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. Patients with known serious hypersensitivity to IV iron preparation should not take Venofer. 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: 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. Summary description of main additional risk minimisation measure DHPC HCP and patient educational materials to be provided to prescribing physicians including advice on: • Information to be provided to patients before administration of the IV iron • Importance of adherence to the recommendations to avoid use of IV iron in patients with an increased risk of experiencing an allergic reaction • Need to have trained staff administering the product to the patient, and adequate facilities and equipment for handling acute allergic reactions • Need to observe the patient 30 minutes after each administration of IV iron Objective and rationale: • 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 • 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: 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. Summary description of main additional risk minimisation measures DHPC HCP and patient educational materials to be provided to prescribing physicians including advice on: • Information to be provided to patients before administration of the IV iron • 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 • Use of the IV iron only in 2nd and 3rd trimester of pregnancy Objective and rationale: • 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: • Hypersensitivity/anaphylactoid reaction • Medication error • Injection/infusion site reactions Important potential risks: • Haemosiderosis Missing information: • Use in paediatric population • Use in elderly patients • Use in pregnant or lactating women • Use in patients with infectious diseases	Initial RMP for Venofer®
2.0	10-Mar-2015	–	Feasibility report for the PASS study Status of additional risk minimisation measures (distribution of educational material)

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