ Brown; Dark Brown; Black

**2. Previous Exposure to any Iron Product**

☐ YES (Please specify and complete table below) ☐ NO

| Name of Product (Trade Name AND Active Ingredient) | Dosage Regimen | Dilution (if applicable) | Start date (dd/mmm/yyyy) | Stop date (dd/mmm/yyyy) | If an adverse event occurred, please specify |
|---|---|---|---|---|---|
| | | | | | |

**3. Information on Suspect Iron Product**

Trade name: Active Ingredient:
Batch Nr.:
Indication (with underlying disease):

**Administration:** Dosage: mg Iron Frequency of administration:
Start Date: (dd/mmm/yyyy) End Date: (dd/mmm/yyyy)
Start Time: : (hours:min) Stop Time: : (hours:min)

**Mode of Application:**

☐ IV drip infusion Dilution: ml in ml sterile 0.9% NaCl solution
Duration of administration (hours:min): :
☐ IV bolus injection Duration of administration (hours:min): :
☐ intramuscular Duration of administration (hours:min): :

IV line was inserted by a: ☐ Physician ☐ Physician Assistant ☐ Nurse
☐ Other (specify):

Was IV line flushed and checked for patency? ☐YES ☐ NO

What was the exact anatomical site of IV line?

What type of IV access was used (e.g.: Butterfly, Venflon)?

What gauge was used (e.g., 16G, 18G, 20G)?

Were other co-medications administered through the same IV line? ☐ YES (Please specify below) ☐ NO

| Name of Product (Trade Name or Active Ingredient) | Indication | Dosage Regimen | Duration of Administration (hours:min) | Start Date (dd/mmm/yyyy) | Stop Date (dd/mmm/yyyy) |
|---|---|---|---|---|---|
| | | | : | | |
| | | | : | | |

**4. Adverse Event Information – Extravasation/Paravasation**

**Did an extravasation occur?** ☐ YES ☐ NO (proceed to Section 5.)
Start Date: (dd/mmm/yyyy) End Date: (dd/mmm/yyyy)

**When was the extravasation detected?** ☐ During administration ☐ After administration

**If** detected **during administration**, was administration stopped immediately? ☐ YES ☐ NO

What was the amount of administered solution at the time of stopping the infusion? ml

**If after administration**, please specify the duration: Day(s): Hour(s):Minute(s): :

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How was extravasation discovered?

| **Additional information on extravasation/paravasate** | **Severity Grade[1]** | **Outcome[2]** |
|---|---|---|
| | | |

(1) For specifying Severity Grade please use the coding system below:
1 = Mild 2 = Moderate 3 = Severe
(2) For specifying Outcome please use the coding system below:
1 = Ongoing 2 = Recovering 3 = Recovered without Sequelae 4 = Recovered with Sequelae 5 = Fatal 6 = Unknown

**Co-manifestation:**

Did this patient experience any infusion/injection site reaction (e.g., swelling, pain, erythema,...)?

☐ YES (Please specify below) ☐ NO

**Treatment:**

Did patient receive any drug treatment for extravasation? ☐YES (Complete table below) ☐ NO

| Name of Product (Trade Name or Active Ingredient) | Indication | Daily Dose | Route of Administration | Start Date (dd/mmm/yyyy) | Stop Date (dd/mmm/yyyy) |
|---|---|---|---|---|---|
| | | | | | |

**Did this patient receive any non-drug treatment?** ☐ YES (Please specify below) ☐ NO

**Did this patient also experience a skin discolouration?**

☐ YES (Please complete section 5) ☐ NO (Please complete section 6)

**5. Adverse Event Information – Skin Discolouration**

Start Date (dd/mmm/yyyy): End Date (dd/mmm/yyyy): ☐ Ongoing

| **Additional information on skin discolouration** | **Severity Grade[1]** | **Outcome[2]** |
|---|---|---|
| | | |

(1) For specifying Severity Grade please use the coding system below:
1 = Mild 2 = Moderate 3 = Severe
(2) For specifying Outcome please use the coding system below:
1 = Ongoing 2 = Recovering 3 = Recovered without Sequelae 4 = Recovered with Sequelae 5 = Fatal 6 = Unknown

**When was the skin discolouration detected?** ☐ During administration ☐ After administration

**If after administration**, please specify the duration: Day(s): Hour(s):Minute(s): :

**What was the location and distribution of skin discolouration?**

☐ At administration site. Specify location

☐ Other site(s). Specify number

**What was the actual aspect and location of the skin discolouration(s), administration site included?**

| Location | Size | Shape | Colour | Texture |
|---|---|---|---|---|
| | cm by cm | | | |
| | cm by cm | | | |
| | cm by cm | | | |
| | cm by cm | | | |

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**Did patient receive any drug treatment for skin discolouration?**

☐ YES (Please complete table below) ☐ NO (Please complete section 6)

| Name of Product (Trade Name or Active Ingredient) | Indication | Dosage Regimen | Start Date (dd/mmm/yyyy) | Stop Date (dd/mmm/yyyy) |
|---|---|---|---|---|
| | | | | |

**Did this patient receive any non-drug treatment?** ☐ YES (Please specify below) ☐ NO

**Date of most recent contact with the patient (dd/mmm/yyyy):**

**What is the outcome of skin discolouration?** ☐ No change ☐ Worsening/Spreading

☐ Resolving/Receding ☐ Complete recovery ☐ Unknown (No contact with patient since the last evaluation)

**Does the discolouration cause cosmetic impairment to the patient?** ☐ YES ☐ NO

**6. Reporter Details**

**Name of Reporter:** **Profession of Reporter:**

**Name & Address of the Institution:** **Country:**

**Telephone:**

**Fax:**

**e-mail:**

**Handwritten signature of reporting person:**

Date: _____ (dd/mmm/yyyy)

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# Targeted Questionnaire for Evaluating Infection Related Events

Enter the Vifor Coding Number for this Questionnaire:

Please check the following sections to include in the Targeted Questionnaire:

1. **Patient Demography** ☐
2. **Medical History and Risk Factors** ☐
3. **Relevant Drug History** ☐
4. **Information on Suspect Iron Product** ☐
5. **Adverse Event Information** ☐
6. **Laboratory Text/Investigation Results** ☐
7. **Reporter Details** *(Required)* ☑

Generate Questionnaire

**NOTE**: Macros must be enabled in order to create Questionnaires using this template.

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**Targeted Questionnaire for Evaluating Infection Related Events**

**Vifor Coding Number:**

**1. Patient Demography**

Gender: ☐ Male ☐ Female Age: Year of Birth:

Weight: kg Height: cm Body Mass Index:

**2. Medical History and Risk Factors**

Information on medical history incl. concomitant disorders (diagnoses, family medical history, pregnancies, risk factors):

Please indicate if the following conditions are either part of the patient's medical history or are still active conditions.

| **Diagnosis/Disease** | | |
|---|---|---|
| Diabetes mellitus | ☐ Yes (specify): | ☐ No |
| Renal disease | ☐ Yes (specify): | ☐ No |
| Hepatitis/liver diseases | ☐ Yes (specify): | ☐ No |
| Auto-immune disease | ☐ Yes (specify): | ☐ No |
| HIV infection | ☐ Yes (specify): | ☐ No |
| Malnutrition | ☐ Yes (specify): | ☐ No |

| **Procedures/Treatments** | | |
|---|---|---|
| Endoscopic procedures | ☐ Yes (specify): | ☐ No |
| Splenectomy | ☐ Yes (specify): | ☐ No |
| Organ transplantation | ☐ Yes (specify): | ☐ No |
| Haematological stem cell transplantation | ☐ Yes (specify): | ☐ No |
| Dialysis:<br>☐ Haemodialysis<br>☐ Peritoneal Dialysis | ☐ Yes (tick one and specify): | ☐ No |
| Other surgical procedures | ☐ Yes (specify): | ☐ No |
| Blood transfusion | ☐ Yes (specify): | ☐ No |

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| | | |
|---|---|---|
| Steroid treatment | ☐ Yes (specify): | ☐ No |
| Anti-TNF antibodies treatment | ☐ Yes (specify): | ☐ No |
| Cytotoxic therapy | ☐ Yes (specify): | ☐ No |
| Other immunosuppressant drugs | ☐ Yes (specify): | ☐ No |
| **Catheter/Port Use** | | |
| Short-term urinary catheter | ☐ Yes (specify): | ☐ No |
| Long-term urinary catheter | ☐ Yes (specify): | ☐ No |
| Other catheter/port | ☐ Yes (specify): | ☐ No |
| **Other** | | |
| Recent foreign travel | ☐ Yes (specify): | ☐ No |
| Previous infection | ☐ Yes (specify): | ☐ No |
| IV drug abuse | ☐ Yes (specify): | ☐ No |

Please specify any other relevant medical history or risk factors for infections in this patient:

**3. Relevant Drug History**

**Enter medication other than those taken to treat the AE:** (If required please complete a separate page or attach the patient's drug list)

| Name of Product (Trade Name or Active Ingredient) | Dosage Regimen | Duration of Administration (hours:min) | Start Date (dd/mmm/yyyy) | Stop Date (dd/mmm/yyyy) | Indication |
|---|---|---|---|---|---|
| | | : | | | |
| | | : | | | |
| | | : | | | |
| | | : | | | |
| | | : | | | |

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| **Previous exposure to any iron product (PO; IM; IV)?** | ☐ YES (please specify below) | ☐ NO |
|---|---|---|

| Name of Product (Trade Name AND Active Ingredient) | Dosage Regimen | Dilution (if applicable) | Start date (dd/mmm/yyyy) | Stop date (dd/mmm/yyyy) | If an adverse event occurred, please specify |
|---|---|---|---|---|---|
| | | | | | |

**4. Information on Suspect Iron Product**

Trade name: Active Ingredient:

Batch Nr.:

Indication (with underlying disease):

| **Administration:** | Dosage: mg Iron | Frequency of administration: |
|---|---|---|
| Start Date: | (dd/mmm/yyyy) | End Date: (dd/mmm/yyyy) |
| Start Time: : | (hours:min) | Stop Time: : (hours:min) |

**Mode of Application:**

| | |
|---|---|
| ☐ IV drip infusion | Dilution: ml in ml sterile 0.9% NaCl solution |
| | Duration of administration (hours:min): : |
| ☐ IV bolus injection | Duration of administration (hours:min): : |
| ☐ intramuscular | Duration of administration (hours:min): : |
| ☐ oral | Dosage form: |

**5. Adverse Event Information**

**Enter information about adverse event(s) which occurred during/after administration of suspected iron product:**

| Nr. | Adverse event (AE) | AE occurred during or after administration? | AE Start Date/ AE Start Time | AE Stop Date/ AE Stop Time | Outcome(1) | If outcome was considered as 4 or 6, please specify | Serious(2) | Serious Criteria (3) | Causal Relationship(4) | Baseline/post-event investigations (if appropriate, please attach investigational results) |
|---|---|---|---|---|---|---|---|---|---|---|
| I. | | | | | | | | | | |
| II. | | | | | | | | | | |
| III. | | | | | | | | | | |
| IV. | | | | | | | | | | |
| V. | | | | | | | | | | |
| VI. | | | | | | | | | | |
| VII. | | | | | | | | | | |
| VIII. | | | | | | | | | | |
| IX. | | | | | | | | | | |
| X. | | | | | | | | | | |

(1) For specifying Outcome, please use the coding system below:
1 = Ongoing 2 = Recovering 3 = Recovered without Sequelae 4 = Recovered with Sequelae 5 = Fatal 6 = Unknown

(2) For specifying Serious Assessment for an adverse event, please use the coding system below:
S = Serious NS = Not serious

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| Nr. | Adverse event (AE) | AE occurred during or after admini-stration? | AE Start Date/ AE Start Time | AE Stop Date/ AE Stop Time | Outcome(1) | If outcome was considered as 4 or 6, please specify | Serious(2) | Serious Criteria (3) | Causal Relationship(4) | Baseline/post-event investigations (if appropriate, please attach investigational results) |
|---|---|---|---|---|---|---|---|---|---|---|

(3) For specifying Serious Criteria, please use the coding list (1-6) below. According to ICH-E2A guidelines a serious adverse event is any untoward medical occurrence that at any dose:
1 = Results in death 2 = Life-threatening 3= Requires inpatient hospitalisation or prolongation of existing hospitalisation
4 = Results in persistent or significant disability/incapacity 5 = Congenital anomaly/birth defect
6 = Considered a medical important event (e.g., patient requires intervention to prevent one of the other outcomes listed above)

(4) For specifying Causal Relationship please use the coding system below:
NR = Not related R = Related

**If patient died**, please enter date: (dd/mmm/yyyy) Was an autopsy performed? ☐ YES ☐ NO

Did patient receive treatment for any of the reported AE(s)? ☐ YES (please enter AE and medication administered for treatment below) ☐ NO

| Adverse Event (use corresponding roman numerals from table on page 4) | Name of Product (Trade Name or Active Ingredient) | Dosage Regimen | Start Date (dd/mmm/yyyy) | Stop Date (dd/mmm/yyyy) |
|---|---|---|---|---|

Did this patient receive any non-drug treatment? ☐ YES (please specify below) ☐ NO

**6. Laboratory Test/Investigation Results**

**Please provide SI (International Systems of Units) if available. Otherwise, as reported.**

☐ Labs Attached (tick box if lab results are attached).

Please indicate if any of the following tests have been performed, and provide the results:
Lab results should be attached whenever possible. If lab results cannot be attached, please **type** (DO NOT handwrite) the results in the space below.

| | Baseline Values (Prior to the Event) | | Values (After the Event) | | Reference Range (if applicable) | Pending? |
|---|---|---|---|---|---|---|
| | Date (dd/mmm/yyyy) | Value (include units) | Date (dd/mmm/yyyy) | Value (include units) | | |
| CRP (C-reactive protein) | | | | | | ☐ Yes |
| ESR (Erythrocyte sedimentation rate) | | | | | | ☐ Yes |
| White Blood Cell count | | | | | | ☐ Yes |
| Neutrophil count | | | | | | ☐ Yes |

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| | Baseline Values (Prior to the Event) | | Values (After the Event) | | Reference Range (if applicable) | Pending? |
|---|---|---|---|---|---|---|
| | Date (dd/mmm/yyyy) | Value (include units) | Date (dd/mmm/yyyy) | Value (include units) | | |
| Eosinophil count | | | | | | ☐ Yes |
| Lymphocyte count | | | | | | ☐ Yes |
| PCR (specify): _____ | | | | | | ☐ Yes |
| Blood culture | | | | | | ☐ Yes |
| Histology (specify): _____ | | | | | | ☐ Yes |
| Chest x-ray | | | | | | ☐ Yes |
| CT scan | | | | | | ☐ Yes |
| MRI | | | | | | ☐ Yes |
| Ultrasound | | | | | | ☐ Yes |
| Other<br>Please specify below all other relevant tests: | | | | | | |
| _____ | | | | | | ☐ Yes |
| _____ | | | | | | ☐ Yes |
| _____ | | | | | | ☐ Yes |

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| **7. Reporter Details** | |
|---|---|
| **Name of Reporter:** | **Profession of Reporter:** |
| **Name & Address of the Institution:** | **Country:**<br>**Telephone:**<br>**Fax:**<br>**e-mail:** |

**Handwritten signature of reporting person:**

Date: _____ (dd/mmm/yyyy)

## Annex 8 Protocols for Proposed and Ongoing Studies in RMP Part IV

Not applicable.

# Evaluation of European Databases for Studies Evaluating the Risk of Hypersensitivity Reactions in Users of Intravenous Iron Compounds

## Database Feasibility Evaluation (Final)

**December 1, 2014**

Prepared for

**Jan-Willem van der Velden, Dr. Med.**
**(on behalf of the IV Iron Consortium)**

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**RTI-HS Project No.: 0303773**

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# ABBREVIATIONS

| | |
|---|---|
| ATC | Anatomic Therapeutic Chemical (classification system) |
| BIPS GmbH | Leibniz Institute for Prevention Research and Epidemiology |
| CI | confidence interval |
| CIP | French pharmacy coding system |
| CNAM-TS | French health care insurance system for salary workers except civil servants and students [Caisse Nationale de l'Assurance Maladie des Travailleurs Salariés] |
| CPR | Central Personal Register (Danish identification number) |
| CPRD | Clinical Practice Research Datalink, UK |
| DDD | defined daily dose |
| DNPR | Danish National Patient Registry |
| DTM | specialized outpatient transfusion departments of hospitals [Dipartimenti di Medicina Trasfusionale], Italy |
| EGB | General Sample of Beneficiaries [Échantillon Généraliste de Bénéficiaires], France |
| EMA | European Medicines Agency |
| EMR | electronic medical record |
| FAAN | Food Allergy and Anaphylaxis Network |
| FDA | US Food and Drug Administration |
| FVG | Friuli Venezia Giulia, region in Italy |
| GePaRD | German Pharmacoepidemiology Research Database |
| GHS | cost-coding system in France |
| GP | general practitioner |
| HES | Hospital Episode Statistics, UK |
| IACS | Aragón Health Sciences Institute [Instituto Aragonés de Ciencias de la Salud], Spain |
| ICD-10 | *International Classification of Diseases, 10th Revision* |
| ICD-10-CM | *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification* |
| ICD-10-GM | *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, German Modification* |
| ICD-9 | *International Classification of Diseases, 9th Revision* |
| ICD-9-CM | *International Classification of Diseases, 9th Revision, Clinical Modification* |
| ICPC | International Classification of Primary Care |
| IDIAP | Institute of Primary Care Research [Institut D´Investigació en Atenció Primària], Spain |
| ISAC | Independent Scientific Advisory Committee (of the CPRD) |
| IV | intravenous |
| MAHs | Marketing authorisation holders |
| MREC | Multi-centre Research Ethics Committee, UK |
| MSA | French health care insurance system for agricultural workers [Mutualité Sociale Agricole] |
| NCAs | National Competent Authorities |

| | |
|---|---|
| NHS | National Health Service, UK |
| NIAID | National Institute of Allergy and Infectious Disease |
| OXMIS | Oxford Medical Information System, UK |
| PASS | postauthorisation safety study |
| PHARMO | PHARMO Institute for Drug Outcomes Research, the Netherlands |
| PMSI | national hospital discharge summaries database system [Programme médicalisé des systèmes d'information], France |
| PPV | positive predictive value |
| PRAC | Pharmacovigilance Risk Assessment Committee (of the EMA) |
| RMP | risk management plan |
| RSI | French health care insurance system for self-employed workers [Régime Social des Indépendants] |
| SHI | statutory health insurance (providers), Germany |
| SIDIAP | Information System for the Development of Primary Care Research [Sistema de Información para el Desarrollo de la Investigación Primaria], Spain |
| SNIIRAM | National Information System Inter Plans Health Insurance [Système National d'Informations Inter Régimes de l'Assurance Maladie], France |
| THIN | The Health Improvement Network, UK |
| UK | United Kingdom |
| US | United States |

# ACKNOWLEDGEMENTS

The authors would like to express their sincere appreciation to the following individuals and institutions for providing information for this report:

- Vera Ehrenstein MPH, DSc; Lars Pedersen, MSc, PhD; and Troels Munch, MD; Dept. of Clinical Epidemiology-Aarhus University Hospital, Denmark
- Pasi Korhonen, CEO, PhD; EPID Research, Finland
- Patrick Blin, MD, MSc; Bordeaux University, France
- Federica Pisa, MD, MStat; Udine University Hospital, Italy
- Tania Schink Dr. rer. medic, MPH, and Kathrin Jobski, MSc Epidemiology; BIPS-Bremen University, Germany
- Irene Bezemer, PhD; PHARMO Institute, The Netherlands
- Amaia Calderón Larrañaga, MPH, PhD, and Alexandra Prados Torres MD, MPH, PhD; Instituto Aragonés de Ciencias de la Salud, Spain
- Maria Giner Soriano, PharmD, MSC; IDIAP Jordi Gol, Spain
- Helle Kieler, MD, PhD; Centre for Pharmacoepidemiology, Karolinska Institutet, Sweden
- Daniel Dedman, BSc, MPhil, MSc, and Antonis Kousoulis, MD, MSc; CPRD, United Kingdom

# EXECUTIVE SUMMARY

**Background:** In the context of the European Medicines Agency (EMA) benefit-risk assessment of iron-containing intravenous (IV) medicinal products (Article 31 referral procedure), the EMA recommended further characterisation of the risk of hypersensitivity reactions known to be associated to IV iron treatments through a post-authorisation safety study (PASS).

**Objectives**: (1) To summarise the research literature on anaphylaxis/hypersensitivity reactions in database studies and (2) to perform an evaluation of European candidate data sources for the feasibility of conducting a PASS.

**Methods**: Targeted literature search via Medline (2000 through June 2014, English language). Feasibility evaluation of 10 European population-based databases in nine countries. We assessed key elements related to the capture of patients receiving prescriptions/dispensings for IV iron compounds in each country and capture of hypersensitivity reactions or anaphylaxis. The databases and countries were The Central Denmark Region database in Denmark, the Finnish national health registers in Finland, the National Inter Plans Health Insurance Information System (SNIIRAM) and the General Sample of Beneficiaries (EGB) in France, the Friuli Venezia Giulia health databases (FVG) in Italy, the German Pharmacoepidemiology Research Database (GePaRD) in Germany, the PHARMO Institute for Drug Outcomes Research databases in the Netherlands, the Aragón Health Science Institute database (IACS) in Spain, the Information System for Primary Care Research (SIDIAP) in Spain, the Swedish national health registers in Sweden, and the Clinical Practice Research Datalink (CPRD) in the United Kingdom (UK).

**Results:** The literature review showed that the incidence of anaphylaxis varies across studies due to differences in the definition of anaphylaxis, the populations studied, and the health care setting from which diagnoses originate. Drug-induced anaphylaxis accounts for up to 30% of all anaphylaxis cases. The frequency of drug-induced severe hypersensitivity/anaphylactic reactions is rare, with incidences of up to 0.3 per 10,000 dispensings for antibiotic-related events. The studies that provide data on the validation of anaphylaxis have applied different definitions, coding systems, and algorithms for the identification of cases. The published reported positive predictive values (PPVs) ranged from 32% to 73% (US and CPRD databases). The use of complex algorithms to identify anaphylaxis cases resulted in somewhat higher PPVs, although the overall range of PPVs was similar in studies that used more simple algorithms.

The evaluation of candidate European data sources confirmed that IV iron treatments are predominantly administered in hospitals or specialised outpatient treatment settings. As a result, of the data sources explored, those that are primarily based on primary health care/general practice and/or non-hospital ambulatory data either do not capture or minimally capture IV iron use (databases in Finland, Italy, Spain, and the UK). Data sources with partial capture of use of IV iron compounds and diagnosis of

hypersensitivity reactions include the databases in Denmark, France, Germany, the Netherlands, and Sweden. The capture of IV iron use in each data source is related to the specific compounds with market authorization in each country and to the type of setting (e.g., inpatient, outpatient) covered by each data source. Overall, the results obtained during the time periods evaluated in the feasibility study showed that approximately 140,000 users of IV iron compounds were captured. This number is a cumulative number and does not refer to unique patients (patients with at least one prescription) because in some databases patients may be counted in multiple years. Counts of unique patients for IV iron use were available in the Central Denmark Region database in 2013 (1,442 treated patients). Data on IV iron use from the Central Danish region are available for the years 2010-2014, which could increase the numbers by 2- to 3-fold, depending on chronic use of medications and indication mix. In Germany, the indirectly estimated number of non-unique IV iron users (N = 76,273) from 2010 through 2012 for three of the IV iron compounds of interest suggests that the size of the population of IV iron users from the entire period of data available in GePaRD (since 2004) may be among the largest in Europe since data from more years are available, although estimates are based on assumptions with limitations. In the PHARMO database in the Netherlands, 8,643 patients had at least one dispensing/prescription of an IV iron compound from 1998 through 2013. This number does not refer to unique patients because some patients may be counted in multiple years. In Sweden, 56,434 non-unique patients had at least one prescription of an IV iron compound from 2006 through 2013. Data on potential hypersensitivity reactions are available across data sources but source record validation is limited to the smallest populations, the regional database in Denmark and potentially only for subpopulations in the Netherlands and Sweden.

**Conclusions:** Drug-induced hypersensitivity/anaphylactic reactions are rare events. In summary, five European data sources provide partial capture of IV iron use. While there are important numbers of treated patients in the ambulatory setting in France, Germany, and Sweden, in the context of the low frequency of severe hypersensitivity reactions, a study based on these data will result in imprecise rate estimates. Furthermore, across all data sources, only case ascertainment using algorithms or electronic profile review could be conducted. The potential to validate the diagnosis of hypersensitivity reactions of potential cases through source record review is limited to the Central Denmark Region, which has the lowest number of patients, and subpopulations in the Netherlands and Sweden, but the approval processes for accessing medical record information are complex. Validation of cases through source record review cannot be conducted in Germany or France, the countries with the largest number of treated patients captured in databases.

Therefore, a PASS as originally envisioned, with comprehensive capture of the available IV iron use in Europe and with source medical record validation of potential cases of anaphylaxis/hypersensitivity reactions, is not feasible. A study based on analyses of available data from data sources that provide partial capture of IV iron use would be

highly complex. Some of the data collected could be informative, but relevant limitations will remain regarding the precision and validity of the estimates.

# 1 BACKGROUND

Intravenous (IV) iron therapy was introduced in the 1950s for the treatment of severe anemia (Auerbach and Ballard, 2010). In the last decades, the use of IV iron has been growing worldwide due to a better understanding of the management of moderate and severe anemia related to numerous conditions such as chronic kidney disease, heavy uterine bleeding, pregnancy and postpartum anemia, chemotherapy-induced anemia, elective surgery, and chronic heart failure (Bailie and Verhoef, 2012).

The benefit-risk balance of iron-containing IV medicinal products has been evaluated by the European Medicines Agency (EMA) in the context of a referral under Article 31 of Directive 2001/83/EC completed in September 2013. While the benefit/risk of all IV iron products was confirmed, the occurrence of severe acute hypersensitivity reactions that are known to be associated with IV iron administration was to be further elucidated (Auerbach and Ballard, 2010).

The various iron preparations contain complexes of iron bound to other molecules such as sugar molecules. The iron complexes involved in the EMA's referral procedure were ferric carboxymaltose, iron dextran, sodium ferric gluconate, iron isomaltoside, and iron sucrose, which are authorised in European Union Member States (EMA, 2013a).

In addition to a labelling update reinforcing risk information on hypersensitivity reactions, the EMA formulated the following "conditions to marketing authorization":

- The Marketing Authorisation Holders (MAHs) should circulate the agreed Direct Healthcare Professional Communication (DHPC) in coordination with the National Competent Authorities (NCAs).
- The MAHs should update or develop the risk management plan (RMP).
- The MAHs should submit annual cumulative reviews of hypersensitivity case reports, all fatal cases, and all pregnancy cases, together with usage data yearly. These should be harmonized among the MAHs.
- The MAH(s) should provide within the risk management plan educational material for prescribers and patients.

All these conditions have been fulfilled and/or discussions are ongoing with selected NCAs on RMPs and/or educational materials.

In addition, the EMA Pharmacovigilance Risk Assessment Committee (PRAC) recommended that *"MAHs shall conduct a post-authorisation safety study (PASS) to further characterise the safety concerns on the hypersensitivity reactions. The study will also have to be reflected in the updated/new RMP submission*" (EMA, 2013a).

To address the EMA PRAC's recommendation and as committed during the referral procedure, a consortium of MAHs of IV iron compounds has been established with the

objective of assessing the **feasibility of conducting a European multinational PASS** on the utilisation of IV iron compounds and the risk of severe hypersensitivity reactions among users of IV iron compounds, to be conducted in several existing population-based automated health care data sources. A common protocol synopsis for the PASS feasibility assessment was submitted to European Union NCAs in November 2013 by each concerned MAH of each IV iron medicinal product within their RMP submission.

# 2 OBJECTIVES

The objectives of this feasibility assessment were as follows:

1. To summarise the literature on research on anaphylaxis/hypersensitivity reactions and frequency in users of other medications and the general population in prior database studies targeting these endpoints and
2. To perform an evaluation of candidate data sources in selected European countries—Denmark, Finland, France, Germany, Italy, Netherlands, Spain, Sweden and the United Kingdom (UK)—for a study to evaluate the use of selected IV iron compounds and the associated risk of hypersensitivity reactions.

# 3 METHODS

## 3.1 Literature Search

In June 2014, a targeted search of the published literature was performed using the Medline (PubMed) database to identify research on hypersensitivity reactions, with a particular focus on studies that aimed at the identification and validation of the endpoint in European data sources. The search covered the period from 2000 up to June 2014 and was limited to studies published in the English language. The detailed search strategy is included in Appendix A. Additional articles were identified through the review of references of relevant studies or were provided by consortium members. Key findings from the published literature are discussed in Section 4.1 and summarised in Appendix B.

## 3.2 Feasibility Evaluation

The feasibility evaluation focused on key elements related to the capture of counts of patients exposed to and/or prescriptions/dispensings for selected IV iron compounds marketed in each country by MAHs participating in the consortium and capture of hypersensitivity reactions or anaphylaxis in each data source. A standard feasibility questionnaire was prepared to facilitate obtaining the information of interest in each country and was sent to all data sources custodians (Appendix C).

The following specific aspects were evaluated:

- Extent to which information on use/dispensing/prescription of IV iron compounds in different settings (ambulatory, specialised clinics, hospitals) was captured through the data sources.
- Impact of reimbursement and setting status on capture of IV iron use.
- Availability of data on dose and duration of treatment.
- Potential for additional linkages, databases, and registers that could be used in case a positive decision is made to conduct a PASS.
- Brief assessment of the capture of diagnosis of hypersensitivity reactions.
- History of previous research on hypersensitivity reactions in the data source.
- Basic counts of ever users (users with at least one prescription/dispensing during a given year and since product launch to latest available period) for all IV iron compounds and per specific IV iron compound in each data source.
- Requirements for data access and research approval.

This feasibility evaluation was based on direct contacts with data source custodians and researchers, publicly available information, and our research experience.

# 4 RESULTS

## 4.1 Published Research on Hypersensitivity Reactions

Due to the previous lack of a universally accepted definition and criteria for the diagnosis of hypersensitivity reactions/anaphylaxis, in 2006, the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network (NIAID/FAAN) proposed a consensus definition of anaphylaxis as "a serious allergic reaction that is rapid in onset and may cause death" and criteria to meet the definition (Sampson et al., 2006). Medicines, insect stings, and food are thought to be the most common causes of anaphylaxis (Worm et al., 2014). Drug-induced anaphylaxis accounts for up to 30% of all cases of anaphylaxis (Peng and Jick, 2004; Worm et al., 2014).

Several studies based on spontaneous reports have evaluated hypersensitivity reactions in association with IV iron preparations (Bailie et al., 2005; Bailie and Verhoef, 2012; Chertow et al., 2004; Chertow et al., 2006). The most recent estimates are those reported to the World Health Organization Uppsala Monitoring Center in Sweden based on data collected from the first quarter of 2003 through the second quarter of 2009 from 16 European countries and North America. Serious allergic adverse events were defined as anaphylaxis plus other serious allergic reactions. Anaphylaxis was defined using the WHO's Adverse Reaction Terminology standardized coding system. Other serious allergic reactions were classified as any other events where the reports included any terms or

codes for systemic allergy combined with any term with cutaneous evidence of bradykinin or histamine release. Reported rates of serious allergic reactions per 100 milligrams of iron used per million x 100,000 inhabitants were between 0.01 and 1.05 events for sodium ferric gluconate, between 0.09 and 4.7 events for iron dextran, and between 0.02 and 0.27 events for iron sucrose (Bailie and Verhoef, 2012). These results suggest that events of anaphylaxis due to IV iron administration are rare.

### 4.1.1 Disease Frequency

Anaphylaxis is a rare event, with an estimated frequency of 5 to 200 episodes per 10,000 persons or a lifetime prevalence of 0.05% to 2% (Lieberman et al., 2006) The incidence of anaphylaxis varies greatly across studies depending on the definition of anaphylaxis used, the study setting, and the population studied. In Appendix B, a summary of study designs and incidence rate results appears in Table B-1. In Europe, there is a large number of published studies either based on electronic medical records of general practitioners (GPs), emergency departments, or hospital discharges. Estimates of incidence rates of anaphylaxis range between 1.5 and 32 per 100,000 person-years (Panesar et al., 2013). In the US, most of the published studies are based on emergency department medical records, and incidence rates range between 2.8 and 90 per 100,000 person-years. The differences in the definitions of outcomes and in design-related aspects hinder direct comparison of incidence rates across studies (see Table B-1 for further information and references). The most common drugs reported as potential triggers of anaphylaxis are painkillers (44%) and antibiotics (21.5%) (Campbell et al., 2012; Peng and Jick, 2004; Worm et al., 2014). The incidence of anaphylaxis induced by fluoroquinolone antibacterials per 10,000 dispensings was 0.3 for moxifloxacin and levofloxacin, 0.2 for gatifloxacin and cephalosporins, and 0.1 for ciprofloxacin and penicillin (Johannes et al., 2007). In summary, data from population-based studies indicate that hypersensitivity/anaphylactic reactions are rare events.

### 4.1.2 Endpoint Validation

Studies performing validation of the diagnosis of anaphylaxis/hypersensitivity reactions as an endpoint are scarce. Endpoint validation has been performed mainly by enquiry to the physician or through review of medical records. In Appendix B, findings from published validation studies are summarised in Table B-2. Overall, studies defined anaphylaxis based on general ICD-9 codes such as the 995.0 code (anaphylactic shock) or when evaluating anaphylaxis of all causes, specific anaphylaxis codes such as ICD-9 995.4 (anaphylactic shock due to anesthesia), 995.6 (anaphylactic shock due to adverse food reaction), and 999.4 (anaphylactic shock due to serum). In studies that used a simplistic approach for the identification of the endpoint based mainly on algorithms of anaphylaxis-related diagnostic codes, the positive predictive value (PPV) ranged from 52% to 73% (Bohlke et al., 2004; González-Pérez et al., 2010; Iribarren et al., 2010; Johannes et al., 2007; Peng and Jick, 2004). In studies that used more sophisticated

algorithms based on the NIAID/FAAN criteria, which includes respiratory compromise, skin-mucosal involvement, gastrointestinal symptoms, and reduced blood pressure, the PPVs ranged from 38% to 69% (Campbell et al., 2012; Erlewyn-Lajeunesse et al., 2010; West et al., 2007). Some studies have also used the ICD-10-CM and other classification systems, although few performed validation of the anaphylaxis endpoint (Liew et al., 2009; Tanno et al., 2012; Vetander et al., 2011). Of particular relevance to the feasibility evaluation of data sources for a potential PASS, most published studies on anaphylaxis, with or without validation of the endpoint, have identified patients based on hospital and/or emergency department records. Although some US studies using claims databases from managed care settings included outpatient data (Bohlke et al., 2004; Iribarren et al., 2010; Johannes et al., 2007), only four studies reported data from primary care databases (Avillach et al., 2013; González-Pérez et al., 2010; Peng and Jick, 2004; Sheikh et al., 2008). Studies based on general practice settings have not used the algorithm proposed by the NIAID/FAAN for the identification of anaphylaxis cases, whereas studies conducted in emergency department and inpatient settings have used the NIAID/FAAN definition and performed validation.

In 2012, the US FDA Mini-Sentinel pilot program published a review of four studies published between 1990 and May 2010 that used administrative and claims health data to identify anaphylaxis and performed validation of the coding algorithms (Schneider et al., 2012). The review reported that the ICD-9-CM 995.0 code (anaphylactic shock) was the most commonly used anaphylaxis-specific code. The PPVs for this code reported in the studies by West et al. (2007) (emergency departments in South Carolina, US), Iribarren et al. (2010) (US Kaiser Permanente Northern Carolina database, US), Bohlke et al. (2004) (Group Health Cooperative database, US), and Johannes et al. (2007) (Ingenix Research Data Mart, US) were 38%, 52%, 55.4%, and 57.1%, respectively. However, the authors also highlighted that the algorithms were simplistic and dependent on diagnostic and procedural codes applied individually and that improvement would be possible by incorporating more complicated algorithms. For studies aiming to evaluate anaphylaxis following a specific trigger, Schneider et al. (2012) recommended incorporating the exposure of interest in the algorithm, whenever possible.

Our literature search identified four additional studies that performed endpoint validation but were not included in the Mini-Sentinel review. The UK studies, performed in The Health Improvement Network (THIN) and the General Practice Research Database[1] (González-Pérez et al., 2010; Peng and Jick, 2004), still used what the authors of the Mini-Sentinel study called a simplistic definition based on codes with the term anaphylaxis in their description; both studies showed a PPV of 73%. Two other studies used more complicated algorithms: Campbell et al. (2012) used the NIAID/FAAN criteria in a US emergency department setting and reported a PPV of 68.6%. The study by Erlewyn-Lajeunesse et al. (2010) performed validation using both the NIAID/FAAN

[1] Forerunner of the Clinical Practice Research Datalink.

anaphylaxis criteria and the Brighton Collaboration Criteria in a UK emergency department setting and reported a PPV of 61.7% and 68.1%, respectively.

During the course of this feasibility assessment, researchers from the Department of Clinical Epidemiology at Aarhus University Hospital in Denmark provided information from an ongoing multinational research project on postmenopausal women diagnosed with osteoporosis in which validation of potential hypersensitivity reactions was performed through review of medical records. Validation of potential hypersensitivity reactions identified by ICD-10 codes had an overall positive predictive value (PPV) of 14%, lower than estimates from published research (Aarhus University Hospital, personal communication, 2014).

In summary, the incidence of anaphylaxis varies due to differences in the definition of anaphylaxis, the populations studied, and the health care setting from which diagnoses originate. The studies that provide data on the validation of anaphylaxis have applied different definitions, coding systems, and algorithms for the identification of cases. The published studies that performed validation of anaphylaxis reported PPVs ranging from 32% to 73% (US and CPRD data sources). Data from an unpublished study reported a PPV of 14% (Aarhus University Hospital, personal communication, 2014). The use of complex algorithms to identify anaphylaxis cases resulted in somewhat higher PPVs, although the overall range of PPVs was similar to the range in studies that used more simple algorithms. The use of data from emergency departments and the use of non-specific ICD codes that potentially indicate hypersensitivity reactions tend to result in low PPVs. Based on these studies and the Mini-Sentinel validation report, the recommendation is to validate potential cases of anaphylaxis through source record verification (Walsh et al., 2013).

## 4.2 Candidate European Population Data Sources for Pharmacoepidemiology Research of Iron Intravenous Compounds

Intravenous iron-containing medicinal products are indicated for the treatment of iron deficiency and anemia associated with low iron levels when oral iron preparations are ineffective or cannot be used, especially in patients receiving dialysis for kidney failure, before and after surgery, or in case of absorption disorders affecting the gut (EMA, 2013). Due to the nature of the conditions underlying the administration of IV iron treatments, the use of these compounds is expected to be initiated and concentrated mainly in hospital settings or in specialised ambulatory treatment centers of hospitals (e.g., dialysis units, transfusion units, IV treatment administration units). However, the potential to capture IV iron use in databases containing health data from the ambulatory setting and their linkage capabilities to data from specialised treatment settings needs to be explored. This feasibility evaluation investigated the capture of data on IV iron use and hypersensitivity reactions in targeted population-based data sources in nine

European countries and their linkage capabilities to data from hospital/ambulatory hospital outpatient settings and to patient registries capturing treatment information from specialised treatment settings. The following data sources were explored:

- The Danish national health registries
- The Finnish national health registries
- The National Information System Inter Plans Health Insurance (SNIIRAM) and the General Sample of Beneficiaries (EGB), France
- The Friuli Venezia Giulia health databases (FVG), in Italy
- The German Pharmacoepidemiology Research Database (GePaRD)
- The PHARMO Institute for Drug Outcomes Research (PHARMO) databases, the Netherlands
- The Aragón Health Science Institute database (IACS), Spain
- The Information System for Primary Care Research (SIDIAP), Spain
- The Swedish national health registers
- The Clinical Practice Research Datalink (CPRD), the UK

The selection of countries was made in consideration of countries where IV iron compounds had been marketed by marketing authorisation holders participating in the IV Iron Consortium and where established population-based data sources were available for a potential PASS. In Appendix D, Table D-1 summarises information on all country-specific IV iron-containing products investigated in each of the targeted data sources: iron(III)-hydroxide dextran, iron(III)-isomaltoside, iron as ferumoxytol, ferric carboxymaltose, iron sucrose/iron hydroxide sucrose, and sodium ferric gluconate complex.

The following sections provide detailed information on the characteristics of and type of data available at each of the data sources explored for the feasibility assessment, ordered alphabetically by country.

### 4.2.1 The Danish National Health Registries, Denmark

Denmark, a Nordic country with a population of 5.6 million (Eurostat, 2014), is a welfare state whose national health service provides universal tax-funded health care to all Danish residents. Health care coverage includes visits to GPs and specialists, hospital admissions, and outpatient visits. The Danish centralised Civil Registration System assigns a unique 10-digit Central Personal Register (CPR) number to all persons at birth or immigration, which is used in all public registries and databases in Denmark and allows for individual-level record linkage of data from all Danish registers and databases (Sørensen et al., 2009). Data collected in these registries can be made available for

research purposes. The specific databases of interest for this project are described below.

Prescription medicine in Denmark is sold to patients through outpatient pharmacies (including outpatient pharmacies located within hospitals) or is administered directly to patients during hospital encounters. The Danish National Prescription Registry collects information on individual-level dispensation records generated by outpatient pharmacies. Information on the patient's CPR number, dispensing date, active substance (Anatomical Therapeutic Chemical [ATC] code), brand name, strength, and package size are collected. Medications administered to patients during hospital encounters are reported to the drug registry only in the form of aggregated sales data. The public-domain online tool www.medstat.dk, maintained by the Danish State Serum Institute, provides continuously updated aggregate statistics on prescription medications sold in Denmark from 1996 onwards. Data on the number of users are available for the primary care sector only (which includes drug dispensings in outpatient hospital pharmacies). As of the date of this report, data from this source were available through 2013.

The Danish National Patient Registry (DNPR) contains information on all inpatient stays at all somatic hospitals in Denmark since 1977. From 1995 onwards, visits to specialists at outpatient departments and emergency rooms are also reported. Each record contains data on the patient's CPR number, dates of admission and discharge, type of visit (inpatient, outpatient, emergency), and up to 20 discharge diagnoses coded using ICD-10 since 1993, with one diagnostic field for the primary diagnosis. In addition to the diagnoses, all procedures and certain in-hospital treatments are likewise recorded. Data on reason for treatment are used for reimbursement purposes. Some treatment codes identify only a drug class and some specify the active substance, but they do not encode strength or route of administration.

The Central Denmark Region electronic medical record (EMR) database (for research), maintained at the Department of Clinical Epidemiology of Aarhus University, is based on EMRs from hospitals in the Central Denmark Region. This database contains individual-level data on medications prescribed and administered in the region's hospitals, including specialist outpatient clinics. Available data include active substance (ATC code), strength, brand name date of prescription, and date of administration. On 1 January 2013, the population of the Central Denmark Region was 1,272,510 individuals, or about one-fourth of the total Danish population (Statistics Denmark, www.statistikbanken.dk). The EMR research database has no data on diagnoses.

#### 4.2.1.1 Prior Research on Hypersensitivity Reactions

In evaluating the incidence of "anaphylactic shock," we identified one study that included data from the Aarhus University Hospital Database record linkage system (Avillach et al., 2013). Identification of cases relied on ICD-10 codes specific for anaphylactic shock and exposure-related anaphylactic shock. The incidence of anaphylactic shock was 5.7 per

100,000 using only primary discharge diagnoses and 6.4 per 100,000 when secondary diagnoses were included. No data on validation of the endpoint were provided.

Aarhus researchers informed us of a currently unpublished research project on postmenopausal women diagnosed with osteoporosis in which validation of potential hypersensitivity reactions was performed through review of medical records. Potential cases were identified by an algorithm of ICD-10 codes for primary discharge diagnoses of hypersensitivity-related events associated with an inpatient stay or an emergency department visit. The overall PPV was 14% for all diagnostic codes, and the PPV was 40% for the ICD-10 code T886 (anaphylactic shock due to adverse effect of correct drug or medicament properly administered), lower than published PPVs in other countries. It was noted that in this cohort of women, hypersensitivity reactions were expected to occur among users of medicinal products given outside of the hospitals.

### 4.2.2 The National Finnish Health Databases, Finland

Finland, a Nordic European country with a population of 5.4 million in 2013 (Eurostat, 2014), provides unrestricted access to health services, independent of socioeconomic status, to all Finnish citizens and residents through a tax-supported public health care plan (Furu et al., 2010). Several health and social welfare registers are available for epidemiological research (Gissler and Haukka, 2004). A system of unique identification numbers was launched in 1964 and allows automated data linkage across health registers. Researchers at EPID Research in Finland provided information for the feasibility assessment.

Finnish statutory health care and prescription registers, together with personal identification numbers, can be used for epidemiological research. The National Prescription Register, available since 1994, contains data on reimbursed drugs dispensed at pharmacies to individuals receiving ambulatory care (Furu et al., 2010). The National Hospital Discharge Registry was established in 1967 and has a data lag time of about 9 months. The Finnish Central Population Register was founded in 1964. Statistics Finland, computerised since 1969, compiles the Cause-of-Death Register (Gissler and Haukka, 2004). The nationwide Primary Care Register has been available since 2011. Other disease-specific registers (e.g., renal, liver) and regional health databases are also available for research purposes. Of potential interest to this project, the Helsinki regional database, covering approximately 20% of the Finnish population, contains hospital care data including drugs used in the inpatient setting and drugs dispensed by hospital pharmacies. Dose and duration of treatments may be captured in this database.

The literature search did not identify publications on the validation of anaphylaxis in Finland. The Finnish investigator confirmed this and reported that studies have been conducted evaluating allergic reactions, mainly focused on allergies in environmental settings (Lammintausta et al., 2002; Lauerma et al., 2001; Salonen, 1990).

### 4.2.3 Health Care Databases in France

#### 4.2.3.1 The French National Information System Inter Plans Health Insurance

The French National Information System Inter Plans Health Insurance (SNIIRAM) database contains individual anonymous information of all non-hospital reimbursed claims linked to the national hospital discharge summaries database system (PMSI) and the national death registry. The database currently covers the 3 main health care insurance systems (the CNAM-TS for salary workers except civil servants and students, the MSA for agricultural workers, and the RSI for self-employed workers), representing 87% of the French population. The following information is available for each individual:

- Demographics and general information: sex, year of birth, area of residence.
- Medical and pharmaceutical expenses related to long-term illness qualifying for full insurance coverage based on a list of 31 conditions, with ICD-10 codes and start and end dates of illness.
- Outpatient reimbursed health care expenditures with dates (prescription and dispensing) and codes: visits, medical procedures, lab tests, drugs, and medical devices. Drug information includes ATC code, CIP code (French pharmacy coding system), dosage, number of units per box, and number of boxes dispensed. Data on underlying medical indication and test results are not available.
- Hospital discharge summaries from PMSI: ICD-10 diagnosis codes for main and associated diagnosis for all medical, obstetric, and surgical hospitalisations, including date and duration of hospitalisation, medical procedures; diagnosis-related group; and cost-coding system (GHS). Drug information is available only for drugs prescribed out of the GHS cost-coding system, mainly expensive drugs, and does not include data on IV iron.
- Date of death.

SNIIRAM data are released for a 3-year period in the third quarter of the following year included in each period (i.e., data extracted for the period from 2012 through 2014 will be available in the third quarter of 2015). Researchers at the INSERM CIC Bordeaux CIC1401 pharmacoepidemiology research unit have conditional access to the SNIIRAM database with an authorisation process (6 to 12 months before data extraction by the CNAM-TS, database operator), based on the scientific protocol, as well as regulatory requirement/public health considerations. Approval by the Institute of Health Data and the French data protection commission is required before data extraction.

#### 4.2.3.2 The General Sample of Beneficiaries Database

The General Sample of Beneficiaries (EGB [Échantillon Généraliste de Bénéficiaires]) database consists of a 1/97 random sample of the SNIIRAM database and currently includes information from approximately 700,000 French residents. The EGB database is fully representative of the French population in terms of sex, age, and mean expenditure reimbursed for individuals. Non-hospital ambulatory health care data are available since

2003 for the population covered by the CNAM-TS health insurance system and since 2011 for the MSA and RSI insurance systems. Hospital discharge information is available since 2005 for CNAM-TS and since 2010 for MSA and RSI populations. Non-hospital data are updated on a monthly basis, and hospital-discharge summaries are updated yearly (at end of the third quarter for the previous year).

In 2007, following a ministerial decree, access to the EGB database was authorised to certain entities. The Service of Clinical Pharmacology of Bordeaux University has full access to the EGB via the INSERM CIC Bordeaux CIC1401 pharmacoepidemiology research unit. For projects financed by the private health care sector, a study synopsis has to be provided for information 1 month before data extraction.

No studies evaluating the risk of anaphylaxis or hypersensitivity reactions performed using the SNIIRAM or EGB databases were identified through the literature search or reported by the researchers at Bordeaux University.

### 4.2.4 The Friuli Venezia Giulia Database, Italy

The health databases of the Friuli Venezia Giulia (FVG) region in Italy, covering a population of 1.2 million, contain diagnoses from hospital discharge records from all hospitalisations (including 1-day hospitalisations) and emergency department encounters in public and private hospitals in the region. Diagnoses are coded according to the *International Classification of Diseases, 9th revision, Clinical Modification* (ICD-9-CM). Minor variations in the format of diagnosis data have occurred over time: prior to 2000, only four secondary diagnoses were recorded; the 1997 version of ICD-9-CM was used until 2003, and subsequently the 2002 version of ICD-9-CM has been used. The FVG Outpatient Prescription Database captures all dispensed and reimbursed ambulatory prescriptions (including nursing-home prescriptions).

Databases registering patient-level data on drug use during in-hospital stays are not available, but these data are registered in medical records (on paper) with the exception of oncology departments of FVG hospitals, where patient-level data are captured in the electronic medical records (Cartella Oncologica) database, available since 2004. For each patient, the electronic database registers all the medications administered.

Outside of the automated data sources available for research, specialised outpatient transfusion departments (DTMs) of hospitals in the FVG region are also responsible for the administration of IV iron treatments. Data from the DTMs can be accessed for research purposes. Medical records are available in paper form in some DTMs and in electronic format in other DTMs. Therefore, the data available in paper form would need to be abstracted from the medical records and entered manually onto an electronic database to be used for research purposes. Compliance with local policies and procedures for patient confidentiality protection and Ethics Committee review are required.

No studies assessing the risk of anaphylaxis or hypersensitivity reactions or validating this endpoint using data from the FVG databases were identified through the literature search or reported by the researchers at Udine University.

### 4.2.5 The German Pharmacoepidemiological Research Database, Germany

The German Pharmacoepidemiological Research Database (GePaRD), which has been built by the Leibniz Institute for Prevention Research and Epidemiology (BIPS GmbH), consists of claims data for reimbursement of diagnostic and therapeutic services from four German statutory health insurance (SHI) providers covering over 17 million insured people throughout Germany. The population contained in this database represents approximately 21% of the German population of 80.5 million inhabitants in 2013 (Eurostat, 2014). The database covers all SHI members who have been enrolled in one of the four SHIs since 2004 and contains core data; hospitalisation data; outpatient prescription data for all dispensed drugs prescribed in ambulatory settings, which are reimbursed by the SHIs; and ambulatory care data/diagnoses starting 1 January 2004. The database covers all geographic regions of Germany. The database is updated every year, with a data availability lag time of approximately 2 years.

Access to data counts on prescriptions and patients are available only for approved research projects; this requires endorsement of the project by the SHI and the Ministry of Health for SHIs that operate nationwide. Researchers at the GePaRD provided data on IV iron use from an approved retrospective cohort study of cancer patients receiving epoetin from 1 January 2004 through 31 December 2009. Dispensings of IV iron products were identified up to 31 December 2010 by the ATC code BO3AC. For the year 2010, data are from only one of the two large SHIs that each cover a population of about 8 million. Data on compound-specific frequency of defined daily doses (DDDs), number of patients with at least one dispensing, and number of DDDs per patient were provided.

Data from the National Pharmaceutical Reference Database published in the Drug Annual Reports on the total annual DDDs for the years 2010 through 2012 (Schwabe and Paffrath, 2011; Schwabe and Paffrath, 2012; Schwabe and Paffrath, 2013) are available for Ferrlecit (sodium ferric gluconate complex), Ferinject (ferric carboxymaltose complex) and FerMed (iron sucrose complex). Compound-specific data on the mean DDDs per patient from the cancer cohort were used to indirectly estimate the total number of annual prescriptions that would be available in the GePaRD, assuming that the population covered in the GePaRD represents approximately 17% of the general population in Germany.

No studies evaluating the risk of anaphylaxis or hypersensitivity reactions or validating this endpoint performed using the GePaRD were identified through the literature search or reported by the researchers at BIPS GmbH.

### 4.2.6 The PHARMO Database Network, The Netherlands

The PHARMO Institute for Drug Outcomes Research (PHARMO) in the Netherlands (http://www.pharmo.com/) has access to the PHARMO Database Network, a population-based network of health care databases that combines data from different health care settings, including general practice, inpatient and outpatient pharmacy, clinical laboratory, hospitals, cancer registry, pathology registry, and perinatal registry. Data sources are linked on a patient level through validated algorithms.

The longitudinal nature of the PHARMO data enables follow-up on more than 4 million residents of a well-defined population in the Netherlands (25% of the Dutch population) for an average of 10 years. All electronic patient records in the PHARMO Database Network include information on age, sex, socioeconomic status, and mortality. Availability of other information is dependent on the data source. Access to medical charts and other clinical data is available within the prerequisites of the Dutch privacy regulations.

The drug dispensings originate from outpatient pharmacies and, for inpatient drug dispensings given during a hospitalisation, from the hospital pharmacy database. Drug dispensings and prescriptions are coded using ATC codes. The Outpatient Pharmacy Database, covering a catchment area of about 3.6 million residents, comprises GP- or specialist-prescribed health care products dispensed by the outpatient pharmacy. The dispensing records include information on type of product, date, strength, dosage regimen, quantity, route of administration, prescriber specialty, and costs. Currently, data are available up to mid-2013. The dispensing records in the Inpatient Pharmacy Database (covering a catchment area representing 2.0 million residents) include information on type of drug, start and end date of use, strength, dosage regimen and route of administration. Currently, data are available up to end of 2012.

The Hospitalisation Database comprises hospital admissions for more than 24 hours and admissions for less than 24 hours for which a bed is required from the Dutch Hospital Data Foundation. The records include information on discharge diagnoses, procedures, and hospital admission and discharge dates. Diagnoses are coded according to ICD-9 and ICD-10, and procedures are coded according to the Dutch Classification of Procedures. Currently, data are available through the end of 2012.

The GP database, covering a population of about 1.5 million, consists of data from electronic patient records registered by GPs. The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists, and drug prescriptions (product, date of prescription, strength, dosage, regimen, quantity, and route of administration). Drug prescriptions are coded in ATC codes, and diagnoses and symptoms are coded according to the International Classification of Primary Care (ICPC), which can be mapped to ICD codes. Data are currently available from 2002 through the end of 2012.

The linked databases in the PHARMO Database Network are updated every year. Databases are linked when the hospital admission data of the preceding calendar year become available; the updated database becomes available in the second half of the year. In between updates of the linked databases, the outpatient pharmacy data are updated every month. Dates of death returned from the Central Bureau of Genealogy have a lag time of 2 years.

#### 4.2.6.1 Prior Research on Hypersensitivity Reactions

Through the literature search we identified one study that included data from PHARMO in the evaluation of the incidence of "anaphylactic shock" (Avillach et al., 2013). Identification of cases, in data from regional drug dispensing records, hospitalisation claims, and laboratory values, relied on ICD-9-CM codes specific for anaphylactic shock and exposure-related anaphylactic shock. The incidence of anaphylactic shock was 1.9 per 100,000 using only primary discharge diagnoses and 2.4 per 100,000 when secondary diagnoses were included. No data on validation of the endpoint were provided. Endpoint validation studies were not identified.

### *4.2.7 IACS, Aragón Health Sciences Institute, Spain*

Linked data from the electronic medical and administrative databases in the region of Aragon in Spain are available for research purposes through the EpiChron Research Group of the Aragón Health Sciences Institute (IACS). Primary health care medical record data with linkage to hospital and pharmacy data are available for 2010 and 2011 and currently cover the 1,300,000 population of Aragon, which represents 3% of the Spanish population (Instituto Aragonés de Estadística, 2013). Administrative and clinical information from primary care health centres, administrative and clinical information from specialty clinics, emergency department diagnoses and care, hospital procedures and discharge diagnoses, and pharmacy prescription data are available. The data availability lag time is 1 year.

Ethics committee approval is needed to handle data from the IACS.

No studies evaluating the risk of anaphylaxis or hypersensitivity reactions performed using the IACS databases were identified through the literature search or reported by the researchers at the IACS.

### *4.2.8 SIDIAP, Information System for the Development of Primary Care Research, Spain*

SIDIAP (Information System for the Development of Primary Care Research) is a primary care database established by the Institute of Primary Care Research and the Catalan Institute of Health in 2010. It covers 5.8 million Catalonian residents (80% of the population in Catalonia) from 274 primary care centres in Catalonia. Visits are recorded

into electronic medical records. Information has been recorded in the database since 1998; in 2005, the use of this electronic medical record system was mandated for all visits within the health care system. It contains information from the primary care computerized clinical records software used by the Catalan Institute of Health (eCAP) and other complementary sources such as laboratory results, pharmacy invoices, hospital discharge data on inpatient care, and other possible sources depending on the aim of the study. (Bolibar et al., 2012).

No studies evaluating the risk of anaphylaxis or hypersensitivity reactions performed using the SIDIAP database were identified through the literature search or SIDIAP researchers.

### 4.2.9 Swedish National Health Databases, Sweden

Sweden, a Nordic country with a population of 9.5 million inhabitants in 2013 (Eurostat, 2014), has a tax-supported health care system that provides universal health coverage to all Swedish residents. All citizens have unrestricted access to health services, including partial or complete reimbursement of purchased medicines. Health care coverage includes visits to general practitioners and specialists, hospital admissions, and outpatient visits. The National Board of Health and Welfare is responsible for a number of health data registers including the Swedish Prescribed Drug Register, which contains information on all prescription medicines dispensed at pharmacies since 2005 to individuals receiving ambulatory care (Wettermark et al., 2007). The unique personal identification number allows for the possibility of linking data collected in all Swedish registries containing civil registration numbers. Data collected in these registries can be made available for research purposes.

The Swedish National Patient Register contains data on hospital inpatient and outpatient diagnosis codes recorded as ICD-10 codes and procedure codes. Drugs administered in the hospital can be recorded in the register as a procedure code together with the ATC code for the drug. However, the Swedish investigator reports that there is limited experience on assessing the availability of data on drug treatments in the Swedish National Patient Register.

Regarding prior research on anaphylaxis, the Swedish researcher referred to results of the same ongoing Nordic study provided by the Danish researchers (see details under Denmark).

### 4.2.10 Clinical Practice Research Datalink, United Kingdom

The Clinical Practice Research Datalink (CPRD) contains anonymised diagnostic and prescribing information recorded by GPs as part of their routine clinical practice in the UK. The database coverage is approximately 5 million active patients (between 4% to 7% of the UK population, depending on calendar year) and over 13 million active and

inactive patients. These data are linkable, at least partially, with other health care data sets (e.g., hospitalisation records, national mortality data, cancer registry data) via the patient's National Health Service (NHS) number, sex, date of birth, and postal code. Approximately 65% of the English practices contributing to the CPRD have consented to have their patient information linked to other health care data sets. Approximately 75% of English practices contributing to the CPRD are linked individually and anonymously to Hospital Episode Statistics, England's national statistical data warehouse for care provided by NHS hospitals (Gallagher et al., 2011; Van Staa et al., 2011). This linkage represents about 50% of patients in the CPRD from all regions in the UK.

Detailed information on prescriptions written by GPs, including prescribed dose and duration, is automatically recorded in the database. Read codes are used to record diagnoses. Additional diagnostic and treatment information can be found in free-text fields, letters from specialists and hospitals, and other sources. Identifying patients who have both CPRD and Hospital Episode Statistics (HES) data enables access to the hospitalisation data, including diagnosis and procedural coding. However, data on drugs prescribed/administered in the hospital setting are not available.

The CPRD group has obtained ethical approval from a Multi-centre Research Ethics Committee (MREC) for all observational research using CPRD data without patient involvement. Study protocols need to be submitted to and approved by the CPRD's Independent Scientific Advisory Committee (ISAC). ISAC is responsible for reviewing protocols for scientific quality, but may recommend that study-specific MREC approval be sought if ethical issues arise in relation to an individual study.

#### 4.2.10.1 Prior Research on Hypersensitivity Reactions

One study using data from the General Practice Research Database (forerunner to the CPRD, which was established in 2012) evaluated the incidence, associated cause, and severity of anaphylaxis and validated the endpoint (Peng and Jick, 2004). The estimated crude incidence of anaphylaxis, based on 675 cases, was 8.4 per 100,000 person-years in people aged 80 years and younger during the period from 1994 to 1999. Anaphylaxis events were ascertained using a list of general and exposure-related anaphylaxis OXMIS (Oxford Medical Information System) codes (e.g., anaphylactic shock or reaction, medication causing an anaphylactic shock, anaphylactic reaction to bite/insect sting, anaphylactic reaction to medicine or drug) or anaphylaxis noted in the comments field. Anaphylaxis related to medicines was estimated to represent 30% of all anaphylaxis cases, with penicillin and non-steroidal anti-inflammatory drugs being the main causes of medicine-related anaphylaxis. The study highlighted the potential underrecording of anaphylaxis events in computerised GPs medical records that do not capture events occurring in the hospital setting and estimated that 65% to 70% of patients were either hospitalised or seen in the emergency department.

Endpoint validation was performed for a random sample of 120 cases by enquiry to the GP for further details and to ascertain severity of the anaphylaxis, which resulted in

confirmation of 73% of cases. A record of history of anaphylaxis was the most common reason for exclusion of cases initially identified.

## 4.3 Intravenous Iron Use

Researchers from the 10 candidate data sources contacted in nine European countries contributed information for this feasibility evaluation and provided data on the use of targeted IV iron-containing products in each country. As expected, the use of IV iron compounds in data sources that are primarily based on primary health care/general practice and/or non-hospital ambulatory data, is either not captured or minimally captured. This is linked to the predominant administration of IV iron treatments in in-hospital and/or specialised outpatient treatment settings. Furthermore, year of drug approval and reimbursement decisions are key factors that directly influence capture and availability of data on IV iron use in European health care data sources.

### *4.3.1 Data Sources With Minimal or No Capture of Intravenous Iron Use*

In the Spanish databases (IACS and SIDIAP), which contain data mainly from primary care settings, IV iron is not recorded because these products are approved only for in-hospital use in the regions covered by the databases. In the CPRD in the UK, the use of IV iron is minimally captured, indicating that these products are primarily prescribed by specialists and not by GPs, and only the minimal number of repeat prescriptions by GPs are available. In the UK, capture of use of drugs from care settings other than primary care is not possible through the CPRD system. In Finland, the National Prescription Register does not capture data on IV iron use because products are administered in the hospital. Inpatient use of IV iron and possibly dose information can be available only through the regional Helsinki database, which covers 20% of the Finnish population. Access to patient counts from the Helsinki regional registry is not possible without submitting a request for data access and gaining approval. In Italy, minimal capture of IV iron use (referring to Ferlixit vials) was found through a search of the prescription database of the FVG region. Intravenous iron use is captured in the three hospital-based DTMs in the FVG. Product-specific type, dose, and duration of treatment is recorded. Table 1 summarises results of the feasibility assessment of IV iron use from these data sources.

**Table 1. Data Sources With No or Minimal Capture of Intravenous Iron Use**

| IV Iron Use | Finnish Health Databases | Italy, Friuli Venezia Giulia Databases | Spain, IACS | Spain, SIDIAP | UK, CPRD |
|---|---|---|---|---|---|
| Data availability on prescrip-tions/ dispensing | None in National Prescription Register<br>Possible only through regional databases (Helsinki 20% total population) | ▪ Minimal in FVG health databases<br>▪ Patient-level data through records kept by DTMs in the region (10 total) in paper form and EMR | Not captured<br>Hospital only use | Not captured<br>Hospital only use | Minimal |
| Population[a] | — | 1.2 million | — | — | 13 million |
| Cumulative annual counts of unique patients (time period) | — | ▪ 18 in FVG database (2001-2013)<br>▪ 295 in 5 DTMs (2013) | — | — | 4,000 prescription events (entire database period) |
| Compound breakdowns | — | ▪ In FVG, all use was for Ferlixit vials (first prescription in 2007) | — | — | — |

CPRD = Clinical Practice Research Datalink (UK); DTMs = outpatient transfusion departments (Italy); EMR = electronic medical record; FVG = Friuli Venezia Giulia region of Italy; IACS = Aragón Health Sciences Institute; IV = intravenous; SIDIAP = Information System for the Development of Primary Care Research (Spain); UK = United Kingdom.

[a] Population is provided only for populations where data on IV iron use were available.

### 4.3.2 Data Sources Capturing Intravenous Iron Use

In the other five data sources explored (Danish health databases, EGB in France, GePaRD in Germany, PHARMO in the Netherlands, and Swedish health registers), the preliminary numbers of users of IV iron compounds indicate that use of IV iron compounds is at least partially captured. In the following sections, we provide details on the available sources and product-specific user counts for some of the targeted IV iron compounds (see Appendix D for country-specific compounds of interest). Overall, the data indicate that approximately 140,000 mostly non-unique users of IV iron compounds are captured in these databases. None of the data sources provide data for all the IV iron compounds of interest to the European Referral. Table 2 provides the product-specific breakdowns, the time periods for the estimates, and the overall estimates.

**Table 2. Data Sources Capturing Patients With More Than Minimal Capture of Prescription/Dispensing of Intravenous Iron**

| Data Source | | Iron Sucrose Complex | | | Ferric Carboxymaltose (Ferinject) | Iron(III) Hydroxide Dextran Complex (CosmoFer/ Ferrisat) | Iron(III) Isomaltoside Complex (Monofer) | Sodium Ferric Gluconate Complex (Ferrlecit) | Number of Users With at Least One Prescription During a Given Year |
|---|---|---|---|---|---|---|---|---|---|
| | | Venofer/ Fer Mylan | FerMed/ FerActavis | Saccharated Iron Oxide | | | | | |
| Denmark, DNPR and EMR Central Region | Patient counts | 470 | — | — | 614 | 2[a] | 356 | — | 1,442 |
| | Year 2013 (data available since 2010) | —2013 | — | | 2013 | 2013 | 2013 | — | |
| France, EGB | Patient counts | 410/104 | 29 | | 784 | 30[a] | | | 1,357[b] |
| | Period (partial data available since 2003) | 2008-2013 | 2012-2013 | | 2011-2013 | 2009-2013 | | | |
| Germany, GePaRD,[c] | Patient counts | 1,644 | 76 | — | 598 | 482 | — | 8,224 | 6,645 |
| | Period | 2004-2010 | 2009-2010 | — | 2007-2010 | 2004-2010 | — | 2004-2010 | |
| Germany, GePaRD,[d] | Patient counts | — | 5,297 | — | 21,360 | — | — | 49,616 | 76,273[b] |
| | Period (data available since 2004) | — | 2010-2011 | — | 2010-2012 | — | — | 2010-2012 | |
| The Netherlands, PHARMO,[e] | Patient counts | 3,863 | — | 12 | 1,432 | 3,164[a] | 172 | — | 8,643[b] |
| | Period (all available data) | 1998-2013 | — | 2012-2013 | 2009-2013 | 2002-2013 | 2011-2013 | — | |
| Sweden, Swedish Prescribed Drug Register[f] | Patient counts | 35,651 | — | — | 18,014 | 2,769 | — | — | 56,434[b] |
| | Period (all available data) | 2006-2013 | — | — | 2008-2013 | 2006-2013 | — | — | |
| Total | Patient counts | | | | | | | | 144,149[g] |

DNPR = Danish National Patient Registry; EGB = General Sample of Beneficiaries (France); EMR = electronic medical record; GePaRD = German Pharmacoepidemiology Research Database; PHARMO = PHARMO Institute for Drug Endpoints Research (the Netherlands).

[a] May include intramuscular use.

[b] This number is not the sum of patients in each year since some patients may have received prescriptions in more than 1 year.

[c] From the cohort of cancer patients treated with epoetin.

[d] Estimates derived from mean defined daily doses per compound from the cancer cohort and estimates of country-specific defined daily doses in annual reports (Schwabe and Paffrath, 2011; Schwabe and Paffrath, 2012; Schwabe and Paffrath, 2013).

[e] Intravenous iron dispensing from inpatient, outpatient, and general practitioner prescriptions.

[f] Data from ambulatory prescriptions.

[g] Total number of users excluding the number in the German cancer cohort. This is a cumulative number and does not refer to unique patients because some patients may be counted in multiple years.

#### 4.3.2.1 Danish Health Databases, Denmark

In Denmark, aggregate statistics for 2002 through 2013 obtained from www.medstat.dk (based on sales volume) showed that approximately 1.2% of DDDs of parenteral iron preparations were sold through outpatient pharmacies, indicating that IV iron treatments are administered primarily in hospital settings. All targeted compounds of interest have been marketed in Denmark with the exception of Jerndextran (Pharmacosmos). Route of administration is not available; however, with the exception of CosmoFer, all parenteral iron preparations must be administered intravenously.

Data on IV iron use from the Central Denmark Region EMR database and the DNPR were obtained. Compound-specific data on parenteral iron users from the EMR database in 2013 are presented in Table 3. In addition, data from either the DNPR or the EMR database for the year 2013 were also provided. There were 1,571 ever-users of an IV iron preparation in a hospital of the Central Denmark Region according to either the DNPR or the EMR database. Of the 1,571 ever-users, 1,442 (92%) users and a total of 6,684 treatment events were captured by both the EMR database and the DNPR, including 1,099 (70%) ever-users captured by the EMR database alone. Only 343 of the 1,442 (24%) of the users identified by the EMR database were also captured by the DNPR, indicating a substantial underascertainment of users in the DNPR. These data indicate that although the DNPR treatment code had a high PPV, its sensitivity is low. The EMR database has data on medication use for 2010-2014. The Central Denmark Region EMR database can be used to identify treatment, and linkage to the DNPR for identification of diagnostic codes is possible.

**Table 3. Users of Parenteral Iron in the Central Denmark Region, 2013**

| Parenteral Iron Compound | Number of Users | Percentage |
|---|---|---|
| CosmoFer[a] | 2 | 0.1 |
| Ferinject Renapharma | 614 | 42.6 |
| Monofer | 356 | 24.7 |
| Venofer | 354 | 24.5 |
| Venofer 2care4 | 32 | 2.2 |
| Venofer Vifor | 84 | 5.8 |
| **Total** | **1,442[b]** | **100.0** |

Note: Based on data from the electronic medical records of the Central Denmark Region.

[a] May be administered as an intramuscular injection.

[b] This number represents a count of unique users.

#### 4.3.2.2 SNIIRAM Database and EGB, France

In France, there were 1,357 non-unique users of IV iron compounds in the EGB database (covering a population of 700,000 inhabitants) from 2008 through 2013 based on dispensings from community practices. Use of only a few IV iron compounds is captured:

Ferinject represented 58% of the use, followed by Venofer (30%). These data indicate that use of IV iron is primarily administered in hospital settings. However, access to the entire SNIIRAM database (representing 87% of the French population), could mean more than 100,000 patients with IV iron administration. Access is possible via Researchers at the INSERM CIC Bordeaux CIC1401 pharmacoepidemiology research unit with an authorisation process that takes 6 to 12 months before data extraction can occur. The authorisation process takes into account the scientific protocol, as well as regulatory requirement/public health considerations.

#### 4.3.2.3 GePaRD, Germany

Data on IV iron use were obtained from a cohort of 142,911 patients with an inpatient or outpatient diagnosis of cancer (other than non-melanoma skin cancer) recorded in the GePaRD from January 2001 through December 2009. In this cohort, 6,645 patients had an IV iron prescription during the study period or in the available follow-up time. Compound-specific numbers are provided in Table 4. Ferrlecit patient counts represented 75% of all IV iron use in this cohort, followed by Venofer (15%). Data on the compound-specific DDDs per patient in 2010 from this cohort were used for the estimations that follow. However, the prevalence of IV iron use is substantially higher in oncology patients than in the general patient population. Therefore, the numbers below are likely to be an underestimate of potential users.

We estimated that there were 76,273 users of IV iron compounds (i.e., Ferrlecit, Ferinject, and FerMed) with at least one prescription in the GePaRD during 2010 through 2012. This was based on information from the total annual DDDs reported in the Drug Annual Reports for 2011, 2012, and 2013, the fact that the GePaRD covers 25% of the German insured population, and application of the product-specific mean DDDs per patient from the cancer cohort in 2010, which resulted in higher-than-expected DDDs per patient (Table 4). Ferrlecit represented 65% of the use, followed by Ferinject (28%).

**Table 4. Indirect Estimates of Intravenous Iron Use in GePaRD (2010-2012)**

| | Ferrlecit | Ferinject | FerMed | Total |
|---|---|---|---|---|
| Total annual DDDs in Germany[a] | | | | |
| 2010 | 1,105,500 | 279,900 | — | 1,385,400 |
| 2011 | 985,600 | 401,500 | 162,300 | 1,549,400 |
| 2012 | 932,600 | 576,300 | 193,200 | 1,702,100 |
| Estimated annual DDDs in GePaRD[b] | | | | |
| 2010 | 268,479 | 67,976 | — | 336,454 |
| 2011 | 239,360 | 97,507 | 39,416 | 376,283 |
| 2012 | 226,489 | 139,959 | 46,920 | 413,367 |
| Mean DDDs per patient[c] | 15 | 14 | 16 | |
| Estimated number of patients in GePaRD | | | | |
| 2010 | 18,140 | 4,754 | — | 22,894 |
| 2011 | 16,173 | 6,819 | 2,418 | 25,410 |
| 2012 | 15,303 | 9,787 | 2,879 | 27,969 |
| Estimated number of patients in GePaRD (2010-2012) | 49,616 | 21,360 | 5,297 | 76,273[d] |

DDDs = defined daily doses; GePaRD = German Pharmacoepidemiology Research Database

[a] Sources: Schwabe and Paffrath (2011), Schwabe and Paffrath (2012), and Schwabe and Paffrath (2013).. Note that each annual report provides data from the prior year.

[b] Estimated assuming that insured members in the GePaRD represent about 17,000,000 of the total 70,000,000 insured members in Germany (statutory health insurance providers).

[c] Mean DDDs from the cancer patient cohort in 2010. Note that these mean DDDs are substantially higher than those typically recommended for oncology patients.

[d] The cumulative number does not refer to unique patients because some patients may be counted in multiple years.

#### 4.3.2.4 The PHARMO Database Network, the Netherlands

In PHARMO, data on IV iron use were obtained from inpatient and outpatient dispensings and GP prescriptions registered from 1998 through 2013 by searching on the product-specific ATC codes. The following ATC codes were searched: B03AC02, Venofer; B03AC06, CosmoFer; B03AC01, Ferinject; B03AC02, saccharated iron oxide; and B03AC, Monofer. Rienso was launched in 2013; thus, no data are currently available in the databases. In the Netherlands, all these IV iron compounds are dispensed and administered in inpatient settings, with the exception of CosmoFer, which can also be administered in the outpatient setting for intramuscular administration.

A total of 8,643 individuals had at least one IV iron dispensing/prescription during a given year in the period evaluated. This number does not refer to unique patients

because some patients may be counted in multiple years. Venofer had the longest period of information (launch in 1999), and its use accounted for 45% of IV iron use, followed by CosmoFer (37%) (Table 2). CosmoFer is available as intramuscular or IV injection, so the number may include some intramuscular use. Although the route of administration is not available, this might be derived from the dosing information.

#### 4.3.2.5 The Swedish National Health Databases, Sweden

In Sweden, data on number of users of specific IV iron compounds were obtained from the publicly available Swedish Prescribed Drug Register website for 2006 through 2013 (Socialstyrelsen, 2014). The data are based on prescriptions dispensed at pharmacies since 2005 to individuals receiving ambulatory care. Use in inpatient settings and one-time-only drug use are likely not covered by the register.

Annual numbers of patients for three of the IV iron compounds of interest are available and were obtained (see Table 5). A total of 56,434 patients had at least one prescription for one of the three compounds of interest during a given year from 2006 through 2013 in ambulatory settings in Sweden. This number does not refer to unique patients because some patients may be counted in multiple years. The choice of IV iron treatment varies across Swedish counties and is dependent on local treatment recommendations. The observed changes in the annual numbers of IV iron users during the years when data are available reflect the timing of marketing availability of the compounds in Sweden (e.g., Venofer launch in 2002, Cosmofer launch in 2007, Ferinject launch in 2008). Data on Monofer and Rienso are not available.

**Table 5. Annual Number of Patients With at Least One Intravenous Iron Prescription, Sweden (2006-2013)**

| Intravenous Compound/ATC | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2006-2013[a] |
|---|---|---|---|---|---|---|---|---|---|
| Ferinject/B03AC01 | 0 | 0 | 97 | 1,265 | 2,944 | 3,726 | 4,886 | 5,096 | 18,014 |
| Venofer/B03AC02 | 5,638 | 5,659 | 5,397 | 4,953 | 4,263 | 3,730 | 3,223 | 2,788 | 35,651 |
| CosmoFer/ B03AC06 | 2 | 250 | 598 | 497 | 368 | 319 | 292 | 443 | 2,769 |
| Total | 5,640 | 5,909 | 6,092 | 6,715 | 7,575 | 7.775 | 8,401 | 8,327 | 56,434 |

ATC = Anatomical Therapeutic Chemical (classification system).

Source: Socialstyrelsen (2014).

[a] The cumulative number does not refer to unique patients because some patients may be counted in multiple years.

## 4.4 Capture of Hypersensitivity Reactions in Data Sources Where Intravenous Iron Use is Captured

In this section, data on the capture of anaphylaxis/hypersensitivity reactions will focus on the data sources where IV iron use is available. Table 1 summarises information on the sources available for the identification of clinical diagnosis of hypersensitivity reactions, the coding systems used, the number of anaphylaxis/hypersensitivity reaction and information on the potential for endpoint validation. Identification of the endpoint of interest is possible for all data sources through hospital discharge diagnoses coded as ICD-9 or ICD-10 codes.

**Table 6. Capture of Anaphylaxis/Hypersensitivity Reactions in Data Sources With Data on Intravenous Iron-Containing Medications**

| Data Source | Diagnosis Availability; Disease and Procedure Coding | Endpoint Validation; Prior Research on Anaphylaxis | Counts of Codes for Anaphylaxis |
|---|---|---|---|
| Danish databases, Denmark | For patients in the Central Denmark Region EMR database, diagnosis is available from hospital inpatients in the DNPR<br>ICD-10 codes | Validation possible through review of medical records<br>Information from ongoing study[a] in women suggests the following PPVs for ICD-10 codes for inpatient stay or emergency department visit:<br>▪ 14% for all hypersensitivity codes<br>▪ 40% for anaphylactic shock (T886) | Cumulative recording of codes[b] of anaphylaxis/hypersensitivity reactions at any time (before/after prescription) during the patient's entire medical recorded information among 1,442 users of IV iron in the Central Denmark Region EMR database in 2013:<br>▪ 55 (3.8%): any code for anaphylaxis/ hypersensitivity<br>▪ 3 (0.2%): specific anaphylaxis code<br>▪ 48 (3.3%): non-specific anaphylaxis code<br>▪ 9 (0.6%): a drug-triggered anaphylaxis/ hypersensitivity reaction |
| SNIIRAM and EGB, France | Available from hospitalisation data<br>ICD-10 codes | Validation through hospital record review is possible in SNIIRAM.<br>An algorithm could be developed based on hospital codes identified in the records | In EGB, 10,339 patients with at least one hospitalisation with specific and non-specific ICD-10 codes for anaphylaxis/hypersensitivity reactions from 2008 through 2012 recorded as primary or secondary diagnosis on discharge summary. Anaphylaxis-specific codes totalled 398 cases. |
| GePaRD, Germany | Available from hospital and outpatient settings<br>Precise date of diagnosis for outpatients estimated through procedure or drug dispensing codes<br>ICD-10-GM codes | Validation through medical record review not possible due to data protection laws<br>No research conducted on anaphylaxis | Not available (requires approvals/linkages) |

| Data Source | Diagnosis Availability; Disease and Procedure Coding | Endpoint Validation; Prior Research on Anaphylaxis | Counts of Codes for Anaphylaxis |
|---|---|---|---|
| PHARMO, the Netherlands | Available in the PHARMO Hospitalisation Database and Outpatient Pharmacy Database. Less severe reactions might not be captured<br>ICD-9 up to 2010<br>ICD-10 codes from 2010 onwards | No validation studies performed. Prior research conducted for anaphylaxis shock based on inpatient data (incidence 1.9 per 100,000)<br>ICD-9-CM codes<br>Endpoint validation through review of medical records for some subgroups is possible under special circumstances | Number of diagnosis codes entries from hospitalisation database[c]:<br>▪ ICD-9 code 995.0:<br>−2010 = 261[d]<br>−Ever = 2,289[d]<br>▪ ICD-10 codes T78.2 and T88.6:<br>−2010 = 0[d]<br>−2011-2012 = 81[d] |
| Swedish Health Registers, Sweden | Available from the Swedish National Patient Register<br>ICD-10 codes. | Same data from the ongoing study in Denmark, Sweden, and Norway[a]<br>Validation through medical records is possible after ethics approval and approval from the executive directors in each clinic | Not available (requires approvals/linkages) |

DNPR = Danish National Patient Registry; EGB = General Sample of Beneficiaries (Échantillon Généraliste de Bénéficiaires in French); EMR = electronic medical record; GePaRD = German Pharmacoepidemiological Research Database; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; ICD-10-GM = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, German Modification*; ICD-9 = *International Classification of Diseases, 9th Revision*; ICD-9-CM = *International Classification of Diseases, 9th Revision, Clinical Modification*; IV = intravenous; PHARMO = PHARMO Institute for Drug Endpoints Research; PPV = positive predictive value.

[a] Aarhus University Hospital, personal communication, 2014.

[b] Counts of anaphylaxis codes identified without any temporal sequence in relation to IV iron use.

[c] Transition from ICD-9 to ICD-10 codes occurred in 2010 in the PHARMO Database Network.

[d] Primary plus secondary diagnoses added ICD-9 code 995.0, Other anaphylactic shock not elsewhere classified; ICD-10 code T78.2, anaphylactic shock, unspecified; and T88.6, anaphylactic shock owing to adverse event of correct drug or medicament properly administered.

Based on preliminary data for IV iron users (N = 1,442) in the Central Denmark Region EMR database in 2013 linked to the DNPR data, 0.6% of patients had an ICD-10 code for "diagnosis of a drug-triggered anaphylaxis/hypersensitivity reaction" and 3.8% had a code that qualified as "any anaphylaxis" in the DNPR at any time during an individual patient's entire recorded medical information. Therefore, it is important to highlight that these numbers do not include a time interval between exposure to IV iron and recording of the diagnostic code, nor do they intend to reflect an association between the exposure and the recording of the event. Endpoint validation through review of medical records is possible.

In the EGB database in France, specific and non-specific diagnoses of anaphylaxis/ hypersensitivity reactions were identified through ICD-10 codes from 2008 through 2012. There were 10,339 cases with at least one hospitalisation during a given year with a main or associated diagnosis of anaphylaxis/hypersensitivity reaction from primary and secondary hospital discharge summary data. Anaphylaxis-specific codes (T78.2, anaphylaxis shock unspecified; T88.6, anaphylaxis shock owing to adverse event of correct drug or medicament; L27.0, generalized skin eruption due to drug; and Y44.0, adverse effects in therapeutic use, iron preparations and other anti-hypochromic anemia) yielded a total of 398 cases. Indirect validation of diagnostic codes through hospital record review is possible for a subset database and only for some codes. An algorithm could be developed based on hospital codes identified in the records.

In the GePaRD in Germany, data on anaphylaxis/hypersensitivity reactions are available through hospital discharge diagnosis codes and outpatient diagnosis codes or through prescriptions for treatments specific for anaphylaxis/hypersensitivity reactions. Endpoint validation through review of records is not possible due to data protection regulations. Therefore, only indirect validation approaches could be implemented. These would be based on the clinical review of patient profiles (regarding treatment, diagnostic procedures, endpoints) and comparison with literature-based incidence rates and/or data from cohort studies.

PHARMO researchers in the Netherlands, provided yearly counts for 2010 and for the entire period covered in the database for ICD-9 and ICD-10 codes related to anaphylaxis/hypersensitivity reactions and identified by a search of primary and secondary discharge diagnoses in PHARMO data. Secondary hospital discharge diagnoses are either diagnoses that occurred during the admission or prevalent diagnoses that were relevant for the admission, such as a comorbidity. In 2010, transition of coding from ICD-9 to ICD-10 occurred in PHARMO. Consequently, counts for ICD-10 codes are linked to hospital data in 2011 and 2012 (current end of data in the Hospitalisation Database). There were 2,289 counts of primary and secondary anaphylaxis-specific diagnoses (ICD-9 code 995.0, other anaphylactic shock not elsewhere classified) in the entire database and 261 in 2010. There were 81 diagnoses for the ICD-10 codes T78.2, anaphylactic shock, unspecified, and T88.6, anaphylactic shock owing to adverse event

of correct drug or medicament properly administered, for the years 2011 and 2012. Endpoint validation through review of medical records is possible for some subgroups under special circumstances.

In Sweden, anaphylaxis/hypersensitivity reactions are recorded in the Swedish National Patient Register using ICD-10 codes, and linkage of data with other registers is feasible. No data on cases with the endpoint of interest among users of IV iron products were provided, as this requires data linkages and approvals. Endpoint validation through medical records is possible after regional ethics approval and approval from the executive directors in each clinic.

# 5 CONCLUSIONS

- As expected, there are important challenges for the evaluation of hypersensitivity reactions linked to the administration of IV iron-containing treatments, including study size, data source coverage, exposure capture, and endpoint identification and validation.
- European data sources that are primarily based on primary health care/general practice and/or non-hospital ambulatory data either do not capture or minimally capture IV iron use. This is linked to the predominant administration of IV iron treatments in hospitals or specialised outpatient treatment settings. This rules out conducting a PASS in Finland, Italy, Spain, and UK.
- Data for all IV iron compounds of interest are not captured by any of the data sources. Data are available for a few compounds, reflecting differences in regulatory status and medical practice in the countries investigated.
- Five European data sources capture use of IV iron compounds and data on the endpoint of interest.
  - In Denmark, data on IV iron use and clinical diagnoses of anaphylaxis/ hypersensitivity reactions are available in the DNPR and the Central Denmark Region EMR database and can be accessed for a potential PASS. The Central Denmark Region EMR database has 1,442 unique patients treated in 2013 with a medication of interest, and data on medication use are available for the years 2010-2014, which could increase the numbers by 2- to 3-fold, depending on chronic use of medications and indication mix. While there is potential for source record validation, the expected number of outcomes will be very low, which will limit the precision of the estimates.
  - In France, data on IV iron use from community pharmacies and clinical diagnoses of anaphylaxis/hypersensitivity reactions are available in the EGB database, which is a sample of the SNIIRAM database. Data on inpatient IV iron use are not captured. Although the number of IV iron users is limited in this database, with 1,357 non-unique patients from 2008 through 2013, the possibility of accessing the entire SNIIRAM database, representing 87% of the French population, is of interest as the total number of treated patients could

be over 100,000. Only indirect validation of hypersensitivity reaction codes through source medical record review is possible for a subset database and for only some of the codes.

- In Germany, the GePaRD captures data on all dispensed IV iron drugs prescribed in ambulatory settings. The estimated number of non-unique users with at least one prescription during a given year from 2010 through 2012 (N = 76,273) suggests that the size of the population of IV iron users for the entire period of data available in GePaRD (since 2004) may be among the largest in Europe for a potential PASS since data from more years are available. However, these estimates are based on a cohort of cancer patients and assumptions regarding DDDs. Endpoint validation through review of medical records will not be possible due to data protection regulations; therefore, only indirect endpoint validation approaches, with their inherent limitations, are possible.
- In the Netherlands, the PHARMO database captures data on IV iron compounds dispensed in the inpatient and outpatient settings and prescribed by GPs (for a subpopulation). Available data showed 8,643 non-unique patients with at least one dispensing/prescription of an IV iron compound from 1998 through 2013. Data on the endpoint of interest are available through hospital discharge diagnoses. Endpoint validation through review of medical records for some subgroups is possible under special circumstances.
- In Sweden since 2005, the Swedish Prescribed Drug Register captures data on prescriptions dispensed at pharmacies to individuals receiving ambulatory care. Publicly available data from this register showed 56,434 non-unique patients with at least one prescription of an IV iron compound from 2006 through 2013. Data on the endpoint of interest (anaphylaxis/hypersensitivity reactions) are recorded in the National Patient Register in ICD-10 codes, and linkage of data with other registers is feasible. Endpoint validation through review of medical records would be possible for selected projects deemed to be in the interest of public health.

Drug-induced hypersensitivity/anaphylactic reactions are rare events. In summary, five European data sources provide partial capture of IV iron use. There are important numbers of treated patients in the ambulatory setting in France, Germany, and Sweden. However, the number of patients in the context of the low frequency of severe hypersensitivity reactions will result in imprecise rate estimates. Furthermore, the potential to validate the diagnosis of hypersensitivity reactions through source record review is limited to the Central Denmark Region, which has the lowest number of patients, or subpopulations in the Netherlands and Sweden, but with complex approvals only for selected projects. Endpoint validation through source record review cannot be conducted in Germany or France, the countries with the largest number of treated patients captured in databases. Case ascertainment using only an algorithm or electronic profile review would be the only approach that could be conducted across all data sources. This indirect validation approach will have some limitations. Therefore, a PASS,

as originally envisioned covering all IV iron compounds used in Europe with source record validation of potential cases is not feasible. A study performed based on analyses of available data from data sources that provide partial capture of IV iron use would be highly complex. Some of the data collected could be informative, but relevant limitations will remain regarding the precision and validity of the estimates.

**Table 7. Summary Data on Intravenous Iron Use and Hypersensitivity Reactions in Potential Candidate Databases for a PASS**

| Data Source | Intravenous Iron Use | Anaphylaxis/Hypersensitivity Reactions |
|---|---|---|
| Central Denmark Region EMR database and DNPR, Denmark | Central Denmark Region EMR database population: approximately 1.2 million<br>▪ 1,442 users of IV iron in 2013 for Venofer, Monofer, Ferinject, and Cosmofer<br>Data available from 2010 through 2014, so a larger number of IV iron users could be obtained, potentially increasing the total by 2- or 3-fold | Identification through hospital discharge diagnoses in the DNPR linked with Central Denmark Region EMR database<br>Endpoint validation through medical record review is possible |
| EGB and SNIIRAM, France | EGB database population: 700,000<br>▪ 1,357 users of IV iron compounds from 1998 through 2013 for Fer Mylan, Ferrisat, FerActavis, Ferinject, and Venofer, based on dispensings from community pharmacies<br>Access to the entire SNIIRAM database (87% of total French population for a 3-year period) is possible after authorization and approvals; potentially over 100,000 patients | Identification through hospital discharge diagnoses. |
| GePaRD, Germany | The GePaRD covers approximately 17 million insured people<br>Indirectly derived estimates of IV iron users for Ferrlecit, Ferinject, and Fermed from 2010 through 2012: 76, 273 non-unique patients<br>Data are available from 2004 onwards, so the total number of IV iron users would be larger, well over 100,000 patients | Identification through hospital discharge codes and outpatient diagnoses.<br>Endpoint validation through medical record review is not possible |
| PHARMO, Netherlands | Drug use from inpatient and outpatient dispensings and GP prescriptions<br>Total number of IV iron users for Venofer, Cosmofer, Ferinject, Saccharated iron oxide, and Monofer from 1998 through 2013 was 8,643 non-unique users, which would be the cohort of IV iron users available for a PASS | Identification through hospital discharge diagnoses<br>Endpoint validation through review of medical records for some subgroups is possible under special circumstances |

| Data Source | Intravenous Iron Use | Anaphylaxis/Hypersensitivity Reactions |
|---|---|---|
| Prescribed Drug Register and National Patient Register, Sweden | Over 56,000 IV iron users for Venofer, Cosmofer, and Ferinject, captured in the Swedish Prescribed Drug Register from 2006 through 2013. This number does not refer to unique patients, so the actual number would be lower. | Identification through hospital discharge diagnoses in the National Patient Register.<br>Endpoint validation through review of medical records is possible after ethics approval and approval from executive directors of the clinics responsible for the records. |

DNPR = Danish National Patient Register; EGB = General Sample of Beneficiaries (France); EMR = electronic medical record; GePaRD = German Pharmacoepidemiological Research Database; GP = general practitioner; IV = intravenous; PASS = postauthorisation safety study; PHARMO = PHARMO Institute for Drug Outcomes Research (the Netherlands); SNIIRAM = French National Information System Inter Plans Health Insurance (France).

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# Appendix A: Literature Search Strategy

## Table A-1. PubMed Search Terms

| Search Number | Search Terms |
|---|---|
| Condition | |
| #1 | "Drug Hypersensitivity"[Mesh] OR "Anaphylaxis"[Mesh] OR "Hypersensitivity, Immediate"[Mesh] OR "Drug Hypersensitivity/Diagnosis"[Mesh:NoExp] OR "Severe Drug-Induced Hypersensitivity"[Text Word] OR "Anaphylactic Reaction"[Text Word] OR "Severe Hypersensitivity Reaction"[Text Word] OR "Anaphylaxis"[Text Word] OR "Hypersensitivity"[Text Word] OR "Hypersensitivity, Type I"[Text Word] OR "Type I Hypersensitivity"[Text Word] OR "Severe allergic reactions"[Text Word] – 290,231 |
| Descriptive epidemiology | |
| #2 | "Validation"[Title] OR "Sensitivity and Specificity"[Mesh] OR "Medical Records Systems, Computerized"[Mesh] OR "Validation Studies as Topic"[Mesh] OR "Validity"[Text Word] OR "Validation"[Text Word] OR "International Classification of Diseases"[Mesh] OR "ICD Codes"[Title/Abstract] OR "Positive predictive value"[Text Word] OR "Predictive Value"[Text Word] OR "PPV"[Text Word] OR "ICD-9-CM 995.0"[Text Word] OR "ICD-9-CM 995.2"[Text Word] OR "ICD-9-CM 995.27"[Text Word] OR "Algorithm"[Text Word] OR "Clinical Practice Research Datalink"[Text Word] OR "CPRD"[Title/Abstract] OR "GPRD"[Title/Abstract] OR "GPRD"[Text Word] OR "Swedish Health Registers"[Text Word] OR "Swedish National Patient Register"[Text Word] OR "German Pharmacoepidemiological Research Database"[Title/Abstract] OR "GePaRD"[Text Word] OR "Danish National Patient Registry"[Text Word] OR "PHARMO database"[Text Word] OR "PHARMO"[Title/Abstract] OR "PHARMO"[Text Word] OR "French Health Insurance Database"[Text Word] OR "SNIIRAM"[Text Word] OR "SNIIRAM"[Title/Abstract] OR "Database"[Text Word] – 875,281 |
| Limits: human subjects, publication date, language, and type of publication | |
| #3 | ("2000/01/01"[PDAT] : "2015/12/31"[PDAT]) NOT ("Comment"[Publication Type] OR "Letter"[Publication Type] OR "Clinical Trial"[Publication Type] OR "Clinical Trials as Topic"[Mesh] OR trial*[Title] OR "Editorial"[Publication Type]) AND English[lang] AND ("Humans"[Mesh] NOT "Animals"[Mesh:NoExp]) - 3,876,174 |
| #4 | #1 AND #2 AND #3 – 4,308 |

# Appendix B: Summary Findings From Published Literature

**Table B-1. Incidence of Anaphylaxis in Population-Based Studies**

| Reference | Setting | Anaphylaxis Definition | Anaphylaxis Incidence Rate (per 100,000 Person-years) |
|---|---|---|---|
| Avillach et al. (2013) | Europe,1996 to 2007, EMRs<br>2 general practice (GP)–based databases:<br>▪ Health Search CSD (Italy)<br>▪ IPCI (the Netherlands)<br>4 record linkage systems:<br>▪ Aarhus (Denmark)<br>▪ Tuscany regional (Italy)<br>▪ Lombardy regional (Italy)<br>▪ PHARMO (the Netherlands) | ▪ ICD-9 codes: 995.0, 995.6, 995.4<br>▪ ICD-10 codes: T78.2, T78.0, T80.5, T88.6<br>▪ ICPC codes: A12004, A92005 | GP-based databases:<br>▪ HSD 5.2<br>▪ IPCI 7.9<br>Using primary discharge diagnosis:<br>▪ Aarhus 5.7<br>▪ Tuscany 12.0<br>▪ Lombardy 2.2<br>▪ PHARMO 1.9<br>Adding secondary discharge diagnosis:<br>▪ Aarhus 6.4 (+12%)<br>▪ Tuscany 12.7 (+6%)<br>▪ Lombardy 2.8 (+27%)<br>▪ PHARMO 2.4 (+26%)<br>Adding death registries:<br>▪ Aarhus 6.4% (+0%)<br>▪ Tuscany 12.8 (+0%) |
| Gibbison et al. (2012) | UK, all critical care units, EMRs, 2005-2009 | Anaphylaxis if they had "anaphylaxis" coded as either the primary or secondary reason for admission | Incidence of anaphylaxis admissions over total admissions for the year 2009:<br>▪ Adults: 331 of 95,196 (0.3%)<br>▪ Children: 23 of 17,111 (0.1%) |
| Tejedor Alonso et al. (2012) | Spain, Alcorcon region, EMRs from primary care clinics, allergy clinics, ED visits, and hospitalisations, 2004-2005 | NIAID/FAAN criteria | ▪ Crude IR: 103<br>▪ Standardized IR: 112<br>▪ Due to drugs IR: 32 |
| Tejedor Alonso et al. (2011) | Spain, single hospital EMRs, 1999-2005 | NIAID/FAAN criteria | 0.2 per 5,000 admission days |
| Iribarren et al. (2010) | US, EMRs for ambulatory visits, ED visits, hospitalisations (KPNC), 1996-2006 | ICD-9 codes: 995.6, 999.4, 995.0, 708.0, 989.5 and 995.1 | 109 among patients with asthma, 19.9 among patients without asthma |

| Reference | Setting | Anaphylaxis Definition | Anaphylaxis Incidence Rate (per 100,000 Person-years) |
|---|---|---|---|
| González-Pérez et al. (2010) | UK, GP database EMRs (THIN), 1996-2005 | ICD-9-CM codes: 995.0, 995.4, 995.6, 693.1, 695.1, 708.0, 708.9, 989.5, 995.1, and 995.3 | 50.45 among patients with asthma, 21.28 among patients without asthma |
| Harduar-Morano et al. (2010) | US, Florida, ED EMRs, 2005-2006 | ▪ Method I: ICD-9 codes: 995.60-995.69, 995.0<br>▪ Method II: NIAID/FAAN criteria | ▪ Method I: 3.3<br>▪ Method 2: 4.4 |
| Calvani et al. (2008) | Italy, ED and hospital EMR databases, 2000-2003, children aged 0-17 years | ICD-9-CM codes: 995.0, 995.2, 995.3, 995.4, 995.6, 999.4, 708.2, 989.5 | 5.9 cases per 100,000 resident children per year |
| Sheikh et al. (2008) | UK, GP database EMRs (QRESEARCH), 2001-2005 | Read codes for anaphylaxis (list of codes not provided) | 6.7 (2001), 6.6 (2002), 6.8 (2003), 8.5 (2004), 7.9 (2005) |
| Decker et al. (2008) | US, inpatient and outpatient EMRs from all medical providers in Olmsted County, 1990-2000 | ICD-9 codes for at least 1 symptom of generalised mediator release (flushing, pruritus, urticaria, angioedema) and at least 1 gastrointestinal or respiratory or cardiovascular symptom | 49.8<br>IR was higher for children aged 0-9 years (IR, 75.1) and in more recent years—the IR was 58.9 in 2000 and 46.9 in 1990 |
| Poulos et al. (2007) | Australia, EMRs for hospitalisations (AIHW) 1993-1994, and 2004-2005, and mortality (National Mortality Database) 1997-2004 | ▪ ICD-9-CM codes: 995.0, 995.6, and 999.4<br>▪ ICD-10-CM codes: T78.2, T88.6, T78.0, and T80.5 | ▪ 10.8 per 100,000 population during 1 year (2004-2005)<br>▪ 3.7 per 100,000 population during 1 year (1993-1994) |
| Mulla and Simon (2007) | US, Florida, hospital discharge EMRs, 2001 | ICD-9-CM codes: 989.5, 995.0, 995.4, 995.6, E905.0, E905.1, E905.2, E905.4, E905.6, E905.7, and E930.0-E931.0 | 2.8 per 100,000 population during 1 year |
| Johannes et al. (2007) | US, claims for all inpatient and outpatient services, procedures, and outpatient pharmacy dispensings (IRDM), 2000-2004, exposed to antibacterials | ▪ ICD-9 codes: 995.0, 995.2, 995.3<br>▪ CPT code: 92950<br>▪ HCPCS code: J7640 | IR of anaphylaxis (ICD-9 code: 995.0) per 10,000 dispensings of each drug:<br>▪ 0.3 for moxifloxacin and levofloxacin<br>▪ 0.2 for gatifloxacin and cephalosporins<br>▪ 0.1 for ciprofloxacin and penicillin |
| Gupta et al. (2007) | UK, hospital admissions EMRs (HES) 1990-1991 and 2003-2004 | ICD-10 codes: T78.0, T78.2, T80.5, T88.6 | 3.6 |

| Reference | Setting | Anaphylaxis Definition | Anaphylaxis Incidence Rate (per 100,000 Person-years) |
|---|---|---|---|
| Braganza et al. (2006) | Australia, ED EMRs, children aged < 16 years, 1998-2001 | Multisystem involvement with respiratory and cardiovascular features and/or neurological dysfunction with or without features of generalised allergic reaction (confined to cutaneous and/or gastrointestinal symptoms) | 100 (1 in 1,000) |
| Gupta et al. (2004) | UK hospital and ED EMRs (HES), 2000-2001 | ICD for anaphylactic shock; ICD-9 codes: 995.0, 999.4, and ICD-10 codes: T78.0, T78.2, T80.5, T88.5 | 3.8 per 100,000 population during 1 year |
| Helbling et al. (2004) | Switzerland, allergy clinic EMRs, 1996-1998 | Confirmed cases of anaphylaxis based on history, symptoms and signs consistent with a mast cell release, and allergy testing | 8.9 (range, 7.9 to 9.6) |
| Bohlke et al. (2004) | US, hospital, ED, and outpatient EMRs (GHC HMO), aged < 18 years, 1991-1997 | ICD-9 codes: 995.0, 995.6, 999.4, 995.4, 989.5, 708.0, 708.9, 995.1, 995.3, 695.1 | 10.5 (68.4 if non-specific codes for anaphylaxis were included) |
| Peng and Jick (2004) | UK, GP database EMRs (GPRD) 1994-1999 | OXMIS codes: 9779AK, 9779AR, 9894HA, 9894HB, 9894HN, 9899AN, 9994, 9994CC, 9994MN, 9994RM | 8.4 |
| Brown et al. (2001) | Australia, ED EMRs, 1998-1999, adults and children aged > 12 years | ICD-9-CM codes: 995.3, 477.8, 999.4, 995.1, 995.2, 995.0, 977.9, 277.6, 708.9, 708.0, 693.1, 477.9, 999.5, 989.5, 708.8, 708.8, 708.1 | 228 (1 per 439 ED cases per year)<br>2.94 (1 per 3,400 people per year) |
| Sheikh and Alves (2001) | UK, ED admission EMRs (HES), 1991-1995 | ICD-9 codes: 995.0, 999.4 | Average, 17 per 100,000 emergency admissions over 4 years |
| Sheikh and Alves (2000) | UK, hospital discharge EMRs (HES), 1991-1995 | ICD-9 codes: 995.0, 999.4 | 10.2 per 100,000 hospital discharges in 1994-1995, and 5.6 in 1991-1992.<br>Incidence rate: 2,424 per 32,400,000 (0.007%) |
| Yocum et al. (1999) | US, Olmsted County, outpatient and inpatient EMRs, 1983-1987 | 1 symptom of generalised mediator release AND at least 1 symptom involving the oral, gastrointestinal, respiratory, or cardiovascular system | 21 (95% CI, 17-25)<br>Occurrence rate: 30 (95% CI, 25-35) |

| Reference | Setting | Anaphylaxis Definition | Anaphylaxis Incidence Rate (per 100,000 Person-years) |
|---|---|---|---|
| Klein and Yocum (1995) | US Rochester, ED EMRs, May-Aug 1993 | Acute mucocutaneous signs plus at least one respiratory or cardiovascular or gastrointestinal symptom | 90 |

AIHW = Australian Institute of Health and Welfare; CI = confidence interval; ED = emergency department; EMR = electronic medical records; FAAN = Food Allergy and Anaphylaxis Network; GHC = Group Health Cooperative; GP = general practitioner; GPRD = General Practice Research Database (forerunner of the CPRD); HES = Hospital Episode Statistics; HMO = health maintenance organisation; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision;* ICD-9 = *International Classification of Diseases, 9th Revision*; ICPC = International Classification of Primary Care; IPCI = Integrated Primary Care Information database (the Netherlands); IR = incidence rate; IRDM = Ingenix Research Data Mart; KPNC = Kaiser Permanente of Northern California; NIAID = National Institute of Allergy and Infectious Disease; OXMIS = Oxford Medical Information Systems; PHARMO = PHARMO Institute for Drug Outcomes Research (the Netherlands); THIN = The Health Improvement Network; UK = United Kingdom; US = United States.

NIAID/FAAN criteria: signs and symptoms that were considered positive for meeting various organ-system components of the criteria: (1) involvement of skin-mucosal tissue, (2) respiratory compromise, (3) reduced blood pressure or associated symptoms, (4) persistent gastrointestinal symptoms (Sampson et al., 2006).

ICD-9 codes: "Specific anaphylaxis codes": 995.0, Other anaphylactic shock not elsewhere classified; 995.4, Shock due to anesthesia not elsewhere classified; 995.6, Anaphylactic shock due to adverse food reaction; 999.4, Anaphylactic shock due to serum not elsewhere classified. Other codes: "non-specific for anaphylaxis" or "allergy" codes or codes used to identify triggers: 995.1, Angioneurotic edema not elsewhere classified; 995.2, Unspecified adverse effect of drug medicinal and biological substance not elsewhere classified; 995.3, Allergy unspecified not elsewhere classified; 693.0, Dermatitis due to drugs and medicines substances taken internally; 693.1, Dermatitis due to food taken internally; 988, Toxic effect of noxious substances eaten as food; 785.50, Shock unspecified; 785.52, Septic shock; 989.5, Toxic effect of venom; 708.0, Allergic urticaria; 708.9, Unspecified urticaria; 695.1, Erythema multiforme; 960-969, Poisoning by drugs; E905.XX, Venomous animals and plants as the cause of poisoning and toxic reactions; E930.XX, Antibiotics causing adverse effects in therapeutic use; E931.XX, Other anti-infective causing adverse effects in therapeutic use; E930-E949, Drugs causing adverse events in therapeutic use; E850-858.9, Accidental poisoning by drugs; E950.0-E950.9, Self-injected injury; E980-980.5, Poisoning undetermined.

ICD-10-CM codes: T78.0, Anaphylactic shock due to adverse food reaction;T78.2, Anaphylactic shock; unspecified; T80.5, Anaphylaxis due to serum; T88.6, Anaphylactic shock due to adverse effect of correctly administered medication; T50.9, overdose or wrong substance given; T63.2, scorpion sting; T63.4, insect sting; T63.6, marine animal sting; T63.9, sting.

Oxford Medical Information System (OXMIS) Codes: 9779AK, Medication causing anaphylactic shock; 9779AR, Anaphylactic reaction to medicine or drug; 9894HA Bite(s), animal anaphylactic reaction; 9894HB, Allergy bee sting (anaphylactic); 9894HN, Anaphylactic reaction to bite; 9899AN, Anaphylactic reaction to non-medicinal agent; 9994, Anaphylactic shock or reaction; 9994CC, Anaphylactic reaction to vaccination; 9994MN, Anaphylactic reaction to immunisation; 9994RM, Allergy serum (anaphylactic).

ICPC codes: A12004 and A92005 anaphylactic shock.

**Table B-2. Published Studies on Validation of Anaphylaxis**

| Reference | Setting | Anaphylaxis Definition | Positive Predictive Value |
|---|---|---|---|
| Campbell et al. (2012) | US, ED EMRs, Apr-Oct 2008 | NIAID/FAAN criteria | 68.6% |
| Iribarren et al. (2010) | US, EMRs for ambulatory visits, ED visits, hospitalisations (KPNC), 1996-2006 | ICD-9 codes: 995.6, 999.4, 995.0, 708.0, 989.5 and 995.1 | PPV for ICD-9 code 995.0: 52% (57 of 109) |
| Erlewyn-Lajeunesse et al. (2010) | UK, ED EMRs, 2005-2006, aged < 18 years | ▪ Brighton Collaboration criteria<br>▪ NIAID/FAAN criteria | ▪ Brighton: 68.1%<br>▪ NIAID/FAAN: 61.7% |
| González-Pérez et al. (2010) | UK, GP database EMRs (THIN), 1996-2005 | ICD-9 codes: 995.0, 995.4, 995.6, 693.1, 695.1, 708.0, 708.9, 989.5, 995.1, and 995.3 | ▪ 72% (444 of 609)<br>▪ PPV for codes 995.0 + 995.4 + 995.6: 85.3%<br>▪ PPV for the other codes: 70.2% |
| West et al. (2007) | US, ED claims (SCERHDD), aged < 19 years, 2000-2002 | ▪ Probable anaphylaxis (ICD-9 codes): 995.0 and any drug code (D, E, P).<br>▪ Possible anaphylaxis (ICD-9 codes): 785.5 (except 785.51 and 785.59), or involvement of at least two systems (dermatologic, respiratory, or cardiovascular) and any drug code (D, E, P). Other drug-related allergic reactions: 995.1 and a Drug-E code and at least 1 of the following: allergic reaction or allergy unspecified, another dermatologic code, or a code from the Drug-D group.<br>−Drug-D: 693.0, 995.2<br>−Drug-E: E930-E949<br>−Drug-P: 960-969, E850-E858.9, E950.0- 950.5, E962.0, E980-E980.5 | Probable or possible anaphylaxis: PPV: 32% |
| Johannes et al. (2007) | US, claims for all inpatient and outpatient services, procedures, and outpatient pharmacy dispensings (IRDM), 2000-2004, exposed to antibacterials | ▪ ICD-9 codes: 995.0, 995.2, 995.3<br>▪ CPT code: 92950<br>▪ HCPCS code: J7640 | PPV for code 995.0: 57.1% |

| Reference | Setting | Anaphylaxis Definition | Positive Predictive Value |
|---|---|---|---|
| Bohlke et al. (2004) | US, hospital, ED, and outpatient EMRs (GHC HMO), aged < 18 years, 1991-1997 | ICD-9 codes: 995.0, 995.6, 999.4, 995.4, 989.5, 708.0, 708.9, 995.1, 995.3, 695.1 | PPV for code 995.0: 55.4% (57 of 103) |
| Peng and Jick (2004) | UK, GP database EMRs (GPRD) 1994-1999 | OXMIS codes: 9779AK, 9779AR, 9894HA, 9894HB, 9894HN, 9899AN, 9994, 9994CC, 9994MN, 9994RM | 72.5% (87 of 120) |

CPT = Current Procedural Terminology; ED = emergency department; EMR = electronic medical records; GHC = Group Health Cooperative; GP = general practitioner; GPRD = General Practice Research Database (forerunner of the Clinical Practice Research Datalink); HCPCS = Healthcare Common Procedure Coding System; HMO = health maintenance organisation; ICD = International Classification of Diseases; ICD-9 = International Classification of Diseases, 9th Revision; IRDM = Ingenix Research Data Mart; KPNC = Kaiser Permanente of Northern California; NIAID/FAAN = National Institute of Allergy and Infectious Disease and Food allergy and Anaphylaxis Network; OXMIS = Oxford Medical Information Systems; PPV = positive predictive value; SCERHDD = South Carolina Emergency Room Hospital Discharge Database; THIN = The Health Improvement Network; UK = United Kingdom; US = United States.

NIAID/FAAN criteria: signs and symptoms that were considered positive for meeting various organ-system components of the criteria: (1) involvement of skin-mucosal tissue, (2) respiratory compromise, (3) reduced blood pressure or associated symptoms, (4) persistent gastrointestinal symptoms (Sampson et al., 2006).

Brighton Collaboration criteria: the sudden onset and rapid progression of symptoms involving major and minor dermatological, cardiovascular, or respiratory symptoms (Erlewyn-Lajeunesse et al., 2010).

ICD-9 codes: "Specific anaphylaxis codes"; 995.0, Other anaphylactic shock not elsewhere classified; 995.4, Shock due to anesthesia not elsewhere classified; 995.6, Anaphylactic shock due to adverse food reaction; 999.4, Anaphylactic shock due to serum not elsewhere classified. Other codes: "non-specific for anaphylaxis" or "allergy" codes or codes used to identify triggers: 995.1, Angioneurotic edema not elsewhere classified; 995.2, Unspecified adverse effect of drug medicinal and biological substance not elsewhere classified; 995.3, Allergy unspecified not elsewhere classified; 693.0, Dermatitis due to drugs and medicines substances taken internally; 693.1, Dermatitis due to food taken internally; 988, Toxic effect of noxious substances eaten as food; 785.50, Shock unspecified; 785.52, Septic shock; 989.5, Toxic effect of venom; 708.0, Allergic urticaria; 708.9, Unspecified urticaria; 695.1, Erythema multiforme; 960-969, Poisoning by drugs; E905.XX, Venomous animals and plants as the cause of poisoning and toxic reactions; E930.XX, Antibiotics causing adverse effects in therapeutic use; E931.XX, Other anti-infective causing adverse effects in therapeutic use; E930-E949, Drugs causing adverse events in therapeutic use; E850-858.9, Accidental poisoning by drugs; E950.0-E950.9, Self-injected injury; E980-980.5, Poisoning undetermined.

Oxford Medical Information System (OXMIS) Codes: 9779AK, Medication causing anaphylactic shock; 9779AR, Anaphylactic reaction to medicine or drug; 9894HA Bite(s), animal anaphylactic reaction; 9894HB, Allergy bee sting (anaphylactic); 9894HN, Anaphylactic reaction to bite; 9899AN, Anaphylactic reaction to non-medicinal agent; 9994, Anaphylactic shock or reaction; 9994CC, Anaphylactic reaction to vaccination; 9994MN, Anaphylactic reaction to immunisation; 9994RM, Allergy serum (anaphylactic).

CPT code: 92950, cardiopulmonary resuscitation.

HCPCS code: J7640, adrenaline injection.

# Appendix C: Feasibility Questionnaire for the Evaluation of European Databases for a PASS of Intravenous Iron Use and Hypersensitivity Reactions

RTI(h)(s)™ RTI HEALTH SOLUTIONS®

# MEMO:

**Date:** July 14, 2014

**To:** Candidate database research contact

**From:** Lia Gutiérrez, Susana Perez-Gutthann (RTI-Health Solutions)

**Re:** Feasibility Assessment of PASS IV iron compounds and hypersensitivity reactions

## FEASIBILITY ASSESSMENT OF EUROPEAN DATABASES

Dear XX, we are reaching out to you to request your collaboration in the regulatory driven feasibility evaluation of the use of IV iron compounds and the risk of hypersensitivity reactions. Please find the details following.

Before initiating the work, kindly provide

- the cost associated to the administrative handling and data processing of this request
- the approximate turnaround time for the evaluation response and if different for the data table.

Please do not hesitate to contact me for any clarification on the regulatory, scientific or financial aspects.

Many thanks in advance.

### Background

The benefit risk of iron containing intravenous (IV) medicinal products is under evaluation in the context of the European Medicines Agency (EMA) referral under Article 31 of Directive 2001/83/EC. A consortium of marketing authorisation holder(s) (MAHs) of these compounds is exploring the feasibility of a post authorization safety study (PASS) to estimate the risk of hypersensitivity reactions among users of IV iron compounds to be conducted in several existing population based automated health care databases. There are important challenges including study size, database coverage, exposure capture, and endpoint identification and validation. We have been asked to lead this evaluation. The results will be used in regulatory communications and Consortium decision making.

We are reaching out to you to request your collaboration in this evaluation for exploration of the *"database name"*.

## Targeted IV Iron Compounds (Country)

Table 1 presents information on the iron containing IV products marketed in *Country* that are of interest to the feasibility evaluation in *"database name"*. Information on the MAH, the international non-proprietary name (INN) and brand name of IV iron compounds, launch and reimbursement dates and status of reimbursement are also included. Please note that in Country some of the IV iron compounds of interest have been excluded from reimbursement.

**Table 1. Targeted IV Iron Compounds: *Country***

| Marketing Authorization Holder | INN | Invented Name | Launch Date (MMYY) | Reimbursement Date (MMYY) & Status |
|---|---|---|---|---|
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |

INN = international non-proprietary name; MMYY = month year

## Specific Request

The feasibility evaluation aims at learning how use of IV iron compounds is captured in the databases, obtaining estimations of patient and/prescription counts and how hypersensitivity reactions/anaphylaxis can be captured.

Can you please provide information on the following aspects:

- To which extent can use/dispensing/prescription of each of these medications in different settings (ambulatory, clinics, hospitals) be captured through the databases?
- Is there any impact of reimbursement and setting status that would impact capture?
- Are there special additional linkages, databases, registries that could be used in case that the PASS moves ahead in Country?
- Availability of data on dose and duration of IV iron treatments
- How can hypersensitivity reactions/anaphylaxis be captured. Please see Tables 2 & 3 as orientation.

**Table 2. ICD-9 Codes Used in Health Research Database Studies on Drug-Related Hypersensitivity Reactions**

| ICD-9 codes | Descriptor |
|---|---|
| **"Anaphylaxis-specific codes"** | |
| 995.0 | Other anaphylactic shock not elsewhere classified |
| **Other "non-specific for anaphylaxis" or "allergy" codes, or codes used to identify triggers** | |
| 995.1 | Angioneurotic edema not elsewhere classified |
| 995.2 | Unspecified adverse effect of drug medicinal and biological substance not elsewhere classified |
| 995.3 | Allergy unspecified not elsewhere classified |
| 785.50 | Shock unspecified |
| 708.0 | Allergic urticaria |
| 708.9 | Unspecified urticaria |
| 693.0 | Dermatitis due to drugs and medicines taken internally |
| 695.1 | Erythema multiforme |
| E947.9 | Unspecified drug or medicinal substance causing adverse effects in therapeutic use |

**Table 3. ICD-10 Codes Used in Health Research Database Studies on Drug-Related Hypersensitivity Reactions**

| ICD-10 codes | Descriptor |
|---|---|
| **"Anaphylaxis-specific codes"** | |
| T78.2 | Anaphylactic shock, unspecified |
| T88.6 | Anaphylactic shock owing to adverse effect of correct drug or medicament properly administered |
| **Other "non-specific for anaphylaxis" or "allergy" codes, or codes used to identify triggers** | |
| J38.4 | Edema of larynx |
| L50 | Urticaria |
| T78.3 | Angioneurotic edema |
| T78.4 | Allergy, unspecified |
| T78.8 | Other adverse effects, not elsewhere classified |
| T78.9 | Adverse effect, unspecified |
| T88.7 | Unspecified adverse effect of drug or medicament |
| **SUBTYPES based on trigger** | |
| **Drugs** | |
| L27.0 | Generalized skin eruption due to drugs and medicaments |
| L27.1 | Localized skin eruption due to drugs and medicaments |
| T88.6 | Anaphylactic shock owing to adverse effect of correct drug or medicament properly administered |
| Y40-Y59 | Drugs, medicaments and biological substances causing adverse effects in therapeutic use |
| Y83-Y84 | Surgical and other medical procedures as the cause of abnormal reaction of the patient, or of later complication, without mention of misadventure at the time of the procedure |
| **Or "adverse effects" of iron preparations of blood-affecting constituents** | |
| Y44 | Adverse effects in therapeutic use: agents primarily affecting blood constituents |
| Y44.0 | Adverse effects in therapeutic use: iron preparations and other anti-hypochromic-anaemia preparation |
| Y44.9 | Adverse effects in therapeutic use: other and unspecified agents affecting blood constituents |

- Has previous research on hypersensitivity reactions/anaphylaxis in general population or associated with exposure to drugs been conducted? Can you provide references
- If special sources need to be linked to obtain fuller information on IV iron compounds, do they have a longer availability lag time that the normal prescription data?
- If special sources need to be linked to obtain fuller information on IV iron compounds, do they have special requirements for data access or study approval?
- Frequency counts of ever users (users with at least one prescription/dispensing during a given year and since product launch to latest available period) for all IV iron compounds and per

specific IV iron compound (see Table 4 for the specific data of interest). Please provide data on annual ever users or ever users for the full period, whatever is easier. We understand that not all details may be available. Please let us know if approvals or special permissions need to be requested and timelines before engaging in such requests.

- Please provide any other information, caution, that you feel it is relevant and important for this assessment.

**Table 4. Frequency Counts of Ever Use of Targeted Iron Intravenous Compounds[a] *(COUNTRY)***

| IV Iron Compound (INN/Brand Name) | Time Since Launch | Annual Counts | Full Period Counts |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| **All targeted compounds** | | | |

[a] Based on at least one annual prescription/dispensing.

IV = intravenous; INN = international nonproprietary name.

# Appendix D: Country-Specific IV iron Compounds Targeted in each Database

**Table D-1. Country-Specific Intravenous Iron Compounds and Year of Launch in the Selected European Databases**

| INN/Invented Name | Danish Health Databases | Finnish Health Databases | France, SNIIRAM | Germany, GePaRD | Italy, Friuli-Venezia Giulia Databases | Netherlands, PHARMO database | Spain, IACS | Spain, SIDIAP | Swedish Health Databases | UK, CPRD |
|---|---|---|---|---|---|---|---|---|---|---|
| **Iron(III)-hydroxide dextran complex** | | | | | | | | | | |
| Jerndextran "Pharmacosmos" | NA | — | — | — | — | — | — | — | — | — |
| CosmoFer | Sep 2003 | Jun 2002 | — | Nov 2001 | — | Jan 2002 | Mar 2004 | Mar 2004 | Jan 2007 | Aug 2001 |
| FERRISAT | — | — | Mar 2008 | — | — | — | — | — | — | — |
| **Iron(III)-isomaltoside complex** | | | | | | | | | | |
| Diafer | — | — | — | — | — | — | — | — | — | Feb 2014 |
| Monofer | Jun 2010 | Mar 2011 | — | Oct 2011 | — | Mar 2011 | — | — | Jan 2011 | Aug 2010 |
| Monoferro | — | — | — | — | — | — | Oct 2012 | Oct 2012 | — | — |
| **Iron as ferumoxytol** | | | | | | | | | | |
| Rienso | Sept 2013 | Nov 2013 | — | — | — | Nov 2013 | — | — | Apr 2013 | Nov 2012 |
| **Ferric carboxymaltose** | | | | | | | | | | |
| Ferinject | Dec 2008 | Dec 2008 | Jan 2011 | Nov 2007 | May 2012 | Mar 2009 | Mar 2009 | Mar 2009 | Oct 2008 | May 2008 |
| **Iron sucrose complex** | | | | | | | | | | |
| Venofer | 2002 | 2002 | 1999 | Jun 2005 | 2005 | 1999 | 2001 | 2001 | 2002 | 1999 |
| Ferro Saccarato FME | — | — | — | — | May 2011 | — | — | — | — | — |
| Hierro Sacarosa FME | — | — | — | — | — | — | Feb 2011 | Feb 2011 | — | — |

| INN/Invented Name | Danish Health Databases | Finnish Health Databases | France, SNIIRAM | Germany, GePaRD | Italy, Friuli-Venezia Giulia Databases | Netherlands, PHARMO database | Spain, IACS | Spain, SIDIAP | Swedish Health Databases | UK, CPRD |
|---|---|---|---|---|---|---|---|---|---|---|
| FERIV | — | — | — | — | — | — | Sep 2005 | Sep 2005 | — | — |
| Hierro Sacarosa NORMON | — | — | — | — | — | — | Feb 2009 | Feb 2009 | — | — |
| Ferrologic | March 2011 | — | — | Mar 2011 | — | — | — | — | — | Oct 2010 |
| FerMed | Dec 2009 | — | — | Dec 2009 | — | — | — | — | — | — |
| Venotrix | — | Jan 2010 | — | — | — | — | — | — | — | — |
| IJzerhydroxide sacharose compl | — | — | — | — | — | Nov 2010 | — | — | — | — |
| FER MYLAN | — | — | Jan 2009 | — | — | — | — | — | — | — |
| FER ACTAVIS | — | — | Dec 2010 | — | — | — | — | — | — | — |
| **Iron hydroxide sucrose complex** | | | | | | | | | | |
| FER SANDOZ | — | — | Jan 2011 | — | — | — | — | — | — | — |
| **Iron (III) sucrose complex** | | | | | | | | | | |
| Fer Panpharma | — | — | May 2014 | — | — | — | — | — | — | — |
| **Sodium ferric gluconate complex** | | | | | | | | | | |
| FERLIXIT | — | — | — | — | NA | — | — | — | — | — |
| Ferrlecit 40 mg | — | — | — | 1954 | — | — | — | — | — | — |
| Ferrlecit | — | — | — | 1954 | — | — | — | — | — | — |

— = not launched; CPRD = Clinical Practice Research Datalink; GePaRD = German Pharmacoepidemiological Research Database; IACS = Aragón Health Sciences Institute; INN = international non-proprietary name; NA = not available; PHARMO = PHARMO Institute for Drug Outcomes Research; SIDIAP = Information System for the Development of Primary Care Research, Spain; SNIIRAM = French National Information System Inter Plans Health Insurance; UK = United Kingdom.

## Annex 10A Details of Proposed Additional Risk Minimisation Measures

All EU registered intravenous (IV) iron medicinal products, including Ferinject®, have been evaluated as part of an Article 31 referral procedure (EMEA/H/A-31/1322) by the EMA, whereby the risk of serious allergic reactions with the use of these products was investigated. The CHMP adopted an opinion on 27 June 2013, which was endorsed by the European Commission (EC) on 13 September 2013.

The conclusion of the EMA referral procedure was that the benefit/risk balance of IV iron containing medicinal products remained positive as the benefits continue to outweigh the risks in the treatment of iron deficiency when the oral route is insufficient or poorly tolerated. However, additional risk minimisation measures were requested in order to address the risk of hypersensitivity events to all patients including administration in pregnancy. These measures included the distribution of a Direct Healthcare Professional Communication (DHPC) as well as educational materials for prescribers and patients.

A consortium of Marketing Authorisation Holders (MAH) was formed (including Vifor Pharma, Sanofi, Pharmacosmos, Takeda, Mylan, Fresenius Medical Care, Medice, Alternova, Teva, Rafarm & EMP, Pharmamatch, Actavis (Arrow Generics), Normon, Combino-Pharm and Genfarma) to distribute one single common DHPC. The resulting joint DHPC was approved by National Competent Authorities (NCAs) and distributed to relevant healthcare professionals at the end of 2013 in line with the communicated action plan (refer to Risk Management Plan Version 8.1). More companies joined the consortium subsequently (Panpharma, Acino, Sandoz France).

The educational materials were also a joint effort of the consortium, and, to date (18 February 2015), NCA approval of the translated material has been received in 26 countries, and distribution is completed or ongoing.

Please refer to the tracker in Annex 10B for further details on the educational material distribution per country.

The healthcare professional and patient educational material represent the English language versions on which the translations were based (see Annex 11). Some of the NCAs have made revisions to the translations resulting in deviations from the English language template.

# Annex 10B RMP EM Tracker IV Iron Products Consortium

| Country concerned | Current status (as of 18.02.2015) | Translated EM submitted to NCA for review/approval | EM approved by NCA | Completion date of EM distribution | Mode of shipment | Number of Shipment | Target population | Follow-up requests |
|---|---|---|---|---|---|---|---|---|
| Completion instruction are included on the top of each column. Please use the following format to enter dates : DD.MM.YYYY | | Insert the date when the translated Educational Material (EM) was initially submitted to the NCA for review | Insert the date when NCA communicated the approval of the EM | Insert the date when distribution of EM has been completed | Insert the mode of shipment, e.g. by letter mail or by eMail or... | Insert the number of folders mailed | Insert the specialties, organisations where the EM has been sent | Describe the method(s) how requests for more material will be handled |
| **Austria (AT)** | 25.09.2014 - re-submission of the educational material (EM) to AT Health Authority (HA); AT HA confirmed that review will be done by the week of 29.09.2014<br>07.10.2014 - AT HA approved the texts without revisions<br>01.11.2014 - Vifor to contact AT HA to agree on distribution details<br>02.12.2014 - Vifor validating the distribution list with the AT HA<br>17.12.2014 - distribution start | 28.07.2014 (via Eudralink)<br>25.09.2014 re-submission via e-mail | 07.10.2014 | Mailing on 17.12.2014 | Postal delivery | 1371 - pharmacies including all AT Hospital Pharmacies; 264 - chief physicians of all AT Hospitals; 118 - department heads of university hospitals;<br>28 - Eisencheck centers | Pharmacies including all AT Hospital Pharmacies; chief physicians of all AT Hospitals; department heads of university hospitals, Eisencheck centers | The material has also been published in the public and health care professional (HCP) section on the Vifor Pharma website http://www.viforpharma.at/de/downloads/index.php |
| **Belgium (BE)** | 06.08.2014 - BE HA request (e-mail) to submit via a different pathway<br>26.09.2014 - Vifor BE consultant currently working on the EM and accompanying cover letter together with Sterop<br>14.10.14 - re-submission (mail) of dossier to BE HA<br>02.12.2014 - comments received from BE HA (both on cover letter and EM)<br>10.02.2015 - preparation of response to BE HA | 28.07.2014 (via Eudralink)<br>14.10.14- re-submission via mail | | Planned start mid-March 2015 | | | Same as for the DHPC | |
| **Bulgaria (BG)** | 29.07.14 - HA request (e-mail) that Vifor local representative (rep) should complete the procedure together with Ewopharma (Pharmacosmos local rep). Further, BG HA communicated that all ongoing variation procedures need to be finalized and only then they can review the EM<br>09.10.2014 - review of variations still ongoing, awaiting finalization<br>25.11.2014 - comments received from HA for the HCP EM , local partner has corrected accordingly and BG HA has approved the HCP<br>01.12.2014 - Vifor partner to contact BG HA to get the patient EM approved<br>10.02.2015 - feedback received from BG HA on patient EM, currently response in preparation | 28.07.2014 (via Eudralink) | 25.11.2014 (HCP EM) | Planned start 15.03.2015; finish 3-4 days later | By courier | 240 | Nephrologists, obstetricians and gynecologists, gastroenterologists, hematologists, oncologists | |
| **Croatia (HR)** | 17.09.2014 - Vifor local rep to contact HR HA for status update<br>25.09.2014 - re-submission of texts to HR HA (e-mail)<br>05.11.2014- phone call with HR HA: review has not yet started (HR HA has a big backlog for reviewing EMs currently)<br>24.11.2014 - still no comments from HR HA (Vifor LPPV is in close contact with them) | 28.07.2014 (via Eudralink)<br>25.09.2014 - re-submission via e-mail to HR HA | | | | | | |
| **Cyprus (CY)** | 31.07.2014 - HA request to re-submit hard copies including information on distribution / dissemination (re-submission: 14.08.2014; received at CY HA - 18.08.2014)<br>27.08.2014 - EM is still under review<br>16.09.2014 - the EM has been reviewed and the reviewer will organize a meeting with all marketing authorization holders (MAHs) to discuss the method of dissemination (meeting: 07.10.2014)<br>20.10.2014 - revisions requested to the EM as well as the distribution list<br>03.11.2014 - Vifor partner currently preparing the accompanying cover letter and will submit it to the CY HA at the end of the week.<br>27.11.2014 - cover letter and EMs have been approved (see dates to the right). The EM will be sent on behalf of all the MAHs by a third party. Plan to dispatch the EM start of the week of 01.12.2014.<br>04.12.2014 - distribution done | 28.07.2014 (via Eudralink) | 18.10.2014 (date of approval of EM)<br>18.11.2014 (date of approval of the cover letter) | 04/12/2014 | Postal delivery | 3295 | Hematology<br>Radiological Oncology<br>Gastroenterology<br>General practitioners 1<br>Endocrinology<br>Cardiology<br>Paediatric Cardiology<br>Obstetrics Gynecology<br>Neurology<br>Neurology Psychiatry<br>Nephrology<br>Pediatric Nephrology<br>Orthopedics<br>Urology<br>Pathology<br>Pathological Oncology<br>Pediatric<br>Pediatric Intensive<br>National Pulmonology<br>Rheumatology<br>Surgery General<br>Surgery Neurosurgery<br>Plastic Surgery<br>Facial Oral Jaw | |

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| **Czech Republic (CZ)** | 01.08.2014 - CZ HA requested to revise texts, provide list of recipients, assumed date of distribution / 14.08.2014 - revised texts and responses sent to CZ HA / 15.08.2014 - revised texts and further questions from CZ HA / 19.08.2014 - responses and new texts sent<br>02.09.2014- Approval<br>03.10.2014 - Distribution started during the week of 29.09.2014<br>30.11.2014 - distribution done | 28.07.2014 (via Eudralink) | 02/09/2014 | Start: 01.10.2014<br>Completion: 30.11.2014 | Done by Vifor local rep 4LifePharma: electronic dissemination to HCPs of the following specialities: internal diseases, cardiology, gastroenterology, surgery, gynecology, nephrology, dialysis centres, hematology and oncology.<br>Postal delivery to internal and surgery hospital departments.<br>Distribution by Vifor/Sanofi/Frensenius sales representatives to specialists in nephrology, dialysis centres and gynecology. | Total number of HCPs targeted: 1800<br>Total number of patient EMs distributed: 7000 | Internal disease specialists, gastroenterologists, cardiologists, hematologists, nephrologists, gynecologists, dialysis centres, surgery | |
| **Denmark (DK)** | 22.08.2014 - approved<br>week 40 2014 - distribution completed | 18/07/2014 | 22.08.2014 | Week 40-2014 | Postal delivery | 1760.00 | Nephrologists, dialysis centers (prescribers and pharmacists), obstetrician-gynaecologists, gastroenterologists, orthopedics/trauma, pharmacists in public and private hospitals/clinics, Other HCPs relevant according to DK HA. | More folders have been distributed to a couple of hospitals after requests |
| **Estonia (EE)** | 24.07.2014 - it has been agreed with the EE HA that the EM translations will be submitted to EE HA after the approval of the lead company´s respective variation (incl. EM) expected in October 2014. Subsequently, the resulting EM will be sent to the other involved companies for comment. The target group of the EM will be the same as it was for the DHPC. The EM will be distributed by Fresenius local affiliate<br>30.09.2014 - expected finalization of review procedure 08.10.2014.<br>08.10.2014 - lead company´s variation approved.<br>09.10.2014 - national EM and distribution plan submitted to EE HA<br>29.10.2014 - national EM approved by EE HA<br>31.10.2014 - distribution completed | 09/10/2014 | 29/10/2014 | 31.10.2014 | By e-mail | 1 e-mail; around 30 adresses including the professional societies | Estonian Nephrologists' Society; Estonian Gynaecologists` Society; Estonian Gastroenterologists' Society; Estonian Traumatology and Orthopaedics Society; Estonian Family Practice Physicians' Society; Estonian Haematologists' Society; Pharmacies in health care institutions: Tartu University Hospital, PERH (Regionaalhaigla), LTKH (Lääne-Tallinna Keskhaigla), ITK (Ida-Tallinna Keskhaigla), Narva Hospital, Saaremaa Hospital, Läänemaa Hospital, IVKH (Ida-Viru Keskhaigla), Rapla Hospital, Pakvere | EM distributed via e-mail to relevant organisations with the request to forward concerned HCPs and that the Patient EM should be printed out for the patient |
| **Finland (FI)** | 28.09.2014 - There is a delay in the assessment of the material as FI HA requested the approved RMP.<br>14.10.2014 - approved<br>December 2014 - distribution done | 18/08/2014 | 14/10/2014 | December 2014 | Postal delivery | 2848 | Nephrologists, dialysis centers,obstetrician-gynaecologists, gastroenterologists, hematologists, hospital pharmacists, specialists in internal medicines | |

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|---|---|---|---|---|---|---|---|---|
| **France (FR)** | Dispatched to FR HA directly through Vifor France affiliate / 27.08.2014 - FR HA response expected around 29.08.2014 / 09.09.2014 - revision of texts requested by FR HA<br>10.10.2014 - response sent to FR HA<br>24.11.2014 - approval<br>31.12.2014 - distribution | 28.07.2014 (via Eudralink) | 24/11/2014 | 31.12.2014 | Postal delivery and via sale representatives during medical visits | 34034 HCPs | Anesthesiologists, gynecologists, obstetricians, oncologists, haematologists, gastroenterologists, specialists in orthopedics and traumatology, internists, hospitals pharmacists, private clinics pharmacists and dialysis centers pharmacists | sales force |
| **Germany (DE)** | DE HA (pre-)approved the material during week 32 2014. The companies had to officially submit the material as approved by DE HA via CESP (Vifor submitted on 11.08.2014).<br>24.10.2014 - EM approved for Vifor (the distribution will start after every company has their CESP-approval)<br>28.11.2014 - distribution | Vifor: 11.08.2014 via CESP;<br>Fresenius: 13.08.2014 via CESP<br>Sanofi: 12.08.2014 via CESP;<br>Medice: 11.09.2014 via CESP<br>(Every company had to send their submission individually) | 24.09.2014 for Sanofi<br><br>24.10.2014 for Venofer and Ferinject | 28.11.2014 | Postal delivery<br>Downloadable pdf's of the material have been activated 28.11.2014 on Viforpharma.de homepage in the DocCheck protected area. | 44390 | resident doctors for internal medicine (including nephrologists, gastroenterologists, oncologists / hematologists), gynecologists, orthopedic surgeons (approx 44500 will be targeted) | Downloadable pdf's of the material have been activated 28.11.2014 on Viforpharma.de homepage in the DocCheck protected area. |
| **Greece (EL)** | 06.08.2014 - EL HA requested that all IV iron product MAHs in Greece confirm directly to EL HA in writing that they agree on the use of common educational materials and common distribution of these materials to HCPs, as those proposed by VIFOR and under the coordination of Genesis. After received confirmation a new submission should be made<br>27.08.2014 - EL HA is still trying to obtain confirmation from all EL MAHs that the common educational materials approach is acceptable.<br>11.09.2014 - re-submission<br>20.10.2014 - revisions requested from EL HA<br>31.10.2014 - response submitted to EL HA<br>16.12.2014 - approved | 28.07.2014 (via Eudralink) | 16/12/2014 | Planned February 2015 | Postal delivery; EL HA has requested the we send about 10 patient leaflets per HCP + information on how to order additional copies | Nephrologists: 744<br>Oncologists: 545<br>Hematologists: 568 | Nephrologists, oncologists, hematologists | EL HA has requested the we send about 10 patient leaflets per HCP + information on how to order additional copies |
| **Hungary (HU)** | 28.08.2014 - approved<br>12.09.2014 - distribution | 17.07.2014 | 28.08.2014 | 12.09.2014 | Postal delivery | | All hospital pharmacies, nephrologists, gynecologist-obstetricians, orthopedists, traumatologists, gastroentorologists | Upon request by postal delivery |
| **Iceland (IS)** | IMA has not had time to look at the material yet | | | | | | | |
| **Ireland (IE)** | 29.07.2014 - requests for revision from IE HA / 29.07.2014 -1st set of responses / 12.08.2014 - 2nd set of responses sent<br>13.08.2014 - Approved<br>20.01.2015 - distribution done | 28.07.2014 (via Eudralink) | 13/08/2014 | 20.01.2015 | Postal delivery (hardcopies); HCPs to receive 1 HCP EM and 2 patient EM with information on how to order more if needed. | 1215 | Specialists in renal, obstetrics and gynaecology, gastroenterology, orthopaedics, haematology, oncology, hospital pharmacists and renal departments | Clinicians will be able to obtain additional patient leaflets via company websites.The material will be on the corporate websites of Iron Consortium members; Vifor, Pharmacosmos; FMC |
| **Italy (IT)** | IT HA made only minor changes to the Italian translation and not in the content of the EM.<br>02.09.2014 - approved<br>16.09.2014 - distribution | 27June 2014 | 02/09/2014 | 16.09.2014 | Postal delivery | 33546 | Nephrologists (n=4144); traumatologists (n=9328); gastroenterologists 3446; gynecologists | |

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| **Latvia (LV)** | 21.07.2014 - LV HA has been asked for detailed information concerning the procedure. Pharmacosmos A/S and Vifor have been asked to provide the confirmation letter (as approval that they agree to participate in a common project of the EM in Latvia) and been asked for their approval concerning the EM drafts (as a templates). Upon approval, the respective translations (joint EM - both in ENG and Latvian) will be submitted to LV HA for evaluation and approval.<br>22.09.2014 - Fresenius partner is currently checking the distribution plan with LV HA. Final approval of NCA and starting of EM distribution not before October 2014.<br>03.11.2014 - EM approved on 02.10.2014, BUT not before the complete "package" (EduMat, communication plan, list of HCPs, distribution way, control mechanism) has been approved by LHA the distribution can be started. The final reconcilation concerning the "package" with the LHA is still in process.<br>18.12.2014 - distribution completed. | 28.07.2014 (by Vifor via Eudralink)<br><br>25.08.2014 (EM and distribution plan (by Fresenius partner) | 24.11.2014 | According to Communication (Distribution) Plan agreed with LV HA , the proposed completion date of EM distribution: 01.03.2015.<br><br>EM distribution completed: 18.12.2014 | Postal delivery | >3000 | Gastroenterologists; nephrologists; gynecologists and obstetricians; family and general practice doctors | The contact information of the Fresenius Medical Care Nephrologica Deutschland GmbH local representative SIA Baltijas Dializes Serviss has been indicated in the common cover letter (attached to EduMat package) for the ordering the additional copies of EduMat! As well as the approved EduMat will be inserted in the website of the company SIA Baltijas Dializes Serviss (www.dialize.lv) and freely available for printing, if necessary. This information is indicated in the common cover letter, as well |
| **Lichtenstein (LI)** | Lichtenstein is in a mutual recognition procedure with Switzerland. The Educational material has been submitted to Swiss HA on 30.09.2014 and so far no feedback has been received. | 30/09/2014 | | | | | | |
| **Lithuania (LT)** | 23.07.2014 - National translations sent to LT HA<br>29.08.2014 - distribution plan is already agreed but there is currently no concrete timetables for the necessary activities for LT<br>22.09.2014 - EM approved<br>03.11.2014 - distribution is intended to be started in November 2014<br>08.12.2014 - distribution completed | 23/07/2014 | 22/09/2014 | 08.12.2014 | By e-mail and during the visits of HCPs when possible. | 138 | Nephrologists, HD specialists. | |
| **Luxemburg (LU)** | 25.09.2014 - re-submission of EM to LU HA<br>09.10.2014 - no feedback from the LU HA yet<br>24.11.2014 - status update inquiry sent to LU HA<br>10.02.2015 - still no news from the LU HA<br>12.02.2015 - Vifor decision to inform LU HA upon approval of EM in BE (as BE is the reference country) and use the same materials in LU (although revised with regards to ADR reporting addresses) | 28.07.2014 (via Eudralink)<br>25.09.2014 - re-submission to LU HA via e-mail | | Planned start mid-March 2015 | | | Same as for the DHPC | |
| **Malta (MT)** | 25.08.2014 - liaision has been made between Vifor and FMC<br>06.10.2014 - EM approval<br>05.11.2014 - distribution done | 28.07.2014 (via Eudralink) | 06/10/2014 | Started 03.11.2014<br>Completed 05.11.2014 | By e-mail; and additionally:<br>1. MT HA shall upload the EM on their website.<br>2. the state hospital shall upload the EM on the hospital's intranet. | 49 target HCPs | Pharmacists, gastroenterologists; several directors of health institutions | |
| **Netherlands (NL)** | Review by NCA, response regarding HCP and distribution plan expected week 32. Patient material was submitted later and according to MEB this will be processed as a separate case. This will be followed up with MEB after receipt of response on HCP material and distribution plan.<br><br>13.08.2014: feedback on HCP EM and distribution plan received. Distribution to same target groups as DHPC approved. Textual changes proposed to material<br>21.08.2014: feedback on patient EM received. Text changes proposed by NL HA. Response sent to MEB today (HCP and patient EM)<br>12.09.2014: final PDF has been sent for final approval to NL HA<br>26.09.2014: EMs approved and sent together with the cover letter to Cegedim, who will do the distribution. The materials will be printed and sent by regular email to the target group.<br>07.10.2014 - distribution completed | 06/05/2014 | 23/09/2014 | 07/10/2014 | Postal delivery | 6747 letters (each including 1 HCP and 1 patient EM) | Nephrologists/ dialysis centres (prescribers and pharmacists), obstetrician gynaecologists, gastroenterologists, internists, orthopaedic surgeons and trauma doctors, hospital pharmacists and all listed specialists in training | Fresenius, Vifor and Teva have a set of additional printed brochures. PDFs of the material have been sent to all companies who participated in the distribution of the educational material. |

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| **Norway (NO)** | 18.08.2014 - approved<br>Week 41-2014: distribution done | 18/07/2014 | 18/08/2014 | Week 41-2014 | Postal delivery | 6498.00 | Nephrologists, dialysis centers (prescribers and pharmacists), obstetrician-gynaecologists, gastroenterologists, orthopedics/trauma, pharmacists in public and private hospitals/clinics, other healthcare professionals relevant according to NCA. | |
| **Poland (PL)** | 25.07.2014 - Involved companies are still waiting for the approval of their individual variations incl. the EM. Upon approval, common national translations will be submitted to PL HA<br>28.08.2014 - EM approved<br>17.12.2014-EM distribution completed | 28.07.2014 (via Eudralink) | 28/08/2014 | started: 15.11.2014<br>completed: 17.12.2014 | Postal delivery | 15900 | Nephrology, gastroenterology, gynecology, orthopedics, clinical transfusiology, hematology | |
| **Portugal (PT)** | 31.07.2014 - HA request (List of recipients, assumed date of distribution requested, etc)<br>19.08.2014 - responses sent to PT HA<br>17.09.2014 - update from PT HA: review ongoing and request for provision of RMPs<br>09.10.2014 - revision of texts requested by PT HA. Agreement on distribution target group and timelines.<br>04.11.2014 - responses sent to PT HA<br>04.11.2014 - further revisions requested by PT HA<br>12.11.2014- EM approved<br>28.11.2014 - distribution of the EMs assigned. Distribution after assignment will take 1 week.<br>26.12.2014 - distribution completed | 28.07.2014 (via Eudralink) | 12/11/2014 | start: 19.12.2014<br>end: 26.12.2014 | Postal delivery:<br>Each HCP will receive 3 laminated copies (re-usable) of the patient's EM (additional material can be ordered via any of the IV iron MAHs). The HCPs are responsible for sharing the patient's EM with their patients, when prescribing or prior to administration, enabling and promoting the reading of the EM and the clarification of any queries. PT HA also placed the cover letter on the website together with the EM | 1030 | Dialysis clinics;<br>Public or private hospitals:<br>Clinical Directors<br>Directors of:<br>Nephrology Service, Gastroenterology, Gynecology, Orthopedics, Internal Medicine, General Haematology and Hematology;<br>Hospital Pharmaceutical Services<br>Health Centres managers. | It was agreed with PT HA the cont of the cover letter, which mentions: " in case that additional educational materials are needed, you can request them to any of the signatories of this letter", this includes B Braun, Combino; Fresenius Medical care PT, Generis and OM Pharma PT, all the MAH/distributors of iron i.v. medicinal products in Portugal. |
| **Romania (RO)** | 01.09.2014 - Vifor affiliate informed fee needs to be paid for review -re-submission of materials with application form and payment to be done / 10.09.2014 - re-submission<br>20.10.2014-approved<br>Distribution ongoing | 28.07.2014 (via Eudralink) | 20/10/2014 | 15.12.2014 | Postal delivery; 1 copy of the educational material for HCP and 4 copies of the educational material for patients | In total: 2932: nephrologists (233), gastroenterologists (297), orthopedic surgeons (548) and gynecologists (1854) | Nephrologists, gastroenterologists, orthopedic surgeons and gynecologists | The educational materials for patients are available on Vifor Pharma's and EwoPharma's websites |
| **Slovakia (SK)** | 09.09.2014 - Vifor partner informed re-submission is needed as SK HA does not have the 1st submission / 09.09.2014- re-submission by partner via e-mail 10.09.2014 - re-submission by partner via post / 12.09.2014 - comments from SK HA on the texts, approved by partner and sent back to SK HA<br>12.09.2014 - Approval<br>30.12.2014 - distribution completed | 28.07.2014 (via Eudralink) | 12.09.2014 | start: 01.11.2014<br>end: 30.12.2014 | Local representative visits to HCPs and postal delivery, | Total targeted HCPs: 1800<br>Total distribution of patient EM: 7000 | Specialists in internal diseases, gastroenterology, cardiology, hematology, nephrology, dialysis centres, surgery, gynecology | |
| **Slovenia (SI)** | 07.08.2014 - SI HA requested revisions to the texts / 12.08.14- translations will be checked by Vifor partner / 19.09.2014 - revisions to the texts made according to HA request and sent back to SI HA.<br>23.09.2014 - further comments from SI HA received<br>07.10.2014 - revised texts sent to SI HA<br>14.10.2014 - further revisions requsted and response sent<br>24.11.2014 - Vifor partner informed there are still no news regarding the approval.<br>05.12.2014-approved<br>18.12.2014 - distribution completed | 28.07.2014 (via Eudralink) | 05/12/2014 | Edu Mat letter to doctors and pharmacies (retail and hospital) sent out on 17 Dec 2014. received 18th of December 2014 | Postal delivery | 1501 | Nephrologists, gynecologists, gastroenterologists, orthopedic and trauma surgeons as it was recommended by EMA. We added hematologists, cardiologists and internists as they also use Iroprem a lot in their daily practice | Educational material will be distributed via wholesalers, as they will add one EM to every package of IV iron product, to all pharmacies which will order IV iron. This way the material will be distributed from the pharmacy to the final user who will give it to the patient |

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| **Spain (ES)** | 22.09.2014 - Normon has received feedback from ES HA who will need us to resend our materials submitted via Eudralink and also confirm which companies are involved in the EM consensus.<br>21.10.2014 - ES HA came back with some minor changes that all affected companies have considered acceptable. We will now propose a target and electronic distribution channel identical to that of the DHPC<br>24.11.2014 - ES HA has accepted the texts; Vifor affiliate is sending the final version and a proposal of target and distribution pathway.<br>10.02.2015 - no response yet from ES HA regarding the distribution | 28.07.2014 (via Eudralink) | 24/11/2014 | | By email through medical associations | Societies: de Farmacia Hospitalaria (SEFH) 3000;de Farmacología Clínica (SEFC) 300; de Ginecología y Obstetricia (SEGO) 6000; de Hematología y Hemoterapia (SEHH) 2000; de Medicina Interna (SEMI) 5880; de Nefrología (SEN)1415; de Oncología Médica (SEOM) 1500;de Patología Digestiva (SEPD) 2200; de Cirugía Ortopédica y Traumatológica (SECOT) 4850 | Nephrologists; gynecologists; gastroenterologists; traumatologists; hospital pharmacists; internists; clinical pharmacologists; hematologists; oncologists | |
| **Sweden (SE)** | 28.07.2014 - EM approved<br>28.10.2014 - distribution completed | 18/07/2014 | 28.07.2014 | 28.10.2014 | Postal delivery | 10393.00 | Nephrologists, dialysis centers (prescribers and pharmacists), obstetrician-gynaecologists, gastroenterologists, orthopedics/trauma, pharmacists in public and private hospitals/clinics, other healthcare professionals relevant according to NCA. | |
| **United Kingdom (UK)** | 13.08.2014 - comments received from UK HA, texts revised / All comments will be accepted as agreed by all consortium members. Additional revisions requested by UK HA (referencing to which products the EMs apply and pagination) is currently in progress.<br>09.09.2014 - revised texts sent back to UK HA<br>18.09.2014 - EM approved<br>20.01.2015 - distribution completed | 28.07.2014 (via Eudralink) | 18/09/2014 | 20.01.2015 | Postal delivery (hard copies),<br>clinicians will be able<br>to obtain additional patient leaflets via company websites. | 19328 | Specialists in Renal, Obstetrics and Gynaecology, Gastroenterology, Orthopaedics, Haematology, Oncology, Hospital Pharmacists and Renal departments | The material will be on the corporate websites of Iron Cons members; Vifor, Pharmacosmos; FMC |

## Annex 11 Mock-up of Proposed Additional Risk Minimisation Measures

Further to the European Medicine Agency (EMA) referral, IV iron medicinal products are under additional monitoring. The EMA considers the benefit/risk of IV iron products favourable when oral route is insufficient or poorly tolerated.

Parenterally administered iron medicinal products are used to treat iron deficiency when oral preparations are ineffective or cannot be used.

Parenterally administered iron preparations can cause hypersensitivity reactions including serious and potentially fatal anaphylactic/anaphylactoid reactions.

This essential prescription information guide can assist you in managing and minimising this risk.

**Contraindications to the use of IV iron include:**

- hypersensitivity to the active substance or any of its excipients.
- known serious hypersensitivity to other parenteral iron products.
- anaemia not caused by iron deficiency
- evidence of iron overload or disturbances in the utilisation of iron.

See the Summary of Product Characteristics of individual IV iron medicinal products for full product information.

Reporting adverse drug reaction is mandatory by law and allows continued monitoring of the benefit/risk balance of the medicinal product. Please report any suspect adverse drug reaction to either the marketing authorisation holder (MAH) or to the local regulatory authority according the local requirements in your country. When reporting please ensure to include the name of the specific product administered. The contact details of MAH and local representative are mentioned in the Summary of Product Characteristics as well as Patient Information Leaflet.

# IV iron ▼

## Essential Prescription and Administration Information to Minimise the Risk of Serious Hypersensitivity Reactions

This essential prescription information guide is brought to you by the European IV iron suppliers.

**Please read carefully and review each time when prescribing IV iron medicinal products.**

## BEFORE each administration of IV iron, you should inform your patient so that they are aware that…

…parenterally administered iron preparations can cause hypersensitivity reactions including serious and potentially fatal anaphylactic/anaphylactoid reactions.

…these reactions have also been reported after previously uneventful doses of IV iron.

…they may have an increased risk of experiencing a hypersensitivity reaction if they have:

- known allergies including drug allergies*
- a history of severe asthma*, eczema* or other atopic allergies* or
- immune or inflammatory conditions (e.g. rheumatoid arthritis, lupus erythematosus)*.

*In these patients, IV iron products should only be used if the benefit is clearly judged to outweigh the potential risk.

…IV iron should not be used during pregnancy unless clearly necessary. Treatment should be confined to the 2nd-3rd trimester if the benefit is judged to outweigh the potential risk for both the mother and the foetus.

…they should report any signs or symptoms suggestive of a hypersensitivity reaction (e.g.: hives, pruritus, dyspnoea, wheezing, swelling of the lips, tongue, throat or body) to their doctor/nurse immediately.

The patient should also be given a copy of the patient information leaflet provided with the individual IV iron product to be administered.

## …and remember that IV iron is contraindicated and should not be administered if your patient…

…has known hypersensitivity to the IV iron product, the active substance or to any of its excipients.

…has previously experienced a serious hypersensitivity reaction to any IV iron preparations.

…has anaemia not caused by iron deficiency.

…has evidence of iron overload or disturbances in the utilisation of iron.

See the Summary of Product Characteristics of individual IV iron medicinal products for full product information.

## BEFORE each administration of IV iron make sure that…

…staff trained to evaluate and manage anaphylactic reactions are immediately available.

…cardio-pulmonary resuscitation facilities and equipment for handling acute anaphylactic/anaphylactoid reactions, including an injectable 1:1000 adrenaline solution, are immediately available onsite. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

## DURING administration of IV iron remember that…

...if hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately and appropriate management initiated.

…IV iron products should be administered in accordance with the posology and method of administration described in the product information for each individual product.

## AFTER you have administered IV iron…

…. the patient must be closely observed for signs and symptoms of a hypersensitivity reactions for at least 30 minutes after each administration.

**IV Iron is** used to treat iron deficiency when oral preparations are ineffective or cannot be used.

**IV Iron** can cause allergic reactions and must be administered by persons trained to evaluate and manage these reactions.

In some patients these allergic reactions can become severe or life-threatening (known as anaphylactic reactions) and can cause problems with your heart and blood pressure and/or cause you to faint or lose consciousness.



**Reporting of side effects**

If you get any side effects, talk to your Doctor or nurse. This includes any possible side effects even if they are not listed in this leaflet. You can also report side effects directly via {the national reporting system}.

# Intravenous (IV) Iron

**Important Information for Patients About the Possible Risk of Serious Allergic Reactions with IV iron (medication given by needle into the vein)**

This information has been prepared and provided to you by the makers of IV iron in Europe.

**Please read this leaflet carefully and discuss any questions you may have with your Doctor.**

**You may have an increased risk of having an allergic) reaction if you have**:

- known allergies including drug allergies
- a history of severe asthma, eczema or other allergies (for example dust, pollen, pet dander) or
- immune or inflammatory conditions (e.g. rheumatoid arthritis, lupus erythematosus and others)

**You should tell your doctor before they prescribe or give you IV Iron** if you have any of these allergies or conditions.

Your Doctor will decide whether the benefit to you is greater than the risk

**You should not be prescribed or given an IV Iron if**:

- you are allergic (hypersensitive) to the product or any of the other ingredients of this medicine
- you have experienced serious allergic (hypersensitive) reactions to other I.V iron treatments in the past*
- you have iron overload (too much iron in your body)
- your anaemia is not caused by iron deficiency

**You should tell your doctor before they prescribe/administer an IV Iron** if you have any of these allergies or conditions.

*** It is important to know that a reaction can still happen even if you have not had any problems in the past with IV iron.**

**Pregnancy:** IV iron should not be used during pregnancy unless clearly necessary. If you are pregnant or think you could be pregnant, it is important to discuss this with your doctor.

**You should contact your Doctor or Nurse immediately if:**

- you have any signs or symptoms of an allergic reaction during or shortly after treatment with IV Iron

For example: hives or rash, itching, dizziness, light-headedness, swelling of the lips, tongue, throat or body, difficulty breathing, shortness of breath or wheezing.

- Your Doctor will monitor you for signs and symptoms of an allergic reaction for at least 30 minutes after each time IV iron is given to you.