SUMMARY OF THE RISK MANAGEMENT PLAN (RMP) FOR FERINJECT® (FERRIC CARBOXYMALTOSE)

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SUMMARY OF RISK MANAGEMENT PLAN FOR FERINJECT

This is a summary of the Risk Management Plan (RMP) for Ferinject. The RMP details important risks of Ferinject, how these risks can be minimised, and how more information will be obtained about Ferinject's risks and uncertainties (missing information).

Ferinject's Swiss Summary of Product Characteristics (SmPC) and its Package Leaflet give essential information to healthcare professionals and patients on how Ferinject should be used.

Important new concerns or changes to the current ones will be included in updates of Ferinject's RMP.

I. The Medicine and What it is Used for

According to Swiss Label

Ferinject is indicated for the treatment of iron deficiency in patients in whom oral iron therapy is not sufficiently effective, is ineffective or cannot be undertaken, such as cases where oral iron preparations cannot be tolerated or in the presence of inflammatory gastrointestinal diseases, e.g., ulcerative colitis, which may be exacerbated by oral iron therapy, or in the case of treatment-refractory iron deficiency states where it is suspected that the oral iron preparations are being taken unreliably. Ferinject should only be administered if the diagnosis of iron deficiency has been established and confirmed through appropriate laboratory investigations (e.g., plasma ferritin levels, transferrin saturation, haemoglobin, haematocrit, red cell count, mean corpuscular volume and mean corpuscular haemoglobin).

According to EU SmPC

Ferinject is indicated for the treatment of iron deficiency when:

- Oral iron preparations are ineffective.
- Oral iron preparations cannot be used.
- There is a clinical need to deliver iron rapidly.

The diagnosis of iron deficiency must be based on laboratory tests.

It contains ferric carboxymaltose as the active substance, and it is given as 50 mg iron/ml solution for injection/infusion.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Ferinject, together with measures to minimise such risks and the proposed studies for learning more about Ferinject's risks, are outlined below. Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the Package Leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size - the amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly
- The medicine's legal status - the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks

Together, these measures constitute routine risk minimisation measures.

In the case of Ferinject, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Ferinject is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Ferinject are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Ferinject. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Hypersensitivity/anaphylactic reaction
	Hypophosphataemic osteomalacia (formerly hypophosphataemia)
	Medication error
Important potential risks	Not applicable
Missing information	Use in children under 1 year of age
	Use in pregnant or lactating women
	Use in patients with hepatic impairment
	Use in patients with infectious diseases
	Long-term usage

II.B Summary of Important Risks

Important Identified Risk: Hypersensitivity/Anaphylactic Reaction	
Evidence for linking the risk to the medicine	The EMA evaluated the benefit/risk relationship of iron-containing IV medicinal products in the context of a referral under Article 31 of Directive 2001/83/EC completed in September 2013. As a result of this evaluation, the EMA imposed a labelling update reinforcing risk information on HSRs and formulated a series of "conditions to marketing authorisation", which included the recommendation by the EMA PRAC for the "MAHs to 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" (EMA, 2017a). The conducted available results of the PASS study showed that the sensitivity analyses results may suggest that there is an increased risk related to dextran products compared to iron non-dextran products which is comparable to the literature. The design of the study, particularly the absence of negative control as well as its numerous limitations, did not conclude that there is no high risk among the users of IV iron.
Risk factors and risk groups	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.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.2, 4.3, 4.4, 4.6 and Section 4.8 • PIL Sections 2, 3 and 4 • Legal status: Prescription only medicine
Additional pharmacovigilance activities	DHPC and Educational Materials for prescribers and patients
Important Identified Risk: Hypophosphataemic Osteomalacia (Formerly Hypophosphataemia)	
Evidence for linking the risk to the medicine	Vifor has conducted an extensive analysis of the available clinical data, post-marketing data and literature sources to investigate the proportion of HP severity, underlying risk factors potentiating the risk of HP, the relationship between the repeated use of high FCM use and HP severity, as well as the possible consequences of severe HP for patients (trends in associated unlisted AEs, HP OM/OM). Evidence of OM from post-marketing and literature data seems to be impacted by the underlying conditions (risk factors) such as Vitamin D deficiency, calcium and phosphate metabolism, secondary hyperparathyroidism, IBD, HHT, and osteoporosis. Currently, there is no precisely defined correlation between the HP experienced by certain FCM patients and the development of OM

	which can be made with any certainty. However, in patients with the underlying risk factors mentioned above and taking high dose repetitive administration of FCM, the risk cannot be excluded and warrants monitoring of this subgroup of patients. The 4th EU PSUSA procedure for iron (parenteral preparations, except for iron dextran), PSUSA/00010236/202001, was ongoing in parallel and also involved assessment of this IIR for Ferinject in relation to the development of OM. The PRAC considered that the benefit/risk balance of medicinal products containing the active substances iron sucrose, FCM, iron isomaltoside, and sodium ferric gluconate remains unchanged, but recommended that the terms of the marketing authorisation for Ferinject should be varied. In view of a plausible mechanism of action, the PRAC considered a causal relationship between FCM and HP OM is at least a reasonable possibility. The PRAC concluded that the product information of products containing FCM should be amended accordingly, and the CMDh endorsed their position on 23-Jul-2020.
Risk factors and risk groups	**Risk Groups** HP OM was observed in cases with the risk factors listed below taking high repetitive doses of Ferinject treatment. Thus, this risk cannot be excluded, and warrants monitoring of this subgroup of patients with aforementioned risk factors. **Risk Factors** HP OM was observed in patients who had the following risk factors: Vitamin D deficiency, calcium and phosphate malabsorption, secondary hyperparathyroidism, IBD, HHT and osteoporosis.
Risk minimisation measures	Routine risk minimisation measures: • Proposed SmPC Section 4.4 and Section 4.8 • Proposed PIL Section 4 Legal status: Prescription only medicine
Important Identified Risk: Medication Error	
Evidence for linking the risk to the medicine	The prevalence of medication errors is difficult to calculate due to the varying definitions and classification systems employed. However, any patient under the care of medical staff in any facility, is susceptible to the potential of a medication error of any form, when drugs are prescribed and administered. The hospital care system can lead to errors and result in failure to detect these errors.
Risk factors and risk groups	**Risk Groups** 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. **Risk Factors** The hospital care system can lead to errors and result in failure to detect these errors. Higher error rates and overwork, fatigue, stress, work environment, poor systems of care, and many other factors beyond an individual's control can lead to medication errors. These factors increase the probability for an individual to make an error and decrease the probability that another person will discover the error. Of importance for the administration of Ferinject are the use of an inappropriate dilution, followed by overdose and wrong technique in drug usage process. Among the other medication errors most were reported as incorrect infusion rate reported as an infusion rate too fast. The remaining medication errors could be classified as isolated events.

Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.2, 4.3, 4.4, 4.8, 4.9 • PIL Section 2 Legal status: Prescription only medicine
Missing Information: Use in children under 1 year of age	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2 and Section 4.4 • PIL Section 2 • Legal status: Prescription only medicine Additional risk minimisation measures: None
Missing Information: Use in pregnant or lactating women	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.6, 5.1 and 5.3 • PIL Section 2 • Legal status: Prescription only medicine Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activity: DHPC and Educational Materials for prescribers and patients
Missing Information: Use in patients with hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 • PIL Section 2 • Legal status: Prescription only medicine Additional risk minimisation measures: None
Missing Information: Use in patients with infectious diseases	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 • PIL Section 2 • Prescription only medicine Additional risk minimisation measures: None
Missing Information: Long-term usage	
Risk minimisation measures	Routine risk minimisation measures: None

Notes: AE=Adverse event; CMDh=Coordination Group for Mutual Recognition and Decentralised Procedures; DHPC=Direct Healthcare Professional Communication; FCM=Ferric carboxymaltose; HHT=Hereditary haemorrhagic telangiectasia; HP=Hypophosphataemia; HP OM=Hypophosphataemic osteomalacia; HSR=Hypersensitivity reaction; IBD=Inflammatory bowel disease; IIR=Important identified risk; IV=Intravenous; MAH=Marketing Authorisation Holder; OM=Osteomalacia; PASS=Post-authorisation Safety Study; PIL=Patient Information Leaflet; PRAC=Pharmacovigilance Risk Assessment Committee; PSUSA=Periodic Safety Update Report Single Assessment; RMP=Risk Management Plan; SmPC=Summary of Product Characteristics.

II.C Post-authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation for Ferinject.

II.C.2 Other Studies in Post-authorisation Development Plan

There are no studies required for Ferinject.