COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

IJzer(III)carboxymaltose Sandoz 50 mg/ml, solution for injection or infusion (ferric carboxymaltose)

NL/H/5359/001/DC

Date: 18 January 2023

This module reflects the scientific discussion for the approval of IJzer(III)carboxymaltose Sandoz 50 mg/ml, solution for injection or infusion. The procedure was finalised at 20 October 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PD	Pharmacodynamics
PK	Pharmacokinetics
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of medicinal Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for IJzer(III)carboxymaltose Sandoz 50 mg/ml, solution for injection or infusion, from Sandoz B.V.

The product 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.

A comprehensive description of the up-to-date indications and posology is given in the current SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Ferinject 50 mg ijzer/ ml, solution for injection/infusion, from Vifor France. Ferinject has been registered by the decentralised procedure (SE/H/1816/001/DC) since 06 July 2007, with the Netherlands included as concerned member state.

The concerned member states involved in this current procedure were Austria, Belgium, Bulgaria, Croatia, Finland, Germany, Ireland, Italy, Malta, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

IJzer(III)carboxymaltose Sandoz is a dark brown, non-transparent, aqueous solution. One mL solution contains as active substance 50 mg of iron (as ferric carboxymaltose).

The solution is packaged in a vial (type I glass) with a grey chlorobutyl rubber stopper and an aluminium cap. It is packaged as 100 mg/2 mL, 500 mg/10 mL or 1,000 mg/20 mL solution (all containing a strength of 50 mg/mL).

The excipients are: sodium hydroxide (E524) (for pH adjustment), concentrated hydrochloric acid (E507) (for pH adjustment) and water for injection.

II.2 Drug Substance

The active substance is ferric carboxymaltose, an established active substance, not described in the European Pharmacopoeia. The active substance is a brown powder, very dispersible in

water and has multiple chiral centres. The akaganeite (β-FeOOH) polymorph is manufactured.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process of ferric carboxymaltose consists of carbohydrate synthesis, iron complex formation and isolation of the final drug substance. The process has adequately been described and the starting materials are acceptable. The active substance, including the carbohydrate structure, has been adequately characterised and controlled, and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the in-house specifications. The specification of a substance is the total of quality tests, analytical procedures and acceptance criteria (limits) this substance has to adhere to. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance for 12 months at long-term conditions (2-8°C) and accelerated conditions (25°C/60% RH). This was part of the ASMF. Based on the data submitted, a re-test period of 12 months is acceptable when stored in the stated conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The aim of the development is to develop a product similar to the reference product. The choice of excipients is justified and their functions explained. The proposed product is qualitatively the same as the reference product. The active substance and water quantity are identical to the proposed product. The remaining components, sodium hydroxide and hydrochloric acid, are added to achieve a pH of 5.0-7.0. Therefore, the proposed product closely matches the reference product in terms of quantities. The development was guided by risk assessments to identify the critical drug substance attributes, critical material attributes and critical process parameters. To mitigate the identified risks, an adequate control strategy was implemented.

The main formulation development studies were the characterisation of the test and reference product and physicochemical comparison. The *in vitro* comparative studies are acceptable based on the results of qualitative and quantitative tests. The main manufacturing process development studies were the optimization of preparation of the bulk solution, purging and sterilisation. The drug product is terminally sterilised by steam. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. The main steps of the manufacturing process are compounding, filtration (bioburden reduction), filling, purging, stoppering, capping and terminal sterilization. Process validation data on the product has been presented for three full scale batches for each packaging volume (i.e. 100mg/2mL, 500mg/10mL and 1000mg/20mL). The manufacturing process of the drug product is non-standard.

Control of excipients

The excipients comply with Ph.Eur. requirements. These specifications were acceptable.

Quality control of drug product

The finished product specifications were adequate to control the relevant parameters for the dosage form. The specification includes tests for: colour of content, appearance of content, identification (by infrared, by X-ray powder diffraction), total iron content, total and unbound carboxymaltose content, average molecular mass, particle size, foreign visible particles, particulate matter, pH, degradation products, osmolality, density, iron(II) content, free iron content, uniformity of dosage units, extractable volume, bacterial endotoxins, sterility, relative labile iron content and iron reduction kinetics.

A CMD(h) referral was triggered as the objecting CMS considered that comparability with the reference product was not sufficiently demonstrated as the specification limits for some quality attributes of the test product were marginally different from the limits of the reference product. Secondly, justification was requested for a difference between test and reference product of one parameter of the comparative physicochemical study. The MAH presented their responses to the questions raised with supporting data. There was a discussion, followed by a vote in the CMDh, with a majority in agreement with the position of the RMS to conclude the procedure positively. Agreement was reached and the procedure was closed positively. The specification was acceptable and considered appropriate for adequate quality control of the product.

All potential sources of nitrosamine impurities currently listed in the EMA Q&A on “Information on nitrosamines for marketing authorisation holders” have been considered in the risk evaluation by the MAH. No confirmatory testing is needed.

The analytical methods have been adequately described and validated. Batch analytical data for three full scale batches for each packaging volume have been provided, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided on three production scale batches for each packaging volume (i.e. 2 mL, 10 mL and 20 mL) stored at 25°C/60% RH (24 months), 30°/75% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. A shelf life of 24 months is acceptable based on stability data at 24 months long-term conditions and 12 months intermediate conditions, with storage conditions "Do not store above 30 °C. Do not freeze.".

In-use stability data have been provided, demonstrating that the product remains stable for 24 hours following dilution in polyethylene bottles to concentrations of 2mg/mL, 4mg/mL and 5mg/mL and undiluted in a polypropylene syringe, when stored at room temperature (20°C - 25°C).

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE could be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that IJzer(III)carboxymaltose Sandoz has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since IJzer(III)carboxymaltose Sandoz is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Ferinject, which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. The overview justifies why there was no need to generate additional non-clinical pharmacology, pharmacokinetics and

toxicology data. Therefore, the member states agreed that no further non-clinical studies were required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ferric carboxymaltose is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the bioequivalence study discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product IJzer(III)carboxymaltose Sandoz 50 mg/ml, solution for injection or infusion (Sandoz B.V., The Netherlands) was compared with the pharmacokinetic profile of the reference product Ferinject 50 mg ijzer/ ml, solution for injection/infusion (Vifor France, France). The design of the study is in line with the advice as stated in *EMA Reflection paper on the data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product (EMA/CHMP/SWP/620008/2012)*.

Bioequivalence study

Design

A single-centre, randomised, single-dose, laboratory-blinded, two-arm, parallel study was carried out under fasted conditions in 143 healthy subjects (87 male and 56 female), aged 21-50 years. The subjects were randomised into either the test or reference group and there was one dosing period. Each subject received a single dose (1000 mg) of one of the two ferric carboxymaltose formulations after an overnight fast of at least 10 hours. In order to ensure adequate hydration of the subjects prior to dosing, 250 mL of normal saline solution was administered intravenously (IV) over 60 minutes prior to dosing. The dose of 1000 mg (20 mL) was administrated by IV injection at a continuous rate of 1 mL/minute (50 mg/min) over 20 minutes.

Blood samples were collected pre-dose at -24, -12 and 0 hours, and post-dose at 0.17, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 28, 32, 36, 48, 72, 96, 120 and 144 hours after administration of the products.

The design of the study was acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and was considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation were considered acceptable.

Results
Three subjects discontinued from the study (two for Covid-19 related symptoms and one for a positive Covid-19 test). This left 140 subjects eligible for pharmacokinetic analysis (72 subjects received the test product and 71 subjects received the reference product).

The ratio (90% confidence interval) presented in the table below represents the similarity between the two products, with an acceptance range of 0.80 to 1.25. This is presented for the area under the curve (AUC) value, which represents the plasma concentration in test subjects over time, and for C_{max}, which is the maximum plasma concentration.

Table 1. Pharmacokinetic parameters (ln-transformed ratio) of ferric carboxymaltose under fasted conditions.

Treatment N=140	**AUC_{0-t}**	**C_{max}**
Ratio (90% CI) baseline-corrected transferrin-bound iron	1.01 (0.91-1.12)	0.99 (0.92-1.06)
Ratio (90% CI) baseline-corrected total iron	1.07 (1.01-1.13)	0.97 (0.93-1.01)
Ratio (90% CI) baseline-*un*corrected transferrin-bound iron	1.01 (0.96-1.07)	0.99 (0.95-1.04)
Ratio (90% CI) baseline-*un*corrected total iron	1.06 (1.01-1.13)	0.97 (0.93-1.01)

AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration
C_{max}	Maximum plasma concentration
CI	Confidence interval

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} were within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study IJzer(III)carboxymaltose Sandoz is considered bioequivalent with Ferinject.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to IJzer(III)carboxymaltose Sandoz.

Table 2. Summary of safety concerns as approved in RMP

Important identified risks	• Hypersensitivity/anaphylactoid reaction • Hypophosphatemic osteomalacia • Medication error
Important potential risks	None
Missing information	• Use in children under 14 years of age • Use in pregnant or lactating women • Use in patients with hepatic impairment • Use in patients with infectious diseases • Long-term usage

The member states agreed that additional pharmacovigilance activities and routine risk minimisation measures are needed for the risks. Treating physicians and patients themselves will be provided with educational information on the important identified risk of a hypersensitivity/ anaphylactoid reaction. This is applicable for active treatment and for cases where therapy with ferric carboxymaltose is proposed.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Ferinject. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management was adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Ferinject 50 mg ijzer/ ml, solution for injection/infusion (SE/H/1816/001/DC). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

IJzer(III)carboxymaltose Sandoz 50 mg/ml, solution for injection or infusion has a proven chemical-pharmaceutical quality and is a generic form of Ferinject 50 mg ijzer/ ml, solution for injection/infusion. Ferinject is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

The procedure was discussed in the CMD(h) meeting on 11 October 2022. Based on the evidence presented, it was agreed by the member states that the Benefit/Risk for IJzer(III)carboxymaltose Sandoz was positive.

The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for IJzer(III)carboxymaltose Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 October 2022.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
N/A	N/A	N/A	N/A	N/A	N/A