EMADOC-1700519818-3419982
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for parenteral iron-containing medicinal products

Referral under Article 31 of Directive 2001/83/EC

Procedure number: EMA/REF/0000369747

INN/active substance: ferric carboxymaltose, ferric derisomaltose, ferric gluconate, ferric hydroxide polymaltose complex, iron dextran, iron sucrose

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1. Questions

The marketing authorisation holders (MAHs) are requested to address the following questions:

Question 1

Concerning your parenteral iron-containing medicinal product(s), please provide in the annexed table:

a) Figures on patient exposure (with a cut-off date on 3 September 2026) by product and route of administration (IV or IM, if applicable), EU Member State, and age group. Data on the use in clinical practice should also be provided, including information on dose, treatment duration and concomitant treatments.

b) Information included in the summary of product characteristics (SmPC) and package leaflet (PL) on posology and method of administration, and, regarding the risk of hypophosphataemia and its skeletal complications, on contraindications, warnings and precautions, and undesirable effects. Please highlight the main differences between the product(s) information (PI) in the different EU Member States.

Question 2

Please provide all available safety data relevant to evaluate the risk of hypophosphataemia and its skeletal complications with your parenteral iron-containing medicinal product(s), with data lock point of 3 September 2026. This analysis should include the following:

- Data from all available sources, including non-clinical, clinical trial data (including both MAH sponsored and non-sponsored studies), pharmaco-epidemiological studies, published literature, and spontaneous reports from the post-marketing setting.
- A case search including all reported cases for which a parenteral iron-containing medicinal product is reported as suspect or interacting product. The search strategy should include all relevant MedDRA Preferred Terms (PTs), including, but not limited to, hypophosphataemia, blood phosphorus decreased, hyperphosphaturia, hypophosphataemic osteomalacia, osteomalacia, osteopenia, osteolysis, osteoporosis, myalgia, bone pain, stress fracture, fracture, and pseudofracture.
- A detailed analysis of all the identified cases should be performed, including a causality assessment performed using the WHO-UMC scoring system. Where available, information on age and sex of patient, treatment duration and dose, route of administration, time to onset, de-challenge and/or re-challenge, medical history, concomitant medication, relevant investigations performed (e.g. laboratory findings, MRI results), seriousness, outcome should be provided, along with a short narrative for each identified case.

Question 3

Please discuss the possible mechanisms underlying hypophosphataemia and its skeletal complications with your parenteral iron-containing medicinal product(s). Additionally, please discuss any additional mechanisms affecting bone metabolism beyond hypophosphataemia.

Question 4

Please discuss possible risk factors for hypophosphataemia and its skeletal complications following use of parenteral iron-containing medicinal products based on the review of relevant and available data.

Question 5

a) Please discuss how healthcare professionals can identify and diagnose skeletal complications and their warning signs at an early stage, including the appropriate clinical, biochemical and imaging investigations, considering that osteomalacia may not be detectable by standard radiographic imaging.

b) Please discuss the challenges associated with the correction of phosphate levels in cases of hypophosphataemia. The discussion should also address the clinical relevance and therapeutic strategies of phosphate correction.

Question 6

Please provide details of any specific measures that have already been taken in order to minimise the risk of hypophosphataemia and its skeletal complications for your parenteral iron-containing medicinal product(s), and assess their effectiveness, including any available evidence supporting their impact on the occurrence, severity and/or early detection of hypophosphataemia and its skeletal complications.

Question 7

Please provide proposals and justifications for any further measures (including changes to the SmPC/PL, as well as additional risk minimisation measures (RMM), as considered appropriate) to minimise the risk of hypophosphataemia and its skeletal complications. For any proposed risk minimisation measure, please discuss their feasibility and how their effectiveness can be monitored.

Question 8

Please provide a full benefit-risk balance assessment of your parenteral iron-containing medicinal product(s) in the currently approved indication in the EU. This should include an assessment on the impact of treatment-induced hypophosphataemia and its skeletal complications on the benefit-risk balance and consider how the benefit-risk balance may differ depending on the dose and route of administration.

Annex

Question 1

a)

EU/EEA member state	INN	Product name	Indication	Method of administration	Pharmaceutical forms and strengths	Estimated patient exposure[1]	Doses (in clinical practice)	Treatment duration (in clinical practice)	Concomitant treatment (in clinical practice)

[1] Expressed in patient years and stratified by Member State, by indication and by age group (<12, 12-18, and >18). Reasonable efforts should be made to obtain this information; potential sources in addition to sales data include registries and healthcare databases. If no precise data is available an estimate can be provided.

b)

PI	SmPC	PL	Main differences in SmPCs/PLs between the different EU Member States
Posology (incl. max. daily dose)			
Method of administration			
Contraindications			
Warnings and precautions			
Undesirable effects			