CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

IJzerhydroxide sacharose complex 20 mg/ml PCH, solution for injection/concentrate for solution for infusion Pharmachemie B.V., the Netherlands

iron(III)-hydroxide sucrose

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.
It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 33727

7 June 2010

Pharmacotherapeutic group:	iron trivalent, parenteral preparations
ATC code:	B03AC02
Route of administration:	intravenous
Therapeutic indication:	parenteral treatment of iron deficiency when not correctable with oral treatment.
Prescription status:	prescription only
Date of authorisation in NL:	18 February 2009
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for IJzerhydroxide sacharose complex 20 mg/ml PCH, solution for injection/concentrate for solution for infusion from Pharmachemie B.V. The date of authorisation was on 18 February 2009 in the Netherlands.

The product is indicated for parenteral treatment of iron deficiency when not correctable with oral treatment.
This may be the case in:

- Patients known to be intolerant to oral iron preparations,
- Patients who are non-compliant,
- Patients for whom there is a specific clinical need to deliver iron rapidly to the iron stores,
- Patients for whom oral iron preparations are ineffective (e.g. as a result of active inflammatory bowel disease).

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

A comprehensive description of the indications and posology is given in the SPC.

The polynuclear iron(III)-hydroxide cores are superficially surrounded by a large number of non-covalently bound sucrose molecules resulting in a complex whose molecular mass M_w is approx. 43 kDa. This is sufficiently large to prohibit renal elimination. The resulting complex is stable and does not release ionic iron under physiological conditions. The iron in the polynuclear cores is bound in a similar structure as in the case of physiologically occurring ferritin.

This national procedure concerns a generic application claiming essential similarity with the innovator product Venofer solution for infusion 20 mg/ml which has been marketed in the EU since 1975. In the Netherlands, Venofer 20 mg/ml ijzer, solution for injection or concentrate for solution for infusion (NL License RVG 20690) has been registered by Vifor France SA since 30 October 1997.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As IJzerhydroxide sacharose complex 20 mg/ml PCH is a product for parenteral use in aqueous solution, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is iron(III)-hydroxide sucrose, an established active substance, however not described described in the European Pharmacopoeia (Ph.Eur.*). The substance is a hygroscopic brown-reddish powder, which is freely soluble in water.

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/EMEA 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 MAH has provided a flow sheet of the manufacturing process. The product developed is a lyophilized powder. The process has been sufficiently described, and is under appropriate control.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and is generally in accordance with the DMF. However, the MAH has set some limits which are wider than the DMF limits. The MAH committed to adopt the tighter limits. If higher limits will be proposed, these should be justified from a toxicological point of view. Analytical procedures have been sufficiently described. Batch analytical data demonstrating compliance with this specification have been provided for 3 production-scale batches. The certificates of analysis will be amended with the correct limits.

Stability of drug substance
Stability data on the active substance have been provided in accordance with applicable European guidelines, justifying a retest period of 36 months.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
IJzerhydroxide sacharose complex 20 mg/ml PCH is a dark brown, unclear aqueous solution. One ml contains 20 mg of iron(III)-hydroxide sucrose complex. Osmolarity is specified at 1150-1350 mOsmol/L, and pH at 10.5-11.1.

The solution for injection/concentrate for solution for infusion is packed in 5 ml type I colourless vials.

The excipients are: sodium hydroxide (E524), water for injection.

Pharmaceutical development
The development of the product has been based on specific documentation, the official United States Pharmacopoeia (USP) monograph of the finished product (Iron Sucrose injection, USP) and literature, as

well as on the particular characteristics and properties of the originator product. No particular alterations to the master formula of the innovator product have been made.
Equivalence is claimed based on *in vitro* data. Results of comparative *in vitro* studies did not reveal relevant differences between the product at issue and the innovator. A sterile filtration method is used during manufacturing in order to obtain a sterile final product. The product is not sterilized in the final packaging. The choice of sterilizing filtration and aseptic processing has been well justified. The MAH has sufficiently shown that the product at issue can be considered equivalent to the innovator product.

Manufacturing process
The manufacturing process has been adequately described and validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for full-scale batches in accordance with the relevant European guidelines. Based on these results it is concluded that the manufacturing process of the product at issue is controlled and consistently demonstrates compliance to the finished product specification. The MAH does not sterilize the product in the final packaging, but is applying an aseptic manufacturing process and a final sterile filtration.

Container closure system
Adequate information on the container closure system has been provided. A declaration that the packaging material complies with the Ph. Eur. has been provided.

Control of excipients
The excipient specification comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, specific gravity, particular matter, alkalinity, osmolarity, turbidity, pH, assay, uniformity of volume, related substances, sterility and endotoxins. The requirements are acceptable in view of the official USP monograph. The release and end-of-shelf-life specifications are identical. This is acceptable in view of the stability data. Satisfactory validation data for the analytical methods have been provided.
Batch analytical data from 1 pilot-scale and 2 production-scale batches have been provided, demonstrating compliance with the specification.

Comparative *in vitro* studies
The product at issue is claimed to be essentially similar to the innovator product (Venofer®). The following techniques to demonstrate similarity to the innovator product were provided (tested in accordance with the USP monograph):
- Sucrose content
- Fe^{3+} content
- Molecular weight distribution
- pH
- Turbidity point.

The results of these tests did not reveal relevant differences between the product at issue and the innovator product. As iron sucrose is a highly complex colloidal macromolecule, the following evidence has been provided for similarity versus the innovator:
- Photon Correlation Spectrometry (particle size)
- Atomic Force Microscopy (size and shape/morphology)
- Fourier Transformation Infrared Spectrometry (chemical structure)
- X-ray Diffraction analysis (chemical structure, polymorphic form)
- Reduction kinetics of the finished product.

Stability of drug product
Stability data on the product have been provided for 3 batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). All 24 months normal stability results and 6 months accelerated stability results meet the set requirements; no particular or significant trends regarding stability indicating parameters could be observed. Photostability testing was performed in accordance with the ICH guidelines. No

evidence of product degradation due to light exposure was found. Based on these results, the claimed shelf life of 24 months could be granted. The labeled storage conditions are *Store in the original packaging* and *Do not refrigerate or freeze.*

Compatability/In-use stability
In-use stability was demonstrated for the product after dilution in 100 ml of NaCl 0.9 %. The diluted product was tested after 24 hour storage at 2-8°C and 25°C. These in-use conditions are acceptable.

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 can be excluded.

II.2 Non clinical aspects

This product is a generic formulation of Venofer 20 mg/ml, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of iron(III)-hydroxide sucrose released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Iron(III)-hydroxide sucrose is a well-known active substance with established efficacy and tolerability.

IJzerhydroxide sacharose complex 20 mg/ml PCH, solution for injection/concentrate for solution for infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of IJzerhydroxide sacharose complex 20 mg/ml PCH is entirely the same as the originator. *In vitro* studies has confirmed comparability of IJzerhydroxide sacharose complex 20 mg/ml PCH compared to Venofer. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

Risk management plan
Iron(III)-hydroxide sucrose was first approved in Europe in 1975, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of iron(III)-hydroxide sucrose can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the national procedure is in accordance with that accepted for the reference product Venofer.

Readability test

The package leaflet has not been evaluated via a user consultation study. The PIL has been brought in accordance with the approved text for procedure SE/H/0627/01/DC, concerning another iron sucrose generic. User testing was performed on this PIL, and a sufficient level of readability was demonstrated. Therefore, the PIL for the product at issue could be exempted from user testing.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

IJzerhydroxide sacharose complex 20 mg/ml PCH, solution for injection/concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Venofer 20 mg/ml ijzer. Venofer is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. IJzerhydroxide sacharose complex 20 mg/ml PCH was authorised in the Netherlands on 18 February 2009.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to adopt the tighter limits as stated on the DMF and amend the certificates of analysis with the correct limits. If higher limits will be proposed, these should be justified from a toxicological point of view (taking into account the administration route).

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Update to a current DMF.	--	II	30-3-2009	28-4-2009	Approval	N