Public Assessment Report

Decentralised Procedure

Sucrofer 20 mg iron/ml, Solution for injection /infusion

(iron sucrose)

Procedure No: UK/H/6369/001/DC

UK Licence No: PL 20568/0083

Claris Lifesciences UK Limited
LAY SUMMARY

Sucrofer 20 mg iron/ml, Solution for injection /infusion
(iron sucrose)

This is a summary of the Public Assessment Report (PAR) for Sucrofer 20 mg iron/ml, Solution for injection /infusion (PL 20568/0083; UK/H/6369/001/DC). It explains how Sucrofer 20 mg iron/ml, Solution for injection /infusion was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Sucrofer 20 mg iron/ml, Solution for injection /infusion.

The product will be referred to as Sucrofer throughout the remainder of this lay summary.

For practical information about using Sucrofer, patients should read the package leaflet or contact their doctor or pharmacist.

What is Sucrofer and what is it used for?
Sucrofer is a ‘hybrid medicine’. It is similar to a ‘reference medicine’ containing the same active substance and its authorisation is supported by new non-clinical studies that describe distribution and fate of iron sucrose particles. The reference medicine for Sucrofer is Venofer 20 mg iron per ml, solution for injection or concentrate for solution for infusion (Vifor France SA).

Sucrofer is used to treat patients who do not have enough iron in their body. This is called “iron deficiency”. Sucrofer is given when:

- The patient cannot take iron by mouth – such as when iron tablets make the patient feel ill.
- The patient has taken iron by mouth – and it has not worked.

How does Sucrofer work?
This medicine contains iron in solution, which allows the medicine to be injected or infused. The iron in Sucrofer can supplement natural iron levels aiding the production of red blood cells.

How is Sucrofer used?
The pharmaceutical form of this medicine is a solution for injection or infusion and the route of administration is by a slow injection or infusion into the patient’s vein.

The doctor will decide how much Sucrofer to give their patient. He or she will also decide how often it is needed and for how long. The doctor will do a blood test to help work out the dose.

The doctor or nurse will administer Sucrofer by slow injection into a vein, 1 to 3 times per week or as an infusion (drip) into a vein, 1 to 3 times per week.

During dialysis – it will be put into the venous limb of the dialysis machine. Sucrofer will be administered under conditions where any imunoallergic events can receive appropriate and prompt treatment. The patient will be observed for at least 30 minutes by their doctor or nurse after each administration. Sucrofer is a brown liquid and so the injection or infusion will look brown.

Use in children
Sucrofer is not recommended for use in children and adolescents under 18 years of age.
Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

**What benefits of Sucrofer have been shown in studies?**

It was concluded that, in accordance with EU requirements, Sucrofer has been shown to have comparable quality and to be be comparable to Venofer 20 mg iron per ml, solution for injection or concentrate for solution for infusion (Vifor France SA). Therefore, the MHRA decided that, as for Venofer 20 mg iron per ml, solution for injection or concentrate for solution for infusion the benefits are greater than its risk and recommended that it can be approved for use.

**What are the possible side effects of Sucrofer?**

The most common side effects with Sucrofer (which may affect more than 1 in 10 people) are:

- Changes in your taste such as a metallic taste. This does not usually last very long.
- Low blood pressure or high blood pressure.
- Feeling sick (nausea)
- Reactions around the site of injection/infusion such as pain, irritation, itching, haematoma or discolouration following the leakage of the injection into the skin.

**Allergic reactions** (may affects up to 1 in 100 people) if the patient has an allergic reaction, their doctor or nurse should be informed straight away. The signs may include:

- Low blood pressure (feeling dizzy, light-headed or faint).
- Swelling of your face.
- Difficulty breathing.

For the full list of all side effects reported with Sucrofer, see section 4 of the package leaflet available on the MHRA website.

For the full list of restrictions, see the package leaflet.

**Why was Sucrofer approved?**

The MHRA decided that the benefits of Sucrofer outweigh the identified risks and it was recommended that it be approved for use.

**What measures are being taken to ensure the safe and effective use of Sucrofer?**

A risk management plan (RMP) has been developed to ensure that Sucrofer is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Sucrofer including the appropriate precautions to be followed by healthcare professionals and patients.

This medicine is subject to additional monitoring (medicines under additional monitoring are called ‘black triangle’ medicines). This will allow quick identification of new safety information. The patient can help by reporting any side effects they may get. Please refer to the end of section 4 of the package leaflet for information on how to report side effects.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.
Other information about Sucrofer
Germany, France and the UK agreed to grant a Marketing Authorisation for Sucrofer on 01 June 2018. A Marketing Authorisation was granted in the UK on 22 June 2018.

The full PAR for Sucrofer follows this summary.

For more information about treatment with Sucrofer, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in August 2018.
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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Sucrofer (PL 20568/0083; UK/H/6369/001/DC) could be approved. The product is a prescription only medicine (POM) indicated for the intravenous treatment of iron deficiency in the following indications:

- Where there is a clinical need for a rapid iron supply
- In patients who cannot tolerate oral iron therapy or who are non-compliant
- In active inflammatory bowel disease where oral iron preparations are ineffective
- In chronic kidney disease when oral iron preparations are less effective.

The diagnosis of iron deficiency must be based on appropriate laboratory tests (e.g. haemoglobin (Hb), serum ferritin, transferrin saturation (TSAT), serum iron, etc.),

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) with Germany and France as the Concerned Member States (CMS). The application was submitted under Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application. The reference medicinal product for this application is Venofer 20 mg iron per ml, solution for injection or concentrate for solution for infusion licenced to Vifor France SA, France (PL 15240/0001) on 8 June 1998.

Iron sucrose injection is a haematinic agent. Iron is essential to the formation of haemoglobin and to the function and formation of other haem and non-haem compounds. Untreated depletion of iron stores leads to iron-deficient erythropoiesis and, in turn, to iron deficiency anaemia. Administration of iron sucrose replenishes tissue iron stores, reverses iron depletion and iron-deficient erythropoiesis, and corrects or prevents iron deficiency anaemia.

Iron sucrose is a nano-colloidal solution consisting of polynuclear iron cores, composed of iron oxy hydroxide stabilised by a sucrose complex. In response to debate over what data should accompany generic applications for such products the following document was published; “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)”. This document clarifies that the following data are required as a minimum:

1. Quality data demonstrating comparable properties to the reference are provided
2. Non-clinical biodistribution studies
3. Human pharmacokinetic studies

The applicant has supplied the following data:

1. Quality data which draw comparisons between the test and reference product.

2. New non-clinical data to supporting the claim that Sucrofer 20 mg iron/ml, Solution for injection /infusion is sufficiently similar to that of the reference product, Venofer 20 mg iron per ml, solution for injection or concentrate for solution for infusion (see section III non-clinical aspects of this report).

3. A single bioequivalence study in healthy adult volunteers under fasting conditions was submitted to support this application. The applicant has stated that the bioequivalence study was conducted in accordance with Good Clinical Practice (GCP).
The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and the CMS considered that the application could be approved at the end of procedure on 1 June 2018. After a subsequent national phase, a licence was granted in the UK on 22 June 2018.

II QUALITY ASPECTS

II.1 Introduction
Each ml of solution for injection/infusion contains 20 mg iron. Other ingredients consist of the pharmaceutical excipients water for injections and sodium hydroxide.

The finished product is presented as a type I glass ampoule containing 5ml of solution and is available in pack sizes of 5, 10 or 25 ampoules.

Not all pack sizes may be marketed; however, the marketing authorisation holder has agreed to provide mock-ups of any pack size to the relevant regulatory authorities before marketing.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance
BAN: Iron sucrose
Chemical name: Iron (III) hydroxide sucrose complex
Structural formula:

**STRUCTURAL FORMULA**

![Structural formula image]

Molecular formula: \([(\text{Na}_2\text{Fe}_5\text{O}_8(\text{OH}))^3(\text{H}_2\text{O})]n^m(\text{C}_{12}\text{H}_{22}\text{O}_{11})\]

Where, ‘n’ is the degree of iron polymerisation and ‘m’ is the number of sucrose molecules associated with the iron (III) hydroxide.

Molecular weight: The molecular weight of iron sucrose, ranges from 34,000 – 60,000 Dalton

Appearance: Brown to dark brown powder

Solubility: Freely soluble in water and practically insoluble in absolute ethanol and isopropyl alcohol

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

Appropriate specifications have been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.
Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data that comply with the proposed specification are provided.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate a safe and efficacious solution for injection or infusion containing 20 mg iron per ml that could be considered a hybrid medicinal product of Venofer 20 mg iron per ml, solution for injection or concentrate for solution for infusion licenced to Vifor France SA, France. A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at the commercial-scale batch size and shown satisfactory results.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 3 years for the unopened product with the storage conditions “Do not store above 25°C. Do not freeze. Keep the ampoule in the outer carton in order to protect from light”.

From a microbiological point of view, the product should be used immediately.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.
III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of iron are well-known, an overview based on the literature review has been provided.

To further support the safety of the medicinal product the following studies were primarily considered:

1. *In vitro* testing

The purpose of these studies was to detect potential differences between the test and reference products.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
A biodistribution study has been designed as per CHMP reflection paper on the data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product. Before performing the biodistribution study, the protocol was shared with the RMS (MHRA) for the confirmation and quantitative statistical approaches developed for showing similarity or equivalence are used. The criteria for compatibility were clearly defined.

Results
Distribution patterns and extent of total iron in a range of tissues and organs show similarity between Sucrofer 20 mg iron/ml, Solution for injection /infusion and Venofer. A comprehensive explanation of recorded deviations was provided, leading to the acceptance of the argument for similarity.

III.4 Toxicology
A comparative safety pharmacology/toxicity study was performed between the test and reference product. The study compared, haemodynamic and oxidative stress markers, inflammatory parameters, tissue histologies and biochemical processes in normal rats.

Results
Biochemical changes such as those in oxidative markers, were not significantly different between the test and reference product. Staining for ferritin in tissues (kidney and liver, less so for the heart) was also more apparent in the treated rats (both for the test and reference product). This would be expected due to them being target organs for this product. There was no significant difference between iron sucrose products in terms of inflammatory response markers (IL-6 and TNF-α).

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Sucrofer 20 mg iron/ml, Solution for injection /infusion is intended to be used in place of other similar products, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical viewpoint.
IV CLINICAL ASPECTS

IV.1 Introduction
No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of iron.

Based on the results of the bioequivalence study, Sucrofer 20 mg iron/ml, Solution for injection /infusion can be considered bioequivalent to the reference product, Venofer Injection (Iron Sucrose 20 mg / mL, Vifor France SA).

IV.2 Pharmacokinetics
To support the application, the applicant has submitted the data from one bioequivalence study as below.

An open label, balanced, randomised, single-dose, two-treatment, single-period, parallel bioequivalence study comparing the pharmacokinetics of the reference product Venofer Injection (Iron Sucrose 20 mg / mL, Vifor France SA) to the applicant’s test product Sucrofer 20 mg iron/ml, Solution for injection /infusion (Claris Lifesciences UK Limited) in adult, human subjects under fasting conditions.

A single dose [100 mg (5 mL x 20 mg/mL)] slow intravenous injection over 5 minutes was administered after a fast of at least 10 hours. Post dose, 8 mL of blood samples were collected within 1 minute of the end time of intravenous injection of the drug, and up to 36 hours post dose in each period. To provide a pharmacokinetic profile of Total Iron (TI) and Transferrin bound Iron (TBI). Blood samples of 8mL each were drawn at -24.00, -12.00 and 0.00 hours (just prior to dosing) to assess TI and TBI estimation for baseline correction.

The use of a parallel study as opposed to a cross-over design to demonstrate bioequivalence (BE) of the test and reference products was acceptable. However, when this study design is used, it is important that the baseline characteristics are verified to be comparable between the test and reference treatment groups. The applicant provided the summary of subjects’ baseline characteristic for each group and overall for both the test and reference products. The results indicate that baseline characteristics (gender, age, height, weight, BMI, TBI, and TI) are generally comparable between subjects who received the test product and those who received the reference product.

The applicant provided the maximum value of the difference in concentration between TI and TBI over all time points measured. The data indicate that the difference between TBI and TI is consistently higher for the test product compared to the reference product. The mean differences (SD) for Cmax were: 32.01 (4.61) for the Test product and 30.86 (4.01) for the reference product. The mean differences (SD) for AUC were 96.48 (24.17) and 91.92 (25.77) for the test and reference products respectively.
Summary of bioequivalence results

Table No. 01: ANOVA output for Transferrin Bound Iron (including term for treatment and Group) the study results

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<th>Parameter</th>
<th>Cmax</th>
<th>AUC0-t</th>
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<td>T/R Ratio</td>
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<tr>
<td>90% CI Lower Limit</td>
<td>93.50</td>
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<tr>
<td>90% CI Upper Limit</td>
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<td>109.32</td>
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<td>Power</td>
<td>100.00</td>
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Table No. 02: ANOVA output for Total Iron (including term for treatment and Group) the study results

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<th>Parameter</th>
<th>Cmax</th>
<th>AUC0-t</th>
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<tr>
<td>T/R Ratio</td>
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<td>90% CI Lower Limit</td>
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<td>Power</td>
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</table>

The results indicate that TI does appear to return to baseline values by the end of sampling which supports the length of the sampling period.

Conclusion

The 90% confidence intervals of the test/reference ratio for AUC and Cmax values for iron lie within the acceptable limits of 80.00% to 125.00%, in line with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product Sucrofer 20 mg iron/ml, Solution for injection/infusion (Claris Lifesciences UK Limited), is bioequivalent to the reference product Venofer Injection (Iron Sucrose 20 mg / mL, Vifor France SA).

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy

No new efficacy data were submitted, and none were required for an application of this type.

IV.5 Clinical safety

No new safety data were submitted and none were required for this application.

IV.6 Risk Management Plan (RMP)

The marketing authorisation holder (MAH) has submitted an RMP, 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 Sucrofer.

An updated RMP should be submitted:

- At the request of the national competent authority;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of the RMP coincide, they can be submitted at the same time.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application from a clinical view point.
V  User consultation
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI  Overall conclusion, benefit/risk assessment and recommendation
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with iron is considered to have demonstrated the therapeutic value of the compound and the claim of bioequivalence with the reference product is accepted. The benefit-risk balance is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The labelling for Sucrofer 20 mg iron/ml, Solution for injection/infusion is below:
Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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<th>Product information affected</th>
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<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
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