LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Ferofix
(ferric hydroxide polymaltose complex)

SE/H/1632/01/DC

This module reflects the scientific discussion for the approval of Ferofix. The procedure was finalised on 2017-07-05. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories S.A. has applied for a marketing authorisation for Ferofix, 100 mg, chewable tablet. The active substance is ferric hydroxide polymaltose complex.

For approved indications, see the Summary of Product Characteristics.

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

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Since this is a WEU application, the non-clinical section is based solely on bibliographical data.

III.2 Pharmacology

Ferofix contains trivalent iron (Fe^{3+}) in a so called ferric hydroxide polymaltose complex (also known as ferric polymaltose, iron dextrin and iron polymaltose complex or IPC). The polymaltose complex is a sugar complex which provides protection against the acidic milieu in the stomach and helps the iron to reach the duodenum. There, the complex then gradually releases Fe^{3+} which is absorbed by active transport into enterocytes. In the enterocyte cells, Fe^{3+} then becomes altered to Fe^{2+} and is then either secreted into the blood or stored bound to ferritin.

III.3 Pharmacokinetics

No negative effects on IPC radiolabelled iron availability in rats have been reported when the IPC has been combined with various medical drugs substances: aluminium hydroxide, acetylsalicylic acid, bromazepam, calcium acetate, calcium carbonate, auranofin, magnesium-L-aspartate hydrochloride, methyldopa sesquihydrate, paracetamol, penicillamine, sulfasalazine, tetracycline hydrochloride, calcium phosphate in combination with vitamin D3, and multi-vitamin preparations. Based on published nonclinical information, the impact of food on IPC iron bioavailability remains unclear.

Intravenously administrated IPC in male rats led to a tissue distribution 14 d days later where 84.6% of the iron was present in the blood, 8.5% in the liver, 0.9% in the kidneys, 1.2% in the spleen, 3% in the faeces and 0% in the urine. Iron in the body usually exists in the ferrous (Fe^{2+}) or ferric (Fe^{3+}) state, with Fe^{2+} readily being oxidized to Fe^{3+}. The fate of the polymaltose complex (e.g. degradation in the lumen, uptake into cells) remains unclear.

When administered intravenously to non-anaemic male rats, IPC was more rapidly eliminated from the serum than ferrous sulphate preparations. However, in anaemic rats no difference could be demonstrated.

Overall, there is only limited non-clinical pharmacokinetic information available concerning IPC but the uncertainty is considered acceptable given the well-established use history of IPC products.

III.4 Toxicology

The acute toxicity NOAEL of oral IPC in Long-Evans rats is above 1000 mg/kg. Acute toxicity studies in Sprague-Dawley rats indicate that oral IPC is less toxic than intravenous IPC administrations and that oral IPC is less toxic than oral ferrous sulphate (which generates gastrointestinal toxicity).

No adverse effects from IPC were reported after repeatedly exposing Sprague-Dawley rats orally (via stomach tube) for 280 mg/kg over 28 days. Exposure for up to four months did not measure any increase in oxidative stress markers in liver or intestines.

No direct IPC genotoxicity publications have been provided but it is known that iron ions have genotoxicity potential. That being said, the iron from ferric-sugar complexes like IPC is very slowly absorbed and there are no indications of oxidative stress for five biomarkers in the two main solid tissues of iron uptake and accumulation (intestines, liver) after four months continuous exposure in rat. The genotoxicity risk of Ferofix is therefore considered low. No carcinogenicity data has been provided for IPC but there is clinical experience from oral iron supplements such as IPC since the late 1970s (e.g. Maltofer). The carcinogenicity risk is therefore also considered low and the absence of such literature reports acceptable.

A full term (Gd0 to Gd21) oral gavage exposure of anaemic pregnant rats at 2 mg/kg/day IPC complemented with 7 µg/kg/day folic acid did not produce any significant differences between control animals and IPC treated animals. Overall, the data is insufficient for a full non-clinical evaluation of the developmental and reproductive toxicity of Ferofix. This is acceptable considering the clinical experience and that there are several clinical studies available.

III.5 Ecotoxicity/environmental risk assessment

No environmental risk assessment (ERA) has been conducted. The polymaltose part of the IPC is a carbohydrate and therefore very unlikely to pose an environmental risk. The active moiety in IPC, iron, is also unlikely to provide a risk to the environment, given that iron is found ubiquitously in the environment and that the administration is primarily to iron deficient patients.

III.6 Discussion on the non-clinical aspects

The non-clinical documentation provided for Ferofix is limited but this is considered acceptable based on the well-established usage aspect of the product. Oral repeat-dose toxicity studies in rats for 4w did not produce any clear toxicity. While excessive iron may influence redox metabolism and therefore lead to potential for genotoxicity, a four month long oral exposure in rats did not increase oxidative stress markers in the intestines or liver. Based on the nature of Ferofix, no ERA is considered necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Iron deficiency with or without anaemia is a common medical problem worldwide especially in women with child-bearing potential. Iron treatment is given orally or intravenously depending on the severity of the iron deficiency and co-morbidities of the patient.

A common oral treatment is the Fe (II) form of iron, most common ferrous sulphate. In several countries of the EU there are also formulations where the ferric form of iron, Fe(III), is used together with polymaltose complex (IPC).

Ferofix is formulated as a ferric hydroxide polymaltose complex (corresponding to Iron III) or Iron polymaltose complex – IPC. Maltofer 100 mg chewable tablets, also an IPC, have been available for at least 20 years (first authorized in Finland 1992) and are currently marketed in many EU member states.
The iron (III)-hydroxide polymaltose complex (IPC) is a macromolecular complex in which polynuclear ferric oxyhydroxide is complexed with polysaccharide groups. For further information regarding the drug substance and product see the Quality assessment report.

Since this is a WEU application it is based solely on bibliographical data.

IV.2 Pharmacokinetics

Absorption of iron from the gut is carefully regulated. Because there is no active excretory process for iron once it has entered the bloodstream, the body's control of iron levels is undertaken at the level of the enterocyte. Absorption is increased when IPC is administered with food.

About 60% of iron is found in the erythrocytes within hemoglobin. The remainder is found in myoglobin in the muscles, in a variety of different enzymes and in storage form.

There is no active excretory process for iron once it has entered the bloodstream and iron in the body is in a dynamic equilibrium between different compartments. Increasing doses of iron were associated with decreased bioavailability, as measured by iron incorporation into haemoglobin which suggests that iron has a less than dose proportional increase in absorbed iron.

Impaired renal and hepatic function does not affect iron exposure as iron is not eliminated via the liver or kidneys to a large extent.

The applicant has presented literature data on a low potential for drug interactions between IPC and other drugs.

IV.3 Pharmacodynamics

Serum iron (i.e., iron bound to transferrin) represents only a very small proportion of total body iron (<0.2%). There is no correlation between the serum iron AUC values (area under the curve values) and the utilisation ratio after application of radio-labelled original IPC but a correlation has been found between RBC iron incorporation and whole-body counts.
The pharmacodynamic effect of iron(III)-polymaltose seems to be equal to the effect of ferrous sulfate, although there is no linear relationship between serum iron increase (Cmax and AUC) and the given dose. However, as iron must be in the ferrous state (Fe++) to be absorbed, this product, likewise to dietary iron is in the ferric form (Fe+++). The gastric secretions dissolve the iron in food and provide a milieu favourable to its reduction to the ferrous form. It is plausible that gastric secretions are needed to convert iron(III)-polymaltose to be absorbed.

IV.4 Clinical efficacy

Iron deficiency is an area with a medical need for better tolerated oral products. IPC is a ferric (FeIII) form of iron supplement. There has been a substantial scientific interest in IPC during many years and IPC has been approved in many EU countries for several years. In Finland it has been approved as oral drops since 1967 and as chewable tablets since 1992. The effect of iron (III) polymaltose complex in normalizing Hb and replenishing iron store levels has been studied in randomised, placebo or reference-therapy controlled clinical trials conducted in adults and adolescents (greater than 12 years of age) with varying iron status. The Applicant has therefore submitted only bibliographical data.

The applicant has presented eight (8) controlled clinical studies that have been performed with IPC in adult subjects, including 6 trials where IPC was compared to treatment with ferrous preparations [Jacobs, 1993; 2000; Langstaff, 1993; Sas, 1984; Rosenberg, 1979; Reddy, 2001], 2 placebo-controlled trials [Tuomainen, 1999; Mackintosh, 1988], and one trial comparing IPC to no treatment [Vetter, 2000]. These trials included a total of approximately 800 subjects, with approximately 480 receiving IPC. The clinical data available for iron deficiency anaemia are

up to 3 months of treatment, and up to 6 months of treatment for iron deficiency without anaemia.

For example, Tuomainen et al. [1999] conducted a 6-month placebo-controlled trial in 48 men with serum ferritin ≤ 30 μg/L. Patients were randomized to receive IPC (containing 200 mg of iron as chewable tablets) plus placebo resembling FeSO4, microencapsulated FeSO4 (180 mg of iron) plus placebo IPC, or both placebo. At 6 months, serum ferritin concentrations had increased 2.2-fold in the FeSO4 (FS) group ($p < 0.001$) and 1.3- fold in the IPC group ($p < 0.001$ versus placebo). Erythrocytic ferritin, however, which is considered a better marker for iron stores, increased equally under both active treatments. Haemoglobin also increased in both groups (by 1.0 % with FeSO4 and by 2.2 % with IPC, $p < 0.001$ vs placebo in both cases). Three subjects receiving 180 mg of iron as microencapsulated ferrous sulphate and 2 receiving 200 mg of iron as IPC reported gastric disturbances. This resulted in treatment discontinuation in one case in each group, while the dose was halved for the other three subjects. Furthermore, it was shown in the Toumainen study that oral preparations of ferrous sulphate increase the susceptibility for oxidation of plasma lipoproteins.
[Tuomainen, 1999]

Mackintosh and Jacobs [1988] studied 46 blood donors, 23 had low iron stores (ferritin <20 μg/L) but Hb ≥13.5 g/dL, and the other 23 (ferritin 50–150 μg/L) served as controls. Both groups were randomised to 100 mg IPC or placebo twice a day for 8 weeks. In the iron-deficient group, iron therapy resulted in a significant rise in haemoglobin (14.3 to 15.0 g/dl, $p = 0.03$) and serum ferritin (16.2 to 43.2 μg/L, $p = 0.002$). In the placebo group, there was no significant change in the haemoglobin level, and a small but significant rise in ferritin. This increase was significantly lower than the increase seen in the IPC group. In the non-iron deficient control group, neither IPC nor placebo produced a significant change in haemoglobin or ferritin levels. This study shows that IPC effectively refilled depleted iron stores and simultaneously produced an increase in haemoglobin in iron deficient subjects without overt anaemia. Gastrointestinal disturbances were not reported despite specific enquiries about adverse effects such as anorexia and nausea [Mackintosh, 1988].

Six (6) controlled studies were identified in literature comparing IPC with ferrous salts and only one study using different doses of IPC. Of the subjects treated with IPC, 160 received IPC in the form of chewable tablets.

Jacobs et al, [1993] investigated the effect of iron therapy on 159 blood donors with overt iron deficiency anaemia (Hb <133 g/L for men, <116 g/L for women). Subjects were randomised to either 60 mg of iron twice daily as FeSO4 (group 1), 100 mg iron once daily as IPC (group 2), or 100 mg iron twice daily as IPC (group 3). Both IPC groups took tablets with meals. 80% of the subjects in groups 1 and 3 reached normal Hb levels by 12 weeks, but in group 2 this figure was only 50 %. Similarly, the proportion of subjects improving their percentage transferrin saturation to within the normal range was significantly better in groups 1 and 3 than in group 2 ($p < 0.01$). The progression to normal was somewhat slower in group 3 than in group 1, but there was no difference by 12 weeks. Nausea and vomiting occurred in all 3 groups, but to a higher extent with ferrous sulphate administration. Treatment had to be stopped because of side effects in 11 cases (20%) in the ferrous sulphate group but in no patients receiving IPC. The incidence of mild gastrointestinal adverse events was similar with both IPC dosages [Jacobs, 1993].

In Jacobs et al, [1993] the treatment subjects were found among blood donors as well but in this study there was preponderance for females included (137 of 159). Please see the figure of the hemoglobin results below.

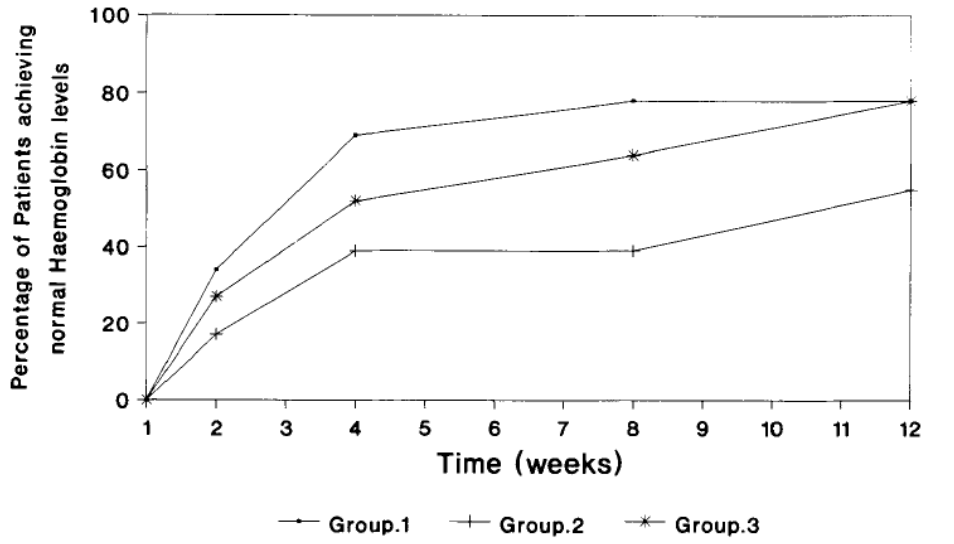
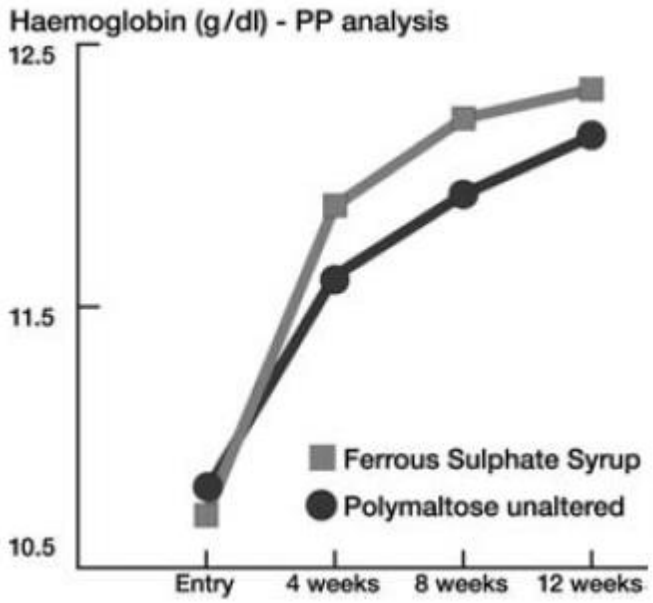


Fig. 1. Percentage of patients achieving normal haemoglobin values over time. Group 1: 60 mg ferrous sulphate, twice a day. Group 2: 100 mg iron as ferric polymaltose daily. Group 3: 100 mg iron as ferric polymaltose twice a day. Although haemoglobin levels rose in all groups, this had reached 80% in Groups 1 and 3 at 12 weeks, but only 55% in Group 2. It is notable that with both doses of ferric polymaltose no plateau had been reached in the last 4 weeks of replacement therapy.

Jacobs et al. [2000] compared IPC and FeSO4 for the treatment of IDA in 143 regular blood donors in an open, randomised trial. Both preparations were given on a 100 mg bid schedule. Hb levels increased to a similar extent in both groups (with no statistically significant difference at either 4 or 8 weeks) (Fig. 6) and similar increases in mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV) and decreases in the percentage of hypochromic red cells were also observed. The withdrawal rate due to adverse events considered at least possibly drug-related was significantly higher (15/48) with FeSO4 than with IPC (16/125; $p = 0.007$). Nausea was the main reason given for interrupting treatment in the FeSO4 group. Tolerance was rated either good or adequate in about 80% of the patients in IPC groups, and in about 60% of patients receiving ferrous sulphate. The authors also noted that serum ferritin levels were higher with the ferrous salt and that this may indicate oxidative stress [Jacobs, 2000]. See the figure below with data retrieved from this publication.



V. Haemoglobin concentration in per-protocol patients with 12 weeks of treatment with IPC or ferrous sulphate [Jacobs, 2000].

More than 130 adolescents have been treated with IPC in clinical trials. The efficacy results seen in adolescents seem to be comparable to the results seen in adults. [Devaki, 2007; 2008; 2009] No adverse events were reported in these studies.

The applicant has performed a literature search and submitted a clinical overview and summary. There is a reasonable amount of data supporting a clinical relevant efficacy of IPC. During the procedure the applicant provided a discussion and justification on the similarities and diversities of the applied product compared to the products used in the clinical studies. This was considered acceptable in a clinical point of view to reassure that the data provided gave a solid ground for the applied product with reference to for example iron release and clinical efficacy and safety.

The Applicant has accepted all proposed amendments to the SmPC during the procedure this is why the product is approvable from a clinical point of view.

V.1 Clinical safety

The safety profile of IPC seems to be quite beneficial. Gastro-intestinal side effects are the most common in oral therapy. The literature points to that the frequency of some of these side effects for example nausea, vomiting and heartburn are less common with IPC compared to ferrous salts. However, the most common side effects like diarrhoea and obstipation the results are more unclear. Strikingly, in some of the published studies especially in adolescents, no side effects at all were reported. However, there is no reason to believe that the effect and safety differs in between adults and adolescents and children from the age of twelve.

The applicant claimed that there is no risk of overdosage because the active substance iron (III)-hydroxide-polymaltose complex is not present in the gastro-intestinal tract as free iron

and is not taken up by passive diffusion. This was further discussed in the procedure and described in the SmPC section 4.9.

V.2 Risk Management Plans

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 Ferofix.

Safety specification

Summary table of safety concerns as proposed in the RMP

Important identified risks	N/A
Important potential risks	Poisoning.
Missing information	N/A

The summary table of safety concerns as proposed in the RMP is accepted.

Pharmacovigilance Plan

Safety concerns and overview of planned pharmacovigilance actions

Poisoning		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None.	Routine pharmacovigilance.	To minimize/monitor an increase of incidence or severity, or changes in the clinical presentation of these effects.

Summary of Safety Concerns and Planned Risk Minimisation Activities as proposed/ approved in RMP

VI.1.4 Summary table of risk minimisation measures-updated

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important potential risk		
Poisoning	Risk minimisation activities consist to describe in the relevant section of the SmPC relevant information to minimize the risk: ***4.4 Special warnings and precautions for use*** *Iron-based preparations can cause poisoning,*	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	especially in children. Particular attention should be paid in case of iron supplementation. ***4.9 Overdose*** *<Invented Name> contains the ferric form of iron, which is not present in the gastro-intestinal tract as free iron and therefore it is anticipated to be less toxic than iron products with ferrous compounds. There have been no reported cases of accidental poisoning with fatal consequences, however it should be taken into consideration that the data on overdosage with the ferric form of iron are limited.* *In case of overdosage the clinical status should be assessed and general routines for suspected overdose cases should be followed. Symptoms of overdosage include: vomiting, hematemesis, abdominal pain, lethargy, acute liver failure, coagulopathy, acute tubular necrosis, metabolic acidosis, shock, gastric scarring and pyloric stricture. Acute liver failure and cardiovascular collapse are the main causes of death due to iron overdose.* Legal Status: Prescription only product.	

Summary of the RMP

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

The RMP is approved

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- 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 dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

VI. 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.

VII. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Iron deficiency (ID) with or without anaemia (IDA) is a common clinical problem especially in women of child-bearing age but also in relation to chronic diseases and malignancies. There are several registered products used to treat ID and IDA. The most commonly used oral product is formulations with ferrous sulphate. The effect of this treatment is good but its use is somewhat hampered by side effects of predominately gastrointestinal nature. In addition to this, iron in the form of ferrous sulphate is very poisonous, in particularly for small children.

In cases where oral ferrous is not suitable, for example in severe anaemia with empty iron storages, intravenous formulas are used. These are very effective in replenishing iron deficiency and the iron storages. However, they are associated with a relatively high frequency of severe allergic reactions.

Therefore there is a clinical need for oral iron formulations with a more favourable safety profile but with an efficacy profile effect compared to ferrous sulphate.

For a WEU application (Article 10a of Directive 2001/83/EC) a medical substance should have been used within the EU with a recognised efficacy and an acceptable level of safety for at least 10 years. IPC is approved in several EU countries and in Finland, Greece, Germany, Ireland, Hungary, Slovakia, and Switzerland, chewable tablets 100 mg, and has been available for at least 10 years. In this WEU application, the presented review of the literature data points to a milder safety profile with IPC compared to ferrous sulphate. On the other hand the clinical response, with regard to haematological values (hemoglobin) may be slower with oral ferric forms of iron compared to oral ferrous salts.
In addition, some data suggests that the load of oxidative stress is less with a ferric iron compound than with the ferrous compound and the applicant put forward that this is a reason for a higher serum ferritin levels obtained with ferrous compounds.

Since, in this application reference is made to bibliographical data of products containing “iron polymaltose complex” (IPC) the similarity between these IPC products and the product applied with regard to release of the active substance ferric hydroxide polymaltose complex must be justified. During the registration procedure the applicant has presented an acceptable discussion and justification that the under registration product in this application is reasonably comparable to the products used in the bibliographical data from a clinical point of view.

In conclusion, there is a reasonable amount of published data that supports the applicant’s position that IPC may be as effective in optimised doses as ferrous sulphate compounds in treating iron deficiency seemingly with fewer side effects.

All quality questions have been acceptably addressed and approval is recommended from a chemical-pharmaceutical view-point.

To conclude, the quality of Ferofix is found adequate. There are no objections to approval of Ferofix from a non-clinical and clinical point of view. The product information is acceptable. The application is therefore recommended for approval for the indication:

"*Treatment of iron deficiency in adults and adolescents above the age of 12.*"

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VIII. APPROVAL

The Decentralised procedure for Ferofix, 100 mg, chewable tablet was positively finalised on 2017-07-05.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

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

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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