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

Invented Name:	Ferinject
Active Substance:	Ferric Carboxymaltose
Version Number of RMP Summary:	2.0
Date of the Document:	24 August 2023
Marketing Authorisation Holder:	Vifor (International) Inc. Rechenstrasse 37 9014 St. Gallen Switzerland

Disclaimer: The RMP is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Ferinject is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation/Information sur le médicament" approved and published in Switzerland, e.g., by mentioning risks occurring in populations or indications not included in the Swiss authorisation.

Please note that the reference document which is valid and relevant for the effective and safe use of Ferinject in Switzerland is the "Arzneimittelinformation/Information sur le médicament" (see www.swissmedic.ch) approved and authorised by Swissmedic.

Vifor Pharma is fully responsible for the accuracy and correctness of the content of this published Summary of RMP for Ferinject.

TABLE OF CONTENTS

Page

LIST OF ABBREVIATIONS

EU	European Union
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

SUMMARY OF RISK MANAGEMENT PLAN FOR FERINJECT

This is a summary of the Risk Management Plan (RMP) for Ferinject (hereafter also referred to as ferric carboxymaltose). 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 (Swiss 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 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)
Important potential risks	Not applicable
Missing information	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 Sep-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 HSRs". The final results and conclusion were received from PRAC and endorsed by the CMDh. Having considered the results of the study and on the basis of the PRAC recommendation and the PRAC assessment report, the CMDh agreed with the variation to the terms of the marketing authorisation concerning the following changes: • Removal of the condition to conduct a PASS to further characterise the safety concerns of HSRs with regard to the safe and effective use of the medicinal product. The MAH shall remove the below condition: "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-Jul-2016". • Consequently, since this imposed PASS was the only criteria for additional monitoring, MAH(s) should submit a variation to request the deletion of the black symbol and the related statement in the Product Information. In this regard, PRAC considered that routine pharmacovigilance could be considered as appropriate to monitor the risk of hypersensitivity and this topic should continue to be closely monitored through the respective PSURs. Accordingly, Vifor Pharma has submitted on 02-Dec-2021 in the EEA a variation to remove the black triangle and also proceeded to remove the educational materials related to this risk.
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 HSRs.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.2, 4.3, 4.4, 4.6 and 4.8 • PIL Sections 2, 3 and 4 • Legal status: Prescription only medicine Additional risk minimisation measures: None

Additional pharmacovigilance activities	Cumulative annual review of HSRs (commitment from the Article 31 EMA referral procedure; EMEA/H/A-31/1322), to be included within the PSUR for FCM in the EEA.
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 adverse events, 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 correlation between the level of HP experienced by certain FCM patients and the development of OM that can be made with 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 involved assessment of this IIR for FCM 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 FCM 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. Vifor Pharma has submitted accordingly a variation on 19-Oct-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 FCM 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: • SmPC Sections 4.4 and 4.8 • PIL Section 4 • 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	Cumulative annual review of pregnancies (commitment from the Article 31 EMA referral procedure; EMEA/H/A-31/1322), to be included within the PSUR for FCM in the EEA.
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: CMDh=Coordination Group for Mutual Recognition and Decentralised Procedures – Human; EEA=European Economic Area; FCM=Ferric carboxymaltose; HHT=Hereditary haemorrhagic telangiectasia; HP=Hypophosphataemia; 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; PSUR=Periodic Safety Update Report; 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.