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Research Article

Intravenous Iron Formulations: Drug Selection by Means of the SOJA Method

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Abstract

Objectives: This analysis was performed to compare intravenous iron formulations for the treatment of iron deficiency anaemia when oral iron preparations are ineffective, contraindicated or not tolerated in any other way.

Methods: In this study intravenous iron formulations are compared by means of the SOJA method.

The following selection criteria were applied: licenced indications, contraindications, warnings and precautions, number of formulations, drug interactions, clinical efficacy, adverse effects, safety, tolerability, ease of admininstration and documentation.

Results: Overall SOJA scores differed slightly, with Ferric derisomaltose showing the highest score, followed by Ferric carboxymaltose. The scores for the other formulations were lower, especially because of the lower ease of administration.

Acquisition cost was not taken into account, because this varies with time. In practice acquisition cost is of course an important selection criterion. Exclusion of this criterion also makes this comparison more internationally applicable..

Conclusion: The present matrix may be of use for hospital formulary committees in determining preferences for specific iron formulations from a clinical practice, prior to the procurement phase.

Keywords: Intravenous Iron Formulations; Drug Selection; Ferric Carboxymaltose; Ferric Dextran Complex; Ferric Derisomaltose; Iron Sucrose

Introduction

Formerly, intravenous iron formulations were based on dextran-binding to prevent uncontrolled release of free iron into the systemic blood circulation upon administration. However, high molecular weight dextran was frequently associated with serious adverse effects. Therefore, it was worldwide withdrawn from the market in 2009. Meanwhile, several alternative intravenous iron formulations had been introduced, characterized by a better safety profile than high molecular weight dextran iron derivatives.

This analysis was performed to compare intravenous iron formulations for the treatment of iron deficiency anaemia when oral iron preparations are ineffective, contraindicated or not tolerated in any other way.

Applied methodology

In this study, the currently available intravenous iron formulations are compared by means of the System of Objectified Judgement Analysis [SOJA] method.

The SOJA method is a structured procedure to rationalize drug selection. The relevant selection criteria for intravenous iron formulations are defined and judged by a panel of experts and each selection criterion is given a relative weight [based on expert consensus]. The more important a selection criterion is considered, the higher the relative weight that is given to that criterion. The ideal properties for these medicines are agreed upon and each intravenous iron formulation is scored as a percentage of the score of the ideal medicine for all selection criteria. The medicines with the highest overall score are most suitable for formulary inclusion [1].

In the published SOJA scores, 1000 points are subdivided over the criteria that are considered to be relevant for a particular group of medicines. In the interactive program, the scores for each drug have been determined by a group of experts and the user is free to assign his own relative weight to each criterion adapting to any scale deemed [locally] relevant, thereby calculating a personal score.

Methods

The following medicines were included in the analysis:

- Ferric carboxymaltose, FCM [Ferinject®]
- Low Molecular Weight ferric dextran complex, FDC [CosmoFer®]
- Ferric derisomaltose, FDM, previously called iron isomaltoside [Monofer®, Diafer®]
- Iron sucrose, IS [Venofer, Ferracin®, generic®]

Ferumoxytol [Rienso®] and ferric gluconate [Ferrlicit®], which are not available in the Netherlands, were not included in the analysis.

The main characteristics of iron formulations are shown in table 1.

The selection criteria and authors' weighting are presented in table 2.

Selection criteria

Licenced indications

The number of licensed indications is a good measure of the applicability and documentation of the medicines. The fact that a drug is approved for [almost] all indications listed below is, from a formulary point of view, advantageous to another drug, that is approved for only one or two applications.

	FCM	FDM	FDC	IS
Molecular weight (Dalton)	233,000	150,000	165,000	35,000-60,000
Half-life (h)	9.4	20-35 hours	27-30	5.3
Free iron % of dose	1-2	<1	1-2	4-5
Concentration iron	50 mg/ml	100 mg/ml	50 mg/ml	20 mg/ml
Carbohydrate	Carboxymaltose (branched polysaccharide)	Isomaltoside (linear oligosaccharide)	Dextran (branched polysaccharide)	Sucrose (disaccharide)
Test dose required	No	No	Yes	No
Approved max. daily dose	1000 mg	20 mg/kg	20 mg/kg	200 mg

Table 1: Main properties.

Selection Criterion	Relative Weight Factor
Licenced indications	60
Contraindications	40
Warnings and precautions	20
Number of formulations	60
Drug interactions	20
Clinical efficacy	300
Adverse effects	200
Ease of administration	200
Documentation	100
Total	1000

Table 2: Selection criteria and authors' weighting.

Contraindications

A large number of contraindications limits the clinical use of medicines. Fewer clinically relevant contraindications imply higher scores.

Special precautions and warnings

Special precautions and warnings may also limit the clinical use of medicines. Fewer precautions and warnings, result in higher

scores.

Number of available formulations

A large number of available ready to use formulations offer the possibility to give each patient an optimal dosage with minimal handling of the product.

This was scored as follows [percentage of the relative weight].

Strength (mg iron)	Score
50 mg	10%
100 mg	10%
200 mg or 250 mg	20%
500 mg	30%
1000 mg	30%

Table a

Drug interactions

Interactions play a role only in patients who use other medicines which may interact with iron formulations. However, it is a relevant criterion from a formulary point of view.

The score for each drug was dependent on the number, frequency and severity of observed drug interactions.

Clinical efficacy

Clinical efficacy is a very important selection criterion for all groups of medicines. The score was dependent on the relative efficacy of each iron formulation, taking into account results from direct comparative studies between iron formulations, comparative studies with other treatments [such as oral iron] or [to a lesser extent] non-comparative studies.

Side effects

The number, the extent and the severity of adverse effects were in combination another major selection criterion for medicines. A distinction was made between "minor" side effects, such as gastrointestinal disturbances or skin reactions, occurring in clinical trials and severe or even life-threatening adverse reactions observed with large scale use of the medicines. The evaluation of the "minor" adverse effects was based on results of double blind comparative clinical studies.

Ease of administration

It is an advantage when the full dose of an intravenous iron formulation can be administered as a short time infusion.

This was scored as follows.

Administration	Rate	Score
IV bolus injection possible		20%
IV infusion possible		20%
IM injection possible		5%
Injection into dialyser possible		5%
Max daily dose of at least 1000 mg allowed		10%
Max daily dose of 20 mg/kg allowed		10%
Duration of infusion: dose ≥1000 mg	15 minutes-30 minutes	30%
	1 hour	20%
	2 hours	10%

Table b

Documentation

The score for this criterion was subdivided in four topics: The first two topics are indicative of the overall clinical documentation of the medicines in randomized controlled clinical studies. A large number of clinical studies and a large number of patients included in these studies signified robust evidence clinical efficacy and safety of this drug in the studied population. The latter two topics were indicative of the overall clinical experience with the drug.

Number of randomized comparative studies

The number of randomized comparative clinical studies is an important determinant of the clinical documentation. Five % of the relative weight for this topic was granted for each randomized comparative study.

Number of patients in these studies

Besides the number of clinical studies, the number of patients that were treated with the drug in question had also tot be taken into consideration.

One percent of the relative weight for this topic was awarded for every ten patients enrolled in randomized comparative studies.

Number of years marketed

The number of years that a product has been marketed in any country of the world provided information on the clinical experience with the drug. If a product was on the market for more than 10 years it is very unlikely that serious adverse reactions will be observed that have not been seen in the first ten years after its introduction.

Ten percent of the relative weight for this subcriterion was awarded for every year that the product was available on the market.

Number of patients treated worldwide

Besides the number of years that a product was on the market, also the number of patient days experience with the drug was taken into account.

One percent of the relative weight for this topic was calculated for 100,000 patients treated with the drug in question worldwide.

Results

Licenced indications

The exact Summary of Product Characteristics SPC texts regarding the licensed indications are summarized below.

FCM [Ferinject®]

Indicated for treatment of iron deficiency, when oral iron preparations are ineffective or cannot be used. The diagnosis of iron deficiency must be based on laboratory tests.

FCM [Diafer®]

Diafer® is indicated in adults for the treatment of iron deficiency in patients with chronic kidney disease on dialysis, when oral iron preparations are ineffective or cannot be used.

The diagnosis of iron deficiency should be based on appropriate laboratory tests [e.g. serum ferritin, serum iron, transferrin saturation or hypochromic red cells].

FDM [Monofer®]

Indicated for the treatment of iron deficiency in the following conditions when oral iron preparations are ineffective or cannot be used or where there is a clinical need to rapidly administer iron.

Again, iron deficiency must be objectified by laboratory tests.

FDC [CosmoFer®]

Indicated for the treatment of iron deficiency in the following indications:

- When oral iron preparations cannot be used, e.g. due to intolerance, or in case of demonstrated lack of effect of oral iron therapy
- If there is a clinical need to rapidly restore iron stock.

The diagnosis of iron deficiency must be based on appropriate laboratory tests.

IS [Venofer®, generic]

IS is indicated for the treatment of iron deficiency in the following indications:

- If 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 documented as above.

None of the formulations is licensed for use in children under the age of 18.

Although the SPC indications are not entirely identical [IS is explicitly licensed in IBD and kidney disease and FDM [Diafer®]], there are no relevant differences in the clinical applicability based on the licensed indications.

Therefore all formulations are awarded 100%.

Contraindications

All formulations are contraindicated in case of:

- Hypersensitivity to the active substance, or any of its excipients
- Known serious hypersensitivity to other parenteral iron products.
- Anaemia not attributable to iron deficiency, e.g. Aplastic anaemia
- Evidence of iron overload or disturbances in the utilisation of iron.

Specific contraindications

FDM

- Decompensated liver disease

FDC

- Decompensated liver cirrhosis and hepatitis
- Acute or chronic infection, because parenteral iron administration may exacerbate bacterial or viral infections
- Acute renal failure.

No additional contra-indications are applicable to FCM and IS. These formulations are awarded 80%.

One extra contraindication applies to FDM. This product is awarded 75%.

Most contraindications are applicable for FDC. This formulation is awarded 50%.

Special precautions and warnings

All formulations have the following precautions and warnings in the SPCs:

SPC Cosmofer https://www.medicines.org.uk/emc/product/48/smpc;

SPC Ferinject https://www.medicines.org.uk/emc/product/5910/smpc;

SPC Monofer https://www.medicines.org.uk/emc/product/5676/smpc;

SPC Venofer https://www.medicines.org.uk/emc/product/5911/smpc [all: accessed 25 March 2021].

Hypersensitivity reactions may occur with all formulations, including serious and potentially fatal anaphylactic or anaphylactoid reactions. Hypersensitivity reactions have also been reported after previously uneventful doses of parenteral iron complexes. The risk is enhanced for patients with known allergies including drug allergies, including patients with a history of severe asthma, eczema or other atopic allergy or patients with immune or inflammatory conditions [e.g. systemic lupus erythematosus, rheumatoid arthritis].

All formulations should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available, in an environment where full resuscitation facilities can be assured. Each patient should be observed for adverse effects for at least 30 minutes following each iron administration. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Facilities for cardio respiratory resuscitation and equipment for handling acute anaphylactic or anaphylactoid reactions should be available, including an injectable adrenaline solution. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

Infection

It is recommended that the treatment with iron is stopped in patients with ongoing bacteraemia. Therefore, in patients with chronic infection a benefit/risk evaluation has to be performed, taking into account the suppression of erythropoiesis.

Another relevant warning applies to FCM regarding hypophosphataemic osteomalacia. This is discussed as a safety criterion. Serum phosphate should be monitored in patients who receive multiple administrations at higher doses or long-term treatment, and those with existing risk factors for hypophosphataemia [SPC Ferinject https://www.medicines.org.uk/emc/product/5910/smpc [accessed 25 March 2021]]. This results in a 10% lower score for FCM: 40%.

All other formulations are awarded 50%.

Number of available formulations

The following presentations are presented in table.

Available formulations

FCM [Ferinject®]

- 2 mL solution with100 mg iron. Available in pack sizes of 1, 2 and 5 vials.
- 10 mL solution with 500 mg iron. Available in pack sizes of 1, 2 and 5 vials.
- 20 mL solution with 1,000 mg iron. Available in a pack size of 1 vial.
- Not all pack sizes may be marketed.

FDM [Monofer®]

- 1 ml solution with 100 mg iron as FDM
- 2 ml solution with 200 mg iron as FDM

- 5 ml solution with 500 mg iron as FDM
- 10 ml solution with 1,000 mg iron as FDM

FDC [CosmoFer®]

- 2 ml solution with 100 mg iron[III] as Iron[III]-hydroxide dextran complex
- 5 ml solution with 250 mg iron[III] as Iron[III]-hydroxide dextran complex
- 10 ml solution with 500 mg iron[III] as Iron[III]-hydroxide dextran complex
- Each ml contains 50 mg Iron[III].

IS [Venofer®, generic]

- Ampoule 1 ml solution with 20 mg of iron as IS [iron[III]-hydroxide sucrose complex].
- Ampoule 5 ml solution with 100 mg iron as IS [iron[III]-hydroxide sucrose complex].
- Vial 2.5 ml solution with 50 mg iron as IS [iron[III]-hydroxide sucrose complex].
- Vial 5 ml solution with 100 mg iron as IS [iron[III]-hydroxide sucrose complex].

The score is presented in table 3.

Formulation	50 mg	100 mg	200/250 mg	500 mg	1000 mg	Score
FCM		+		+	+	70%
FDM		+	+	+	+	90%
FDC		+	+	+		60%
IS	+	+				20%

Table 3: Formulations.

Drug interactions

Virtually no relevant drug interactions have been described for any of the parenteral iron formulations. The absorption of oral iron is reduced when administered concomitantly with parenteral iron preparations. Therefore, [additional or continuation of] oral iron therapy should discouraged, whilst intravenous iron therapy is indicated or ongoing.

All formulations are awarded 90%.

Clinical efficacy

Only studies with at least 25 patients per treatment arm were taken into account. Many small scale studies were therefore excluded [2-21]. Of these, 16 studies were performed with IS [2-17], 3 with FDC [18-20] and one with FCM [21]. Studies were also excluded when it was unclear which iv iron formulation was studied [22].

Direct comparative studies between two iv iron formulations

FCM vs FDC

In one study FCM and FDC were compared in patients with iron deficiency anaemia. The primary endpoint was safety. hHemoglobin concentrations increased from baseline value with 2.8 g/dl, and 2.4 g/dl for FCM and FDC, respectively, being statistically insignificantly different. The increase in each cohort [efficacy] was statistically highly significant, p = 0.001. Ferritin increased more in the FCM cohort [543] compared to the FDC cohort [319], p = 0.001. Transferrin saturation increased less in FCM users [30%] than in FDC users [38%], p = 0.001 [23].

FCM vs IS

The REPAIR-IDA trial was by far the largest direct comparative trial performed between two intravenous iron formulations. The study included over 2500 patients with iron-deficiency anaemia and impaired renal function. The primary endpoint was the maximal haemoglobin increase from baseline during an eight-week study period. The mean haemoglobin increase was 1.13 g/dl in the FCM group and 0.92 g/dl in the IS group [95% Confidence Interval of this difference 0.13-0.28], indicating noninferiority of FCM. The study was designed to show noninferiority of FCM, but incidentally superiority was observed. haemoglobin concentration increment was numerically higher for all subgroups in case of FCM use [various baseline haemoglobin levels, EPO use and stage of chronic kidney disease]. The proportion of patients showing an increase of haemoglobin of more than 1.0 g/dl was greater in the FCM group [48.6%] than in the IS group [41.0%], with a 95% CI of the difference: amounting 3.6 to11.6%. Mean increases in serum ferritin, transferrin saturation and serum iron were also statistically significantly greater in the FCM group [24].

In the FERGIcor study FCM was also compared with IS. The study was performed in patients with iron deficiency anaemia caused by IBD. The primary endpoint was haemoglobin response [defined as an increase of at least 2 g/dl] at week 12.The primary

endpoint was achieved in 66% of patients treated with FCM vs 54% of patients treated with IS, 95% CI for the difference 3.07 to 20.97, p = 0.004] in the full analysis set, with similar results in the per protocol set. The overall iron dose in the FCM group however was higher than in the IS group: 1377mg vs 1160 mg. Reference values of haemoglobin [gender dependent > 12 of 13 g/dl], transferrin saturation levels [20-50%] and ferritin [>100 microg/L] were reached in more patients treated with FCM [25].

In an Indian study FCM and IS were compared again. The study was performed in gynaecological and obstetric patients. The primary endpoint was haemoglobin response [defined as an increase of at least 2 g/dl] at week 4. An increase in the mean haemoglobin was observed from 7.76 g/dl ± 0.709 to 13.25 g/dl ± 0.606 in patients treated with FCM and 7.64 g/dl ± 0.710 to 11.59 ± 0.733 g/dL [P < 0.001] in patients treated with IS after four weeks of therapy [26].

FDM vs IS

In the PROPOSE study FDM and IS were compared in patients undergoing haemodialysis. The primary efficacy endpoint was the proportion of patients with haemoglobin concentration between 9.5 and 12.5 g/dl at six6weeks. Patients were randomized to either a single injection of 500 mg or 500 mg in split doses of FDM or 500 mg IS in split doses. In both treatment arms, similar efficacy was shown with more than 82% of patients with haemoglobin in the target range [non-inferiority, p = 0.01]. The effects of both formulations on quality of life were also similar [27].

In the PROVIDE study, efficacy and safety of FDM and IS were compared in patients with iron deficiency anaemia who were intolerant of, or unresponsive to, oral iron. Five hundred and eleven patients with iron deficiency anaemia from different causes were randomized 2:1 to FDM or IS and followed for 5 weeks. The mean cumulative dose of FDM was 1640.2 mg, and of IS 1127.9 mg. The primary endpoint was the proportion of patients with a haemoglobin increase 2 g/dL from baseline at any time between weeks 1-5. Both non-inferiority and superiority in favour of FDM were confirmed for the primary endpoint, and a shorter time to haemoglobin increase 2 g/dL was observed with FDM. For all biochemical efficacy parameters, faster and/or greater improvements were found with FDM [28]. Similar results were seen in a subpopulation of gynaecological patients [29].

The FERWON-NEPHRO study was an open-label, comparative, randomized, multi-centre trial conducted in over 1500 non-dialysis dependent chronic kidney disease patients with iron deficiency anaemia randomized 2:1 to either FDM 1000 mg [1027 subjects] or IS administered as 200 mg IV injections repeated up to a cumulative dose of 1000 mg [511 subjects]. For the co-primary efficacy endpoint, the change from baseline to week 8 of haemoglobin concentration was almost identical in both groups, demonstrating non-inferiority of FDM [30].

The FERWON-IDA study was an open-label, comparative, randomized, multi-centre trial conducted in 1512 patients with iron deficiency anaemia randomized 2:1 to either FDM 1000 mg [1009 subjects] or IS in a cumulative dose of 1000 mg [503 subjects]. For the co-primary efficacy endpoint the change from baseline to week 8 of haemoglobin concentration was 1.55 mmol/l in both groups, demonstrating non-inferiority of FDM [31].

Some indirect comparisons between two formulations, using retrospective data were not included in this analysis [32,33].

FDC vs IS

In one small scale study FDC and IS were compared in predialysis patients with anaemia. No statistically significant differences were found considering any predefined efficacy endpoint [34].

Randomized comparative studies with other treatments

FCM

In three studies FCM was investigated in patients with iron deficiency anaemia.

FCM was studied in comparison with oral iron sulphate. All patients were pretreated with oral iron sulphate for 14 days, followed by randomization. The primary efficacy endpoint was change of haemoglobin concentration to the highest observed during 5 weeks. The haemoglobin concentration increase was higher in the FCM group than in the oral iron sulphate group: 1.57 vs 0.80 g/dl, p = 0.001 [35].

Standard medical care [SMC] was compared with FCM in yet another study. Both a single as well as multiple doses of 750 mg FCM were compared to SMC. The single dose study showed greater increases in haemoglobin than SMC [1.15 vs 0.78 g/dl]. Ferritin concentrations also increased more in the FCM group: 146 vs 67 ug/l, as did haematocrit [3.4 vs 2.4] [36].

FCM was studied in patients with iron deficiency anaemia and heart failure in two studies.

In the FAIR-HF trial FCM was compared with placebo. The primary endpoint was a self-reported Patient Global Assessment and NYHA functional class at week 24. Secondary endpoints included 6 minutes walking distance and health-related quality of life. Patient Global Assessment showed a moderate or strong improvement in 50% of patients in the FCM group vs 28% for placebo, with an odds ratio of 2.51, 95% CI 1.75-3.61]. Of patients treated with FCM, 47% had a NYHA functional class of I or II, compared to 30% for placebo [37].

Placebo was compared with FCM in the CONFIRM-HF study during 52 weeks. The primary endpoint was the change in 6 minutes walking test from baseline to week 24. FCM showed an improvement in walking distance [36 m difference with placebo, $p < 0.001$]. From week 24 onwards, FCM showed a statistically significant improvement of NYHA class, Patient Global Assessment Quality of life and fatigue score compared to placebo [38].

FCM was additionally investigated in patients with iron deficiency anaemia caused by IBD.

In one study FCM was compared with oral iron sulphate. The primary endpoint was the change of haemoglobin concentration from baseline to week 12. The study was designed to demonstrate noninferiority. The mean haemoglobin increased from 8.7 g/d lto 12.3 g/d lin the FCM groups, and from 9.1 g/dl to 12.1 g/dl in the iron sulphate group, confirming noninferiority of FCM. The rise of haemoglobin concentration was quicker in the FCM group. Median ferritin levels increased from 5 to 323 ug/lin the FCM at week 2, followed by a gradual decrease to 43 microg/L at week 12 [39].

FCM was compared to iron sulphate in patients who had suffered from upper gastrointestinal bleeding. The primary endpoint was the difference in haemoglobin at the end of treatment. A small [n = 14] placebo group was included as well. The haemoglobin concentration at week 13 was higher in the iv and oral iron groups [13.9 and 13.5 g/dl, respectively], than in the placebo group [11.5 g/dl], $p < 0.01$ [40].

FCM was compared to oral ferrous glycine sulphate in a study in patients who developed postoperative anaemia after total knee arthroplasty. The primary endpoint was change in haemoglobin concentration from day 4 to 30 postoperatively. The target value of haemoglobin [> 12 g/dl] was reached more frequently with FCM [42%] than for ferrous glycine sulphate [24%, $p = 0.04$]. The difference in haemoglobin increase was not statistically significantly different between the two treatments [41].

FCM and oral iron sulphate were compared in women with postpartum anaemia in two studies. FCM was more effective than oral iron sulphate in increasing haemoglobin concentration or achieving target haemoglobin concentration [42-44]. Similar results were achieved in another study in patients with iron deficiency anaemia due to heavy uterine bleeding [45]. FCM was also more effective than iron sulphate in pregnant women with iron deficiency [46].

A good clinical efficacy of FCM to oral iron sulphate or to standard medical care was shown in two studies [including oral or iv iron or no iron] [47,48].

Two dosages of FCM aimed at either higher [400-600 microg/L] or lower [100-200 microg/L] ferritin levels were compared to oral iron. The high ferritin group was more effective than the low ferritin group or placebo in reaching initiation of anaemia treatment [49].

FCM showed superior clinical efficacy in patients with postoperative anaemia compared to standard care on all investigated endpoints, including transfusions [50].

In a meta-analysis superiority of FCM was shown compared with oral iron sulphate in improving both haemoglobin and serum ferritin concentrations as well as transferrin saturation [51].

FDM

In the PROTECT study FDM [n = 30] was compared to placebo [n = 30] to prevent postoperative anaemia in preoperatively non-anaemic patients undergoing elective or subacute coronary artery bypass graft, valve replacement or a combination thereof. Patients were randomized to receive a single dose of either 1000 mg FDM or placebo. The primary endpoint was to demonstrate superiority of FDM regarding haemoglobin concentration at 4 week, postoperatively. Haemoglobin concentrations at baseline were comparable: 14.3 vs 14.0 g/dl. FDM resulted in higher haemoglobin concentrations than placebo at 4 week. Full Analysis Set: 12.6 vs 11.8 g/dl, $p = 0.012$. More patients were non-anaemic in the group treated with FDM: 39% vs 8%, $p = 0.019$ [52].

In the PROCEED study FDM was compared to oral iron sulphate in patients with anaemia caused by IBD. Patients were randomized to receive 1000 mg [given as either 2 infusions of 500 mg or one infusion of 1000 mg] FDM according to the Ganzoni formula or 200 mg of oral iron sulphate. The primary endpoint was the change in haemoglobin concentration from baseline to week 8, using a non-inferiority design. Unfortunately, this could not be demonstrated. There was a trend for oral iron sulphate to be more effective in increasing haemoglobin concentration than FDM. The estimated treatment effect was -0.37 [p = 0.09] in the full analysis set and -0.45 in the per protocol analysis set [p = 0.04]. The mean change in ferritin concentration was higher for FDM, with an estimated treatment effect of 49 microg/l, p = 0.002. Transferrin saturation was lower in the FDM group, with an estimated treatment effect of -4.4, p = 0.005. The dose-response relationship observed with FDM suggested that the true iron demand of IV iron was underestimated by the modified Ganzoni formula. The haemoglobin response [haemoglobin increase of haemoglobin concentration ≥2 g/dl] rate was 93% for patients receiving > 1000 mg FDM [53].

FDM was compared to oral iron sulphate in patients with cancer related anaemia in the PROFOUND study. The primary efficacy outcome was a change in haemoglobin concentration from baseline to week 4. The primary efficacy outcome was tested for noninferiority, whereas the remaining outcomes were tested for superiority. FDM was noninferior to oral iron in change in haemoglobin concentration from baseline to week 4. A statistically significant mean decrease in fatigue score was observed from baseline to week 12 in the FDM group, but not in the oral iron group. No other statistically significant differences were found on other efficacy endpoints [54].

In the PROGRESS study FDM was compared to oral iron sulphate in patients with chronic kidney diseases who were not dialysis dependent in a noninferiority study. The primary efficacy outcome was change in haemoglobin concentration from baseline to week 4. FDM was noninferior to oral iron on all efficacy parameters and was superior to oral iron regarding haemoglobin concentration increase at weeks 3 and 8 [55].

FDM was compared to standard therapy in the prevention of anaemia in patients undergoing total knee arthroplasty [TKA] in a Korean study. The administered dose of FDM in the treatment group was 1136 ± 225 mg. The incidence of anaemia at 30 days after TKA was lower in the treatment group [34.1%, 15/44] than that in the control group [62.2%, 28/45]: relative risk 0.55 [95% confidence interval, 0.34 to 0.88], P = 0.008. In line, haemoglobin and serum ferritin concentrations, and transferrin saturation were also statistically significantly higher in the treatment group at 30 days after TKA [56].

The efficacy of FDM [1 g] in comparison with placebo in first-time female blood donors was evaluated in the PROCESS study. The primary endpoint of the trial was change in haemoglobin concentration from baseline to before the third blood donation. The increase in haemoglobin concentration was higher for FDM compared with placebo before both the second blood donation and the third blood donation [57].

The PROACTIVE study was an open-label, comparative, randomized, single-centre trial conducted in 200 healthy women with postpartum haemorrhage exceeding 700 mL and ≤1000 ml or postpartum haemorrhage >1000 ml and haemoglobin concentration >6.5 g/dl measured >12 hours after delivery. The women were randomized 1:1 to receive either a single dose of 1200 mg FDM or standard medical care. The primary endpoint was the aggregated change in physical fatigue within 12 weeks postpartum. The difference in aggregated change in physical fatigue score within 12 weeks postpartum was -0.97 [p = 0.006], in favour of FDM [58].

FDC

FDC [single total dose infusion or 100 mg at each dose of EPO] was compared to oral iron sulphate 325 mg bid and no iron in patients with chronic kidney disease receiving EPO therapy in one study.The primary efficacy endpoint was change in haemoglobin concentration from baseline to study endpoint [6 weeks]. The mean increase in haemoglobin concentration was 25 g/L for the iv bolus injection, 24 g/L for the total dose infusion, 15 g/L for oral iron sulphate and 9 g/L for no iron, respectively. The mean increases in both FDC groups were statistically significantly higher than in the oral iron and no iron groups [59].

The addition of FDC to either 300 mcg or 500 mcg darbepoetin every 3 weeks was studied in patients with chemotherapy-induced anaemia. The primary endpoint was achievement of target haemoglobin concentration [> 11 g/dl] at the end of study. Statistically significantly more patients receiving iron [82%] than with darbepoetin monotherapy [72%] achieved target haemoglobin concentration [60].

IS

In several, mostly small scale, studies, IS was compared with oral iron [iron sulphate or Iron protein succinate] in pregnant or post-gestational women. IS was as effective [61,62] or more effective [63-68] than oral iron in increasing haemoglobin concentration at the end of the study. IS was as effective as another intravenous iron formulation, Iron sorbitol in a direct comparative study [69]. IS was also more effective than oral iron in the prophylactic use in raising preoperative haemoglobin concentration in women undergoing surgery for menorrhagia [70].

IS was more effective than placebo in reducing fatigue in premenopausal women with fatigue who were non-anaemic at baseline [71]. IS was more effective than oral iron sulphate in reducing blood transfusion in women with gynaecologic cancer receiving platinum-based chemotherapy [72].

IS was compared to oral iron sulphate in patients with anaemia caused by IBD. The primary endpoint was response to treatment at week 20, assessed by haemoglobin concentration increase of more than 2 g/dl, remaining anaemia at 20 week and the proportion of patients reaching the target haemoglobin reference concentration. IS was not statistically significantly more effective than oral iron in increasing haemoglobin concentration more than 2 g/dl [66% vs 47%]. There was no difference in the mean increase of haemoglobin concentration [73].

IS was compared to oral iron in three studies in patients with anaemia caused by chronic kidney disease. In all studies, one in haemodialysis patients and two in predialysis patients, a higher increase of haemoglobin concentration was shown in the IS groups [74-76]. IS was compared to oral iron sulphate in patients with chronic kidney disease who were non-anaemic at baseline in another study. The primary endpoint was change in haemoglobin concentration at 12 months, or at termination after at least 6 months of treatment. At study end, haemoglobin concentration did not differ between the groups [77].

IS was not more effective in reducing postoperative blood transfusion rate than standard treatment alone when used preoperatively in elderly patients undergoing hip fracture surgery. A statistical significant reduction in blood transfusions was seen in a subgroup of patients with intracapsular fractures [78].

IS was compared to ferumoxytol in patients with iron deficiency anaemia who had shown an unsatisfactory response to oral iron. The study was designed to show noninferiority of ferumoxytol compared to IS. The proportion of patients achieving a haemoglobin concentration increase of > 2 g/dl was comparable for IS [81%] and ferumoxytol [84%], demonstrating non inferiority of ferumoxytol. The mean increase in haemoglobin concentration was higher for ferumoxytol [2.7 g/dl vs 2.4 g/dl, p =0.0124] [79].

IS added to erythropoietin increased haemoglobin concentration to a greater extent than standard treatment alone in patients with anaemia due to lymphoproliferative malignancies. The proportion of patients showing a haemoglobin concentration increase of at least 2 g/dl was 93% compared to 53%. The mean erythropoietin dose was also statistically significantly reduced in the IS group [80].

Prophylactic IS was no more effective than oral iron or placebo regarding effects on postoperative haemoglobin concentration or haematocrit in patients undergoing elective cardiac surgery [81]. This was also the case for postoperative use of IS [82].

IS was more effective in reducing iron depletion and restless legs symptoms than oral iron sulphate in blood donors [83].

Noncomparative studies

The efficacy of FCM was confirmed in several non-comparative studies. These studies are not further discussed in this article [84-87].

The use of 1000 mg of FDM was studied in 182 patients with chronic kidney disease [88], in patients with IBD [89] and in patients undergoing urological surgery [90]. FDM was effective and well tolerated in both studies. Because of the non-comparative design, these studies are not discussed in detail.

Non-comparative trials studied the use of FDC in various patient populations [91-93]. Because of the non-comparative design, these studies are not discussed in detail.

Several non-comparative studies were performed with IS [94-99]. These studies are not further discussed.

In one meta-analysis, FCM and FDM were compared. In the study no direct comparative studies were included. The indirect comparison indicated a significantly higher increase from baseline haemoglobin for FDM, but there was no significant difference in the

proportion of patients with a clinically-relevant response [100]. These findings are difficult to interpret due to differences in study design and patient population.

Discussion

The number of direct comparative studies between the intravenous iron formulations is relatively limited, thwarting to draw robust conclusions regarding effectiveness. FCM and FDM were more effective than IS when considering few specific outcomes in several studies. However, dosages of FCM and FDM in these studies differed from that of IS. Generally, in most study designs intravenous iron dose is usually titrated to a desired haemoglobin concentration. Therefore, clinical relevant differences in effectiveness are unlikely to be found in clinical studies.

All intravenous iron formulations offer relevant advantages over oral iron. Intravenous iron works more rapidly than oral iron and can be given in acute GI bleeding, in combination with erythrocyte concentrate. This also applies to chronic blood loss due to oral anticoagulant drugs.

There is no evidence to suggest major or relevant differences between the intravenous iron formulations regarding efficacy. Therefore, all formulations were [arbitrary] awarded 70%.

Adverse effects

Serious anaphylactic reactions have been described for intravenous iron formulations, although formerly more often than with the current formulations. It is of relevance to discern common infusion reactions, that are inconvenient but relatively harmless, from these rare but severe anaphylactic reactions. The US Food and Drug Administration [FDA] concluded in 2010 that there was insufficient data to conclude that there are relevant differences in the incidence of anaphylactic reactions between the formulations [101].

Similar observations were later made by the European Medicines Agency [EMA] [103]. In this article only studies with low molecular weight FDC, marketed as Cosmofer® [Europe] or INFeD™ [US] were included, because other formulations are associated with a higher incidence of serious adverse reactions, although the incidence remains very low in absolute numbers for all iron formulations [103-105]. In one meta-analysis, it was shown that no difference was demonstrable between the iron formulations included in this analysis [106]. By means of an indirect comparison of studies using meta-analysis with FCM, FDM and IS, it was concluded that a lower incidence of serious adverse reactions for FDM was reported when compared to the other formulations [107].

Several studies investigated The risk of infection with iv iron formulations was studied in several studies, which concluded that there is no evidence for an increased risk of infection compared to oral treatment, placebo or no treatment [106,108].

A good tolerability profile of intravenous iron formulations was shown in a meta-analysis including 103 studies with over 10,000 patients treated iv iron formulations showed a good tolerability profile. The incidence of serious adverse events compared to oral iron, placebo or sc iron formulations. A decreased incidence of adverse events was seen for iv iron formulations vs comparators in patients with heart failure. Gastrointestinal reactions were significantly less frequent compared to oral iron formulations and more frequent compared to placebo [106].

Direct comparative studies between two iv iron formulations

FCM vs FDC

FCM and FDC were compared in patients with iron deficiency anaemia in one study. The primary endpoint was safety. The incidence of adverse events was comparable for both medicines. Hypersensitivity reactions were more frequently observed for FDC: 9% vs 0%, p = 0.006. This was also the case for cutaneous and subcutaneous tissue disorders: 24% vs 7%, p = 0.004. Urticaria was the most frequently reported reactions for FDC [in 9% of cases], which was not observed in FCM users. There were no statistically significant differences in changes in laboratory values between both formulations [23].

FCM vs FDM

The effects of FDM and FCM on the occurrence of hypophosphatemia were investigated in two studies. The dosage of FDM was 1000 mg at baseline, whereas FCM was dosed 750 mg at baseline and at 1 week. The primary endpoint was the occurrence of hypophosphatemia [serum phosphate concentration <0.65 mmol/L] between baseline and day 35. In the studies, 245 patients were included. In pooled analysis of both trials, hypophosphatemia was more frequently observed following FCM as compared with FDM [74% versus 8.0%, p < 0.0001]. Hypophosphatemia persisted

at day 35 in 43% of FCM-treated patients compared to 0.9% of FDM-treated patients [p < 0.0001]. Severe hypophosphatemia ≤0.32 mmol/L occurred in 11% of FCM patients compared to 0.0% of FDM treated patients [p < 0.0001].

A total of 21/125 [16.8%] of patients in the FDM and 55/117 [47%] in the FCM group experienced adverse events. Beyond hypophosphatemia, the most common adverse drug reactions [No./total No.] were nausea [FDM: 1/125; FCM: 8/117] and headache [FDM : 4/125; FCM: 5/117]. The percentage of serious or severe hypersensitivity reactions amounted to 0.8% [1/125] in the FDM and 1.7% [2/117] in the FCM group, respectively [no data presented regarding statistics] [109].

These results were corroborated in a meta-analysis including 42 clinical trials. It was shown that FCM induced a statistically significantly higher number of cases of hypophosphatemia than FDM [47% vs. 4%], and higher decreases of serum phosphate [0.40 vs. 0.06 mmol/L]. Hypophosphatemia persisted at the end of the study periods [maximum 3 months] in up to 45% of patients treated with FCM [110]. Clinical relevance however remains debated.

On the other hand, a Dutch single centre cohort observational study showed a lower incidence of hypersensitivity reactions to FCM compared to FDM [2.1% vs 8.7% in over 1300 patients] [111].

FCM vs IS

Over 2500 patients with iron-deficiency anaemia and impaired renal function were included in the REPAIR-IDA trial. The primary safety endpoint was the proportion of study participants experiencing at least one treatment-emergent adverse event as defined in a primary composite safety endpoint, assessed from start of first intravenous iron dosage. The primary composite safety endpoint included all-cause death, nonfatal myocardial infarction, nonfatal stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization or medical intervention, cardiac arrhythmia and hypertensive or hypotensive events as defined by the protocol. There was no difference in the composite safety endpoints between the FCM group [13.7%] and the IS group [12.1%], 95% CI of the difference -1.10-4.25%]. Hypertensive events were more often observed in the FCM group [7.5 vs 4.3%] [24].

Very similar tolerability profiles for both iron formulations were found in the FERGIcor study [25].

FCM vs ferumoxytol

FCM and ferumoxytol were compared in one large scale [n>2000] study. No anaphylactic reactions were observed. Ferumoxytol was noninferior to FCM with respect to tolerability and safety [112].

FDM vs IS

In the PROPOSE trial, FDM and IS were compared in patients undergoing haemodialysis [n = 351]. The primary safety endpoint was the number of patients who experienced any adverse drug reaction. There was no significant difference in the incidence of adverse events: 48% for FDM vs 41% for IS. Adverse drug reactions for FDM were drug intolerance, hypersensitivity, dyspepsia, malaise, muscle spasms, paraesthesia, anxiety, constipation, pruritus and urticaria. Adverse drug reactions to IS were dry mouth, dyspnoea, chills, staphylococcal bacteraemia and limb discomfort [27].

The safety of a single dose of 1000 mg FDM [n = 1027] or IS administered as 200 mg IV injections up to five times within a 2-week period in patients [n = 511] with chronic kidney disease was compared in the FERWON-NEPHRO trial. The co-primary safety endpoint was any serious or severe hypersensitivity reaction. Secondary endpoints included incidence of composite cardiovascular adverse events [AEs]. No differences were observed in the occurrence of serious or severe hypersensitivity reactions in the FDM and IS groups [0.3% versus 0%]. The risk difference between FDM and IS was estimated to 0.29 % [95% CI: -0.19;0.77]. The percentage of composite cardiovascular adverse events was lower in the FDM group [4.1% versus 6.9%; P = 0.025] [30].

The FERWON-IDA trial was an open-label, comparative, randomized, multi-centre trial conducted in 1512 patients with IDA randomized 2:1 to either FDM 1000 mg infused over 20 min [1009 subjects] or IS administered as 200 mg IV injections repeated up to a cumulative dose of 1000 mg [503 subjects]. For the co-primary safety endpoint, a total of 3 treatment emergent serious or severe hypersensitivity reactions in 989 subjects [0.3%] were adjudicated and confirmed by the adjudication committee in the FDM group. The 95 % CI was [0.06% - 0.88%]. As the maximal upper bound was defined at a percentage below 3 %, the primary safety objective was considered met. In the IS group, two treatment emergent serious or severe hypersensitivity reactions in 494 subjects [0.4%] were adjudicated and confirmed by the adjudication committee. The risk difference between FDM and IS was estimated to be -0.10 % [95% CI: -0.91 - 0.71, P > 0.05] [31].

The efficacy and safety of FDM and IS in patients with iron deficiency anaemia who were intolerant of, or unresponsive to, oral iron were compared in the PROVIDE study. Fivehundred-eleven patients with iron deficiency anaemia, due to different causes, were randomized 2:1 to FDM or IS and followed for 5 weeks. In the FDM group, 75 [22.5%] reported 137 ADRs [i.e., treatment-related adverse event], and in the IS group 29 [17.3%] reported 86 ADRs [$p > 0.05$]. Both treatments were well tolerated; 0.6% experienced a serious adverse drug reaction [28].

A low incidence of adverse events for both FDC and FDM in over 1400 patients with chronic kidney disease was found in one large scale comparative study. Only one [mild] hypersensitivity reaction was observed in a FDM using patient, and one patient showed an anaphylactic reaction to FDC [113].

FDC vs IS

The relative safety of FDC, IS and sodium ferric gluconate complex in patients with chronic kidney disease was investigated in one study. It was however unclear which FDC formulation was used in the study [114]. Therefore this study was not included in this analysis. The safety of Iron Dextran and IS were investigated in non-dialysis patients. A generic formulation of FDC was used, which is not available in the UK or the Netherlands. This study was not included in this paper/analysis [115]. No difference in the allergic potencies of FDC and IS was found in a single dose study [116]. No difference in adverse events of both iron formulations was found in a retrospective chart review study, including 167 patients [117].

Safety of the individual formulations

FCM

FCM showed a higher incidence of adverse events than placebo in a direct comparative, crossover study. The overall prevalence of adverse events [29% vs 20%], drug-related adverse events [13 vs 7%], nausea [3.8 vs 1.8%], general disorders [5.7 vs 2.0%], pyrexia [1.3 vs 0.2%], fatigue [1.3 vs 0%], increased ALT activity [1.6 vs 0.4%] or AST activity [1.6 vs 0.2%] and drug-related nervous system disorders [4.7 vs 2.1%] and dizziness [1.6% vs 0.2%] was higher in the FCM group [118].

No statistically significant differences were seen between FCM and placebo in two comparative studies in patients with iron deficiency anaemia and heart failure [37,38].

Several studies compared FCM to oral iron sulphate. The incidence of adverse events was higher [42-45, 48].

The observed adverse events were investigated in a meta-analysis including all clinical studies performed up to 2011. Withdrawal due to adverse events were seen in 1.0% of patients treated with FCM. Adverse events were seen in 41% of patients, serious adverse events were observed in 2.5%. The most frequent adverse events were gastrointestinal disorders [13%], reaction at the injection site [11%], infections [14%] and nervous system reactions [10%]. The most frequent individual reactions were constipation [3%], diarrhoea [2%], nausea [3%] and headache [7%]. Compared to placebo, gastrointestinal disorders and reactions at the injection site were observed more frequently for FCM [51].

A comparable all-cause withdrawal rate for FCM compared to oral iron, other iv iron or placebo [6.3% vs 7.1%]. was found in another study, combining data from 17 FCM studies, the incidence of gastrointestinal reactions was lower than for oral iron [119].

Hypersensitivity reactions were reported in 0.3-0.9% of patients treated with FCM, compared to 0.2% for IS, 0.8% in standard medical care and 0% of oral iron recipients. Most reactions were mild to moderate in nature. No severe anaphylactic reaction was described in clinical trials [120].

FDM

FDM was usually well tolerated.

A lower incidence of serious adverse reactions for FDM compared to the other formulations was found in an indirect comparison of studies using meta-analysis with FCM, FDM and IS. Odds ratios of any serious or severe HSR [all groups] with FDI relative to FCM were 0.41, 0.39, and 0.45 according to the Bayesian, naïve and adjusted approaches [107].

An analysis of the FERWON studies included over 2000 patients, treated with FDM. The incidence of adverse events was comparable for FDM and IS: 8.6% vs 9.0%. Nausea, rash and dysgeusia were the most frequent adverse events reported for FDM [121].

FDC

A higher occurrence of adverse events was found with high molecular weight FDC in a retrospective chart review including

500 infusions from 153 patients treated with either high- or low molecular FDC: 5.5% vs 1.4% [122].

IS

In several, mostly small scale, studies, IS was compared to oral iron [iron sulphate or iron protein succinate] in various patient populations. Reports on adverse events were limited or absent, but a lower incidence of gastrointestinal reactions was seen for IS compared to oral iron [61-74].

A higher incidence of gastrointestinal side effects than placebo was found for IS in a study in premenopausal women [71].

A low incidence of adverse events was found in a large scale study involving over 8,500 doses of IS in 665 patients undergoing haemodialysis. Only 29 adverse drug events were identified, corresponding to 4.4% of patients and 0.3% of infusions. The most "frequent" adverse events were constipation, hypotension and vomiting, occurring in 3 patients each. Only one case of constipation was assessed as "severe" [123].

There are no indications of relevant differences in the safety and tolerability profiles of the formulations. Comparisons of FCM and FDM showed a higher incidence of hypophosphatemia and a lower incidence of hypersensitivity reactions for FCM.

All formulations are awarded 80%.

Ease of administration

The results are presented in table 4.

Documentation

The clinical documentation of the medicines is summarised below:

Formulation	Iv bolus	Iv drip	IM	dialyser	Dose 1000 mg	Dose 20 mg/kg	Duration	Score
FCM	+	+		+	+		15 min (1000 mg)	85%
FDM	+	+		+	+	+	15 min (1000 mg) 30 min (>1000 mg)	95%
FDC	+	+	+	+	+		4-6 hours (total dose infusion)	70%
IS	+	+		+				45%

Table 4: Ease of administration.

Only randomized comparative studies were taken into consideration for calculation of the score. Non-randomized studies were discussed above, but did not add to the number of studies as shown in table 5.

	Studies	Patients	Years	Patients (millions)	Score
FCM	>20	>1000	>10	>10	100%
FDM	18	>1000	>10	>10	98%
FDC	6	>1000	>10	>10	83%
IS	>20	>1000	>10	>10	100%

Table 5: Documentation.

SOJA score

The SOJA score was calculated with above mentioned calculations. It is depicted in table 6.

Outcome

Overall SOJA scores differed slightly, with FDM showing the highest score, followed by FCM. The scores for the other formulations were lower, especially because of the lower ease of administration.

Discussion

Applied methodology

This analysis was done by means of the SOJA method, which is a well-established rational and transparent way of selecting medicines within a therapeutic class from a formulary perspective.

Strength and limitations of the methodology

The evaluation of criteria in the SOJA method is highly standardized in order to promote standardized and transparent [objectified] judgement of medicines from various pharmaco-

	Weight	Ferric carboxymaltose	Ferric derisomaltose	Iron dextran	Iron sucrose
Licenced indications	60	60	60	60	60
Contraindications	40	32	30	20	32
Warnings and precautions	20	8	10	10	10
Number of formulations	60	42	54	36	12
Drug Interactions	20	18	18	18	18
Clinical efficacy	300	210	210	210	210
Adverse effects	200	160	160	160	160
Ease of administration	200	170	190	140	90
Documentation	100	100	98	83	100
Total	1000	800	830	737	692

Table 6: SOJA score.

therapeutic categories based on clinically relevant criteria. Debate whether or not the correct scoring system was used for each criterion is inevitable, and indeed judgement is partly arbitrary for most, if not all, criteria. The SOJA score method however is a transparent process, objectifying the calculated scores which is reproducible if the same criteria and assigned scores are being applied. If necessary, the criteria and scores can be changed if deemed necessary due to different circumstances.

The SOJA method is intended as a tool for rational drug decision making, allowing clinicians [physicians, hospital pharmacists and nurses] as well as procurement officials to include all relevant aspects of a certain group of medicines It precludes formulary decisions being based on only few [selective] criteria.

This paper is therefore intended to structure discussions or decisions within formulary committees in hospitals and is not the absolute truth.

Obviously, the score depends on the relative weight that is assigned to each individual selection criterion. Therefore, an interactive program is available, which makes it easy for local and regional formulary committees to assign personal weights to each selection criterion by individual members. If a physician or hospital pharmacist considers individual criteria as totally irrelevant, this criterion may be assigned nil points, thereby ignoring this criterion.

Acquisition cost was not taken into account, because this varies with time and is highly dependent on volumes used by individual hospitals or by groups of collaborating hospitals [or hospital pharmacists]. Price also varies with time and differs between countries.

The SOJA method therefore focuses on criteria regarding the benefit-risk profile of a medicinal product.

In practice, acquisition cost is of course an important selection criterion, especially due to limited differences, from a clinical perspective, between the discussed iron formulations [FDM vs FCM and FDC vs IS].

Exclusion of this financial criterion is essential to quantify the specific costs of a formulation [and may be helpful to calculate efficiency of a product]. Additionally, the SOJA method allows a more international approach, excluding the financial criterion.

Conclusion

The present matrix may be of use for hospital formulary committees in determining preferences for specific iron formulations from a clinical practice, prior to the procurement phase.

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