EXPERT OPINION

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Iron sucrose – characteristics, efficacy and regulatory aspects of an established treatment of iron deficiency and iron-deficiency anemia in a broad range of therapeutic areas

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Introduction: Iron is a key element in the transport and utilization of oxygen and a variety of metabolic pathways. Iron deficiency is a major cause of anemia and can be associated with fatigue, impaired physical function and reduced quality of life. Administration of oral or intravenous (i.v.) iron is the recommended treatment for iron-deficiency anemia (IDA) in different therapeutic areas.

Areas covered: This article provides an overview of studies that evaluated i.v. iron sucrose for anemia and iron status management, either alone or in combination with erythropoiesis-stimulating agents, across various diseases and conditions.

Expert opinion: Iron sucrose is an established, effective and well-tolerated treatment of IDA in patients with acute or chronic conditions such as chronic kidney disease, inflammatory bowel disease, pregnancy (second and third trimester), postpartum period, heavy menstrual bleeding and cancer who need rapid iron supply and in whom oral iron preparations are ineffective or not tolerated. Available data on patient blood management warrant further studies on preoperative iron treatment. First experience with iron sucrose follow-on products raises questions about their therapeutic equivalence without comparative clinical data in newly diagnosed patients or patients on existing chronic treatment.

Keywords: anemia, efficacy, follow-on products, generics, iron deficiency, iron sucrose, pharmacodynamics, pharmacokinetics, safety, substitution, tolerability

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1. Introduction to iron deficiency and anemia

Iron deficiency (ID) and iron-deficiency anemia (IDA) are leading causes of disability [1] and common complications in a wide range of conditions such as chronic kidney disease (CKD), inflammatory bowel disease and other gastrointestinal disorders, pregnancy/postpartum, heavy menstrual bleeding, cancer and chronic heart failure (CHF) [2-8]. Main pathological contributors to ID and IDA are chronic bleeding, malabsorption and inflammation [9,10]. In addition to the impact on patients, anemia comprises an economic burden in terms of increased average annual health care cost per patient even after adjustment for disease severity [11]. Since the involvement of iron in hemoglobin (Hb)-dependent oxygen transport is only one key role of iron apart from its involvement in essential metabolic pathways [12,13], ID, even

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Box 1. Drug summary.

Drug name	Iron sucrose, Venofer
Phase	Post-marketing, launched
Indication	Where there is a clinical need for a rapid iron supply. In patients who cannot tolerate oral iron therapy or who are noncompliant. In active inflammatory bowel disease where oral iron preparations are ineffective
Pharmacology description	Anti-anemic iron preparation for parenteral use
Route of administration	Intravenous
Chemical formula	$[Na_2Fe_5O_8(OH) * 3(H_2O)]_n * m(C_{12}H_{22}O_{11})$
Pivotal trial(s)	The iron sucrose complex was developed before formal clinical development plans became as usual as today. Therefore, published, representative studies using Venofer in a variety of patient populations were selected for inclusion in this review.

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without anemia, can be associated with fatigue, impaired physical function and reduced quality of life [14,15].

Accordingly, treatment of ID/IDA is an important aspect in reducing morbidity and improving quality of life. Iron administration is recommended by treatment guidelines in different therapeutic areas [4,6,16-21]. In general, the effectiveness of parenteral (intravenous [i.v.]) iron and the time to response are superior or at least equivalent to that with oral iron. Since i.v. iron is directly taken up by the reticuloendothelial system (RES) [22], it can overcome the low intestinal absorption [23] as well as most of the gastrointestinal side effects that limit the use of oral iron. Apart from the better tolerability of parenteral compared to oral iron, the decision for i.v. or oral iron as first-line therapy depends on the type of ID (absolute vs functional), the urgency to achieve a treatment effect, tolerability and costs.

ID can be characterized as absolute ID (i.e., depleted iron stores) or functional ID (FID, i.e., impaired or suboptimal availability of iron despite normal or even elevated iron stores). Absolute ID may be a consequence of chronic blood loss (e.g., due to heavy menstrual bleeding), increased iron needs (e.g., in pregnancy), low dietary iron or impaired absorption. In patients with absolute ID, a trial of oral iron should be considered first [20,24] if resolution of ID is not time critical. Slow response to oral iron (due to low absorption) [23] is particularly limiting in preoperative anemia treatment (also known as patient blood management, PBM) [17,25].

The FID is mainly associated with chronic diseases (inflammation-driven iron sequestration leading to anemia of chronic disease [ACD] [10,26]) and/or rapidly increased iron consumption (e.g., due to treatment with erythropoiesis-stimulating agents, ESAs [10,27]).

In patients with FID due to inflammation, the ferroportin-mediated release of iron from enterocytes and macrophages can be reduced by hepcidin, the main regulator of iron homeostasis, which in turn is upregulated by proinflammatory cytokines [2,10,28]. Consequently, the already low intestinal absorption of orally ingested iron in healthy individuals is further reduced by > 50% in patients with chronic inflammatory conditions [28], which may lead to ACD if left untreated. Conversely, i.v. iron complexes that are directly taken up by macrophages can overcome the reduced (and not fully blocked) iron release in patients with chronic disease [2]. Notably, iron homeostasis can also be influenced by hypoxia and cellular ID via hepcidin-independent factors (e.g., hypoxia-inducible factors [HIFs], especially HIF-2) [26,29]. Therefore, hepcidin levels should not serve as surrogate marker for iron status or response to anemia treatment.

In patients with FID due to erythropoietin therapy, oral iron treatment may be sufficient in individuals with normal iron absorption. However, in patients with impaired iron absorption (e.g., patients with cancer or inflammatory disorders), i.v. iron therapy is required.

2. Market overview of parenteral iron preparations

Currently available iron carbohydrate preparations for i.v. iron treatment are based on six compounds: iron sucrose (IS), ferric gluconate, ferric carboxymaltose, iron dextran (high- and low-molecular-weight dextran), iron isomaltoside and ferumoxytol (**Table 1**) [30]. The use of IS continuously increased from 2003 to 2009, and in 2005, IS became the leading i.v. iron compound surpassing ferric gluconate [31]. In the first quarter of 2009, quarterly sales expressed in 100 mg iron dose equivalents were approximately 4.7 million (IS), 2.6 million (ferric gluconate) and 0.6 million (iron dextran). The other compounds were not included in this analysis since they entered the market at a later stage.

Notably, high-molecular-weight iron dextran has been associated with significantly higher annual reports of total and life-threatening adverse drug events than other i.v. iron compounds [32] and is not approved in Europe.

In the recent years, follow-on products of IS (so-called IS similars) have entered the market. These products have been approved as generics; however, there is growing clinical [33-36] and nonclinical [34,37] evidence questioning the interchangeability of originator IS with such IS similars [38,39]. Since generic follow-on products can be marketed under the same international nonproprietary name as the originator products, no reliable data about the market share of these follow-on products are available.

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Table 1. Some characteristics of approved intravenous iron formulations.

	Iron gluconate	Iron sucrose	HMWID	LMWID	Ferric carboxymaltose	Iron iso-maltoside 1000	Ferumoxytol
Brand name	Ferrlecit	Venofer	Dexferrum	Cosmofer	Ferinject, Injectafer	Monofer	FeraHeme
Manufacturer	Sanofi-aventis	Vifor Pharma	Watson Pharmaceuticals	PharmaCosmos	Vifor Pharma	Pharmacosmos	AMAG Pharmaceuticals
Carbohydrate shell	Gluconate (monosaccharide)	Sucrose (disaccharide)	Dextran (branched polysaccharide)	Dextran (branched polysaccharide)	Carboxymaltose (branched polysaccharide)	Isomaltoside (linear oligosaccharide)	Polyglucose sorbitol (branched polysaccharide)
Molecular weight (kDa)	289 – 440	34 – 60	265	165	150	150	750
Initial distribution (l)	6	3.4	3.5	3.5	3.5	3.4	3.16
Plasma half-life (h)	1	6	60	30	16	20	15
Labile iron (% of dose)	3.3	3.4	-	1.9	0.6	1	0.99
Direct iron donation to transferrin (% of dose)	5 – 6	4 – 5	1 – 2	1 – 2	1 – 2	< 1	< 1
Iron content (mg/ml)	12.5	20	50	50	50	100	30
Maximal single dose (mg)	125	300	20 mg/kg BW	20 mg/kg BW	20 mg/kg BW (max. 1000)	20 mg/kg BW	510

Adapted from [30].
BW: Body weight; HMWID: High-molecular-weight iron dextran; l: Liter; LMWID: Low-molecular-weight iron dextran.

3. Characteristics of the product and its administration

The medicinal product Venofer® (Vifor Pharma Ltd., active substance: iron as iron(III)-hydroxide sucrose complex, average molecular weight 45,700 Da) is a dark brown, colloidal solution that contains 20 mg iron per ml (**Box 1**). It is available in ampoules or vials with 5 ml solution (100 mg iron). The only excipients are water for injection and sodium hydroxide for pH adjustment (pH 10.9) [37,40].

IS should be only given intravenously; either as an i.v. drip infusion (diluted in 0.9% sodium chloride solution), a slow i.v. injection or directly into the venous line of a dialysis machine. The total dose of IS should be individually determined based on the calculated total iron deficit [41]. Like other iron carbohydrate complexes for parenteral use, IS is mainly taken up via endocytosis by the macrophages of the RES [22,26]. It is not suitable for intramuscular administration [42]. In the case of weaker iron carbohydrate complexes such as IS and ferric gluconate, the carbohydrate is largely dissociated in the plasma, and essentially only the polynuclear iron core is taken up by the macrophages [26]. Iron that is released in the blood can be directly taken up by transferrin and other proteins (forming nontransferrin bound iron). Accordingly, IS is given at lower single doses (in general 200 mg iron up to 3 times a week) than the more stable products such as ferric carboxymaltose (**Table 1**) [30]. In patients with hemodialysis-dependent CKD (HD-CKD), the administration of lower doses at short intervals fits well to the usual hemodialysis schemes.

4. Pharmacokinetics and pharmacodynamics

In healthy volunteers (n = 12, 50 – 84 kg), IS (Venofer, single dose, 100 mg iron) was quickly cleared from serum with a terminal half-life of 5.3 ± 1.6 h and the total body clearance was 1.23 ± 0.22 l/h (20.5 ± 3.7 ml/min) [43]. Renal elimination of iron contributed very little to the overall elimination (on average < 5%). Serum ferritin levels increased significantly after 8 – 10 h and had doubled after 24 h.

In anemic patients (n = 6), single-dose administration of 100 mg iron with radiolabeled (^{52}Fe/^{59}Fe) IS complex was followed by rapid uptake into the liver, spleen and bone marrow, reaching maximum rates at 10, 20 and 100 min after administration, respectively [44]. Serum ferritin and transferrin saturation (TSAT) increased within 24 h and 1 week. Up to 97% of the administered iron was utilized for red blood cell (RBC) synthesis and both ferritin and TSAT returned to baseline levels within 3 – 4 weeks.

5. Efficacy

Notably, the IS complex was already developed in the 1940s before formal clinical development plans became as usual as

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today. Therefore, many studies were conducted as investigator initiated trials in different countries using a wide variety of study designs and end points. This limits the comparability and combined analyses of studies and therefore, published, representative studies using Venofer in a variety of patient populations were selected for inclusion in this review on the basis of their patient numbers, study design, and assessed efficacy and safety parameters.

The efficacy of IS in the treatment of ID has been proven in patients with a wide range of underlying conditions that cause or are associated with anemia (e.g., CKD, gastrointestinal disorders, pregnancy/postpartum, CHF and cancer). Overall, IS treatment improved iron status (ferritin, TSAT) and increased Hb levels with or without ESA therapy. When used in combination with ESA therapy, IS reduced ESA dose requirements substantially.

5.1 Chronic kidney disease

A comparison of IS (100 mg iron/dose in hemodialysis patients, 200 mg iron/dose in peritoneal dialysis patients) and oral ferrous succinate in two separate prospective, randomized studies with recombinant human erythropoietin (rHuEPO)-treated patients on maintenance dialysis showed statistically significantly better outcomes in Hb, hematocrit (Hct), serum ferritin and TSAT in the IS groups during the entire study periods (12 and 8 weeks, respectively; all $p < 0.05$) [45,46]. Furthermore, rHuEPO dose requirements at the end of both studies were significantly lower with IS compared to oral iron (-20.1 and -26.6%, respectively; $p < 0.05$). In HD-CKD patients with documented hypersensitivity to iron dextran who received erythropoietin twice weekly at a constant dose, a weekly dose of IS (100 mg iron given over 5 – 10 min for 8 weeks) significantly increased mean Hct (23.8 – 32.3%; $p < 0.0001$), serum ferritin (185 – 599 ng/ml; $p < 0.0001$) and serum iron (29.3 – 76.7 ng/ml; $p < 0.01$) [47].

The effectiveness of IS in anemic nondialysis CKD (ND-CKD) patients without concomitant ESA treatment has been shown in two single-arm studies. Compared to baseline, IS, given as 200 mg iron dose either monthly for 1 year or weekly for 4 weeks, significantly increased mean Hb, serum ferritin and TSAT from the first post-baseline assessment at month 3 onward or after the 4-week study period, respectively [48,49]. In a randomized trial comparing IS (five 200 mg iron doses over 14 days) to oral ferrous sulfate (65 mg iron thrice daily for 56 days) for the treatment of anemic, stage 3 – 5, ND-CKD patients, IS treatment resulted in significantly more Hb responders (44.3 vs 28.0% with Hb increase ≥ 1 g/dl; $p = 0.0344$), more patients achieving Hb levels ≥ 11 g/dl (59.5 vs 43.2%; $p = 0.0165$) and a higher mean Hb increase (0.7 vs 0.4 g/dl; $p = 0.0298$) [50].

5.2 Inflammatory bowel disease

One randomized, controlled, 20-week superiority study compared IS (200 mg iron weekly or biweekly until cumulative dose was reached) and oral ferrous sulfate for the treatment of IDA in patients with inflammatory bowel disease [51]. The study showed significantly better outcomes in the IS arm for two of three primary end points: less IS-treated patients remained anemic (16 vs 41%; $p = 0.007$; Hb < 12 g/dl [females] or < 13 g/dl [males]) and more patients achieved Hb reference levels (42 vs 22%; $p = 0.04$; Hb ≥ 13 g/dl or ≥ 15 g/dl [f/m]). The difference in the percentage of Hb responders (Hb increase > 2 g/dl) at week 20 was in favor of IS and close to significant (66 vs 47%; $p = 0.07$). Notably, all patients in the IS group achieved the recommended serum ferritin target (> 100 ng/ml), whereas only 28% in the oral iron group achieved this target. This might be partly due to the fact that all patients tolerated IS, whereas 24% discontinued ferrous sulfate due to intolerance.

Another study that investigated hematological response to IS and oral ferrous sulfate allocated patients with inflammatory bowel disease and Hb levels < 10 g/dl (mean baseline Hb 8.8 g/dl) to IS (200 mg iron twice a week until calculated iron deficit) and patients with Hb levels ≥ 10 g/dl (mean baseline Hb 11.3 g/dl) to oral ferrous sulfate (106 mg iron per day after the principal meal) [52]. Eighty-nine percent of patients receiving oral iron for moderate anemia normalized Hb levels. Despite their lower baseline Hb, also 77% of IS-treated patients achieved normal Hb levels (Hb ≥ 12 g/dl or ≥ 13 g/dl [f/m]) after 3 months. Furthermore, Hb levels correlated with the quality of life score CCVEII-9 (a 9-item questionnaire including the most representative items of the 36-item Inflammatory Bowel Disease Questionnaire; $p < 0.0001$).

A randomized comparison of IS (200 mg iron twice weekly up to 11 times until calculated iron deficit) and ferric carboxymaltose (once-weekly infusions of 1000 or 500 mg iron depending on baseline Hb and body weight) showed similar response rates to IS as the studies above (61.8% achieving normal Hb, 53.6% achieving Hb increase ≥ 2 g/dl); yet response rates to ferric carboxymaltose were significantly better (72.8 and 65.8%, respectively; $p < 0.015$ and $p = 0.004$) [53].

5.3 Obstetrics and gynecology, women's health

Among three studies that compared IS and oral iron in pregnant women with IDA, two used ferrous sulfate salt [54-56] and one iron polymaltose complex [57] as comparator. In pregnant women with a gestational age < 32 weeks and severe IDA (Hb < 9.0 g/dl, serum ferritin < 20 ng/ml), treatment with IS (200 mg iron every 1 – 3 days until calculated iron deficit) resulted in significantly higher mean Hb levels (12.9 vs 11.1 g/dl; $p \leq 0.001$; baseline 7.6 g/dl in both groups) than oral ferrous sulfate treatment (60 mg iron thrice daily) [54]. IS-treated patients achieved maximum Hb levels in approximately half the time (6.9 vs 14.9 weeks; $p \leq 0.001$) and also significantly higher serum ferritin levels (96 vs 52 ng/ml; $p \leq 0.001$; baseline 12 ng/ml in both groups).

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In pregnant women with less severe IDA (Hb 8 – 10 g/dl, serum ferritin < 50 ng/ml), randomization to a 4-week treatment with IS (6 × 200 mg iron) or a higher oral ferrous sulfate dose (240 mg iron daily) resulted in similar Hb levels (11.0 vs 11.1 g/dl; baseline 9.6 and 9.7 g/dl, respectively) [55]. Iron prophylaxis in pregnant women with Hb ≥ 10.5 g/dl (gestational week 15 – 20) showed similar efficacy among patients randomized to IS (2 – 3 times 200 mg iron) or to oral ferrous sulfate (80 mg iron daily) until delivery [56].

A comparison of IS (400 mg iron daily until calculated iron deficit) and oral iron polymaltose complex (300 mg iron daily) in pregnant women with severe ID (Hb 8 – 10.5 g/dl, serum ferritin < 13 ng/ml; gestational age 26 – 34 weeks) showed a significantly higher Hb increase in the IS group at weeks 2 and 4 after treatment initiation and until delivery (0.6, 1.2 and 2.1 g/dl vs 0.2, 0.6 and 1.5 g/dl, respectively; $p < 0.005$ at all time points) [57]. At birth, the target Hb of 11 g/dl was reached by 95.6% IS- versus 62.2% oral iron-treated patients ($p < 0.001$).

In a randomized study in postpartum women with IDA (Hb < 9 g/dl, ferritin < 15 mg/l at 24 – 48 h post-delivery), treatment with IS (200 mg iron on days 2 and 4) resulted in significantly higher Hb levels at days 5 and 14 (9.9 and 11.1 g/dl vs 7.5 and 9.0 g/dl, respectively; both $p < 0.01$) than oral ferrous sulfate treatment (40 mg iron twice daily) [58]. At day 40, oral iron-treated patients achieved similar Hb levels as those in the IS group (11.2 vs 11.5 g/dl). A randomized comparison of IS (100 mg iron daily for 3 days) and iron protein succinylate (40 mg iron daily for 1 month) in postpartum women with severe IDA (Hb < 8 g/dl, serum ferritin < 10 ng/ml) showed significantly higher Hb levels in IS-treated patients after 1 and 4 weeks (8.8 and 12.6 g/dl vs 8.1 and 10.3 g/dl) [59]. However, in these two trials, the daily oral iron dose was suboptimal.

Finally, a placebo-controlled study in fatigued, nonanemic premenopausal women with low ferritin levels (Hb ≥ 12 g/dl, serum ferritin ≤ 50 ng/ml) showed a trend for greater improvement in fatigue (Brief Fatigue Inventory questionnaire) in patients treated with IS (4 times 200 mg iron over 2 weeks) that reached significance in those with serum ferritin ≤ 15 ng/ml [60].

5.4 Oncology

Two prospective, randomized trials have been performed to assess the efficacy of IS treatment in cancer patients receiving ESAs. In anemic patients with lymphoproliferative malignancies not receiving chemotherapy, addition of IS (100 mg iron once weekly from weeks 0 – 6 followed by 100 mg every second week from weeks 8 to 14) to epoetin-β resulted in significantly faster and greater Hb increase (vs baseline) from week 8 onward when compared to no iron treatment ($p < 0.05$) [61]. Accordingly, end of study Hb levels were also higher in the IS arm (difference in mean Hb 0.99 g/dl; $p = 0.0023$) and a higher percentage of patients achieved a Hb increase ≥ 2 g/dl (87 vs 53%; $p = 0.0014$). From week 5 onward, mean epoetin dose requirements were consistently lower in the IS arm resulting in a 15% lower cumulative epoetin dose over the study period ($p = 0.059$) and a 24% lower epoetin dose at the end of the study. A subsequent cost analysis estimated that the lower epoetin dose requirements in the IS arm translate into cost savings of €670 – 747 over the 16-week study period, depending whether costs for loss of leisure time are considered or not [62].

In multiple myeloma or lymphoma patients after autologous hematopoietic cell transplantation, supplementation of darbepoetin-α with IS (200 mg iron on days 28, 42 and 56 post-transplant) increased the percentage of patients with Hb increase ≥ 2 g/dl from 88 to 100% and reduced the median time to response from 28 to 25 days ($p = 0.0231$) compared to no iron supplementation [63]. The percentage of patients requiring RBC transfusions and the cumulative darbepoetin-alfa dose were significantly lower in the IS arm (0 vs 11.1%; $p = 0.0276$ and 1210 vs 1440 µg; $p = 0.015$, respectively). Overall cost savings for drug acquisition when using IS supplementation were estimated to €444 per patient.

Otherwise, the use of IS without additional ESA treatment could also benefit at least some patients in terms of improved Hb levels and reduction of RBC transfusions as suggested by early studies in patients with gynecological cancers who received chemotherapy [64,65] and a prospective observational study in patients with cancer- and chemotherapy-associated anemia [66].

5.5 Preoperative iron treatment

In the context of perioperative PBM, that is, the prevention of perioperative anemia and minimization of blood transfusions [25], the Network for Advancement of Transfusion Alternatives recommends that nutritional deficiencies such as ID are treated before ESAs are used for anemic patients [17]. Since the underlying conditions in patients scheduled for elective surgery are often associated with inflammation or blood loss that exceeds absorption of oral iron, management of iron status with i.v. iron should be considered in patients lacking a response to oral iron. Despite the importance of this topic, high-quality prospective studies that are sufficiently powered are sparse.

A very small study in 12 patients with normal Hb and iron status that were due for elective surgery showed no significant difference in Hb increase of patients treated preoperatively with rHuEPO and IS (200 mg iron twice weekly) or ferrous sulfate (160 mg daily for 3 weeks) [67]. However, IS was associated with significantly higher reticulocyte counts and prevented iatrogenic iron depletion. In a similar trial, oral iron was as effective as i.v. iron in supporting preoperative EPO-driven stimulation of erythropoiesis, but transfusions were not reported [68].

In anemic, iron-deficient patients (Hct < 34%, serum iron < 700 µg/l) with gastrointestinal or colorectal cancer scheduled for elective surgery, a combination of rHuEPO and IS (200 mg iron on 12 consecutive days) allowed for

preoperative, autologous blood donations by 11/11 patients compared to none among patients treated with IS alone [69]. Furthermore, the proportion of patients with perioperative blood transfusions was reduced from 4/11 to none with the combination treatment.

Patients with IDA (Hb < 9 g/dl) due to menorrhagia who were scheduled for surgery 3 weeks later and received IS (200 mg iron thrice per week until calculated iron deficit) achieved significantly better postoperative Hb levels (10.5 vs 8.6 g/dl; $p < 0.0001$) than those treated with oral iron protein succinylate (80 mg iron daily) [70]. However, the oral iron dose used in this trial was suboptimal.

5.6 Perioperative iron treatment

A pooled analysis of observational data from 2547 patients from a single institution who underwent major orthopedic surgery compared postoperative outcomes of patients who received very-short-term perioperative i.v. iron administration (IS or ferric carboxymaltose with or without rHuEPO) or standard treatment [71]. Intravenous iron was associated with reduced rates of autologous RBC transfusions (32.4 vs 48.8%), postoperative nosocomial infection (10.7 vs 26.9%) and 30-day mortality (4.8 vs 9.4%), and shorter length of hospital stay (11.9 vs 13.4 days) (all $p < 0.01$) in hip fracture patients. Transfusion rates and hospital stay were also reduced in iron-treated arthroplasty patients (8.9 vs 30.2% [$p < 0.01$] and 8.4 versus 10.7 days [$p < 0.05$], respectively). However, the quality of evidence gathered from pooled observational analyses is questionable.

Four randomized controlled trials have examined the impact of perioperative i.v. iron. In a small double-blind trial, including patients with post-operative Hb between 7.0 and 9.0 g/dl on day 1 after cardiac or orthopedic surgery, 38 patients were randomized between no treatment, i.v. IS 200 mg on days 1, 2 and 3, and the same schedule of i.v. IS plus rHuEPO 600 U/kg on days 1 and 3 post-surgery [72]. Hb values on day 7 as well as 6 weeks after surgery were not different in the three groups. In another double-blind trial, 120 anemic (Hb 7 – 10 g/dl) patients after cardiac surgery were randomized between no treatment, i.v. IS and IS plus rHuEPO 300 U/kg once [73]. The i.v. IS dose was 200 mg daily until reaching the total iron deficit as calculated by the so-called Ganzoni formula: total iron deficit (mg) = 2.4 × body weight (kg) × (target Hb [12 g/dl] - lowest Hb). Hb values, measured daily until day 5 and then on days 15 and 30, were not different in the three groups and no significant difference in transfusion needs was observed among the three groups (22, 25, and 17% of patients transfused in the no treatment, i.v. iron alone and i.v. iron + rHuEPO group, respectively). The largest randomized trial compared IS treatment (3 times 200 mg iron at 48 h intervals starting at the day of admission) and standard clinical management in 200 patients undergoing hip fracture repair surgery (no patient received EPO) [74]. In the overall population, there was no significant difference in transfusion requirements, length of stay, morbidity and mortality between the two groups. Only in subgroups of patients with surgery for intracapsular fractures or with preoperative Hb > 12 g/dl, post-hoc analysis showed significant reductions in RBC transfusion requirements in the IS arm (14 vs 46% [$p < 0.005$] and 19 vs 35% [$p < 0.05$], respectively). The last trial was a double-blind study performed in 159 patients undergoing cardiopulmonary bypass surgery [75]. Group 1 received i.v. IS 3 × 100 mg/d pre- and postoperatively plus oral placebo, group 2 i.v. placebo plus oral ferrous fumarate 105 mg/d perioperatively and for 1 month after discharge, and group 3 the oral and i.v. placebos. No intergroup differences in Hb values or in blood transfusion requirements were found during the whole postoperative period.

In conclusion, four randomized controlled trials did not demonstrate benefits of perioperative i.v. iron. However, these trials included no more than 520 patients in total and one study identified some subgroups of patients who may have benefited. Therefore, before the use of perioperative i.v. iron is abandoned, further studies involving large numbers of patients should be performed to evaluate the efficacy and safety of i.v. iron administration in surgical patients.

5.7 Chronic heart failure

A small study (n = 35) in iron-deficient patients with CHF (serum ferritin < 100 ng/ml or serum ferritin 100 – 300 ng/ml and TSAT < 20%) showed significant improvements ($p < 0.05$) of absolute peak oxygen consumption, New York Heart Association (NYHA) functional class, TSAT and ferritin among anemic patients (Hb < 12.5 g/dl) who received a 16-week treatment with IS (200 mg iron weekly until ferritin > 500 ng/ml, followed by 200 mg iron monthly) compared to no treatment [76]. Notably, even nonanemic patients in the IS arm of this small study experienced a strong trend toward improvement in NYHA class compared to controls ($p = 0.08$). Changes in Hb levels were not significantly different between the treatment arms.

5.8 Pediatric populations

Limited, nonrandomized, studies have been performed in children. One retrospective study in pediatric non-CKD patients aged 3 months to 18 years who were treated with IS with individual doses of 25 – 500 mg iron revealed significant improvements in Hb levels compared to oral iron in children who were refractory to oral iron or had malabsorption (+3.1 vs +0.05 g/dl; $p < 0.001$ and +1.9 vs +0.4 g/dl; $p = 0.04$, respectively) [77].

Two studies were performed in iron-deficient children and adolescents with low Hb levels [78,79] and treated with IS at individual doses of 6.5 – 18.1 mg iron/kg and 5 mg/kg, respectively. The study in 18- to 180-month-old children who were scheduled for elective surgery showed significant improvements in Hb from month 1 to the end of the 3-month study period [78]. Children in the control group who were treated with oral ferrous glycine sulfate (no details

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on dosing reported) achieved a similar Hb increase. The second study in IS-treated children (age 11 months to 16 years) who were unresponsive to oral iron, showed significant improvements in Hb from 7.4 g/dl at baseline to 9.3 g/dl on day 14 and 12.4 g/dl after 6 months [79].

6. Safety and tolerability

Since the clinical development of IS started already some 70 years ago, safety-related aspects in early trials were often not reported in the same detail as for newer drugs. More recent trials, when IS was already well-established, rather focused on specific treatment regimens (e.g., combination with ESAs) or patient populations (e.g., patients with prior intolerance to other i.v. iron products). Among the 36 published clinical studies [45-50,55-60,64,65,70,74,76-91] that are included in the clinical dossier of Venofer, 26 reported at least some details about adverse drug events; 3 of those reported at least possibly related serious adverse events (all nonfatal, **Table 2**) [51,76,77]. Three reports included only general statements on safety without further details (e.g., no serious adverse reactions were noted) [47,48,64]. Five reports mentioned that no drug-related adverse events or no adverse events at all have been observed in IS-treated patients [45,46,49,52,65]. Two reports did not provide any safety information [84,88].

Overall, taste disturbance (dysgeusia) is the most common adverse event related to IS that has been reported in 2 – 24% of patients among 12 of the above-mentioned studies (**Table 2**). In general, dysgeusia is of transient and clinically insignificant nature and hardly results in treatment discontinuation. Gastrointestinal adverse events were reported for 1 – 13% of IS-treated patients in 13 of the published studies. In studies that included oral iron as a comparator, gastrointestinal adverse events occurred generally at a lower rate in the IS than in the oral iron arm (17 – 40%). In practice, there is a very low incidence of anaphylactoid or hypersensitivity reactions with IS, and none were reported in the published studies listed here (**Table 2**). In patients with HD-CKD and documented hypersensitivity to iron dextran, a weekly dose of IS (100 mg iron) was well tolerated without reoccurrence of hypersensitivity reactions during the 8-week study period [47]. Hypotension and rash/pruritus were reported in four publications each, flushes or dizziness in two studies each (**Table 2**).

In pediatric non-CKD patients (3 months to 18 years) who received 510 IS administrations (25 – 500 mg iron), individual IS doses < 3 mg iron/kg body weight were well tolerated without drug-related adverse events [77]. Five mild events were observed with individual doses of 3.0 – 5.1 mg iron/kg, and only one serious-related adverse event (body aches, facial swelling, thready pulse and hypotension) was reported after an individual 500 mg iron dose that was given within 35 min (i.e., 200 mg above the recommended dose corresponding to an individual dose of 8.8 mg/kg).

Apart from clinical trial data, three analyses of the US FDA and WHO pharmacovigilance databases covering periods from 1997 to 2009 evaluated adverse event reports of IS, iron dextranes and ferric gluconate [32,92,93]. Across all analyses, the reported adverse event rates appeared to be lowest with IS; particularly when compared to dextran-containing preparations. The most recent analysis of data from 16 European countries, the United States and Canada (Jan 2003 – Jun 2009) showed a significantly lower risk for all adverse events (odds ratio, 0.13; $p < 0.0001$) or serious allergic adverse events (odds ratio, 0.07; $p < 0.0001$) for IS compared to iron dextran [93]. Also compared to sodium ferric gluconate, IS had a significantly lower risk for all adverse events (odds ratio, 0.63; $p < 0.0001$) or serious allergic adverse events (odds ratio, 0.31; $p = 0.001$).

In 2013, the European Medicines Agency (EMA) published an assessment report [94] that reviewed the risk of allergic reactions of all i.v. iron products registered in the European Union and concluded that the benefits of i.v. iron-containing medicinal products continue to outweigh the risks in the treatment of ID situations when the oral route is insufficient (e.g., due to increased hepcidin activity and other inhibitors of cellular iron homeostasis [26]) or poorly tolerated. Notably, no test dose should be applied anymore; however, staff trained to evaluate and manage anaphylactic or anaphylactoid reactions as well as resuscitation facilities should be immediately available.

Since iron can modulate the activity of the immune system and iron sequestration by monocytes and macrophages has been suggested as a mechanism to withhold iron from pathogens or infected cells [10], a frequently raised question is whether i.v. iron increases the risk of infections. However, relevant clinical evidence is sparse and inconclusive [81,95,96]. A large multicenter safety study that evaluated an iron status correction and a maintenance IS dosing regimen in 665 hemodialysis patients (covering 8583 doses of 100 mg iron) reported lower rates of infection-related hospitalizations (relative risk 0.54, $p < 0.001$) and mortality (relative risk 0.61, $p = 0.08$) compared with a historical general hemodialysis population [81]. Conversely, a US cohort study (117,050 HD patients) suggested a higher risk of infection-related hospitalizations with high versus low iron dose (hazard ratio [HR] 1.05 [1.02 – 1.07]) and bolus versus maintenance dose (HR 1.05 [1.05 – 1.11]) [97]. However, the study does not provide any information about the distribution of administered iron compounds. A review of 75 studies (42 of them investigated IS) included a meta-analysis of 24 studies (n = 4400 patients) that suggests an association between i.v. iron and an increased risk of infection (risk ratio 1.33; 95% confidence interval 1.10 – 1.64) [95]. However, the authors of this analysis mentioned themselves that their finding might also be a false positive result since infection is generally not a predefined end point and missing data could have created a bias in the analysis. A study investigating an 'aggressive' IS treatment (100 mg iron doses until a TSAT > 30% and serum

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Table 2. Published clinical studies on the treatment of ID/IDA that are also included in the clinical dossier of iron sucrose (Venofer).

Study	Inclusion criteria	Patients (n)	mg iron/dose, interval, treatment duration	Outcomes and safety information
Non-dialysis chronic kidney disease				
Charytan *et al.* (2005) [87]	Hb < 10.5 g/dl TSAT < 25% SF < 300 ng/ml	IS + EPO: 48 FeS + EPO: 48	200 mg, qwk, 5 wks 65 mg t.i.d., 29 d	Significant Hb increase versus baseline within but not between groups Taste disturbances in 8.4% with IS, none with FeS Less GI side effects with IS versus FeS (constipation 12.5 vs 35.4%; nausea, 4.2 vs 10.4%; vomiting, 0 vs 8.3%; diarrhea 0 vs 6.3%) No deaths, SAEs, hypersensitivity or discontinuation due to drug-related AEs
Van Wyck *et al.* (2005) [50]	Hb < 11.0 g/dl TSAT < 25% SF < 300 ng/ml	IS + EPO: 91 FeS + EPO: 91	2 × 500 or 5 × 200 mg, 14 d 65 mg t.i.d., 56 d	Significant better Hb response (ΔHb ≥ 1.0 g/dl) and increase with IS versus FeS Dysgeusia most prominent IS-related GI complaint (6.6%) Less GI side effects with IS200 (11.5%) and IS500 (3.3%) versus FeS (17.6%)
Mircescu *et al.* (2006) [48]	Hb < 11.0 g/dl SF < 200 ng/ml	IS: 60	200 mg, monthly, 1 y	Significant, continuous and progressive Hb increase No worsening of renal function, blood pressure changes or SAEs
Tagboto *et al.* (2008) [49]	Hb < 11.5 g/dl	IS: 82	4 × 200 mg, qwk	Hb increase in 74% of patients No specific safety results reported
Hemodialysis-dependent chronic kidney disease				
Charytan *et al.* (2001) [85]	Hb < 11.0 g/dl TSAT < 20% SF < 300 ng/ml	IS + EPO: 77	10 × 100 mg, 22 d	78% achieved target Hb > 11.0 g/dl possibly or probably related AEs transient minty taste, diarrhea + abdominal pain, diarrhea + nausea, constipation (1 patient each) No SADR, anaphylaxis or discontinuation due to drug-related AEs
Charytan *et al.* (2004) [86]	Intolerance to iron dextran and/or ferric gluconate	IS + EPO: 130	Summary of four trials 100 or 200 mg, 1 – 3 qwk	14 AEs in eight patients (taste disturbance in three, nausea in two, diarrhea, hypotension, vomiting, constipation + dry mouth + skin irritation in 1 each) One patient experienced seven AEs but continued therapy
Aronoff *et al.* (2004) [81]	Patients requiring EPO and iron as per NKF K/DOQI	IS + EPO: 665	Correction:10 × 100 mg Maintenance: 100 mg qwk Depending on iron status	Taste disturbances most common AE (11); constipation, hypotension, vomiting (3 each); pruritus, nausea (2 each); transaminase elevation, dermatitis, diarrhea, dizziness, dry mouth (1 each); no drug-related SAEs
Li and Wang (2008) [46]	Hb 6.0–9.0 g/dl TSAT < 30% SF < 500 ng/ml	IS + EPO: 70 FeSu + EPO: 66	100 mg 2×/wk then qwk 200 mg FeSu t.i.d., 12 wk	Significant Hb increase versus baseline in both groups and with IS versus FeSu No AEs with IS, 33.3% GI symptoms with FeSu
Haddad *et al.* (2009) [47]	Intolerance to iron dextran	IS + EPO: 15	100 mg qwk	Significant hematocrit increase No hypersensitivity reactions or effects on intradialytic blood pressure

*At study sites in Mexico, prevalence of severe anemia was so high that patients with lower Hb and no prior ESA use were allowed to enroll.

‡Female Hb < 12 g/dl, male < 13 g/dl.

ADE: Adverse drug events; AE: Adverse event; b.i.d.: Twice per day; CKD: Chronic kidney disease; CT: Chemotherapy; d: Day; eod: Every other day; eowk: Every other week; EPO: Erythropoietin; ESRF: End-stage renal failure; FCM: Ferric carboxymaltose; FeGlyS: Ferrous glycine sulfate; FeProtSu: Ferrous protein succinylate; FeS: Ferrous sulfate; FeSu: Ferrous succinate; FG: Ferric gluconate; Gest: Gestational; GI: Gastrointestinal; Hb: Hemoglobin; ID: Iron deficiency; IDA: Iron-deficiency anemia; IPC: Iron polymaltose complex; IS: Iron sucrose; qd: Every day; qwk: Every week; q4wk: Every fourth week; RBC: Red blood cell; SAE: Serious adverse event; SADR: Serious adverse drug reaction; SF: Serum ferritin; t.i.d.: Thrice per day: TSAT: Transferrin saturation; wk: Week.

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Table 2. Published clinical studies on the treatment of ID/IDA that are also included in the clinical dossier of iron sucrose (Venofer) (continued).

Study	Inclusion criteria	Patients (n)	mg iron/dose, interval, treatment duration	Outcomes and safety information
Peritoneal dialysis-dependent chronic kidney disease				
Singh *et al.* (2006) [90]	Hb 9.5–12.5 g/dl or 8.5–12.5 g/dl*	IS + EPO: 75 EPO: 46	2 × 400 + 1 × 300 mg, 29 d	Significant better Hb increase with IS versus no iron 6.7% GI ADEs in IS group, no SADEs, 1 discontinuation due to drug-related AEs (feet swelling and pruritus),
Li and Wang (2008) [45]	Hb 6.0–9.0 g/dl TSAT < 30% SF < 500 ng/ml	IS + EPO: 26 FeSu + EPO: 20	200 mg qwk over 4 wk then eowk 200 mg FeSu t.i.d., 8 wk	Significant Hb increase versus baseline in both groups and with IS versus FeSu No AEs with IS, 40% GI symptoms with FeSu
Inflammatory bowel disease				
Bodemar *et al.* (2004) [82]	IDA and IS treatment	IS: 61	200 mg qwk or eowk until calculated dose	91% Hb response during 12 week One rash and slight fever for 24 h after one infusion that did not reappear during or after subsequent infusions, no SAEs during IS infusions,
Gisbert *et al.* (2009) [52]	Hb < 12 or 13 g/dl‡ TSAT < 12% SF < 30 ng/ml	IS: 22 FeS: 78	200 mg 2×/wk if Hb < 10 until calculated dose 106 mg qd if Hb > 10	77 and 89% response rate in IS and FeS group, respectively No AEs with IS, 5.1% with oral iron intolerance (nausea, abdominal pain and constipation), which led to discontinuation of treatment
Lindgren *et al.* (2009) [51]	Hb < 11.5 g/dl SF < 300 ng/ml	IS: 45 FeS: 46	200 mg qwk or eowk until calculated dose 40 mg b.i.d., 20 wk	66 versus 47% Hb response to IS versus FeS (p = 0.07) One possibly related SAE (thrombocytopenia) with IS, AEs with FeS dominated by GI events
Evstatiev *et al.* (2011) [53]	Hb ≥ 7 g/dl and < 12 or 13 g/dl‡ SF < 100 ng/ml	IS: 239 FCM: 244	200 mg 2×/wk until calculated dose 500 or 1000 mg qwk	Significant better Hb response to FCM versus IS No true hypersensitivity reactions or drug-related SAE with IS, two patients withdrew due to drug-related AEs
Obstetrics and gynecology – pregnancy				
al-Momen *et al.* (1996) [54]	Gest. age < 32 wk Hb < 9.0 g/dl SF < 20 ng/ml	IS: 52 FeS:59	200 mg qd or 3×/wk 60 mg t.i.d.	Significant higher Hb levels with IS versus FeS Self-limiting fever and tightness in skin (1 each) with IS, 30% GI events and 32% non-compliance with FeS, 6% could not tolerate FeS,
Breymann *et al.* (2001) [83]	Gest. age ≥ 21 wk Hb < 10.0 g/dl SF < 15 ng/ml	IS: 20 IS + EPO: 20	200 mg 2×/wk 200 mg 2×/wk	Significant better increase in reticulocytes and hematocrit with IS No SAEs; metallic taste in 3 patients and 2 felt warm for few min, no hypo- or hypertensive reactions
Bayoumeu *et al.* (2002) [55]	Hb 8.0–10.0 g/dl SF < 50 ng/ml	IS: 24 FeS: 23	6× ~200 mg until calculated dose, 21 d 80 mg t.i.d, 4 wk	Hb increase in both groups without significant difference 'Not-unpleasant taste' only AE with IS, during injection (dysgeusia). One treatment interruption due to AE (diarrhea) with FeS
Al *et al.* (2005) [57]	Gest. age 26–34 wk Hb 8.0–10.5 g/dl SF < 13 ng/ml	IS: 45 IPC: 45	200 mg until calculated dose, 5d 100 mg t.i.d., whole pregnancy	Significant better Hb increase with IS versus IPC Possibly related AEs to IS: metallic taste (11), hot flush (12), dizziness (8), nausea (5), arthralgia, vomiting (1 each); significant less GI symptoms with IS versus FeS (13.3 vs 28.9% upper GI events)

*At study sites in Mexico, prevalence of severe anemia was so high that patients with lower Hb and no prior ESA use were allowed to enroll.

‡Female Hb < 12 g/dl, male < 13 g/dl.

ADE: Adverse drug events; AE: Adverse event; b.i.d.: Twice per day; CKD: Chronic kidney disease; CT: Chemotherapy; d: Day; eod: Every other day; eowk: Every other week; EPO: Erythropoietin; ESRF: End-stage renal failure; FCM: Ferric carboxymaltose; FeGlyS: Ferrous glycine sulfate; FeProtSu: Ferrous protein succinylate; FeS: Ferrous sulfate; FeSu: Ferrous succinate; FG: Ferric gluconate; Gest: Gestational; GI: Gastrointestinal; Hb: Hemoglobin; ID: Iron deficiency; IDA: Iron-deficiency anemia; IPC: Iron polymaltose complex; IS: Iron sucrose; qd: Every day; qwk: Every week; q4wk: Every fourth week; RBC: Red blood cell; SAE: Serious adverse event; SADR: Serious adverse drug reaction; SF: Serum ferritin; t.i.d.: Thrice per day: TSAT: Transferrin saturation; wk: Week.

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Table 2. Published clinical studies on the treatment of ID/IDA that are also included in the clinical dossier of iron sucrose (Venofer) (continued).

Study	Inclusion criteria	Patients (n)	mg iron/dose, interval, treatment duration	Outcomes and safety information
Bencaiova *et al.* (2009) [56]	Gest. age 15–20 wk Hb > 10.5 g/dl SF ≤ 100 ng/ml	IS: 130 FeS: 130	200 or 300 mg 80 mg qd	Significant Hb increase versus baseline in both groups Mild anemia (16.2%), infections (6.9%), muscle pains, pruritus (2.3% each), cough, breast disorders (1.5% each) with IS; GI events only with FeS (17.7%), 14 SAEs in IS group (preterm contractions 3, premature rupture of the membranes 3, moderate anemia after delivery 2, threatened preterm delivery because of cervical insufficiency 2, intrauterine growth restriction 2, infection 1, injury 1), 7 SAEs in FeS group (preterm contractions 2, vaginal bleeding 1, premature rupture of the membrane 1, infection 1, gestational diabetes mellitus 1, postpartal pulmonary embolism 1
Krafft *et al.* (2009) [89]	Gest. age > 16 wk Hb < 10.0 g/dl SF ≤ 15 ng/ml	IS: 27 IS + EPO: 57	200 mg, 2×/wk, max 4wk 200 mg, 2×/wk, max 4wk	Significant higher Hb with IS + EPO from beginning versus delayed EPO Most patients reported metallic taste, no SAEs, no hypotensive or allergic reaction
Obstetrics and gynecology – postpartum				
Bhandal and Russell (2006) [58]	Hb < 9.0 g/dl SF < 15 ng/ml	IS: 22 FeS: 21	200 mg eod, 3 d 200 mg b.i.d, 6 wk	Significant. better Hb increase with IS versus FeS 23% metallic taste, 18% facial flushing with IS, 33% GI events with FeS No SAEs, no hemodynamic disturbances during or after infusion
Westad *et al.* (2008) [91]	Hb 6.5–8.5 g/dl	IS: 58 FeS: 70	200 mg qd, 3 d 100 mg b.i.d., 12 wk	Hb increase in both groups Few and transient AEs with IS (phlebitis, pain at injection site), 22.9% withdrew due to drug-related AEs with FeS (GI events most common reason)
Giannoulis *et al.* (2009) [59]	Hb < 8.0 g/dl SF < 10 ng/ml	IS: 78 FeProtSu: 26	100 mg qd, 3 d 800 mg qd, 28 d	Significant better Hb increase with IS versus FeProtSu 2 AEs with IS (headache, nausea), 11 AEs with FeProtSu (constipation 5, hiccup 4, heartburn 2)
Obstetrics and gynecology – women's health (lactating, fatigue)				
Breymann *et al.* (2007) [84]	Hb 10.0–12.0 g/dl TSAT < 15%	IS: 10 No iron: 5	1 × 100 mg	No increase in milk iron and no significant intergroup differences No AE-related details reported
Krayenbühl *et al.* (2011) [60]	Hb ≥ 12.0 g/dl SF ≤ 50 ng/ml	IS: 43 Placebo: 47	4 × 200 mg, 2 wk	Trend for better improvement of fatigue score with IS versus placebo 21% drug-related AEs with IS (nausea, chills, headache, dizziness, chest pain, dysesthesia, dysgeusia), 7% AEs with placebo (nausea, headache, dizziness, diarrhea)
Oncology				
Kim *et al.* (2007) [65]	Hb < 12.0 g/dl	IS: 30 No iron: 45	1 × 200 mg per CT cycle	Significant reduction of RBC transfusions with IS versus no iron No drug-related AEs with IS, transfusion-related allergic reactions with similar frequency in both groups
Dangsuwan and Manchana (2010) [64]	Hb < 10.0 g/dl	IS: 22 FeS: 22	200 mg 200 mg t.i.d.	Significant better Hb and significant less RBC transfusions with IS versus FeS Most common AEs mild nausea and vomiting, no significant difference between groups, no SAEs or hypersensitivity reaction

*At study sites in Mexico, prevalence of severe anemia was so high that patients with lower Hb and no prior ESA use were allowed to enroll.

‡Female Hb < 12 g/dl, male < 13 g/dl.

ADE: Adverse drug events; AE: Adverse event; b.i.d.: Twice per day; CKD: Chronic kidney disease; CT: Chemotherapy; d: Day; eod: Every other day; eowk: Every other week; EPO: Erythropoietin; ESRF: End-stage renal failure; FCM: Ferric carboxymaltose; FeGlyS: Ferrous glycine sulfate; FeProtSu: Ferrous protein succinylate; FeS: Ferrous sulfate; FeSu: Ferrous succinate; FG: Ferric gluconate; Gest: Gestational; GI: Gastrointestinal; Hb: Hemoglobin; ID: Iron deficiency; IDA: Iron-deficiency anemia; IPC: Iron polymaltose complex; IS: Iron sucrose; qd: Every day; qwk: Every week; q4wk: Every fourth week; RBC: Red blood cell; SAE: Serious adverse event; SADR: Serious adverse drug reaction; SF: Serum ferritin; t.i.d.: Thrice per day: TSAT: Transferrin saturation; wk: Week.

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Table 2. Published clinical studies on the treatment of ID/IDA that are also included in the clinical dossier of iron sucrose (Venofer) (continued).

Study	Inclusion criteria	Patients (n)	mg iron/dose, interval, treatment duration	Outcomes and safety information
Preoperative iron treatment				
Gesemann *et al.* (1996) [88]	Hip replacement RBC donation if Hb > 11.5 g/dl	IS: 41 FG: 33 Oral FeS: 123	1 × 200 mg iron (IS) 1 × 125 mg iron (FG) 200 mg qd	Significant more female patients with IS versus FeS could donate 4 RBC units, no significant differences between groups observed in male patients No AE-related details reported
Kim *et al.* (2009) [70]	Menorrhagia Hb < 10.0 g/dl	IS: 39 FeProtSu: 37	200 mg, 3×/wk eod 80 mg qd, 3 wk	Significant better Hb increase and prominent response rate with IS versus FeProtSu Two myalgia, one injection pain events with IS, one nausea, one dyspepsia with FeProtSu, no severe AEs reported
Serrano-Trenas *et al.* (2011) [74]	Hip fracture	IS: 99 No iron: 97	200 mg, 3× eod	No significant difference in RBC transfusions between groups 3.0% AE-related treatment suspension with IS (one skin rash, two general discomfort), overall 14.8% infections (mainly superficial surgical wound infections 5.6%)
Chronic heart failure				
Okonko *et al.* (2008) [76]	Anemic population Hb < 12.5 g/dl TSAT < 20% SF < 100 ng/ml Nonanemic Hb 12.5 – 14.5 g/dl TSAT < 20% SF 100 – 300 ng/ml	IS: 24 No iron: 11	200 mg, qwk until SF ≥ 500 ng/ml, then q4wk, 16 wk	Significant Hb increase versus baseline with IS, no difference versus no iron, significant improved exercise tolerance (pVO_2) with IS in anemic subgroup No symptomatic hypotension or anaphylactic reactions, only unrelated or unlikely related AEs (one unrelated death due to intractable cardiac pump failure)
Pediatric populations				
Anbu *et al.* (2005) [80]	CKD or ESRF, anemic, on EPO, SF < 100 ng/ml or on hemodialysis	IS: 92 (72 from 1999 to 2003 and 20 from 2003 to 2004)	Depending on weight, time period and correction versus maintenance 2–5 mg/kg or 100–200 mg	Three AEs during first time period (abdominal pain, no reoccurrence after further doses), no related SAE Six AEs during second time period (taste perversion 3, smell of coffee, diarrhea, vomiting [1 each])
Akarsu *et al.* (2006) [78]	Low Hb for age TSAT ≤ 16% SF < 12 ng/ml	IS: 62 FeGlyS: 40	6.5–18.1 mg/kg, 2–3 d until calculated dose No dose info for FeGlyS	Significant incremental Hb increases from week 1 onwards 12.9% AEs with IS (facial rashes 4.8%, febrile episodes + irritability + flushing 4.8%, urticarial lesions 1.6%, food craving 1.6%), no withdrawal due to AE
Pinsk *et al.* (2008) [79]	Low Hb for age SF < 16 ng/ml	IS: 45	5 mg/kg, 3×/wk until calculated dose	Significant Hb increase versus baseline One transient hypotension and vomiting 30 min after initiation of IS (resolved after discontinuation), two drug extravasations with skin discoloration
Crary *et al.* (2010) [77]	Treated with IS for any non-CKD condition	IS: 38	25–500 mg	Five mild, related AEs (abdominal pain 2, headache 1, transient hypotension 1, vasovagal syncope 1) with IS at 3.0–5.1 mg/kg, 1 SAE (body aches, facial swelling, thready pulse, hypotension) with IS at 8.8 mg/kg

*At study sites in Mexico, prevalence of severe anemia was so high that patients with lower Hb and no prior ESA use were allowed to enroll.

‡Female Hb < 12 g/dl, male < 13 g/dl.

ADE: Adverse drug events; AE: Adverse event; b.i.d.: Twice per day; CKD: Chronic kidney disease; CT: Chemotherapy; d: Day; eod: Every other day; eowk: Every other week; EPO: Erythropoietin; ESRF: End-stage renal failure; FCM: Ferric carboxymaltose; FeGlyS: Ferrous glycine sulfate; FeProtSu: Ferrous protein succinylate; FeS: Ferrous sulfate; FeSu: Ferrous succinate; FG: Ferric gluconate; Gest: Gestational; GI: Gastrointestinal; Hb: Hemoglobin; ID: Iron deficiency; IDA: Iron-deficiency anemia; IPC: Iron polymaltose complex; IS: Iron sucrose; qd: Every day; qwk: Every week; q4wk: Every fourth week; RBC: Red blood cell; SAE: Serious adverse event; SADR: Serious adverse drug reaction; SF: Serum ferritin; t.i.d.: Thrice per day: TSAT: Transferrin saturation; wk: Week.

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ferritin up to 1200 ng/ml) showed no increase in the incidence of culture positive bacteremias, pneumonias, soft tissue infections or osteomyelitis over a 1-year period [96].

7. Regulatory affairs and experience with IS follow-on compounds

Iron(III)-hydroxide sucrose complex has received the first marketing authorization in December 1949 in Switzerland, where the product was first launched in 1950 (formerly marketed as Ferrum Hausmann®, now Venofer). Until August 2013, Venofer had received marketing authorization in a total of 85 countries worldwide and is marketed in all of them.

A generic follow-on product is considered therapeutically equivalent (and thus eligible for substitution) if it comprises the same active pharmaceutical ingredient and dosage form as well as comparable pharmacokinetic properties demonstrated in a cross-over healthy volunteer study [98]. However, the synthetic IS complex (and iron carbohydrate complexes in general) comprises a macromolecular and nanoparticulate structure that may even exceed the complexity of some biologicals [38,99]. Accordingly, IS is no single substance that can be isolated or fully characterized, and the physicochemical and biological properties of IS preparations (e.g., structure of the iron core, complex stability, biodisposition and bioavailability of iron after infusion) can be affected by subtle differences in the multistep manufacturing process. Therefore, IS might be considered as a nonbiological complex drug (NBCD) [38]. While the originator IS received regulatory approval based on clinically assessed efficacy and safety, regulatory assessment of follow-on products is subject to a lively discussion since the abridged pathway for small-molecule generics does not seem appropriate for follow-on products of a NBCD and the biosimilar pathway cannot be applied to nonbiologicals [39,99].

The EMA highlighted regulatory issues with the assessment of nanoparticle iron follow-on products in a first reflection paper on nonclinical requirements in 2011 and a draft reflection paper on nonclinical and clinical data requirements that has been open for consultation until 28 February 2014 [100]. Also, the US FDA issued a draft guidance on the evaluation of IS follow-on products that recommends conduct of two bioequivalence studies; one study assessing serum iron and serum transferrin-bound iron in healthy subjects after administration of a 100 mg iron dose, and one assessing 'sameness' in physicochemical properties such as 'labile iron determination under physiologically relevant conditions' [101].

Accordingly, experts from academia, industry and regulatory bodies suggest a stepwise similarity approach that includes appropriate clinical and/or nonclinical studies that evaluate pharmacokinetics, pharmacodynamics and safety/efficacy of a nonbiological complex drug's follow-on products in relevant patient populations [38,99,102,103]. As long as proof of therapeutic equivalence and similar safety profiles by appropriate studies is missing, interchange and automatic substitution between nonbiological complex drugs and their follow-on products should be discouraged [39].

Few studies have touched on this topic. A retrospective study of 658 female patients who received the IS originator or a follow-on product in two different dilutions (ISSd1, ISSd2) showed significantly fewer adverse drug reactions with the originator (IS: 1.8%, ISSd1: 11.0%, ISSd2: 14.3%; $p < 0.02$) [33]. The most commonly observed adverse events were injection site reaction (IS: 1.8%, ISSd1: 6.2%, ISSd2 8.2%; $p < 0.05$) and phlebitis (IS: 0%, ISSd1: 4.8%, ISSd2 4.7%; $p < 0.05$). An observational study in 75 consecutive, stable patients with HD-CKD in a French hemodialysis center investigated Hb and iron status parameters during two 27-week periods before and after a switch from the IS originator to a follow-on product [35]. The study showed significantly lower mean Hb levels (11.4 ± 1.1 g/dl vs 11.8 ± 1.0 g/dl; $p = 0.005$), as well as ferritin and TSAT after the switch. Conversely, the mean ESA dose requirements per patient to maintain or re-achieve target Hb levels increased by 13.8% (from 0.58 ± 0.52 to 0.66 ± 0.65 μg/kg/week; $p = 0.13$).

8. Cost-effectiveness

Intravenous iron supplementation can result in substantial ESA dose reductions and corresponding net cost savings to health-care providers [62,104,105]. Furthermore, reducing RBC transfusions needs [65,106] can potentially reduce costs for providing RBC units, hospitalization and management of complications.

Very few studies compared drug costs between i.v. iron preparations [107,108]. Two studies evaluated the effects of IS and ferric gluconate in hemodialysis patients in a switch ($n = 100$) and a parallel group study ($n = 59$), respectively. The first study reported a reduction of iron dosage from 264 to 153 mg iron/month after 9 months of IS treatment and a trend for reduced ESA dosage [108]. The second study, a randomized, controlled comparison (IS: 250 mg iron monthly vs ferric gluconate: 62.5 mg iron weekly), showed no significant difference in ESA dose requirements [107].

Switching from the IS originator to an IS follow-on product in a French hemodialysis center nonsignificantly increased the cumulative anemia drug (ESA + iron) expenditure by 11.9% [35].

9. Conclusion

Clinical experience demonstrates that treatment with i.v. IS corrects both absolute ID (i.e., depleted iron stores) as well as FID (insufficient availability of iron to the bone marrow despite adequate iron stores) and promotes erythropoiesis. IS is effective and well-tolerated in patients who are in clinical need for rapid iron supply, cannot tolerate oral iron therapy or are noncompliant or where oral iron preparations are ineffective. The efficacy and tolerability of IS in the treatment of IDA have been demonstrated in patients with a wide range

of underlying conditions that cause or are associated with anemia, including CKD, gastrointestinal disorders, pregnancy, postpartum, CHF and cancer. In the preoperative or perioperative setting, additional data are warranted.

10. Expert opinion

IS is the most frequently used i.v. iron compound for the treatment of ID and IDA in a broad range of therapeutic areas; particularly in patients with impaired iron absorption (e.g., due to chronic inflammatory conditions) or rapidly increased iron consumption after treatment with ESAs. IS, like available i.v. iron preparations in general, can overcome both the low intestinal absorption of orally ingested iron as well as the reduced release of iron from iron storing cells of the RES.

In contrast to the common misconception that i.v. iron would be trapped in the RES of patients with inflammatory conditions, the release of iron from iron stores is only reduced and not completely blocked. Since iron is still released, though at a lower equilibrium rate, there is no risk of chronic iron overload as long as i.v. iron is administered to individuals with confirmed ID (i.e., serum ferritin < 100 ng/ml or TSAT < 20%).

IS treatment is associated with increases in Hb concentrations with or without ESA therapy and improvements in iron status increasing both TSAT and ferritin. In studies comparing i.v. IS with an oral iron preparation, achievement of hematological response was generally faster (if early time points were recorded) or more frequent. In the long-term and absence of chronic inflammatory conditions, daily treatment with oral iron may compensate the early advantages of i.v IS provided that patients tolerate oral iron and stay compliant with the treatment. Furthermore, the use of IS in addition to an ESA-based anemia therapy can substantially reduce ESA dose requirements and thus improve cost-effectiveness since the costs of ESAs are still major drivers of total anemia treatment costs.

In general, i.v. iron should be considered for patients with FID and impaired iron absorption due to chronic inflammatory conditions and for patients with absolute ID or IDA requiring rapid resolution of ID or anemia. A trial of oral iron should be considered in patients with absolute ID and normal iron absorption if resolution of ID is not time critical.

IS has an extensive safety and tolerability record in a wide range of patients with ID. The most commonly reported adverse event in clinical trials was dysgeusia (taste disturbance), which rarely led to discontinuation of therapy. The incidence of serious drug-related adverse events with IS is low. Three analyses of surveillance data covering the period from 1997 to 2009 confirmed the good tolerability of IS compared to other iron products, particularly iron dextran. In addition, IS has been shown to be well tolerated by patients with documented prior intolerance of iron dextran and/or iron gluconate. No patient with intolerance to iron dextran or iron gluconate had an anaphylactic reaction to IS.

The extensive safety and tolerability record of IS, including a low frequency of hypersensitivity reactions, supports the recent recommendation of the EMA that no test dose needs to be applied prior IS administration provided that trained staff and equipment for the evaluation and management of potential anaphylactic or anaphylactoid reactions and resuscitation are available. Overall, there is no confirmed association between i.v. IS when used according to the label and the rate of infections, but this remains to be further investigated prospectively. In patients with active infection, however, the use of i.v. iron should be generally avoided.

First reports about the clinical experience with follow-on products of the IS originator raise questions whether these products are all therapeutically equivalent and should qualify for automatic substitution without clinical proof of equivalence in the intended patient population.

Declaration of interest

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