# RISK MANAGEMENT PLAN (EU) FOR VENOFER® (IRON SUCROSE)

**RMP version to be assessed as part of this application:**

| | |
|---|---|
| RMP Version Number: | 3.1 |
| Data Lock Point for this RMP: | 1 May 2022 |
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| Rationale for Submitting an Updated RMP: | Changes to safety concerns<br>Presentation of PASS results<br>Alignment with Guidance on the format of the risk management plan (RMP) in the EU – in integrated format¸ EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2 |
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# LIST OF ABBREVIATIONS

| | |
|---|---|
| CHF | chronic heart failure |
| CI | confidence interval |
| CKD | chronic kidney disease |
| CMDh | Coordination Group for Mutual Recognition and Decentralised Procedures - Human |
| ESA | erythropoiesis stimulating agent |
| EU | European Union |
| GCP | Good Clinical Practice |
| GI | gastrointestinal |
| GVP | Good Pharmacovigilance Practice |
| Hb | haemoglobin |
| HR | hazard ratio |
| HSR | hypersensitivity reaction |
| IBD | inflammatory bowel disease |
| ID | iron deficiency |
| IDA | iron deficiency anaemia |
| IIR | important identified risk |
| IPR | important potential risk |
| IS | iron sucrose |
| IV | intravenous |
| MAH | Marketing Authorisation Holder |
| PASS | Post-authorisation Safety Study |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PSUR | Periodic Safety Update Report |
| RMP | Risk Management Plan |
| SmPC | Summary of Product Characteristics |
| TQ | targeted questionnaire |
| TSAT | transferrin saturation |
| US | United States |

# PART I: PRODUCT OVERVIEW

## Table 1 Product(s) Overview

| | |
|---|---|
| Active Substance(s) (INN or Common Name): | Iron sucrose. |
| Pharmacotherapeutic Group(s) (ATC Code): | Anti-anaemic preparation. Iron trivalent, parenteral preparation (B03AC). |
| Marketing Authorisation Holder or Applicant: | Vifor International Inc.<br>Rechenstrasse 37<br>9014 St. Gallen<br>Switzerland |
| Medicinal Products to Which This RMP Refers: | Venofer. |
| Invented Name(s) in the EEA: | Venofer 20 mg iron/ml, solution for injection or concentrate for solution for infusion. |
| Marketing Authorisation Procedure: | Mutual Recognition: Austria, Belgium, Denmark, Finland, Greece, Ireland, Italy, Luxembourg, Spain, Sweden. |
| Brief Description of the Product: | Venofer is a brown, sterile solution of IS containing 2% w/v iron (20 mg iron as iron(III)-hydroxide sucrose complex per ml) bound in a stable polynuclear, non-ionic sucrose complex, the core of which is structurally similar to that of the physiological iron storage protein ferritin. IS belongs to the pharmacotherapeutic group of anti-anaemic preparations. |
| Hyperlink to the Product Information: | Not applicable. |
| Indication(s) in the EEA: | Current indication based on MRP SmPC Version 17.0 (dated 18 March 2022):<br>Venofer is indicated for the treatment of ID in the following indications:<br>• Where there is a clinical need for a rapid iron supply<br>• In patients who cannot tolerate oral iron therapy or who are non-compliant<br>• In active IBD where oral iron preparations are ineffective<br>• In chronic kidney disease when oral iron preparations are less effective<br>The diagnosis of ID must be based on appropriate laboratory tests (e.g., Hb, serum ferritin, TSAT, serum iron, etc.).<br>Proposed: Not applicable. |
| Dosage in the EEA: | Current dosage based on MRP SmPC Version 17 (dated 18 March 2022):<br>5-10 ml of Venofer (100-200 mg iron) 1 to 3 times a week.<br>The cumulative dose and schedule of administration of Venofer must be calculated for each patient individually and must not be exceeded.<br>**Normal Posology**<br>Adults<br>5-10 ml of Venofer (100-200 mg iron) 1 to 3 times a week.<br>**Maximum Tolerated Single and Weekly Doses**<br>Adults<br>As an injection, maximum tolerated dose per day, given not more than 3 times per week:<br>200 mg iron (10 ml of Venofer) injected over at least 10 minutes. |

| | |
|---|---|
| | As an infusion, maximum tolerated dose per day given not more than once per week:<br>• Patients above 70 kg body weight: 500 mg iron (25 ml of Venofer) over at least 3½ hours<br>• Patients of 70 kg body weight and below: 7 mg iron/kg body weight over at least 3½ hours<br>The infusion times given should be strictly adhered to even if the patient does not receive the maximum tolerated single dose.<br>Proposed: Not applicable. |
| Pharmaceutical Form(s) and Strengths: | Current:<br>Solution for injection or concentrate for solution for infusion.<br>One ml of solution contains 20 mg of iron as IS (iron(III)-hydroxide sucrose complex).<br>Each 5 ml ampoule of Venofer contains 100 mg iron as IS (iron(III)-hydroxide sucrose complex).<br>Each 5 ml vial of Venofer contains 100 mg iron as IS (iron(III)-hydroxide sucrose complex).<br>Proposed: Not applicable. |
| Is/Will the Product Be Subject to Additional Monitoring in the EU? | No |

Notes: ATC Anatomical Therapeutic Chemical; EEA European Economic Area; Hb Haemoglobin; IBD Inflammatory bowel disease; ID Iron deficiency; INN International Nonproprietary Name; IS Iron sucrose; MRP Mutual Recognition Procedure; RMP Risk Management Plan; SmPC Summary of Product Characteristics; TSAT Transferrin saturation.

# PART II: SAFETY SPECIFICATION

# SI EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

**Indication**

**Current Indication Based on Mutual Recognition Procedure SmPC Version 17.0 (Dated 18 March 2022)**

Venofer is indicated for the treatment of ID in the following indications:

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

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

## SI.1 Epidemiology of the Disease

ID is characterised by reduced body iron content leading to impaired physiological function of the blood and tissues, such as the brain and muscles. ID is the most common cause of anaemia (nearly 50%) of the estimated 22.8% (around 1.7 billion people) of the global population that is affected by anaemia [1-2]. Whilst ID in many cases exists in the absence of anaemia, it could become evident when the duration and/or its severity affects the process of erythropoiesis leading to reductions of Hb concentration below the "normal" threshold for the specific gender and age group. As iron is required to permit normal function of many enzymes, there is a wide range of symptoms, either as its primary deficiency or secondary to anaemia [3-4]. Symptoms may include fatigue, headache, hair loss, dizziness, breathlessness, palpitations and reduced cognitive function which may all result in decreased quality of life [5-6]. ID may also lead to reduced immune function [7].

**Definition and Diagnosis**

The most accurate initial diagnostic test for laboratory evidence of ID is to measure serum ferritin and TSAT. Ferritin ≤30 µg/l is the currently acceptable threshold for ID with and without anaemia in absence of inflammation or comorbidities [3]. It is much more difficult to identify a clinically useful cut off to define ID in subjects with inflammatory disorders. An expert opinion review of the diagnosis of ID across chronic heart failure (CHF), CKD, and IBD, as examples of chronic inflammatory conditions, provided pragmatic recommendations for diagnosing ID that can be summarised as follows: a) ferritin <100 µg/l or TSAT<20%; b) ferritin between 100 and 300 µg/l and TSAT<20% [8]. In

recent guidelines for the diagnosis and treatment of acute and CHF ID is defined in accordance with those recommendations [9].

## SI.1.1 Incidence and Prevalence

### Incidence in Target Population

An accurate representation of incidence rates regarding ID is currently not available as most literature is focused on the prevalence of anaemia.

### Prevalence in Target Population

Anaemia is a global public health problem affecting both developing and developed countries, with major consequences for human health as well as social and economic development. ID is the most common cause (nutritional or otherwise) of anaemia, and is estimated to contribute to approximately 50% of all cases of anaemia among non-pregnant and pregnant women, and 42% of cases in children under 5 years of age worldwide [10]. It occurs at all stages of the life cycle, however it is more prevalent in pregnant women and young children. Anaemia has been quantified to account for close to 9% of the total global disability burden from all conditions [11]. Pregnant women and young children are at greatest risk. The highest proportion of individuals affected are in Africa and Asia: almost two-thirds of preschool-age children living in Africa are anaemic [12].

For certain therapeutic areas there are incidence/prevalence data on ID available:

- CHF: 45.6% [13]
- CHF and anaemia: 61.2 [13]
- CKD: 57.8 to 58.8% of men and 69.9 to 72.8% of women [14]
- IBD: range from 36 to 90% [15,16]
  - Mean prevalence 68% [15,16]

## SI.1.2 Demographics of the Target Population (Age, Sex, Race/Ethnic Origin)

Some patients are particularly at risk due to malabsorption of dietary iron (e.g., malnutrition, IBD, gastrointestinal (GI) surgery) or increased utilisation or loss from the body (e.g., pregnant women, menstruating or lactating females, haemodialysis patients, patients undergoing surgery who might experience blood loss or trauma). ID adversely affects the cognitive performance, behaviour, and physical growth of children, immune status and morbidity from infections and the physical capacity and work performance of adolescents and adults of all age groups (World Health Organization) [17].

### SI.1.3 Risk Factors for the Disease

The main risk factors for iron deficiency anaemia (IDA) include a low intake of iron, poor absorption of iron from diets high in phytate or phenolic compounds, and period of life when iron requirements are especially high (i.e., growth and pregnancy). Among the other causes of anaemia, heavy blood loss as a result of menstruation, or parasite infections such as hookworms, ascaris, and schistosomiasis can lower blood Hb concentrations. Acute and chronic infections, including malaria, cancer, tuberculosis, and HIV can also cause IDA. The presence of other micronutrient deficiencies, including Vitamins A and B12, folate, riboflavin, and copper can increase the risk of anaemia. Furthermore, the impact of haemoglobinopathies on anaemia prevalence needs to be considered within some populations.

### SI.1.4 Main Existing Treatment Options

ID is a state of reduced body iron content where the physiological function of the blood and tissues, such as the brain and muscles, and many enzymes and neurotransmitters is impaired. Treatment of ID consists of repletion of iron deficit as well as in the treatment of the underlying disease. Iron deficit repletion may be facilitated by various treatment strategies.

Iron supplements intended for oral administration remain the most common treatment option for the majority of ID patients because of the ease of administration and perceived effectiveness. Oral iron is inexpensive, readily available and does not require intravenous (IV) access (a particular concern in CKD patients not on haemodialysis). They contain bivalent (Fe2+; ferrous sulphate, ferrous fumarate, ferrous gluconate) or trivalent (Fe3+; iron polymaltose complex) iron forms. Iron needs to be reduced in order to be absorbed from the GI tract. However, only around 10% of intestinal iron is absorbed on average [18]. Although appropriate for many patients, oral iron (in particular in the bivalent form) can cause dose-dependent, undesirable effects in up to 40% of patients [19]. Choice of individual patient iron therapy is clinically based on careful assessment and benefit/risk evaluation. Patients with severe ID and low Hb levels may require fast iron replenishment which cannot be facilitated by oral iron, especially in case of GI tract impairment or concomitant medication that decreases iron absorption, as only about 10% of the oral dose is absorbed. In pre-operative settings, oral preparations will only have a limited effect on patient's ID. IV iron preparations have a great advantage over oral preparations in this respect. Therapy of ID with Venofer may be initiated:

- Where there is a clinical need for a rapid iron supply
- In patients who cannot tolerate oral iron therapy or who are non-compliant
- In active IBD where oral iron preparations are ineffective
- In CKD when oral iron preparations are less effective

Severe IDA may require a blood transfusion or IV iron therapy. Treatment with IV iron preparations may also be preferred over oral therapy in some other situations. IV iron is more effective in patients with IBD [20] and oncology guidelines suggest that IV iron is superior to oral iron in combination with erythropoiesis stimulating agents (ESAs) for chemotherapy induced anaemia [21-23].

Severe forms of anaemia, resulting from myelosuppression are treated by erythropoietin, anabolic steroids, corticosteroids, pyridoxine or granulocyte colony-stimulating factors (i.e., filgrastim, lenograstim), medication and blood transfusions.

Current medical practice involving red blood cell transfusions or administration of ESAs as anaemia therapy is typically limited to certain patient populations. These therapies are treatment options for management of chronic anaemia in CKD patients or chemotherapy induced anaemia in cancer patients. Several patient conditions outweigh the risks of red blood cell transfusions and in such situations transfusions are indicated (e.g., acute bleeding where rapid correction is required in order to stabilise the patient's condition or when ESA therapy is ineffective due to ESA resistance). ESA and iron supplements are usually co-administered to facilitate the most effective anaemia treatment.

### SI.1.5 Natural History of the Indicated Condition in the Population, Including Mortality and Morbidity

The global age-standardised death rate for IDA was 1.0 per 100,000 (95% confidence interval (CI) 0.8-1.2) in 2010 [24]. In terms of regional ranking of leading causes of years of life lost, IDA ranked 81-83 in high income North America and Western Europe, 89-90 in Eastern and Central Europe, 75 in South Asia, 44-54 in Southern and Eastern sub-Saharan Africa, 26-27 in Western and Central sub-Saharan Africa, and 15 in the Caribbean [25].

Higher mortality rates are observed in patients with anaemia in general. Anaemia is associated with increased mortality in CKD, CHF and acute myocardial infarction patients [26].

- Anaemia alone: 16.6% [27]
- CHF + anaemia: 34.6% [27]

Klip et al, 2013 [13] investigated the predictive value of ID for mortality in CHF patients with or without anaemia in an international pooled analysis. ID but not anaemia remained an independent predictor for mortality (hazard ratio (HR) 1.42, 95% CI 1.14-1.77, p 0.002), even after adjustment for all univariate associated variables. No significant interaction was observed between ID and anaemia (p 0.841). ID remained an independent predictor of mortality in anaemic (HR 1.71, 95% CI 1.24-2.36, p 0.001) and nonanaemic patients (HR 1.44, 95% CI 1.11-1.87, p 0.006) [13].

For more detailed information regarding mortality and incidence in the target population, please refer to Table 2.

The importance of the interaction between chronic kidney injury, CHF and anaemia was suggested by a study conducted in 1.1 million elderly patients, a 5% sample of the Medicare population in the US [28]. The 2-year risk of dying or starting dialysis (end-stage renal disease) is shown in Table 2. Individually, each of these 3 conditions increases the risk of death or end-stage renal disease by 50-100%, and the 3 together increase the probability by up to 300%. This interaction is consistent with the presence of the vicious circle the cardiorenal anaemia syndrome [27,28].

**Table 2 Mortality and Incidence in the Target Population**

| Population | Mortality | Incidence of End-stage Renal Disease |
|---|---|---|
| No anaemia, CHF or CKD (background) | 7.7% | 0.1% |
| Anaemia | 16.6% | 0.2% |
| CHF | 26.1% | 0.2% |
| CHF + anaemia | 34.6% | 0.3% |
| CKD | 16.4% | 2.6% |
| CKD + anaemia | 27.3% | 5.4% |
| CHF and CKD | 38.4% | 3.5% |
| CHF, CKD and anaemia | 45.6% | 5.9% |

Notes: Data provided in the table were adapted from Silverberg et al, 2003 [27].
CHF Chronic heart failure; CKD Chronic kidney disease.

## SI.2 Important Comorbidities

Target population suffering from ID may be very broad including various oncology, gynaecology, nephrology (e.g., CKD) or GI conditions (e.g., IBD). Concomitant medication therefore, may include a large variety of both over-the-counter and prescription medicines.

However, there are some particular conditions which are more often associated with ID and IDA and represent important comorbidities of ID. Concomitant medication may include but is not limited to:

- IBD: aminosalicylates such as sulphasalazine and mesalazine, immunosuppressive medications such as azathioprine, corticosteroids, biological preparations such as infliximab, adalimumab
- CHF: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, digoxin, beta-blockers, diuretics, aldosterone antagonists
- CKD: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, low-dose aspirin, statins, Vitamin D supplements, phosphate binders
- Oncology: chemotherapeutics, corticosteroids, analgesics (including opioids), antiemetics

**Table 3 Important Comorbidities Found in Target Population**

| Comorbidity | IBD |
|---|---|
| Incidence of condition | Incidence rates of IBD in ID patients are not available. |
| Prevalence of condition | ID occurs in about 60-80% of patients with IBD and anaemia manifests in approximately one-third of patients [29]. A recently published review showed study data with the prevalence of anaemia in IBD patients ranging from 16-74%, with a mean value of 16% in outpatients and 68% in hospitalised patients [29].<br>Prevalence of ID in IBD adult outpatients:<br>• IBD - all: 35% [30]<br>• IBD - ulcerative colitis: 32% [30]<br>• IBD - Crohn's disease: 38% [30]<br>Goodhand et al, 2012 [31] demonstrated in a prospective trial that anaemia and IDA are particularly prevalent in children with IBD, the incidence of anaemia being 70% in children, 42% in adolescents, and 40% in adults with IBD. IBD was also found to occur more commonly in children (88%) and adolescents (83%) than in adults (55%) with IBD. |
| Mortality of condition | IBD patients suffering from anaemia have a higher mortality rate than patients without anaemia [32]. |
| **Comorbidity** | **CHF** |
| Incidence of condition | Incidence rates of CHF in ID patients are not available. |
| Prevalence of condition | Estimates of the prevalence of anaemia in patients with CHF and low ejection fraction range widely from 4% to 61% (median 18%), based on the different definitions of anaemia [33].<br>Estimates calculated within the last decade suggest a prevalence of CHF in general population of approximately 1–2% and >10% in the elderly population.<br>ID is present in 61.2% of anaemic patients with CHF [13].<br>It has been estimated that there are currently 6.5 million CHF patients in Europe and 5 million in the US [34]. |
| Mortality of condition | The long-term prognosis associated with CHF is poor.<br>Mortality rates:<br>• Anaemia alone: 16.6% [27]<br>• CHF: 26.1% [27]<br>• CHF + anaemia: 34.6% [27]<br>Klip et al, 2013 [13] investigated the predictive value of ID for mortality in CHF patients with or without anaemia in an international pooled analysis. ID but not anaemia remained an independent predictor for mortality (HR 1.42, 95% CI 1.14-1.77, p=0.002), even after adjustment for all univariate associated variables.<br>No significant interaction was observed between ID and anaemia (p=0.841).<br>ID remained an independent predictor of mortality in anaemic (HR 1.71, 95% CI 1.24-2.36, p=0.001) and nonanaemic patients (HR 1.44, 95% CI 1.11-1.87, p=0.006) [13].<br>CKD is a common comorbidity of CHF [33].<br>Mortality rates:<br>• CHF and CKD: 38.4% [27,28]<br>• CHF, CKD and anaemia: 45.6% [27,28]<br>Please refer to Table 2 for more detailed information. |

**Table 3 Important Comorbidities Found in Target Population (Cont'd)**

| Comorbidity | CKD |
|---|---|
| Incidence of condition | Incidence rates of CKD in ID patients are not available.<br>The incidence and prevalence of CKD in the general population worldwide has risen markedly in the past decade.<br>In the National Health and Nutrition Examination Survey III, among older adults (age 65 and older) with anaemia, about 12% had renal insufficiency [35]. |
| Prevalence of condition | Anaemia was present in 47.7% of 5,222 pre-dialysis patients with CKD in performed cross-sectional survey [36]. Prevalence of anaemia increased as kidney function decreased. |
| Mortality of condition | The importance of the interaction between cardiovascular disease, CKD and anaemia has been discussed in a study conducted in a US Medicare sample of more than one million elderly patients [27,28,14]. Compared with patients who had no known comorbidity, patients with anaemia had a 100% increased risk of death. Patients with CKD had a 100% increased risk of death. For patients with anaemia and CKD, the relative mortality risk was even higher reaching 3.7. Mortality risk was further increased in patients who had multiple comorbidities with anaemia being a significant multiplier of mortality risk.<br>• CKD: 16.4% [27]<br>• CKD + anaemia: 27.3% [27]<br>Please refer to Table 2 for more detailed information. |
| **Comorbidity** | **Oncology – anaemia induced by chemotherapy** |
| Incidence of condition | The incidence of anaemia in cancer patients undergoing chemo- and/or radio-therapy was estimated to be 53.7%, calculated from a subpopulation of the survey that was not anaemic at enrolment and received their first cancer treatment during the survey period with a minimum of 2 cycles of chemotherapy or 2 follow-up data points for radiotherapy. The patients who received chemotherapy had the highest incidence of anaemia, 62.7%, compared with concomitant chemo-radiotherapy, 41.9%, or radiotherapy, 19.5% [37]. |
| Prevalence of condition | European cancer patients were evaluated for up to 6 months. Prevalence of anaemia at enrolment was 39.3% and 67.0% during the survey (Hb <12.0 g/dl) [37].<br>The high prevalence of anaemia in patients with different cancer types (39% at enrolment and 68% becoming anaemic at least once during the 6-month survey period) has been already shown in the European Cancer Anaemia Survey. Conversely, published data on the prevalence of ID in cancer patients are scarce. Prevalence of ID was highest for colorectal cancer (60%, and 69% of those were also anaemic); probably, chronic blood loss may render patients with colorectal or GI cancers more prone to ID and anaemia. Nevertheless, reported prevalence of ID in different cancer populations ranges from 32 to 60% and the prevalence of IDA ranges from 7 to 42% [38]. |
| Mortality of condition | A meta-analysis of 60 clinical studies found a 65% increase in the risk of death and a shortened survival time among patients with cancer treated by chemotherapy and anaemia compared with patients without anaemia [39]. |

**Table 3 Important Comorbidities Found in Target Population (Cont'd)**

| **Comorbidity** | **Dysfunctional uterine bleeding** |
|---|---|
| Incidence of condition | No data on the incidence of dysfunctional uterine bleeding among patients with ID/IDA were found. |
| Prevalence of condition | No data on the prevalence of dysfunctional uterine bleeding among patients with ID/IDA were found. |
| Mortality of condition | Dysfunctional uterine bleeding is not associated with a significant risk of mortality. |
| **Comorbidity** | **Diabetes** |
| Incidence of condition | No data on the incidence of diabetes among patients with ID/IDA were found. |
| Prevalence of condition | No data on the prevalence of diabetes among patients with ID/IDA were found. |
| Mortality of condition | Diabetes is a key risk factor for CKD, which is an important comorbidity of anaemia [40]. Evidence suggests that comorbid diabetes, CKD and anaemia place the patient at particular high risk of mortality [41]. Among patients with diabetes, anaemia as interaction term with CKD was associated with an 88% (HR 1.88, 95% CI 1.33-2.66) greater risk of all-cause mortality compared with patients without anaemia [41]. |

Notes: CHF Chronic heart failure; CI Confidence interval; CKD Chronic kidney disease; GI Gastrointestinal; Hb Haemoglobin; HR Hazard ratio; IBD Inflammatory bowel disease; ID Iron deficiency; IDA Iron deficiency anaemia.

# SII NONCLINICAL PART OF THE SAFETY SPECIFICATION

There was no formal nonclinical development programme of IS at the time of the initial marketing authorisation which was granted in 1949. Single-dose toxicity, absorption, distribution and excretion data were available at this point in time.

A number of nonclinical safety studies have been conducted on IS over the last 20 years that meet the requirements for a novel pharmaceutical product as laid out in the International Council for Harmonisation Guideline M3 (R2) [42].

The nonclinical programme addressed repeat-dose toxicity in rats and dogs which also provided some data on safety pharmacology.

A full programme of developmental and reproductive toxicity studies was conducted, including a study of fertility and early embryonic development in rats, studies of embryo-foetal toxicity in rats and rabbits, and a pre- and post-natal development study in rats.

Four genotoxicity studies have been performed, comprising bacterial cell mutation assays, a mouse lymphoma assay, an in vitro chromosome aberration test and a micronucleus test in mice.

Further studies investigated the local tolerance of IS in rabbits and an antigenicity study was conducted in rabbits.

All pivotal nonclinical toxicology studies were conducted in accordance with Good Laboratory Practice regulations.

The nonclinical data are considered adequate and acceptable for the purpose of conducting a meaningful human risk assessment for IS and there is no need for additional nonclinical data.

## SII.1 Toxicity

Key safety findings originating from this are summarised below in Table 4.

**Table 4 Key Nonclinical Safety Findings - Toxicity**

| Key Safety Findings (From Nonclinical Studies) | Relevance to Human Usage |
|---|---|
| **Repeat-dose Toxicity** | |
| Data from the repeat-dose toxicity studies using high iron doses showed the expected pattern of changes associated with iron excess.<br>Toxic effects were observed only at cumulative doses of >117 mg Fe/kg in rats and dogs. | Data from repeat-dose toxicity studies are not relevant for the assessment of the risk of haemosiderosis in humans, since iron replete animals were administered with high doses of iron, with total exposure up to 1,170 mg Fe/kg. |
| **Reproductive/Developmental Toxicity** | |
| In reproductive and developmental toxicity studies using iron replete animals, IS was associated with minor skeletal abnormalities in the foetus, but only at dosages that caused maternal toxicity. | Nonclinical data showed no special hazards based on conventional studies of toxicity to reproduction and development. |
| **Genotoxicity** | |
| A battery of genotoxicity tests showed no evidence of mutagenic or clastogenic potential for IS. | Based on the results, IS is considered as non-genotoxic substance. |
| **Carcinogenicity** | |
| Carcinogenicity studies have not been performed. | The genetic toxicity data, the knowledge of the nature of the product, its use as a replacement therapy for correction of ID/IDA, and the lack of any findings indicative of pre-neoplastic lesions in the chronic toxicity studies all together suggest a low potential for carcinogenic effects of the product. |

Notes: ID Iron deficiency; IDA Iron deficiency anaemia; IS Iron sucrose.

## SII.2 Safety Pharmacology

General safety pharmacology findings from nonclinical studies are presented in Table 5 below.

**Table 5 Key Nonclinical Safety Findings - General Safety Pharmacology**

| Key Safety Findings (From Nonclinical Studies) | Relevance to Human Usage |
|---|---|
| **Cardiovascular (Including Potential for QT Interval Prolongation)** | |
| No dedicated safety pharmacology studies have been conducted. Data on the effects of IS on cardiovascular systems were obtained as a part of the 13-week toxicity studies in dogs. No effect of IS at dosages up to 30 mg Fe/kg (administered over either 1 or 4 hours as an intravenous infusion) was observed on electrocardiogram, blood pressure or respiration rate in these studies. | N/A |

Notes: IS Iron sucrose; N/A Not applicable.

## SII.3 Other Toxicity-related Information or Data

Other findings from nonclinical studies are presented in Table 6 below.

**Table 6 Other Toxicity-related Information or Data**

| Key Safety Findings (From Nonclinical Studies) | Relevance to Human Usage |
|---|---|
| **Drug Interactions** | |
| Specific drug interactions for Venofer have not been identified during the nonclinical development programme. | No specific drug interactions have been identified during the clinical development programme. The current SmPC considers a known class effect of interaction with oral iron:<br>"As with all parenteral iron preparations, IS should not be administered concomitantly with oral iron preparations since the absorption of oral iron is reduced." [43]. |
| **Cross-reactivity to Anti-dextran Antibodies** | |
| IS showed no cross-reactivity with anti-dextran antibodies. | These findings indicate that it would be safe to administer IS to patients who may have been sensitised to iron dextran. |

Notes: IS Iron sucrose; SmPC Summary of Product Characteristics.

# SIII CLINICAL TRIAL EXPOSURE

Early studies with Venofer were primarily conducted by external Investigators in different countries and did not follow a predefined development plan as used for newer products. Newer studies were performed as a part of a product development plan from the 1990s onwards and conducted according to Good Clinical Practice (GCP).

The clinical data for Venofer are available from more than 150 company sponsored and other studies. Overall, approximately 16,529 patients have been enrolled in Vifor Pharma, American Regent, Inc. (formerly Luitpold Pharmaceuticals, Inc.) and Investigator initiated clinical trials, of which 6,896 patients received Venofer in 27 completed clinical studies or in 42 studies available only in publications as the investigational study drug, or the designated comparator or part of the standard medical care. The majority were treated with individual doses up to 200 mg iron.

**Table 7 Overview of Venofer Clinical Studies in Adult Patients**

| Patient Population | No. of Studies (Study References) | No. on Venofer/ Total No. of Patients |
|---|---|---|
| Nephrology (total=25 studies) | | |
| CKD – not dialysis-dependent | 7 [44-50], [50 safety only](1) | 1,751/3,565 |
| CKD – dialysis-dependent not receiving ESA | 2 [51-52] | 38/38 |
| CKD – dialysis-dependent receiving ESA | 15 [53-67], [55-67 safety only](2) | 1,915/2,287 |
| Renal patients (unspecified) | 1 [68 safety only](3) | 335/335 |
| Gastroenterology (total=7 studies) | | |
| Malabsorption, oral iron intolerance | 1 [69] | 71/121 |
| IBD (Crohn's disease and/or ulcerative colitis) | 6 [70-74] | 427/795 |
| Women's health (total=10 studies) | | |
| Pregnancy | 5 [75-79] | 245/372 |
| Postpartum | 4 [80-83] | 168/290 |
| Anaemia due to menorrhagia | 1 [84] | 39/76 |
| Oncology | 3 [85-87] | 151/343 |
| Cardiorenal syndrome | 1 [88] | 27/72 |
| Symptomatic congestive heart failure | 1 [89] | 24/35 |
| Various conditions | 4 [90-93 safety only](4) | 665/2,699 |
| Blood management (autologous blood donations/need for transfusion) (total=4 studies) | | |
| Elective surgery | 3 [94-96] | 116/332 |
| Hip fracture surgery | 1 [97] | 99/196 |
| Nonanaemic patients (total=2 studies) | | |
| Pregnancy, not anaemic | 1 [98] | 130/260 |
| Premenopausal females, low ferritin | 1 [99] | 43/90 |

1 [50] included 97 CKD patients who were dialysis dependent.
2 15 studies (efficacy and safety: [53 63]. Safety only: [64 67]).
3 [68] did not specifically report efficacy for Venofer.
4 [91 93] did not specifically report efficacy for Venofer.

Notes: Study 1VEN01016 [100] which is part of the safety analysis of 22 studies has not been included in this table because it is a pharmacokinetic study.
CKD Chronic kidney disease; ESA Erythropoiesis stimulating agent; IBD Inflammatory bowel disease.

**Table 8 Overview of Venofer Clinical Studies in Paediatric Patients**

| Patient Population | Age Range | Reference[1] | No. on Venofer/ Total No. of Patients |
|---|---|---|---|
| CKD (dialysis-dependent and not dialysis-dependent) | 2-20 years | [101] | 141/141 |
| CKD and end-stage renal failure | 3 months to 17 years | [102] safety only[2] | 92/92 |
| Post-operative anaemia | 2-20 years | [103] | 16/32 |
| Non-renal conditions with anaemia | 3 months to 18 years | [104] | 38/38 |
| Intolerant of oral iron therapy (underlying conditions not specified) | 8-180 months | [105] | 62/102 |
| Failed oral iron therapy (anaemia due to nutritional iron deprivation, gastritis, coeliac disease, stool parasites, Crohn's disease, chronic diarrhoea, milk allergy, or short gut syndrome) | 11 months to 16 years | [106] | 45/45 |
| Very low birth weight, prevention of anaemia | Neonates | [107] | 10/29 |

1 Table includes 1 study in neonates [107].
2 No efficacy evaluations in this study [102].
Notes: Study 1VEN05033 [108] which is part of the safety analysis of 22 studies has not been included in this table because it is a pharmacokinetic study.
CKD Chronic kidney disease.

## SIII.1 Duration of Exposure

An estimate of cumulative exposure to Venofer by duration of exposure, age group and gender, and dose is provided in Table 9, Table 10, Table 11, Table 12 and Table 13.

**Table 9 Duration of Exposure**

| Duration of Exposure (at Least) | Patients | Person Time (y) |
|---|---|---|
| **Non-SMC Studies** | | |
| ≤2 weeks | 485 | 6.58 |
| >2-4 weeks | 282 | 19.01 |
| >4-6 weeks | 164 | 16.74 |
| >6-12 weeks | 990 | 179.27 |
| >12-24 weeks | 1,672 | 537.06 |
| >24 weeks | 118 | 79.22 |
| **Total** | **3,711** | **837.87** |
| **SMC Studies** | | |
| ≤2 weeks | 22 | 0.57 |
| >2-4 weeks | 99 | 7.46 |
| >4-6 weeks | 329 | 32.14 |
| >6-12 weeks | 70 | 9.98 |
| >12-24 weeks | 207 | 70.53 |
| >24 weeks | 1 | 0.52 |
| **Total** | **728** | **121.21** |

## Table 9 Duration of Exposure (Cont'd)

| Duration of Exposure (at Least) | Patients | Person Time (y) |
|---|---|---|
| **Overall** | | |
| ≤2 weeks | 507 | 7.16 |
| >2-4 weeks | 381 | 26.47 |
| >4-6 weeks | 493 | 48.88 |
| >6-12 weeks | 1,060 | 189.25 |
| >12-24 weeks | 1,879 | 607.59 |
| >24 weeks | 119 | 79.74 |
| **Total** | **4,439** | **959.08** |

Notes: Non SMC studies include where Venofer is the Investigational Medicinal Product or is a comparator with a controlled regimen.
SMC Standard medical care.

## Table 10 By Age Group and Gender

| Age Group | Patients | | Person Time (y) | |
|---|---|---|---|---|
| | Male | Female | Male | Female |
| **Non-SMC Studies** | | | | |
| <18 y | 79 | 58 | 16.63 | 10.92 |
| 18 to <65 y | 862 | 1,265 | 169.23 | 273.72 |
| ≥65 y | 689 | 758 | 165.27 | 202.10 |
| **Total** | **1,630** | **2,081** | **351.13** | **486.75** |
| **SMC Studies** | | | | |
| <18 y | 0 | 0 | - | - |
| 18 to <65 y | 69 | 456 | 8.66 | 88.62 |
| ≥65 y | 58 | 145 | 5.80 | 18.13 |
| **Total** | **127** | **601** | **14.46** | **106.75** |
| **Overall** | | | | |
| <18 y | 79 | 58 | 16.63 | 10.92 |
| 18 to <65 y | 931 | 1,721 | 177.89 | 362.34 |
| ≥65 y | 747 | 903 | 171.07 | 220.23 |
| **Total** | **1,757** | **2,682** | **365.59** | **593.49** |

Notes: Non SMC studies include where Venofer is the Investigational Medicinal Product or is a comparator with a controlled regimen.
SMC Standard medical care.

## Table 11 By Single Maximum Dose

| Dose of Exposure | Patients | Person Time (y) |
|---|---|---|
| **Non-SMC Studies** | | |
| ≤200 mg | 3,495 | 802.21 |
| >200-≤500 mg | 214 | 35.23 |
| >500 mg | 2 | 0.43 |
| Unknown | 0 | - |
| **Total** | **3,711** | **837.87** |
| **SMC Studies** | | |
| ≤200 mg | 524 | 88.63 |
| >200-≤500 mg | 161 | 27.01 |
| >500 mg | 41 | 5.03 |
| Unknown | 2 | 0.53 |
| **Total** | **728** | **121.21** |
| **Overall** | | |
| ≤200 mg | 4,019 | 890.84 |
| >200-≤500 mg | 375 | 62.25 |
| >500 mg | 43 | 5.46 |
| Unknown | 2 | 0.53 |
| **Total** | **4,439** | **959.08** |

Notes: Non SMC studies include where Venofer is the Investigational Medicinal Product or is a comparator with a controlled regimen.
SMC Standard medical care.

## Table 12 By Cumulative Dose

| Dose of Exposure | Patients | Person Time (y) |
|---|---|---|
| **Non-SMC Studies** | | |
| ≤1,000 mg | 2,729 | 570.70 |
| >1,000-≤2,000 mg | 898 | 224.33 |
| >2,000 mg | 84 | 42.85 |
| Unknown | 0 | - |
| **Total** | **3,711** | **837.87** |
| **SMC Studies** | | |
| ≤1,000 mg | 626 | 101.46 |
| >1,000-≤2,000 mg | 79 | 16.47 |
| >2,000 mg | 21 | 2.74 |
| Unknown | 2 | 0.53 |
| **Total** | **728** | **121.21** |

## Table 12 By Cumulative Dose (Cont'd)

| Dose of Exposure | Patients | Person Time (y) |
|---|---|---|
| **Overall** | | |
| ≤1,000 mg | 3,355 | 672.16 |
| >1,000-≤2,000 mg | 977 | 240.80 |
| >2,000 mg | 105 | 45.59 |
| Unknown | 2 | 0.53 |
| **Total** | **4,439** | **959.08** |

Notes: Non SMC studies include where Venofer is the Investigational Medicinal Product or is a comparator with a controlled regimen.
SMC Standard medical care.

## Table 13 By Ethnic or Racial Origin

| Ethnic/Racial Origin | Patients | Person Time (y) |
|---|---|---|
| **Non-SMC Studies** | | |
| White | 1,910 | 458.55 |
| Black or African American | 978 | 198.40 |
| Asian | 266 | 44.98 |
| American Indian or Alaska Native | 9 | 1.54 |
| Native Hawaiian or other Pacific Islander | 3 | 0.68 |
| Other | 545 | 133.72 |
| Unknown | 0 | - |
| **Total** | **3,711** | **837.87** |
| **SMC Studies** | | |
| White | 477 | 74.78 |
| Black or African American | 154 | 29.15 |
| Asian | 17 | 2.32 |
| American Indian or Alaska Native | 3 | 0.24 |
| Native Hawaiian or other Pacific Islander | 3 | 0.33 |
| Other | 73 | 14.30 |
| Unknown | 1 | 0.10 |
| **Total** | **728** | **121.21** |
| **Overall** | | |
| White | 2,387 | 533.33 |
| Black or African American | 1,132 | 227.55 |
| Asian | 283 | 47.30 |
| American Indian or Alaska Native | 12 | 1.78 |
| Native Hawaiian or other Pacific Islander | 6 | 1.00 |
| Other | 618 | 148.01 |
| Unknown | 1 | 0.10 |
| **Total** | **4,439** | **959.08** |

Notes: Non SMC studies include where Venofer is the Investigational Medicinal Product or is a comparator with a controlled regimen.
SMC Standard medical care.

# SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

## SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

The first marketing authorisation for Venofer was issued on 6 December 1949, and no information about the exclusion criteria for the original development programme is available. However, 27 studies sponsored by Vifor or a Vifor partner have been conducted since 1990, and the key exclusion criteria utilised, as well as contraindications listed in the approved Company Core Data Sheet, are broadly reflected in Table 14.

**Table 14 Exclusion Criteria**

| Criteria | Reason for Exclusion | Is It Considered to Be Included as Missing Information? | Rationale |
|---|---|---|---|
| Anaemia not caused by iron deficiency | Contraindications | No | Patients with anaemia not caused by iron deficiency would not benefit from Venofer therapy . There are no special implications expected for the target population. |
| Evidence of iron overload or hereditary disturbances in utilisation of iron | Contraindications | No | Patients with iron overload or hereditary disturbances in utilisation of iron would not benefit from Venofer. |
| Subjects <18 years | Paediatric population was not included in the clinical studies | Yes | The administration of Venofer, its efficacy and safety are not ascertained in this age group. |
| Use in pregnant or lactating women | Data availability from pregnant and lactating women in clinical trials is limited | Yes | The administration of Venofer, its efficacy and safety are insufficiently ascertained in this age group. |
| Elderly patients | Elderly population was not included in the clinical studies | Yes | The administration of Venofer, its efficacy and safety are not ascertained in this age group. |
| Hypersensitivity to iron sucrose, Venofer, or to any of its excipients | Contraindication | Yes | The administration of Venofer, its efficacy and safety are not ascertained in this group. |

## SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The first marketing authorisation for Venofer was issued on 6 December 1949, and no information about the limitations to detect adverse reactions in the original clinical trial development programme is available.

The clinical studies conducted to date were unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

**Table 15 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes**

| Ability to Detect Adverse Reactions | Limitation of Trial Programme | Discussion of Implications for Target Population |
|---|---|---|
| Due to prolonged exposure; due to cumulative effects which have a long latency | Venofer has been studied for periods of up to 6 months of use | The ability to detect ADRs which are due to prolonged exposure, cumulative effects or prolonged latency is widely covered by the duration of conducted clinical trials and by their Venofer administration scheme. |
| | Long-term safety study data are available up to 6 months | The MAH believes that the information regarding the long-term use of Venofer, defined as periods beyond 6 months is well supported by the 70 years of post-marketing experience and active pharmacovigilance activities. |

Notes: ADR Adverse drug reaction; MAH Marketing Authorisation Holder.

## SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Many clinical studies with Venofer were carried out by external Investigators in various different countries, and did not necessarily follow a predefined development plan. The majority of studies were not sponsored by Vifor (International) Inc. (Vifor) and, therefore, data from these studies were derived from the published literature. More recent studies, carried out from the 1990s onwards, were sponsored by Vifor or one of its partners and were conducted as part of a more formal product development plan.

Twenty-seven studies sponsored by Vifor and/or one of its partners that were part of the product development plan carried out from the 1990s onwards were conducted according to GCP.

## Table 16 Exposure of Special Populations Included or Not in the Clinical Trial Development Programmes

| Type of Special Population | Exposure |
|---|---|
| Paediatric population | Not included in the clinical development programme.<br>There is a moderate amount of data in children under study conditions [101-111]. If there is a clinical need, it is recommended not to exceed 0.15 ml of Venofer (3 mg iron) per kg body weight not more than 3 times per week. |
| Pregnant women | Not included in the clinical development programme.<br>There is only a limited amount of data (less than 300 pregnancy outcomes) from the use of IS in pregnant women in the first trimester. A moderate amount of data (between 300-1,000 pregnancy outcomes) from the use of Venofer in pregnant women in the second and third trimester [75-79,98] showed no safety concerns for the mother or newborn. |
| Breastfeeding women | Not included in the clinical development programme.<br>There is limited information on the excretion of iron in human milk following administration of intravenous IS. In one clinical study, 10 healthy breastfeeding mothers with iron deficiency received 100 mg iron in the form of IS [83]. Four days after treatment, the iron content of the breast milk had not increased and there was no difference from the control group (n=5). It cannot be excluded that newborns/infants may be exposed to iron derived from Venofer via the mother's milk, therefore the benefit/risk should be assessed. |
| Patients with relevant comorbidities | |
| • Patients with hepatic impairment | Not included in the clinical development programme. |
| • Immunocompromised patients | Not included in the clinical development programme. |
| • Patients with a disease severity different from inclusion criteria in clinical trials | Not included in the clinical development programme. |
| Population with relevant different ethnic origin | Not included in the clinical development programme. |
| Subpopulations carrying relevant genetic polymorphisms | Not included in the clinical development programme. |

Note: IS Iron sucrose.

# SV POST-AUTHORISATION EXPERIENCE

The first marketing authorisation for Venofer was received on 6 December 1949 in Switzerland, where the product was first launched in 1950. Venofer was then approved in Portugal (November 1964) and Germany (November 1969) but it was not marketed in these countries until 1995.

Up until the data lock point of this RMP, Venofer is authorised in 84 countries worldwide.

## SV.1 Post-authorisation Exposure

For this product no actions were taken for safety reasons, i.e., there have been no license application rejections, no marketing authorisation suspensions, no rejections of marketing authorisation renewal, and no restrictions on distribution. Furthermore, there have been no clinical trial suspensions, no dosage modifications, and no formulation changes for safety reasons.

### SV.1.1 Method Used to Calculate Exposure

The exact numbers of patients exposed to Venofer are not available. The exposure to Venofer was calculated from the number of ampoules/vials sold, expressed in 100 mg equivalents (1 ml of solution in each vial contains 20 mg of iron) or defined daily doses; 1 defined daily dose 100 mg iron as per World Health Organization recommendation. Post-marketing data are available only since 1997.

The total patient-years are calculated based on an estimated annual cumulative dose of iron given as Venofer which is 2,000 mg.

### SV.1.2 Exposure

Cumulative exposure from marketing experience calculated until 30 April 2022 was estimated to be 32,769,408 patient-years based on the method of calculation described above, representing 655,388,165 sold 100 mg iron equivalents. Exposure data sorted by region are presented in Table 17. Post-marketing data for Venofer are only available since 1997.

Details on indication, age, gender or race/ethnic origin in exposed patients are not available.

## Table 17 Cumulative Exposure from Marketing Experience from 1997 Until 30 April 2022

| Region (from January 2012) | Exposure (Units) | |
|---|---|---|
| | **Patient-Years** | **Number of 100 mg Iron Equivalents** |
| North America | 7,939,486 | 158,789,724 |
| Latin America | 2,869,924 | 57,398,475 |
| Europe | 2,999,183 | 59,983,666 |
| Africa | 160,472 | 3,209,430 |
| Middle East | 2,303,663 | 46,073,260 |
| Asia Pacific | 2,672,312 | 53,446,230 |
| Global exposure between 1997-2011[(1)] | 13,824,369 | 276,487,380 |
| **Total** | **32,769,408** | **655,388,165** |

1 Detailed exposure data for the different territories is not available for the period between 1997 2011.
Note: Defined daily dose 100 mg iron.

# SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATIONS

## SVI.1 Potential for Misuse for Illegal Purposes

Venofer has no illicit effect and therefore, the potential for illegal misuse is considered negligible.

Risk of drug abuse is low as Venofer is subjected to medical prescription and is administered by and under the direct supervision of healthcare professionals as an IV administration.

# SVII IDENTIFIED AND POTENTIAL RISKS

## SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable, as this is not the first version of the RMP.

### SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

There are no risks applicable under this section at the time of compiling this report.

### SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

## SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

- Important identified risk (IIR) medication error is removed from the list of safety concerns.

As part of the product life cycle management, the MAH proposes to remove the IIR medication error from the current list of Venofer RMP safety concerns owing to the fact that this risk does not fulfil the criteria for an IIR according to the Good Pharmacovigilance Practices (GVP) Module V Version 2.1 as no additional pharmacovigilance and/or risk minimisation measures were deemed necessary and it does not require further evaluation as part of the pharmacovigilance plan.

Additionally, the IIR medication error is monitored and analysed through Periodic Safety Update Reports (PSURs) in Section 9.2. Medication Error. This risk is also followed up via routine pharmacovigilance activities such as signal detection and adverse reaction reporting. The routine risk minimisation statements in the product information are adhered to by prescribers and the pack size and legal status of IS mitigate this risk.

- IIR injection/infusion site reaction is removed from the list of safety concerns.

As part of the product life cycle management, the MAH proposes to remove the IIR injection/infusion site reaction from the current list of Venofer RMP safety concerns owing to the fact that this risk does not fulfil the criteria for an IIR according to the GVP Module V Version 2.1 as no additional pharmacovigilance and/or risk minimisation measures were deemed necessary and it does not require further evaluation as part of the pharmacovigilance plan. The targeted questionnaire (TQ) specific for IIR injection/infusion site reactions has been removed to match the updates in the Venofer safety concerns of this RMP.

This risk is well-characterised and the root cause is known as extravasation at the injection/infusion site. These occurrences are directly related to the technical skills of the treating healthcare professional. This risk is also followed up via routine pharmacovigilance activities such as signal detection and adverse reaction reporting. The routine risk minimisation statements in the product information are adhered to by prescribers and the pack size and legal status of IS mitigate this risk.

- Important potential risk (IPR) haemosiderosis is removed from the list of safety concerns.

As part of the product life cycle management, the MAH proposes to remove the IPR haemosiderosis as this risk is adequately reflected in SmPC Section 4.9 and Section 4.3 as the product is contraindicated in cases with evidence of iron overload or disturbances in the utilisation of iron. Furthermore, this risk does not require further evaluation as part of the pharmacovigilance plan.

This risk is well-characterised and followed up via routine pharmacovigilance activities such as signal detection and adverse reaction reporting. The routine risk minimisation statements in the product information are adhered to by prescribers and the pack size and legal status of IS mitigate this risk.

## SVII.3 Details of IIRs, IPRs, and Missing Information

### SVII.3.1 Presentation of IIRs and IPRs

Safety concerns relating to the active substance in terms of IIRs and IPRs are specified in Table 18 below.

**Table 18 Important Identified Risk of Hypersensitivity/Anaphylactoid Reaction**

| Important Identified Risk | Hypersensitivity/anaphylactoid reaction |
|---|---|
| Potential mechanisms | There appear to be two types of HSRs to IV iron, a "classical" antibody-mediated anaphylactic reaction and a non-classical mechanism, which may involve a direct activation of complement. Both mechanisms result in release of mast cell and basophil-derived mediators. The pathophysiology of HSRs to Venofer remains unclear [112].<br>Anaphylactic reactions are often life-threatening and almost always unanticipated. Even when there are mild symptoms initially, the potential for progression to a severe and even irreversible outcome must be recognised. Any delay in the recognition of the initial signs and symptoms of anaphylaxis can result in a fatal outcome either because of airway obstruction or vascular collapse. Symptoms of an anaphylactic reaction consist for 90% of cutaneous symptoms followed by respiratory (40-60%) and vascular symptoms (30-35%) and less often abdominal complaints occur (20-25%) [113]. |
| Evidence source(s) and strength of evidence | The Vifor Pharma Clinical Trial Database and Safety Database, together with data from interventional, non-interventional studies and literature [98-117].<br>The EMA evaluated the benefit/risk relationship of iron-containing IV medicinal products in the context of a referral under Article 31 of Directive 2001/83/EC completed in Sep-2013. As a result of this evaluation, EMA imposed a labelling update reinforcing risk information on HSRs and formulated a series of "conditions to marketing authorisation", which included the recommendation by the EMA PRAC for the MAHs to conduct a PASS to further characterise the safety concerns on HSRs. The final results and conclusion were received from PRAC and endorsed by the CMDh (see further information in Section SVII.2 above). Having considered the results of the study and on the basis of the PRAC recommendation and the PRAC assessment report, the CMDh agreed with the variation to the terms of the Marketing Authorisation concerning the following changes:<br>• Removal of the condition to conduct a PASS to further characterise the safety concerns of HSRs with regard to the safe and effective use of the medicinal product. The MAH shall remove the below condition: "The MAHs shall conduct a PASS to further characterise the safety concerns on the HSRs. The study will also have to be reflected in the updated/new RMP submission. Final study report by: 31 July 2016".<br>• Consequently, since this imposed PASS was the only criteria for additional monitoring, MAH(s) should submit a variation to request the deletion of the black symbol and the related statement in the product information. |

## Table 18 Important Identified Risk of Hypersensitivity/Anaphylactoid Reaction (Cont'd)

| Important Identified Risk | Hypersensitivity/anaphylactoid reaction |
|---|---|
| | In this regards, PRAC considered that routine pharmacovigilance could be considered as appropriate to monitor the risk of hypersensitivity and this topic should continue to be closely monitored through the respective PSURs. Accordingly, Vifor Pharma has submitted a variation in March 2022 to remove the black triangle. |
| **Characterisation of the risk** | |
| Frequency with 95% CI | **Related Clinical Trial Population** |

| Number of Venofer Related Cases[1] | Number of Subjects Exposed | Frequency per 10,000 Patients (95% CI) |
|---|---|---|
| 116 (non-serious)<br>8 (serious)<br>124 (total) | 4,439 | 261 (217.3, 313.7)<br>18 (8.4, 37.0)<br>279 (233.8, 333.3) |

**Post-marketing Experience**

| Number of Cases | Exposure Since International Birth Date to DLP | Frequency per 100,000 Patient-Years |
|---|---|---|
| 1,819 (non-serious)<br>1,586 (serious)<br>3,405 (total) | 32,769,408 patient-years | 5.55<br>4.84<br>10.39 |

1 Based on the interim outcomes of now completed referral procedure EMEA/H/A 31/1322, the MAH has proactively broadened the search criteria string for the 'hypersensitivity' case reports to include SMQ 'anaphylactic reactions' and 'angioedema' together with PT 'hypersensitivity'. This broadened search string has been used retrospectively for all the searches within the safety databases since the international birth date. Therefore, the number of respective case reports has significantly increased. This increase is not caused by the changing trend in 'hypersensitivity' case reporting frequency.

Seriousness/outcomes

**From Completed Clinical Trials: in 4,439 patients:**

43 serious cases were reported in clinical trials, of which 8 were related cases and reported as recovered at the end of study. Of the unrelated events 13 had a fatal outcome, 18 were reported as recovered, and 4 were not recovered at the end of study.

510 non-serious cases were reported in clinical trials, of which 116 were non-serious related cases of which 112 reported as recovered and 4 were still ongoing at the end of study. Of the unrelated cases, 297 were reported as recovered, 2 were recovering, 94 were not recovered and 1 was lost to follow-up at the end of study.

**From Post-marketing Experience: in 32,769,408 patient-years until the DLP of this RMP:**

1,586 serious cases (1,482 cases at least possibly related) and 1,722 non-serious cases (1,744 at least possibly related).

Serious cases: 1,586 cases of which 1,482 related to Venofer.

Outcome:

49 cases were reported with fatal outcome.

**Table 18 Important Identified Risk of Hypersensitivity/Anaphylactoid Reaction (Cont'd)**

| Important Identified Risk | Hypersensitivity/anaphylactoid reaction |
|---|---|
| | 1 case was reported "complete recovery", 640 cases were reported "recovered/resolved", 3 cases were reported "recovered/resolved with sequelae", 42 cases were reported "recovering/resolving", 49 cases were reported "not recovered/not resolved", 1 case was reported "lost to follow-up", 381 cases were reported "unknown".<br>For 420 cases the outcome cannot be retrieved from the safety database.<br>Non-serious cases: 1,819 cases of which 1,744 related to Venofer.<br>Outcome:<br>1 case was reported "complete recovery", 726 cases were reported "recovered/resolved", 2 cases were reported "recovered/resolved with sequelae", 66 cases were reported "recovering/resolving", 1 case was reported "continued", 49 cases were reported "not recovered/not resolved", 3 cases were reported "lost to follow-up", 531 cases were reported "unknown".<br>For 440 cases the outcome cannot be retrieved from the safety database. |
| Severity and nature of risk | **From Completed Clinical Trials: in 4, 439 patients:**<br>Of the 8 serious related cases, 4 were moderate and 4 severe. Of the remaining 35 serious unrelated cases, 8 were mild, 6 were moderate and 21 severe.<br>Of the 116 non-serious cases, 78 were mild, 32 were moderate and 6 were severe. Of the remaining 394 non-serious unrelated cases, 251 were mild, 124 were moderate, and 19 were severe.<br>Of 116 non-serious cases, 78 were mild, 32 were moderate and 6 were severe.<br>HSRs in general may be life-threatening conditions with fatal outcome. |
| Background incidence/ prevalence | A general safety concern with regard to all parenteral iron preparations is potential HSRs, based on historical experience with dextran containing iron products. However, iron sucrose is a non-dextran IV iron.<br>Hypersensitivity drug reactions are responsible for significant morbidity, mortality and socioeconomic costs that are often underestimated. Current epidemiological data have to be regarded carefully as different studies used different populations (either adult or paediatric populations or both, inpatients or outpatients), different definitions of HSRs, different methodologies and methods of data analyses. It should also be kept in mind that the assessment of severity, preventability and drug imputability of reactions relies mostly on clinical history, which can sometimes be ambiguous [118].<br>**Hospital-based Population**<br>Currently not many studies have studied the hospital-based population with regards to HSRs. A review performed by Lazarou [118] showed in a meta-analysis of 33 prospective studies from the US between 1966 and 1996, that 15.1% of hospitalised patients suffered an ADR (6.7% severe) and that the incidence of drug-related hospital admissions ranged from 3.1 to 6.2% [59]. In Singapore, a 2-year prospective study by Thong [59], using a network based electronic notification system for which each case was verified by a trained allergist, detected 366 cases of reported drug allergy from a total of 90,910 inpatients. |

**Table 18 Important Identified Risk of Hypersensitivity/Anaphylactoid Reaction (Cont'd)**

| Important Identified Risk | Hypersensitivity/anaphylactoid reaction |
|---|---|
| | After review, 210 were classified as drug allergy. Cutaneous manifestations were the most common clinical presentation (95.7%); systemic manifestations occurred in 30% of the cases and serious adverse reactions such as Stevens Johnson syndrome, toxic epidermal necrolysis and general exfoliative dermatitis occurred in 11 patients (5.2%). Antibiotics and anti-epileptic drugs accounted for 75% of the reactions. They concluded that the frequency of drug allergy in hospitalised patients was 4.2 per 1,000 hospitalisations and mortality attributable to drug allergy was 0.09 per 1,000 hospitalisations [118].<br>**General Population**<br>Until recently, studies have been limited by small sample size or samples that may not represent the general population. Neugut et al, 2001 [119] suggested that the better approach to estimating risk would be to "use estimates specifically calculated from epidemiologic studies measuring anaphylaxis in the general population." Despite the obvious difficulties in estimating the overall incidence of anaphylaxis, the authors addressed this issue via a review of the literature of what they termed were the "four major subtypes of anaphylaxis (food, drugs, latex, and insect stings)" [119]. They calculated an overall estimate of the risk of anaphylaxis using data derived from the incidence of episodes to these specific agents. Then, based on a 1999 US population of 272 million, they attempted to estimate the population at risk; their calculations yielded between 3.3 million and 43 million Americans. They also estimated that a total of 1,443 to 1,503 were at risk for a fatal event attributable to food, medications, latex, and insect stings. Thus, they concluded that the reported frequency of anaphylaxis was not as rare as previously believed and estimated that 1.2% to 15% of the total US population may experience an anaphylactic reaction and that 0.002% of these might experience a fatal event [119].<br>Overall, there is few epidemiological data on hypersensitivity drug reactions, which account for about 33% of all ADRs. They affect 10-20% of hospitalised patients and up to 7% of outpatients. The available information based predominantly on the epidemiology of ADRs, requires cautious interpretation as these reactions are rarely accurately classified or proven. Both under-diagnosis because of underreporting and over-diagnosis due to the common use of the term 'allergy' have also to be considered. |
| Risk factors and risk groups | Although several risk factors have been identified, their clinical importance has not been fully understood. Future progress in immunogenetics and pharmacogenetics may help identify populations at risk for HSRs. |
| Preventability | Drug-related HSRs occur in approximately 33% of all HSRs, with 10-20% occurring in an inpatient setting. This number can be significantly reduced by carefully recording each patient's medical history, especially allergic medical history/other atopy. Careful medical monitoring with regards to early detection of hypersensitivity symptoms could result in prompt medical interventions and subsequently decrease serious HSRs. |

**Table 18 Important Identified Risk of Hypersensitivity/Anaphylactoid Reaction (Cont'd)**

| Important Identified Risk | Hypersensitivity/anaphylactoid reaction |
|---|---|
| Impact on the benefit/risk balance of the product | Hypersensitivity/anaphylactoid reactions represent an identified risk, as reported in Venofer product information. Although uncommon, and in most cases mild to moderate in severity, self-limiting and of short duration, the rarely reported severe cases of HSRs (anaphylactic or anaphylactoid reactions) could be life-threatening and further investigations are needed to understand their potential mechanism. This identified risk is managed by routine and additional pharmacovigilance activities. Moreover procedures to enhance the knowledge on this identified risk are in place. |
| Public health impact | The potential public health impact is probably not high, as HSRs are uncommon, and fatalities occur in 0.002-1% only (figure based on the US population [119]) and depends widely on the comorbidities of the affected patient and the setting in which the HSR occurs.<br>Post-marketing data showed an overall occurrence of 0.08% (figure based on EU and US populations) with no fatalities reported. When the severity of the cases is taken into account only 0.06% was serious of which only 0.01% was of a life-threatening nature, which is significantly below the background incidence of anaphylaxis, which can be as high as 1.2-15%. |
| MedDRA terms | MedDRA SMQ Anaphylactic reaction<br>MedDRA SMQ Angioedema<br>MedDRA PT Hypersensitivity |

Notes: ADR Adverse drug reaction; CI Confidence interval; CMDh Coordination Group for Mutual Recognition and Decentralised Procedures Human; DLP Data lock point; HSR Hypersensitivity reaction; Ig Immunoglobulin; IV Intravenous; MAH Marketing Authorisation Holder; MedDRA Medical Dictionary for Regulatory Activities; PASS Post authorisation Safety Study; PRAC Pharmacovigilance Risk Assessment Committee; PSUR Periodic Safety Update Report; PT Preferred term; RMP Risk Management Plan; SMQ Standardised MedDRA query.

## SVII.3.2 Presentation of the Missing Information

**Table 19 Missing Information**

| Missing Information | What Is Known |
|---|---|
| **Use in paediatric population** | |
| Evidence source | Population in need of further characterisation:<br>Children and adolescents were excluded from the formal clinical development programme of Venofer. However, there is limited information in the published literature about the efficacy and safety of Venofer use in children and adolescents. |
| **Use in elderly patients** | |
| Evidence source | Population in need of further characterisation:<br>Elderly patients were under-represented in the clinical development programme of Venofer. Therefore, the knowledge about efficacy and safety of Venofer in this population is scarce. |

## Table 19 Missing Information (Cont'd)

| Missing Information | What Is Known |
|---|---|
| **Use in patients with infectious diseases** | |
| Evidence source | Population in need of further characterisation:<br>Patients with acute infection or known infectious disease (e.g., hepatitis B, C or HIV) were excluded from the clinical development programme. Therefore, the knowledge about efficacy and safety of Venofer in these patients is limited and the administration of Venofer in patients with an active infection is not recommended. |
| **Use in pregnant or lactating women** | |
| Evidence source | Population in need of further characterisation:<br>There is no or only a limited amount of data (less than 300 pregnancy outcomes) from the use of iron sucrose in pregnant women in the first trimester. A moderate amount of data (between 300-1,000 pregnancy outcomes) from the use of Venofer in pregnant women in the second and third trimester showed no safety concerns for the mother or newborn. It cannot be excluded that newborns/infants may be exposed to iron derived from Venofer via the mother's milk. Therefore, the benefit/risk should be assessed before Venofer is prescribed to a pregnant or nursing woman. |

# SVIII SUMMARY OF THE SAFETY CONCERNS

**Table 20 Summary of Safety Concerns**

| | |
|---|---|
| Important identified risks | Hypersensitivity/anaphylactoid reaction |
| Important potential risks | None |
| Missing information | Use in paediatric population<br>Use in elderly patients<br>Use in patients with infectious diseases<br>Use in pregnant or lactating women |

# PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

## III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- **Specific Adverse Reaction Follow-up Questionnaire for Use in Pregnant Women**

The pregnancy follow-up form has been incorporated into routine follow-up and is presented in this RMP in Annex 4 (Report on Exposure to Medicines During Pregnancy). All pregnancy cases will be carefully followed up and a thorough assessment will be made.

- **Specific Adverse Reaction Follow-up Questionnaire for Hypersensitivity/ Anaphylactoid Reactions**

The follow-up TQ specific for evaluating HSR events has been incorporated into routine follow-up and is presented in this RMP in Annex 4 (Hypersensitivity Reaction Reports). All HSR cases are carefully followed up and a thorough assessment is made.

- **Specific Adverse Reaction Follow-up Questionnaire for Infection Related Events**

The follow-up TQ specific for evaluating infection related events has been incorporated into routine follow-up and is presented in this RMP in Annex 4 (Evaluating Infection Related Events). There are no other specific adverse reaction follow-up questionnaires for the other safety concerns listed in this RMP in Table 20.

In addition, routine processes are employed for the identification of new safety concerns, the further characterisation of known safety concerns (including elucidation of risk factors), the investigation into whether a potential safety concern is real and the search for important missing information.

## III.2 Additional Pharmacovigilance Activities

The overview of the additional pharmacovigilance activities is presented in Table 21 below.

**Table 21 Overview of Additional PV Activities per Safety Concern**

| Safety Concern | Additional PV Activities | Objectives |
|---|---|---|
| Hypersensitivity/ anaphylactoid reaction | Cumulative review of hypersensitivity reactions (commitment from the PSUSA/00010696/201901), to be included within the EU PSUR for IS. | To monitor any increase in frequency and severity of hypersensitivity/ anaphylactoid/anaphylactic reactions. |
| Use in pregnant or lactating women | Cumulative review of pregnancies (commitment from the PSUSA/00010696/201901), to be included within the EU PSUR for IS. | To monitor and determine the safety profile of the medication in pregnant or lactating women. |

Notes: IS Iron sucrose; PSUR Periodic Safety Update Report.

In relation to the Article 31 referral procedure (EMEA/H/A-31/1322; EC decision: 13 September 2013) which involved all EU registered IV iron medicinal products, all IV iron MAHs were obliged to undertake a PASS to further characterise the safety concerns regarding HSRs. To achieve this in a coordinated manner, a consortium of IV iron companies was established. The PASS "Intravenous Iron PASS: Evaluation of the Risk of Severe Hypersensitivity Reactions" was registered in the ENCePP EU PAS Register (EU electronic register of post-authorisation studies), under registration number: EUPAS20720.

Literature data showed that early IV iron formulations were associated with rare but serious HSRs, including anaphylactic reactions and death [57] however, newer formulations of IV iron showed a better safety profile [58-60]. Studies evaluating HSRs in association with IV iron preparations have likewise been previously reported [58].

The results of the PASS study showed that according to the sensitivity analyses there is an increased risk related to dextran products compared to iron non-dextran products which is comparable to the literature. Nevertheless, the design of the study and its limitations did not allow to conclude that there is not a high risk of HSR among the users of IV iron. Following these results and due to the observed limitations of the conducted PASS, the PRAC requested supplementary information to further elucidate the likelihood to obtain more robust results.

In May 2021, the IV Iron Consortium submitted the responses to the questions stated in the request for supplementary information as well as a preliminary report on the feasibility evaluation for a potential new IV iron PASS (Feasibility Study Report). The conclusion of this preliminary report was that "At this stage after having reviewed all but one of the population-based data sources and the few responders from the identified disease and patient registries, the options for an efficient, valid, and timely potential new IV iron PASS for anaphylaxis in Europe using secondary data collection remained low. Pending information is unlikely to change this conclusion."

The PRAC considered that further investigation of anaphylaxis in IV iron treated patients was not feasible at that stage, routine pharmacovigilance could be considered as appropriate to monitor the risk of hypersensitivity and this topic should continue to be closely monitored through the respective PSURs.

No final conclusions with respect to HSRs could be drawn on the basis of the results of this imposed PASS study due to some study limitations. Nevertheless, a higher risk of hypersensitivity/anaphylaxis could not be excluded. Therefore, the results of this PASS did not warrant an update of the current risk minimisation measures.

The CMDh, having considered in accordance with Article 107q(2) of Directive 2001/83/EC the results of the study on the basis of the PRAC recommendation and the PRAC assessment report, reaches its position by consensus on the variation to the terms of the Marketing Authorisation concerning the following change (further information presented in Section SVII.2):

- Removal of the condition to conduct a PASS to further characterise the safety concerns of HSRs with regard to the safe and effective use of the medicinal product. The MAH shall remove the below condition: “The MAHs shall conduct a PASS to further characterise the safety concerns on the HSRs. The study will also have to be reflected in the updated/new RMP submission”.

- Consequently, since this imposed PASS was the only criterion for additional monitoring, MAH(s) should submit a variation to request the deletion of the black symbol and the related statement in the product information.

Following this decision, Vifor Pharma has submitted a variation in March 2022 to remove the black triangle.

## III.3 Summary Table of Additional Pharmacovigilance Activities

### Table 22 Ongoing and Planned Additional Pharmacovigilance Activities

| Study/Activity Type, Title and Category (1-3) Status | Summary of Objectives | Safety Concerns Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| **Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation** | | | | |
| N/A | N/A | N/A | N/A | N/A |
| **Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances** | | | | |
| N/A | N/A | N/A | N/A | N/A |
| **Category 3 - Required additional pharmacovigilance activities** | | | | |
| Cumulative review of hypersensitivity reactions (commitment from the PSUSA/00010696/201901), to be included in the EU IS PSURs. | To monitor any increase in frequency and severity of hypersensitivity/ anaphylactoid/ anaphylactic reactions. | Hypersensitivity/ anaphylactoid reaction. | Ongoing | Reviews will no longer be submitted as a separate report. |
| Cumulative review of pregnancies (commitment from the PSUSA/00010696/201901), to be included in the EU IS PSURs. | To monitor and determine the safety profile of the medication in pregnant or lactating women. | Use in pregnant or lactating women. | Ongoing | Reviews will no longer be submitted as a separate report. |

Notes: IS Iron sucrose; N/A Not applicable; PSUR Periodic Safety Update Report.

# PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

No post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations are planned.

# PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

**Risk Minimisation Plan**

## V.1 Routine Risk Minimisation Measures

The routine risk minimisation measures are listed in Table 23 below.

**Table 23 Description of Routine Risk Minimisation Measures by Safety Concern**

| Safety Concern | Routine Risk Minimisation Measures |
|---|---|
| **Important Identified Risk: Hypersensitivity/Anaphylactoid Reaction** | |
| Routine risk communication | SmPC Section 4.2<br>SmPC Section 4.3<br>SmPC Section 4.4<br>SmPC Section 4.8<br>PL section "Intended for healthcare professionals only"<br>PL Section 2 |
| Routine risk minimisation activities recommending specific clinical measures to address the risk | Guidance on individual dose adjustment and method of administration is included in SmPC Section 4.2 and in PL section "Intended for healthcare professionals only."<br>Warnings against use of Venofer in case of hypersensitivity to iron sucrose, Venofer, or to any of its excipients is included in SmPC Section 4.3 and in PL section "Intended for healthcare professionals only."<br>Recommendation to monitor carefully patients during and following administration, as well as need for the presence of appropriately trained staff, and full resuscitation facilities is included in SmPC Section 4.2 and SmPC Section 4.4 and in PL section "Intended for healthcare professionals only."<br>Precaution message on the use of Venofer in patients with a history of severe asthma, eczema, other atopic allergies or allergic reactions to other parenteral iron preparations is included in SmPC Section 4.4 and in PL Section 2. |
| Other routine risk minimisation measures beyond the Product Information | |
| Pack size | 5 × 5 ml (20 mg iron/ml) |
| Legal status | Prescription only medicine |
| **Missing Information: Use in Paediatric Population** | |
| Routine risk communication | SmPC Section 4.2<br>PL section "Intended for healthcare professionals only" |
| Routine risk minimisation activities recommending specific clinical measures to address the risk | SmPC:<br>If there is a clinical need of Venofer, it is recommended not to exceed 0.15 ml of Venofer (3 mg iron) per kg body weight not more than 3 times per week, as stated in SmPC Section 4.2 and in PL section "Intended for healthcare professionals only". |
| Other routine risk minimisation measures beyond the Product Information | |
| Pack size | 5 × 5 ml (20 mg iron/ml) |
| Legal status | Prescription only medicine |

## Table 23 Description of Routine Risk Minimisation Measures by Safety Concern (Cont'd)

| Safety Concern | Routine Risk Minimisation Measures |
|---|---|
| **Missing Information: Use in Elderly Patients** | |
| Routine risk communication | SmPC Section 4.2<br>PL section "Intended for healthcare professionals only" |
| Routine risk minimisation activities recommending specific clinical measures to address the risk | SmPC:<br>Guidance on the dosage and method of administration including information on normal posology, maximum tolerated doses, method of administration, as well as detailed guidance for the calculation of the total cumulative dose of Venofer is included in SmPC Section 4.2.<br>PL section "Intended for healthcare professionals only". |
| Other routine risk minimisation measures beyond the Product Information | |
| Pack size | 5 × 5 ml (20 mg iron/ml) |
| Legal status | Prescription only medicine |
| **Missing Information: Use in Patients with Infectious Diseases** | |
| Routine risk communication | SmPC Section 4.4<br>PL Section 2 |
| Routine risk minimisation activities recommending specific clinical measures to address the risk | SmPC:<br>Recommendation to use parenteral iron with caution in case of acute or chronic infection is included in SmPC Section 4.4 and PL Section 2. It is recommended that the administration of iron sucrose is stopped in patients with bacteraemia. In patients with chronic infection, a benefit/risk evaluation should be performed. |
| Other routine risk minimisation measures beyond the Product Information | |
| Pack size | 5 × 5 ml (20 mg iron/ml) |
| Legal status | Prescription only medicine |
| **Missing Information: Use in Pregnant or Lactating Women** | |
| Routine risk communication | SmPC Section 4.6<br>PL Section 2 |
| Routine risk minimisation activities recommending specific clinical measures to address the risk | SmPC:<br>Recommendation to use Venofer only during second and third trimester of pregnancy if the benefit is judged to outweigh the potential risk for both the mother and the foetus is found in SmPC Section 4.6.<br>Warning that foetal bradycardia may occur following administration of parenteral irons is included in SmPC Section 4.6. Foetal bradycardia is usually transient and a consequence of a hypersensitivity reaction in the mother.<br>Warnings and precautions regarding pregnancy and breastfeeding are included in PL Section 2.<br>It cannot be excluded that newborns/infants may be exposed to iron derived from Venofer via the mother's milk, therefore the benefit/risk should be assessed. |
| Other routine risk minimisation measures beyond the Product Information | |
| Pack size | 5 × 5 ml (20 mg iron/ml) |
| Legal status | Prescription only medicine |

Notes: PL Package Leaflet; SmPC Summary of Product Characteristics.

## V.2 Additional Risk Minimisation Measures

The following safety concerns required additional risk minimisation measures and these are presented in Table 24 below.

**Table 24 Additional Risk Minimisation Measures**

| Safety Concern | Additional Risk Minimisation Measures |
|---|---|
| **Important identified risk: hypersensitivity/anaphylactoid reaction** | |
| Objective | The objective is to minimise the risk of serious hypersensitivity reactions based on a class label (commitment from the Article 31 EMA referral; EMEA/H/A-31/1322). |
| Rationale for additional risk minimisation activity | To inform healthcare professionals and patients about the outcomes of completed EMA referral procedure (EMEA/H/A-31/1322) and its impact on IV therapy and about the strengthened recommendations for use.<br>Dissemination of DHPC about the risks of IV iron associated with hypersensitivity reactions. |
| Target audience and planned distribution path | All healthcare professionals should follow the recommendations presented in the DHPC (distribution performed Oct-2013 to Nov-2013).<br>Dissemination of educational materials to healthcare professionals and patients was completed (distribution performed Sep-2014 to Aug-2015). |
| Plans to evaluate the effectiveness of the intervention and criteria for success | Effectiveness will be measured by means of routine pharmacovigilance activities, including signal detection, follow-up requests and review of received case reports relevant to this safety concern.<br>The success of the proposed risk minimisation measures will be based on a reporting rate (comparison of product information versus case reports received). Close monitoring of hypersensitivity reports and trends versus previous time period within EU region where distribution of DHPC and educational material has taken place.<br>Assessment will be performed continuously during medical review of case reports and during signal detection evaluation meetings.<br>Results will be presented regularly in PSUR and RMP updates. |
| **Missing information: Use in pregnant or lactating women** | |
| Objective | To inform about this risk and associated risk factors using routine risk minimisation activities. The objective is to minimise the risk of serious hypersensitivity reactions based on a class label (commitment from the Article 31 EMA referral; EMEA/H/A-31/1322).<br>Dissemination of DHPC about the risks of IV iron associated with hypersensitivity reactions. |
| Rationale for additional risk minimisation activity | To inform healthcare professionals and patients about the outcomes of completed EMA referral procedure and its impact on the IV therapy and about the strengthened recommendations for use. |
| Target audience and planned distribution path | All healthcare professionals should follow the recommendations presented in the DHPC (distribution performed Oct-2013 to Nov-2013). Dissemination of educational materials to healthcare professionals and patients was completed (distribution performed Sep-2014 to Aug-2015). |

**Table 24 Additional Risk Minimisation Measures (Cont'd)**

| Safety Concern | Additional Risk Minimisation Measure |
|---|---|
| Plans to evaluate the effectiveness of the intervention and criteria for success | Effectiveness will be measured by means of routine pharmacovigilance activities, including signal detection, follow-up requests and review of received case reports relevant to this safety concern.<br>The success of the proposed risk minimisation measures will be based on a reporting rate (comparison of product information versus case reports received). Close monitoring of hypersensitivity reports and trends versus previous time period within EU region where distribution of DHPC and educational material has taken place.<br>Assessment will be performed continuously during medical review of case reports and during signal detection evaluation meetings.<br>Results will be presented regularly in PSUR and RMP updates. |

Notes: DHPC Direct Healthcare Professional Communication; IV Intravenous; PSUR Periodic Safety Update Report; RMP Risk Management Plan.

## V.3 Summary Table of Risk Minimisation Measures

**Table 25 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| Hypersensitivity/ anaphylactoid reaction | Routine risk minimisation measures:<br>SmPC Section 4.2<br>SmPC Section 4.3<br>SmPC Section 4.4<br>SmPC Section 4.8<br>PL section "Intended for healthcare professionals only"<br>PL Section 2<br>Pack size: 5 × 5 ml (20 mg iron/ml)<br>Legal status: Prescription only medicine<br>Additional risk minimisation measures: DHPC and educational materials for prescribers and patients | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up TQ.<br>Additional pharmacovigilance activities: Cumulative review of hypersensitivity reactions (commitment from the PSUSA/00010696/201901), to be included within the EU PSUR for IS. |
| Use in paediatric population | Routine risk minimisation measures:<br>SmPC Section 4.2<br>PL section "Intended for healthcare professionals only"<br>Pack size: 5 × 5 ml (20 mg iron/ml)<br>Legal status: Prescription only medicine<br>Additional risk minimisation measures: None | None |

**Table 25 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern (Cont'd)**

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| Use in elderly patients | Routine risk minimisation measures:<br>SmPC Section 4.2<br>PL section "Intended for healthcare professionals only"<br>Pack size: 5 × 5 ml (20 mg iron/ml)<br>Legal status: Prescription only medicine<br>Additional risk minimisation measures: None | None |
| Use in patients with infectious diseases | Routine risk minimisation measures:<br>SmPC Section 4.4<br>PL Section 2<br>Pack size: 5 × 5 ml (20 mg iron/ml)<br>Legal status: Prescription only medicine<br>Additional risk minimisation measures: None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up TQ. |
| Use in pregnant or lactating women | Routine risk minimisation measures:<br>SmPC Section 4.6<br>PL Section 2<br>Pack size: 5 × 5 ml (20 mg iron/ml)<br>Legal status: Prescription only medicine<br>Additional risk minimisation measures: DHPC and educational materials for prescribers and patients | Pregnancy follow-up form.<br>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up TQ.<br>Additional pharmacovigilance activities: Cumulative review of pregnancies (commitment from the PSUSA/00010696/201901), to be included within the EU PSUR for IS. |

Notes: DHPC Direct Healthcare Professional Communication; IS Iron sucrose; PL Package Leaflet; PSUR Periodic Safety Update Report; SmPC Summary of Product Characteristics; TQ Targeted questionnaire.

# PART VI: SUMMARY OF THE RMP

**Summary of Risk Management Plan for Venofer (Iron Sucrose)**

This is the summary of the Risk Management Plan for Venofer. The Risk Management Plan details important risks of Venofer, how these risks can be minimised, and how more information will be obtained about Venofer's risks and uncertainties (missing information).

Venofer's Summary of Product Characteristics and its Package Leaflet give essential information to healthcare professionals and patients on how Venofer should be used.

Important new concerns or changes to the current ones will be included in updates of Venofer's Risk Management Plan.

## I. The Medicine and What It Is Used for

Based on Mutual Recognition Procedure Summary of Product Characteristics Version 17.0 (approved 18 March 2022).

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

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

It contains iron sucrose as active substance and it is given intravenously.

## II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Venofer, together with measures to minimise such risks and the proposed studies for learning more about Venofer’s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and Summary of Product Characteristics addressed to patients and healthcare professionals
- Important advice on the medicine’s packaging
- The authorised pack size the amount of medicine in a pack is chosen to ensure that the medicine is used correctly

- The medicine's legal status the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

Important risks of Venofer, together with measures to minimise such risks and the proposed studies for learning more about Venofer's risks, are outlined below.

If important information that may affect the safe use of Venofer is not yet available, it is listed under 'missing information' in below.

## II.A List of Important Risks and Missing Information

Important risks of Venofer are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Venofer. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

**List of Important Risks and Missing Information**

| | |
|---|---|
| Important identified risks | Hypersensitivity/anaphylactoid reaction |
| Important potential risks | Not applicable |
| Missing information | Use in paediatric population<br>Use in elderly patients<br>Use in patients with infectious diseases<br>Use in pregnant or lactating women |

## II.B Summary of Important Risks

### Important Identified Risk: Hypersensitivity/Anaphylactoid Reaction

| | |
|---|---|
| Evidence for linking the risk to the medicine | The Vifor Pharma Clinical Trial Database and Safety Database, together with data from interventional, non-interventional studies and literature [98-113]. |
| Risk factors and risk groups | Although several risk factors have been identified, their clinical importance has not been fully understood. Future progress in immunogenetics and pharmacogenetics may help identify populations at risk for hypersensitivity reactions. |
| Risk minimisation measures | Routine risk minimisation measures:<br>SmPC Section 4.2<br>SmPC Section 4.3<br>SmPC Section 4.4<br>SmPC Section 4.8<br>PL section "Intended for healthcare professionals only"<br>PL Section 2<br>Appropriate posology is listed in SmPC Section 4.2 and PL section "Intended for healthcare professionals only"<br>Appropriate warning about the need for patient monitoring during administration is stated in SmPC Section 4.2 and PL section "Intended for healthcare professionals only"<br>Appropriate contraindications are listed in SmPC Section 4.3 and PL section "Intended for healthcare professionals only"<br>Special warnings and precautions relevant to this risk are present in SmPC Section 4.4, PL section "Intended for healthcare professionals only" and in PL Section 2.<br>Hypersensitivity and anaphylactoid reactions are listed as adverse drug reactions in SmPC Section 4.8. A description of the most common and most severe characteristics of hypersensitivity is provided in the first paragraph of SmPC Section 4.8.<br>Pack size: 5 × 5 ml (20 mg iron/ml)<br>Legal status: Prescription only medicine<br>Additional risk minimisation measures: DHPC and educational materials for prescribers and patients |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities: Cumulative review of hypersensitivity reactions (commitment from the PSUSA/00010696/201901), to be included within the EU PSUR for IS. |

Notes: DHPC Direct Healthcare Professional Communication; IS Iron sucrose; PL Package Leaflet; PSUR Periodic Safety Update Report; SmPC Summary of Product Characteristics.

### Missing Information: Use in Paediatric Population

| | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>SmPC Section 4.2<br>PL section "Intended for healthcare professionals only"<br>Information relevant to this special population is included in SmPC Section 4.2 and in PL section "Intended for healthcare professionals only"<br>Pack size: 5 × 5 ml (20 mg iron/ml)<br>Legal status: Prescription only medicine<br>Additional risk minimisation measures: None |

Notes: PL Package Leaflet; SmPC Summary of Product Characteristics.

### Missing Information: Use in Elderly Patients

| | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>SmPC Section 4.2<br>PL section "Intended for healthcare professionals only"<br>Information relevant to this special population is included in SmPC Section 4.2 and PL section "Intended for healthcare professionals only".<br>Pack size: 5 × 5 ml (20 mg iron/ml)<br>Legal status: Prescription only medicine<br>Additional risk minimisation measures: None |

Notes: PL Package Leaflet; SmPC Summary of Product Characteristics.

### Missing Information: Use in Patients with Infectious Diseases

| | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>SmPC Section 4.4<br>PL Section 2<br>Special warnings and precautions associated with this risk are included in SmPC Section 4.4 and PL Section 2.<br>Pack size: 5 × 5 ml (20 mg iron/ml)<br>Legal status: Prescription only medicine<br>Additional risk minimisation measures: None |

Notes: PL Package Leaflet; SmPC Summary of Product Characteristics.

### Missing Information: Use in Pregnant or Lactating Women

| | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>SmPC Section 4.6<br>PL Section 2<br>All information relevant to pregnancy and lactation is presented in Section 4.6 of the SmPC and Section 2 of PL.<br>Pack size: 5 × 5 ml (20 mg iron/ml)<br>Legal status: Prescription only medicine<br>Additional risk minimisation measures: DHPC and educational materials for prescribers and patients |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities: Cumulative review of pregnancies (commitment from the PSUSA/00010696/201901), to be included within the EU PSUR for IS |

Notes: DHPC Direct Healthcare Professional Communication; IS Iron sucrose; PL Package Leaflet; PSUR Periodic Safety Update Report; SmPC Summary of Product Characteristics.

## II.C Post-authorisation Development Plan

### II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation for IS.

### II.C.2 Other Studies in Post-authorisation Development Plan

Not applicable. There are no other studies in post-authorisation development plan.

# PART VII: ANNEXES

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## Annex 1 EudraVigilance Interface

Interface is available in electronic format only.

## Annex 2 Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Programme

Note: This annex to be reviewed and updated when submitted to Health Authority.

### Table 1 Planned and Ongoing Studies

| Study | Summary of Objectives | Safety Concerns Addressed | Milestones |
|---|---|---|---|
| N/A | N/A | N/A | N/A |

Note: N/A Not applicable.

**Table 2 Completed Studies**

| Study | Summary of Objectives | Safety Concerns Addressed | Date of Final Study Report Submission |
|---|---|---|---|
| Intravenous Iron Post-authorisation Safety Study (PASS) | Intravenous Iron Post-authorisation Safety Study (PASS): Evaluation of the Risk of Severe Hypersensitivity Reactions, Category 1 | Assessment of the risk of anaphylactic or severe immediate hypersensitivity reactions (hereafter, "anaphylactic reactions") on the day of or the day after the first IV iron administration through the following parameters:<br>Incidence proportion of anaphylactic reactions in patients first dispensed/administered IV iron (new users) overall, by group of IV iron product - iron(III)-hydroxide dextran complex versus non-dextran IV iron products - and by the individual IV iron types listed below:<br>Iron(III)-hydroxide dextran complex<br>Iron sucrose complex/iron(III)-hydroxide sucrose complex<br>Ferric carboxymaltose complex<br>Iron(III)-isomaltoside complex<br>Sodium ferric gluconate complex<br>Risk ratios of anaphylactic reactions in patients first dispensed/administered IV iron (new users), by group of IV iron product - iron(III)-hydroxide dextran complex versus non-dextran IV iron products, and by the individual IV iron types listed below using iron sucrose complex/iron(III)-hydroxide sucrose complex as the comparator:<br>Iron(III)-hydroxide dextran complex<br>Ferric carboxymaltose<br>Iron(III)-isomaltoside complex<br>Sodium ferric gluconate complex | March 2020 |

Note: IV Intravenous.

## Annex 3 Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan

### Part A: Requested Protocols of Studies in the Pharmacovigilance Plan, Submitted for Regulatory Review With This Updated Version of the RMP

Not applicable.

### Part B: Requested Amendments of Previously Approved Protocols of Studies in the Pharmacovigilance Plan, Submitted for Regulatory Review With This Updated Version of the RMP

Not applicable.

### Part C: Previously Agreed Protocols for Ongoing Studies and Final Protocols Not Reviewed by the Competent Authority

Not applicable.

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## REPORT ON EXPOSURE TO MEDICINES DURING PREGNANCY Part 1

**Name of Vifor Drug** (Trade name / IMP):

Patients Initials / No: Country: Local Reference No:

### Details of Mother and Pregnancy

Date / Year of Birth: / / (dd/mmm/yyyy) Age: Occupation:

**Previous Pregnancy**

Yes ☐ No ☐ Total no. of pregnancies: Normal Deliveries:

Abortions (Spontaneous ): Abortions (performed):

**Relevant Medical History**:
(including pregnancy risk factors, Pre eclampsia, eclampsia, smoking, alcohol, environmental & occupational exposures etc.)

**Relevant Family History**:
(hereditary diseases e.g. hypertension, diabetes)

### Current Pregnancy

First day of Last Menstruation: / / (dd/mmm/yyyy) Expected Delivery Date: / / (dd/mmm/yyyy)

Gestational age of foetus (specify at time of exposure / time of reporting) :

Ultrasound performed? Yes ☐ No ☐ If yes, findings if any:

Any complications, infections or illnesses during pregnancy? Yes ☐ No ☐

If yes, elaborate:

### Drug Exposure during Pregnancy

| Mother /Father Exposure | Suspect Drug/ Concomitant medication | Product Name (Trade / IMP) Batch no. | Total Daily Dose (Units) | Therapy Start date | Therapy Stop date | Indication for use | Route of application (oral, infusion, injection) |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |

**Reporting Physician:** Name: Profession:

***Privacy Notification:***

The personal data that you provide, such as your name and contact details, will be handled and stored by Vifor Pharma. You can read in detail what information we save and how the information will be handled in our Privacy Notices on the Vifor Pharma website (www.viforpharma.com/dataprivacy) where you also find contact details if you have questions.

***NOTE**:* The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule specifically permits covered entities (such as pharmacists, physicians or hospitals) to use and disclose health information without authorization in order to report adverse events and other information related to the quality, effectiveness and safety of FDA-regulated products both to the manufacturers and directly to FDA. Please submit only that health information which is reasonably necessary to achieve the purpose of the report.

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# REPORT ON EXPOSURE TO MEDICINES DURING PREGNANCY Part 2

## Information on Outcome of Pregnancy

**Name of Vifor Drug** (Trade name/IMP)**:**

Patients Initials / No: Country: Local Reference No:

## Outcome of Pregnancy

☐ Full Term — Normal delivery or Caesarean:

☐ Premature Birth — If premature birth, gestational age: weeks

☐ Spontaneous Miscarriage

☐ Elective termination — Medical Reason? ☐ Yes ☐ No

If yes, specify:

Details / Comments (if any):

☐ Healthy Baby ☐ Multiple Births

☐ Sick Baby (e.g. Birth trauma, infection etc.) ☐ Congenital anomaly or Birth defect ☐ Still Birth

Date of Birth / / (dd/mmm/yyyy) Sex ☐ Male ☐ Female

Size: Weight: APGAR scores, if provided (Birth/5/10 mins.)

Details / Comments (if any):

Please comment on any abnormal condition or occurrence regarding outcome of pregnancy and/or birth/delivery.

**Is there a suspicion that adverse outcome of pregnancy is related to exposure to Product?**

☐ Yes ☐ No

Please elaborate:

**Reporting Physician:** Name: Profession:

**Please provide all available information and send to completed form. Attach any applicable supporting documentation if applicable.** (such as pictures, autopsy report, hospital discharge summary, laboratory values)

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***NOTE:*** The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule specifically permits covered entities (such as pharmacists, physicians or hospitals) to use and disclose health information without authorization in order to report adverse events and other information related to the quality, effectiveness and safety of FDA-regulated products both to the manufacturers and directly to FDA. Please submit only that health information which is reasonably necessary to achieve the purpose of the report.

**Please always send both, Part I and Part II of the form to safety@viforpharma.com or fax to: +41 58851 8659**

**Vifor coding number:** VIT 2022 04046

## 1. Patient details:

Initials (First name / family name): Date of Birth: Age:

Gender: M ☐ F ☐ Weight (in kg): Height (in cm):

**Seriousness criteria** No ☐ Yes ☐ If yes specify:

☐ Patient death
☐ Life threatening
☐ Involved or prolonged patient hospitalization
☐ Involved persistence of significant disability

☐ Congenital anomaly
☐ Medically important/ significant

Was the patient treated in the office No ☐ Yes ☐ Unknown ☐
Did the patient go the Emergency room No ☐ Yes ☐ Unknown ☐
Was the patient hospitalized No ☐ Yes ☐ Unknown ☐

Start of the AE (date): Clearing of the AE (date):

| Adverse Event description: |
|---|
| |

## 2. Eliciting medication:

Indication for use:

**Iron preparation:**

| Brand name / generic name | Administered dose | Route of application | Start date | End date | Duration | Batch number |
|---|---|---|---|---|---|---|
| | | | | | | |
| | | | | | | |

**Pre-medication:** no ☐ yes ☐ unknown ☐ If yes, please specify:

| Substance | Brand name / generic name | Administered dose (mg) | Route of application | Date of use (From-To) | Time of use |
|---|---|---|---|---|---|
| Antihistamines | | | | | |
| Corticosteroids | | | | | |
| Other substances | | | | | |
| | | | | | |

**Other medication (ACE inhibitors, beta blockers etc.):**

| Brand name / generic name | Administered dose | Route of application | Start date | End date | Duration |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |

## 3. Chronology:

3.1 Time to onset (Period between drug start and first symptoms): ☐ minutes: ☐ hours: ☐ days:
3.2 Time to recovery (Duration until symptoms subsided): ☐ minutes: ☐ hours: ☐ days:

3.3 Previous exposure with same iron medication: no ☐ yes ☐ Unknown ☐ If yes, please specify:
Date: Adverse reaction: no ☐ yes ☐ Unknown ☐
3.4 Previous exposure with other iron medication: no ☐ yes ☐ Unknown ☐ If yes, please specify:
Date: Adverse reaction: no ☐ yes ☐ Unknown ☐
3.5 Later exposure with the same iron medication: no ☐ yes ☐ Unknown ☐ If yes, please specify:
Date: Adverse reaction: no ☐ yes ☐ Unknown ☐
3.6 Later exposure with other iron medication: no ☐ yes ☐ Unknown ☐ If yes, please specify:
Date: Adverse reaction: no ☐ yes ☐ Unknown ☐

## 4. Clinical reaction:

4.1 Skin / mucosa associated symptoms:

| | | | | |
|---|---|---|---|---|
| Pruritus (itch): | no ☐ | yes ☐ | Unknown ☐ | If yes: local ☐ generalized ☐ |
| Flush face / upper chest: | no ☐ | yes ☐ | Unknown ☐ | |
| Flush generalized: | no ☐ | yes ☐ | Unknown ☐ | |
| Angioedema skin: | no ☐ | yes ☐ | Unknown ☐ | Location: |
| Urticaria: | no ☐ | yes ☐ | Unknown ☐ | Location: |
| Angioedema lips / eyelids: | no ☐ | yes ☐ | Unknown ☐ | |
| Angioedema oral mucosa: | no ☐ | yes ☐ | Unknown ☐ | |
| Angioedema tongue: | no ☐ | yes ☐ | Unknown ☐ | |

Other skin lesions, e.g. macules, papules, purpuric lesions, vesicles / bullae (blisters), pustules (please specify type, location):

4.2 Respiratory symptoms:

| | | | | |
|---|---|---|---|---|
| Cough: | no ☐ | yes ☐ | Unknown ☐ | |
| Dyspnea: | no ☐ | yes ☐ | Unknown ☐ | |
| Hyperventilation: | no ☐ | yes ☐ | Unknown ☐ | |
| Wheezing / bronchospasm: | no ☐ | yes ☐ | Unknown ☐ | PEFR or FEV1 (if known): l/s |
| Respiratory distress: | no ☐ | yes ☐ | Unknown ☐ | |
| Respiratory arrest: | no ☐ | yes ☐ | Unknown ☐ | |
| Rhinitis: | no ☐ | yes ☐ | Unknown ☐ | |
| Conjunctivitis: | no ☐ | yes ☐ | Unknown ☐ | |

Other (please specify):

4.3 Gastrointestinal symptoms:

| | | | |
|---|---|---|---|
| Nausea / emesis: | no ☐ | yes ☐ | Unknown ☐ |
| Abdominal pain / colic: | no ☐ | yes ☐ | Unknown ☐ |
| Diarrhea: | no ☐ | yes ☐ | Unknown ☐ |
| Stool incontinence: | no ☐ | yes ☐ | Unknown ☐ |

Other (please specify):

4.4 Cardiovascular symptoms:

| | | | | |
|---|---|---|---|---|
| Tachycardia: | no ☐ | yes ☐ | Unknown ☐ | Beats per minute: |
| Arrhythmia: | no ☐ | yes ☐ | Unknown ☐ | |
| Hypotension: | no ☐ | yes ☐ | Unknown ☐ | BP (systolic/diastolic): mmHg |
| Collapse: | no ☐ | yes ☐ | Unknown ☐ | |
| Loss of consciousness: | no ☐ | yes ☐ | Unknown ☐ | |
| Cardiovascular arrest: | no ☐ | yes ☐ | Unknown ☐ | |

- Other (please specify):

4.5 Other / general symptoms:

| | | | | | |
|---|---|---|---|---|---|
| Feeling of impending doom: | no ☐ | yes ☐ | Unknown ☐ | | |
| Metallic taste: | no ☐ | yes ☐ | Unknown ☐ | | |
| Urine incontinence: | no ☐ | yes ☐ | Unknown ☐ | | |
| Lower back pain: | no ☐ | yes ☐ | Unknown ☐ | | |
| Headache: | no ☐ | yes ☐ | Unknown ☐ | | |
| Fever: | no ☐ | yes ☐ | Unknown ☐ | Temperature: | °C |
| Lymph node swelling: | no ☐ | yes ☐ | Unknown ☐ | Localization: | |
| Arthralgia: | no ☐ | yes ☐ | Unknown ☐ | Localization: | |
| Arthritis: | no ☐ | yes ☐ | Unknown ☐ | Localization: | |
| Myalgia: | no ☐ | yes ☐ | Unknown ☐ | Localization: | |

## 5. Prior history / underlying disorders:

5.1 Co factors / risk factors:

| | | | | |
|---|---|---|---|---|
| Concurrent infection: | no ☐ | yes ☐ | Unknown ☐ | If yes, please specify: (e.g. viral, bacterial, other): |
| Exercises / effort / stress: | no ☐ | yes ☐ | Unknown ☐ | If yes, please specify: |
| Pregnancy: | no ☐ | yes ☐ | Unknown ☐ | If yes, week of gestation: |
| Alcohol: | no ☐ | yes ☐ | Unknown ☐ | |
| Smoking: | no ☐ | yes ☐ | Unknown ☐ | |
| Mastocytosis: | no ☐ | yes ☐ | Unknown ☐ | Mast cell tryptase level baseline: ng/ml |
| Other conditions: | no ☐ | yes ☐ | Unknown ☐ | If yes, please specify: |

5.2 Allergic disorders: Allergen:

| | | | | |
|---|---|---|---|---|
| Atopic allergy (hay fever): | no ☐ | yes ☐ | Unknown ☐ | If yes, please specify: |
| Asthma, allergic: | no ☐ | yes ☐ | Unknown ☐ | If yes, please specify: |
| Food hypersensitivity: | no ☐ | yes ☐ | Unknown ☐ | If yes, please specify: |
| Hymenoptera venom allergy: | no ☐ | yes ☐ | Unknown ☐ | If yes, please specify: |
| Drug hypersensitivity: | no ☐ | yes ☐ | Unknown ☐ | If yes, please specify: |
| Recurrent / chronic urticaria, angioedema: | no ☐ | yes ☐ | Unknown ☐ | If yes, please specify: |
| Recurrent / eczematous exanthemas: | no ☐ | yes ☐ | Unknown ☐ | If yes, please specify: |

5.3 Underlying disorders:

| | | | | |
|---|---|---|---|---|
| Cardiovascular disease: | no ☐ | yes ☐ | Unknown ☐ | If yes, please specify: |
| Respiratory disease: | no ☐ | yes ☐ | Unknown ☐ | If yes, please specify: |
| Kidney disease: | no ☐ | yes ☐ | Unknown ☐ | If yes, please specify: |
| Hematological disease: | no ☐ | yes ☐ | Unknown ☐ | If yes, please specify: |
| Malignancy: | no ☐ | yes ☐ | Unknown ☐ | If yes, please specify: |
| Autoimmune disorder: | no ☐ | yes ☐ | Unknown ☐ | If yes, please specify: |
| Psychological condition: | no ☐ | yes ☐ | Unknown ☐ | If yes, please specify: |

## 6. Diagnosis based on:

Clinical manifestation / chronology: no ☐ yes ☐

Photography of skin lesions: no ☐ yes ☐

Laboratory analysis:

| | | | | |
|---|---|---|---|---|
| Mast cell tryptase: | no ☐ | yes ☐ | Date / time: | Level: ng/ml |
| Hematology: | no ☐ | yes ☐ | Date / time: | |
| Chemistry: | no ☐ | yes ☐ | Date / time: | |

Skin test

- Prick test Negative ☐ Positive ☐ Unknown ☐
- Intradermal test Negative ☐ Positive ☐ Unknown ☐
- Lymphocyte Transformation Test Negative ☐ Positive ☐ Unknown ☐

Other (please specify):

## 7. Management of AE:

Stop of infusion: no ☐ yes ☐ Unknown ☐ After, time: minutes

Emergency treatment: no ☐ yes ☐ Unknown ☐ If yes, please specify:

| Substance | Brand name / generic name | Dose | Route of application | Date | Time |
|---|---|---|---|---|---|
| Antihistamines | | | | | |
| Epinephrine/adrenaline | | | | | |
| Corticosteroids | | | | | |
| Bronchodilators | | | | | |
| Shock treatment (plasma expander, IV fluids) | | | | | |

Other emergency treatment (e.g. infusion, oxygen etc.): no ☐ yes ☐ Unknown ☐ If yes, please specify:

Response to emergency treatment (e.g. infusion, oxygen etc.): no ☐ yes ☐ Unknown ☐

If no, please specify:

If yes, please specify (response):

In: ☐ minutes: ☐ hours: ☐ days:

## 8. Outcome:

| | | Date end | Time end |
|---|---|---|---|
| Complete recovery: | no ☐ yes ☐ | | |
| Surveillance: | no ☐ yes ☐ | | |
| Hospitalization: | no ☐ yes ☐ | | |
| Temporary sequelae: | no ☐ yes ☐ | | |
| Permanent sequelae: | no ☐ yes ☐ | | |
| Death: | no ☐ yes ☐ | | |
| Unknown: | ☐ | | |

## 9. Causal relationship between suspected medication and AE:

☐ Certain (definite relationship; plausible time relationship; no other plausible explanations)
☐ Probable/Likely (reasonable time relationship; unlikely to be attributed to other plausible explanations)
☐ Possible (reasonable time relationship; could be attributed to other explanations)
☐ Unlikely (timely relationship improbable (but not impossible); other plausible explanations)
☐ Not related (clearly no relationship)

## 10. Reporting Physician:

Name: E mail: Phone no.

Address: Fax no.

## 11. Comments:

**Please provide all available information and send to completed form. Attach any applicable supporting documentation if applicable** (such as pictures, autopsy report, hospital discharge summary, laboratory values) and send to safety@viforpharma.com or fax to +41 58851 8659.

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| | |
|---|---|
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## Targeted Questionnaire for Evaluating Infection Related Events

| **Vifor Coding Number:** | | | | | | |
|---|---|---|---|---|---|---|
| **1. Patient Demography** | | **Data available** | ☐ **No** | ☐ **Yes (please complete the section below)** | | |
| Initials | Gender: | F ☐ M ☐ | Age: | | Year of Birth: | |
| | Weight: | kg | Age Group: | | Body Mass Index: | |
| | Height: | cm | | | | |
| | Pregnancy: | No ☐ Yes☐ | Trimester: | ☐ 1st ☐ 2nd ☐ 3rd | Estimated date of birth: | |

| **2. Medical History and Risk Factors** | **Data available** | ☐ **No** | ☐ **Yes (please complete the section below)** |
|---|---|---|---|
| Information on medical history incl. concomitant disorders (diagnoses, family medical history, pregnancies, risk factors):<br>Please indicate if the following conditions are either part of the patient's medical history or are still active conditions. | | | |
| **Diagnosis/Disease** | | | |
| Medical history of | ☐ No<br>☐ Yes (specify):<br>☐ Cardiovascular disease<br>☐ Respiratory disease<br>☐ Diabetes mellitus<br>☐ Renal disease<br>☐ Hepatic/liver diseases<br>☐ Pancreatic disorder<br>☐ Auto-immune disease<br>☐ HIV infection<br>☐ Malnutrition<br>☐ Allergies<br>☐ Other | | |
| Procedures/Treatments | ☐ No<br>☐ Yes (specify):<br>☐ Endoscopic procedures<br>☐ Splenectomy<br>☐ Organ transplantation<br>☐ Haematological stem cell transplantation<br>☐ Dialysis<br>☐ Haemodialysis ☐ Peritoneal Dialysis<br>☐ Other surgical procedures<br>☐ Blood transfusion<br>☐ Anti-TNF antibodies treatment<br>☐ Cytotoxic therapy<br>☐ Steroids treatment<br>☐ Other immunosuppressant drugs<br>☐ Other | | |
| Catheter/Port Use | ☐ No<br>☐ Yes (specify):<br>☐ Short-term urinary catheter<br>☐ Long-term urinary catheter<br>☐ Other catheter/port | | |
| Any relevant risk factors for infections in this patient | ☐ No<br>☐ Yes<br>☐ Recent foreign travel<br>☐ Previous infection<br>☐ IV drug abuse<br>☐ Other | | |

Based on the Global Targeted Questionnaire for Evaluating Infection Related Events
Version 1.1 (2017.09)

| | |
|---|---|
| **Vifor Pharma Ltd.**<br>**Fax Nr.: +41 58851 8659**<br>**E-mail: safety@viforpharma.com** | VIFOR PHARMA |

| **3. Relevant Drug History** | **Data available** | ☐ **No** | ☐ **Yes (please complete the section below)** | | |
|---|---|---|---|---|---|
| **Enter medication other than those taken to treat the AE:** (If required please complete a separate page or attach the patient's drug list) | | | | | |
| Name of Product (Trade Name or Active Ingredient) | Dosage Regimen | Duration of Administration (hours:min) | Start Date (dd/mmm/yyyy) | Stop Date (dd/mmm/yyyy) | Indication |
| 1. | | | | | |
| 2. | | | | | |
| 3. | | | | | |
| 4. | | | | | |
| 5. | | | | | |
| Suspected causal relationship also with Product Nr. 1. ☐ 2. ☐3. ☐4. ☐ 5. ☐ | | Previously used? ☐ No ☐ Yes | Tolerated? ☐ No ☐ Yes | Re-exposure? ☐ No ☐ Yes | |
| Previous exposure to any iron product (PO; IM; IV)? | | ☐ YES (please specify below) | | ☐ NO | |
| Name of Product (Trade Name or Active Ingredient) | Dosage Regimen | Dilution (if applicable) | Start Date (dd/mmm/yyyy) | Stop Date (dd/mmm/yyyy) | If an adverse event occurred, please specify |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

| **4. Information on Suspect Iron Product** | **Data available** | ☐ **No** | ☐ **Yes (please complete the section below)** |
|---|---|---|---|
| Trade name: | Active Ingredient: | | Batch Nr.: |
| Indication (with underlying disease): | | | |
| Administration: | Dosage: mg Iron<br>Start Date: (dd/mmm/yyyy)<br>Start Time: (hours:min): | | Frequency of administration:<br>End Date: (dd/mmm/yyyy)<br>Stop Time:(hours:min): |
| Mode of Application | ☐ IV drip infusion<br>☐ IV bolus injection<br>☐ intramuscular<br>☐ oral | | Dilution: ml in ml sterile 0.9% NaCl solution<br>Duration of administration (hours:min):<br>Duration of administration (hours:min):<br>Duration of administration (hours:min):<br>Dosage form: |
| Therapy with suspected drug? | ☐ Withdrawn<br>☐ No<br>☐ Yes (specify):<br>☐ resolution of suspected ADR<br>☐ improvement of suspected ADR<br>☐ no improvement of suspected ADR<br>☐ Reintroduced<br>☐ No<br>☐ Yes (specify):<br>☐ recurrence of suspected ADR<br>☐ Dosage reduced due to ADR?<br>☐ indicate the new dose | | |

| | |
|---|---|
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| **5. Adverse Event Information** | **Data available** | ☐ **No** | ☐ **Yes (please complete the section below)** |
|---|---|---|---|

Enter information about adverse event(s) which occurred during/after administration of suspected iron product: Diagnose or/and any symptoms / signs, body site, progression, reoccurrence after further processing

| **Nr.** | **Adverse Event** | |
|---|---|---|

**Adverse Event Description:**

| | | |
|---|---|---|
| Time<br>of occurrence | Start Date/ Start Time<br>/<br>(dd/mmm/yyyy) /(hours:min) | AE occurred<br>☐ during administration<br>☐ after administration |
| Outcome | ☐ Ongoing<br>☐ Recovering<br>☐ Recovered without Sequelae Stop Date/Stop Time /<br>☐ Recovered with Sequelae (specify):<br>☐ Fatal/Death ☐ Related to Adverse Event Nr. ☐ other<br>☐ Unknown | |
| Seriousness | ☐ Non-serious<br>☐ Serious (If serious, please complete following):<br>☐ Death Date Autopsy ☐ No ☐ Yes (please provide copy of autopsy report)<br>☐ Life-threatening<br>☐ Hospitalisation (> 24 h)<br>☐ Prolongation of existing hospitalisation (> 24 h)<br>☐ Persistent or significant disability/incapacity<br>☐ Congenital anomaly/Birth defect<br>☐ Medical important (e.g., patient requires intervention to prevent one of outcomes listed above) | |
| Causal Relationship | ☐ Certain<br>☐ Probable/ Likely (reasonable time relationship; unlikely to be attributed to other plausible explanation)<br>☐ Possible (reasonable time relationship; could be attributed to other plausible explanation)<br>☐ Unlikely<br>☐ Not related<br>☐ Un-assessable (To be used for, e.g.,Pregnancy, medication errors etc.,) | |
| Baseline/Post-event investigations<br>(if appropriate, please attach results | ☐ No<br>☐ Yes (specify): ☐ Laboratory **(please complete section 6)**<br>☐ other | |
| Corrective therapy (treatment required to treat the reported AE?) | ☐ No<br>☐ Yes (specify medication administered for treatment):<br>Name of product: Daily Dose Route/Form<br>Start Date Stop Date<br>Name of product: Daily Dose Route/Form<br>Start Date Stop Date | |
| Non-drug treatment received? | ☐ No<br>☐ Yes (specify): | |

| | |
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**6. Laboratory Test/Investigation Results** **Data available** ☐ **No** ☐ **Yes (please complete the section below)**

Please provide SI (International Systems of Units) if available. Otherwise, as reported.

☐ Labs Attached
(tick box if lab results are attached)

| **Laboratory Test** | **Baseline Values** (Prior to the Event) | | **Control Values** (After the Event) | | Reference Range (if applicable) | Pending? |
|---|---|---|---|---|---|---|
| | Date (dd/mmm/yyyy) | Value (include units) | Date (dd/mmm/yyyy) | Value (include units) | | |
| C-Reactive Protein (CRP) | | | | | | ☐ Yes |
| Erythrocyte sedimentation rate (ESR) | | | | | | ☐ Yes |
| White Blood Cell count | | | | | | ☐ Yes |
| Neutrophil count | | | | | | ☐ Yes |
| Eosinophil count | | | | | | ☐ Yes |
| Lymphocyte count | | | | | | ☐ Yes |
| PCR (specify): | | | | | | ☐ Yes |
| Blood culture | | | | | | ☐ Yes |
| Histology (specify): | | | | | | ☐ Yes |
| Chest x-ray | | | | | | ☐ Yes |
| CT Scan | | | | | | ☐ Yes |
| MRI | | | | | | ☐ Yes |
| Ultrasound | | | | | | ☐ Yes |
| Other (Please specify below all other relevant tests:) | | | | | | |
| : | | | | | | ☐ Yes |
| : | | | | | | ☐ Yes |
| : | | | | | | ☐ Yes |
| : | | | | | | ☐ Yes |

**7. Other Comments:**

**8. Reporter Details**

| | |
|---|---|
| Name of Reporter: | Profession of Reporter: |
| Name & Address of the Institution: | Country: |
| | Telephone: |
| | Fax: |
| | e-mail: |

**Please provide all available information and send completed form. Attach any applicable supporting documentation if applicable** (such as pictures, autopsy report, hospital discharge summary, laboratory values).

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## Annex 5 Protocols for Proposed and Ongoing Studies in RMP Part IV

Not applicable.

## Annex 6A Details of Proposed Additional Risk Minimisation Activities

All EU registered IV iron medicinal products, including Venofer, have been evaluated as part of an Article 31 referral procedure (EMEA/H/A-31/1322) by the EMA, whereby the risk of serious allergic reactions with the use of these products was investigated. CHMP adopted an opinion on 27 June 2013, which was endorsed by the European Commission on 13 September 2013.

The conclusion of the EMA referral procedure was that the benefit/risk balance of IV iron containing medicinal products remained positive as the benefits continue to outweigh the risks in the treatment of ID when the oral route is insufficient or poorly tolerated. However, additional risk minimisation measures were requested in order to address the risk of hypersensitivity events to all patients including administration in pregnancy. These measures included the distribution of a Direct Healthcare Professional Communication (DHPC) as well as educational materials for prescribers and patients.

A consortium of MAHs was formed (including Vifor Pharma, Sanofi, Pharmacosmos, Takeda, Mylan, Fresenius Medical Care, Medice, Alternova, Teva, Rafarm & EMP, Pharmamatch, Actavis (Arrow Generics), Normon, Combino-Pharm and Genfarma) to distribute 1 single common DHPC. The resulting joint DHPC was approved by National Competent Authorities (NCAs) and distributed to relevant healthcare providers by the end of 2013 in line with the communicated action plan. More companies joined the consortium subsequently (Panpharma, Acino, Sandoz France).

The educational materials were also a joint effort of the consortium and their distribution was completed in 2015.

The DHPC and the healthcare provider and patient educational materials in English which the translations were based on are provided in Annex 6B and Annex 6C. Some of the NCAs made revisions to the translations resulting in deviations from the English template.

**IV Iron is** used to treat iron deficiency when oral preparations are ineffective or cannot be used.

**IV Iron** can cause allergic reactions and must be administered by persons trained to evaluate and manage these reactions.

In some patients these allergic reactions can become severe or life-threatening (known as anaphylactic reactions) and can cause problems with your heart and blood pressure and/or cause you to faint or lose consciousness.

**Reporting of side effects**

If you get any side effects, talk to your Doctor or nurse. This includes any possible side effects even if they are not listed in this leaflet. You can also report side effects directly via {the national reporting system}.

# Intravenous (IV) Iron

**Important Information for Patients About the Possible Risk of Serious Allergic Reactions with IV iron (medication given by needle into the vein)**

This information has been prepared and provided to you by the makers of IV iron in Europe.

**Please read this leaflet carefully and discuss any questions you may have with your Doctor.**

**You may have an increased risk of having an allergic) reaction if you have**:

- known allergies including drug allergies
- a history of severe asthma, eczema or other allergies (for example dust, pollen, pet dander) or
- immune or inflammatory conditions (e.g. rheumatoid arthritis, lupus erythematosus and others)

**You should tell your doctor before they prescribe or give you IV Iron** if you have any of these allergies or conditions.

Your Doctor will decide whether the benefit to you is greater than the risk

**You should not be prescribed or given an IV Iron if**:

- you are allergic (hypersensitive) to the product or any of the other ingredients of this medicine
- you have experienced serious allergic (hypersensitive) reactions to other I.V iron treatments in the past*
- you have iron overload (too much iron in your body)
- your anaemia is not caused by iron deficiency

**You should tell your doctor before they prescribe/administer an IV Iron** if you have any of these allergies or conditions.

*** It is important to know that a reaction can still happen even if you have not had any problems in the past with IV iron.**

**Pregnancy:** IV iron should not be used during pregnancy unless clearly necessary. If you are pregnant or think you could be pregnant, it is important to discuss this with your doctor.

**You should contact your Doctor or Nurse immediately if:**

- you have any signs or symptoms of an allergic reaction during or shortly after treatment with IV Iron

For example: hives or rash, itching, dizziness, light-headedness, swelling of the lips, tongue, throat or body, difficulty breathing, shortness of breath or wheezing.

- Your Doctor will monitor you for signs and symptoms of an allergic reaction for at least 30 minutes after each time IV iron is given to you.

Further to the European Medicine Agency (EMA) referral, IV iron medicinal products are under additional monitoring. The EMA considers the benefit/risk of IV iron products favourable when oral route is insufficient or poorly tolerated.

Parenterally administered iron medicinal products are used to treat iron deficiency when oral preparations are ineffective or cannot be used.

Parenterally administered iron preparations can cause hypersensitivity reactions including serious and potentially fatal anaphylactic/anaphylactoid reactions.

This essential prescription information guide can assist you in managing and minimising this risk.

**Contraindications to the use of IV iron include:**

- hypersensitivity to the active substance or any of its excipients.
- known serious hypersensitivity to other parenteral iron products.
- anaemia not caused by iron deficiency
- evidence of iron overload or disturbances in the utilisation of iron.

See the Summary of Product Characteristics of individual IV iron medicinal products for full product information.

Reporting adverse drug reaction is mandatory by law and allows continued monitoring of the benefit/risk balance of the medicinal product. Please report any suspect adverse drug reaction to either the marketing authorisation holder (MAH) or to the local regulatory authority according the local requirements in your country. When reporting please ensure to include the name of the specific product administered. The contact details of MAH and local representative are mentioned in the Summary of Product Characteristics as well as Patient Information Leaflet.

# IV iron ▼

## Essential Prescription and Administration Information to Minimise the Risk of Serious Hypersensitivity Reactions

This essential prescription information guide is brought to you by the European IV iron suppliers.

**Please read carefully and review each time when prescribing IV iron medicinal products.**

## BEFORE each administration of IV iron, you should inform your patient so that they are aware that…

…parenterally administered iron preparations can cause hypersensitivity reactions including serious and potentially fatal anaphylactic/anaphylactoid reactions.

…these reactions have also been reported after previously uneventful doses of IV iron.

…they may have an increased risk of experiencing a hypersensitivity reaction if they have:

- known allergies including drug allergies*
- a history of severe asthma*, eczema* or other atopic allergies* or
- immune or inflammatory conditions (e.g. rheumatoid arthritis, lupus erythematosus)*.

*In these patients, IV iron products should only be used if the benefit is clearly judged to outweigh the potential risk.

…IV iron should not be used during pregnancy unless clearly necessary. Treatment should be confined to the 2nd-3rd trimester if the benefit is judged to outweigh the potential risk for both the mother and the foetus.

…they should report any signs or symptoms suggestive of a hypersensitivity reaction (e.g.: hives, pruritus, dyspnoea, wheezing, swelling of the lips, tongue, throat or body) to their doctor/nurse immediately.

The patient should also be given a copy of the patient information leaflet provided with the individual IV iron product to be administered.

## …and remember that IV iron is contraindicated and should not be administered if your patient…

…has known hypersensitivity to the IV iron product, the active substance or to any of its excipients.

…has previously experienced a serious hypersensitivity reaction to any IV iron preparations.

…has anaemia not caused by iron deficiency.

…has evidence of iron overload or disturbances in the utilisation of iron.

See the Summary of Product Characteristics of individual IV iron medicinal products for full product information.

## BEFORE each administration of IV iron make sure that…

…staff trained to evaluate and manage anaphylactic reactions are immediately available.

…cardio-pulmonary resuscitation facilities and equipment for handling acute anaphylactic/anaphylactoid reactions, including an injectable 1:1000 adrenaline solution, are immediately available onsite. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

## DURING administration of IV iron remember that…

...if hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately and appropriate management initiated.

…IV iron products should be administered in accordance with the posology and method of administration described in the product information for each individual product.

## AFTER you have administered IV iron…

…. the patient must be closely observed for signs and symptoms of a hypersensitivity reactions for at least 30 minutes after each administration.


# PASS Information

| | |
|---|---|
| **Title** | Intravenous Iron Postauthorisation Safety Study (PASS): Evaluation of the Risk of Severe Hypersensitivity Reactions |
| **Version identifier of the final study report** | Final Report V1.3 |
| **Date of last version of the final study report** | 20 November 2020 |
| **EU PAS Register number** | EUPAS20720 |
| **Active substance** | Intravenous iron products (ATC code: B03AC, Iron, parenteral preparations):<br>Iron(III)-hydroxide dextran complex<br>Iron sucrose complex/iron(III)-hydroxide sucrose complex<br>Ferric carboxymaltose complex<br>Iron(III) isomaltoside complex<br>Sodium ferric gluconate complex |
| **Medicinal product** | Medicinal products in the countries targeted in this study are listed by International Nonproprietary Names and Invented Names (Note: Invented names are those of medicinal products marketed by members of the Iron Consortium. The study will also include equivalent medicinal products of pharmaceutical companies that are not part of the IV Iron Consortium.)<br>**Denmark:**<br>▪ Iron(III)-hydroxide dextran complex: CosmoFer<br>▪ Iron sucrose complex: Venofer<br>▪ Ferric carboxymaltose: Ferinject<br>▪ Iron(III) isomaltoside complex: Monofer<br>**France:**<br>▪ Iron(III)-hydroxide dextran complex: Ferrisat<br>▪ Iron sucrose complex: Venofer, Fer Mylan, Fer Panpharma, Fer Arrow, Fer Sandoz<br>▪ Ferric carboxymaltose: Ferinject<br>**Germany:**<br>▪ Iron(III)-hydroxide dextran complex: CosmoFer<br>▪ Iron sucrose complex: Venofer, FerMed<br>▪ Ferric carboxymaltose: Ferinject<br>▪ Iron(III) isomaltoside complex: Monofer<br>▪ Sodium ferric gluconate complex: Ferrlecit<br>**The Netherlands:**<br>▪ Iron(III)-hydroxide dextran complex: CosmoFer<br>▪ Iron sucrose complex: Ferracin, Venofer, IJzerhydroxide saccharose complex Teva |

| | |
|---|---|
| | ▪ Ferric carboxymaltose: Ferinject<br>▪ Iron(III) isomaltoside complex: Monofer |
| | **Sweden:**<br>▪ Iron(III)-hydroxide dextran complex: CosmoFer<br>▪ Iron sucrose complex: Venofer, Järnsackaros Rechon<br>▪ Ferric carboxymaltose: Ferinject<br>Iron(III) isomaltoside complex: Monofer/Diafer |
| **Product reference** | Note: Product references listed are those for products produced by members of the IV Iron Consortium. The study will also include exposure to equivalent medicinal products of pharmaceutical companies that are not part of the IV Iron Consortium.<br>FerMed: 71610.00.00 (Germany authorisation number)<br>Ferrovin: 96896/13/03-02-16, 78933/11/05-04-2013 (Greece authorisation number)<br>Ferrovin: 021660/ 09-01-2013 (Cyprus authorisation number)<br>Venofer:<br>▪ 31111 (Denmark authorisation number)<br>▪ 3400957128340 (France authorisation number)<br>▪ 6462062.00.00 (Germany authorisation number)<br>▪ RVG 20690 (The Netherlands authorisation number)<br>▪ 15754 (Sweden authorisation number)<br>Ferinject:<br>▪ 39254 (Denmark authorisation number)<br>▪ 66227.00.00 (Germany authorisation number)<br>▪ 33865 (The Netherlands authorisation number)<br>▪ France authorisation numbers:<br>– Ferinject 1 x 2 mL: 34009 386 812 4 6<br>– Ferinject 1 x 10 mL: 34009 386 924 7 1<br>– Ferinject 2 x 2 mL: 34009 219 393 1 6<br>– Ferinject 2 x 10 mL: 34009 219 394 8 4<br>– Ferinject 5 x 2 mL: 34009 386 823 6 6<br>– Ferinject 5 x 10 mL: 34009 386 933 6 2<br>– Ferinject 1 x 20 mL: 34009 585 988 5 2<br>▪ 23738 (Sweden authorisation number)<br>Monofer:<br>▪ 27791 (Sweden authorisation number)<br>CosmoFer:<br>▪ 23462 (Sweden authorisation number)<br>Fercayl:<br>▪ Fercayl 100 mg/2 mL: BE168497 (Belgian authorisation number)<br>▪ Ferrlecit:<br>▪ 638 5744.00.00, 644 1686.00.00 (Germany authorisation numbers)<br>Ferracin:<br>▪ Ferracin oplossing voor injectie/concentraat voor oplossing voor infusie: RVG 112056 (The Netherlands authorisation number) |

| | |
|---|---|
| | **IJzerhydroxide saccharose complex Teva 20 mg/mL, solution for injection/concentrate for solution for infusion: RVG 33727 (The Netherlands authorisation number)** |
| **Procedure number** | EMEA/H/A-31/1322 |
| **Marketing authorisation holder(s)** | IV Iron Marketing Authorisation Holders Consortium, comprising the following marketing authorisation holders (MAHs): Accord Healthcare Limited, Acino AG, Arrow Génériques, Baxter, Generis Farmacéutica SA, Altan Pharmaceuticals SAU, Laboratoires Sterop SA, Medice Arzneimittel Puetter GmbH & Co. KG, Mylan SAS, Orifarm Generics A/S, Panmedica (Panpharma SA), Pharmachemie BV (Teva), Pharmacosmos A/S, Rafarm SA, Sandoz SAS, Sanofi Aventis Groupe, and Vifor France |
| **Joint PASS** | Yes |
| **Research question and objectives** | To assess the risk of anaphylactic or severe immediate hypersensitivity reactions (hereafter, "anaphylaxis" or "anaphylactic reactions") on the day of or the day after the first IV iron use through the following parameters:<br>▪ Incidence proportion of anaphylactic reactions in patients with a first-recorded IV iron (new users) overall, by group of IV iron product—iron(III)-hydroxide dextran complex and non-dextran IV iron products—and by the individual IV iron types listed below:<br>– Iron(III)-hydroxide dextran complex<br>– Iron sucrose complex/iron(III)-hydroxide sucrose complex<br>– Ferric carboxymaltose complex<br>– Iron(III) isomaltoside complex<br>– Sodium ferric gluconate complex<br>▪ Risk ratios of anaphylactic reactions in patients with a first-recorded IV iron (new users), by group of IV iron products—iron(III)-hydroxide dextran complex versus non-dextran IV iron products, and by the individual IV iron types (as listed above) using iron sucrose complex/iron(III)-hydroxide sucrose complex as the comparator. |
| **Country(-ies) of study** | Denmark<br>France<br>Germany<br>The Netherlands<br>Sweden |
| **Author** | Lia Gutierrez, BSN, MPH and Joan Fortuny, MD, PhD; on behalf of the IV iron PASS research team<br>RTI Health Solutions<br>Av. Diagonal 605, 9-1, 08028 Barcelona SPAIN<br>Phone: +34.93.241.77.64<br>Fax: +34.93.760.85.07<br>E-mail: lgutierrez@rti.org |

## Marketing authorisation holder(s)

| | |
|---|---|
| **Marketing authorisation holder(s)** | [redacted] |
| **MAH contact person** | [redacted] |

## Table of Contents

# List of Tables



# List of Figures

# 1 Abstract

**Title**: Intravenous Iron Postauthorisation Safety Study (PASS): Evaluation of the Risk of Severe Hypersensitivity Reactions

Lia Gutierrez, BSN, MPH and Joan Fortuny, MD, PhD; RTI Health Solutions, on behalf of the IV iron PASS research team.

**Keywords**: Intravenous iron, anaphylaxis, severe hypersensitivity reactions, cohort study, multidatabase study

**Rationale and background**: Severe hypersensitivity reactions/anaphylaxis in intravenous (IV) iron treatment are rare. However, this safety concern is poorly characterised in Europe. A multidatabase study approach was required to evaluate this rare outcome. This PASS was requested by the European Medicines Agency Committee for Medicinal Products for Human Use to assess the risk of anaphylaxis in IV iron users in Europe.

**Research question and objectives**: The primary objective of the study was to assess the risk of anaphylaxis, overall and by groups (iron non-dextrans and iron dextran) and types of IV iron (using iron sucrose as the common reference).

**Study design**: Multinational cohort study of patients initiating IV iron treatment, conducted in populations covered by sources of routinely collected health and administrative data in Europe. Given that the risk of anaphylactic reactions rapidly decreases after the first administration of a drug (i.e., due to the depletion of susceptibles), the study used a "new-user" design. Risk was estimated using beta-binomial derived combined incidence proportions (IPs) among patients receiving any IV iron medication overall, by groups and individual types. Risk ratios and 95% confidence intervals (CIs) were calculated to compare the risk of anaphylactic reactions at the first (main analysis), second, and third or subsequent IV iron exposure overall and by IV iron groups and individual types. To put the study findings into context, the risk of anaphylaxis was also assessed among users of IV penicillins.

**Setting**: The study used data from populations covered in six European databases in five countries. Researchers with access to the study databases in Denmark, France, Germany, the Netherlands, and Sweden collaborated with RTI Health Solutions (Spain) as the coordinating centre. The study period varied across data sources, spanning overall from 1999 to 2017.

**Patients and study size, including dropouts**: The study identified 304,210 patients with a first-recorded IV iron treatment of whom 6,367 (2.1%) were iron dextran users. For the second IV iron treatments, there were 148,099 patients of whom iron dextran users represented 2.1% and for the third and subsequent treatments 3,103,486 treatments in 105,634 patients were captured with iron dextran accounting for 0.3%. For the IV penicillins cohort, there were 231,294 first treatments and 984,000 total treatments.

**Variables and data sources**: Data sources were the Danish national and regional linked registers and databases, the Système National des Données de Santé (SNDS, French National Health Care Insurance System Database), the German Pharmacoepidemiological Research Database (GePaRD), the Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme (KfH QiN) registry in Germany, the PHARMO Database Network in the Netherlands (PHARMO-NL) and the Swedish national registers. Data from the Oldenburg University Hospital in Germany were used to validate the case-identification algorithm adapted to the GePaRD data. The German Institute of Medical Documentation and Information (DIMDI-DaTraV database) could not contribute to the study because of lack of resources.

The study outcome was anaphylaxis identified through a case-identification algorithm based on a previously validated algorithm.

Exposure to IV iron was captured through drug-dispensing data from outpatient pharmacy settings and, in two data sources, from inpatient drug administration. Analyses were conducted at first, second, and third or subsequent IV iron treatments. Validation of potential anaphylaxis events was conducted in the Central Denmark Region and the PHARMO-NL by review of medical records. Validation of the case-identification algorithm was performed through Oldenburg Hospital data.

**Results**: IV iron treatment in this study reflects only partial use in each country, mostly from ambulatory drug-dispensing data. A high proportion of all third or subsequent IV iron treatments (84%) occurred in the KfH QiN dialysis registry in Germany.

At first IV iron treatment, between 13 and 16 potential cases of anaphylaxis were identified. The resulting IP ranged from 0.38 (95% CI, 0.17-0.88) to 0.51 (95% CI, 0.28-0.97)[1] per 10,000 first treatments (the IP is reported as a range owing to data-protection rules for counts between 1 and 4). No events among iron dextran users were identified at first IV iron treatment. Risk estimates by groups and types of IV iron were based on a very small number of events.

At first IV penicillins treatment, 30 potential cases of anaphylaxis were identified. The resulting IP was 1.16 (95% CI, 0.78-1.73)[1] per 10,000 treatments.

**Discussion**: The study found an overall IP of anaphylaxis ranging from 0.38 to 0.51 per 10,000 first treatments, from 0.44 to 0.55 for iron non-dextrans and not assessable for iron dextran. These IPs were lower than the estimates of 2 and 6.8 per 10,000 first treatments (IV iron non-dextrans and iron dextran, respectively) reported in studies in the United States (US) (Walsh et al., 2016; Wang et al., 2015). The IP of anaphylaxis in users of penicillins in our study was consistent with the incidences reported in the literature.

[1] IPs and 95% CIs estimates in the abstract have been corrected because they were inadvertently not updated in the previous March 24, 2020 and May 06, 2020 final study reports. Please note that all estimates in the text and tables of the report have been reported correctly in all versions of the report.

Owing to the small number of events, the originally planned adjusted analyses, including comparison of IV iron types, could not be performed. Results presented are potentially subject to confounding.

A potential for misclassification of repeated users of IV iron as first users, because of the impossibility of capturing use in-hospital and in specialty clinics in most data sources, may have resulted in lower IPs of anaphylaxis.

Due to methodological limitations, the study cannot exclude the possibility of a high risk of anaphylaxis associated with the administration of injectable iron and whether there are differences in the risk between the different types of IV iron. Some sensitivity analyses yielded risk ratios above the unity when comparing the risk of anaphylaxis for iron dextran versus iron non-dextrans; however, these analyses were based on very few cases, all of which had important validity concerns, and therefore conclusions cannot be drawn.

**Marketing authorisation holder(s)**: IV Iron Marketing Authorisation Holders Consortium, comprising the following marketing authorisation holders (MAHs): Accord Healthcare Limited, Acino AG, Arrow Génériques, Baxter, Generis Farmacéutica SA, Altan Pharmaceuticals SAU., Laboratoires Sterop SA, Medice Arzneimittel Puetter GmbH & Co. KG, Mylan SAS, Orifarm Generics A/S, Panmedica (Panpharma SA), Pharmachemie BV (Teva), Pharmacosmos A/S, Rafarm SA, Sandoz SAS, Sanofi Aventis Groupe, and Vifor France.

**Names and affiliations of principal investigators**:

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- University of Bordeaux, INSERM CIC1401, Bordeaux PharmacoEpi Research Unit, Patrick Blin, MD, MSc
- Leibniz Institute for Prevention Research and Epidemiology BIPS, Tania Schink, MPH, PhD
- Carl von Ossietzky University Oldenburg, Antje Timmer, MD, MSc, Prof. Dr. med, Clinical Epidemiologist
- University Hospital of Cologne, Gero von Gersdorff, MD, head of QiN-group
- German Institute of Medical Documentation and Information, Jochen Dreß, MD
- Karolinska Institutet, Professor Helle Kieler, MD, PhD, Head of Centre for Pharmacoepidemiology

# Approval Page: Research Partners

**Project Title: Intravenous Iron Postauthorisation Safety Study (PASS): Evaluation of the Risk of Severe Hypersensitivity Reactions**

| | |
|---|---|
| Authors and reviewers | Lia Gutierrez, BScN, MPH; Joan Fortuny, MD, PhD; Catherine Johannes; PhD, Lawrence Rasouliyan, MPH; Kenneth Rothman, DrPH; Susana Perez-Gutthann, MD, MPH, PhD<br>(RTI Health Solutions)<br>Vera Ehrenstein, MPH, DSc; Gunnar Toft, PhD, DMSc; Henrik Sørensen, MD, PhD, DMSc<br>(Aarhus University Hospital, Department of Clinical Epidemiology, Denmark)<br>Nicholas Moore, MD, PhD; Patrick Blin, MD, MSc; Régis Lassalle MSc; Cécile Droz-Perroteau, PhD<br>(University of Bordeaux, INSERM CIC1401, Bordeaux PharmacoEpi Research Unit, France)<br>Tania Schink, MPH, PhD<br>(Leibniz-Institut für Präventionsforschung und Epidemiologie - BIPS, Germany)<br>Antje Timmer, MD, MSc<br>(Carl von Ossietzky University of Oldenburg, Germany)<br>Gero von Gersdorff, MD; Mathias Schaller, PhD; Katherine Rascher, PhD<br>(University Hospital of Cologne, Department II of Internal Medicine – QiN-group in collaboration with Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme [KfH QiN], Germany)<br>Jetty Overbeek, PhD; Lisa Smits, MSc; Fernie Penning-van Beest, PhD; Ron Herings, PharmD, PhD<br>(PHARMO Institute for Drug Outcomes Research, the Netherlands)<br>Jochen Dreß, MD<br>(Information system for health care data (data transparency) of the German Institute of Medical Documentation and Information) (DIMDI-DaTraV), Germany<br>Helle Kieler, MD, PhD, Professor, Marie Linder MSc, PhD, Zoltan Thinsz BSc, Ingvild Odsbu, MScPharm PhD<br>(Centre for Pharmacoepidemiology, Karolinska Institutet)<br><br>**The members of the IV Iron Consortium and Michael Forstner as Coordinator of the Consortium have reviewed this report** |
| Version and date: | Final Report Version 1.3, 20 November 2020 |

On behalf of the IV iron PASS Research team:

Susana Perez-Gutthann

20 NOV 2020

Susana Perez-Gutthann, MD, MPH, PhD, FISPE, FRCP Vice President and Global Head of Epidemiology

*Date*

# Approval Page: IV Iron Consortium

**Project Title: Intravenous Iron Postauthorisation Safety Study (PASS): Evaluation of the Risk of Severe Hypersensitivity Reactions**

| | |
|---|---|
| Authors and reviewers: | Lia Gutierrez, BScN, Joan Fortuny, MD, PhD; MPH; Catherine Johannes; PhD, Lawrence Rasouliyan, MPH; Kenneth Rothman, DrPH; Susana Perez-Gutthann, MD, MPH, PhD<br>(RTI Health Solutions)<br>Vera Ehrenstein, MPH, DSc; Gunnar Toft, PhD, DMSc; Henrik Sørensen, MD, PhD, DMSc<br>(Aarhus University Hospital, Department of Clinical Epidemiology, Denmark)<br>Nicholas Moore, MD, PhD; Patrick Blin, MD, MSc; Régis Lassalle, MSc; Cécile Droz-Perroteau, PhD<br>(University of Bordeaux, INSERM CIC1401, Bordeaux PharmacoEpi Research Unit, France)<br>Tania Schink, MPD, PhD<br>(Leibniz-Institut für Präventionsforschung und Epidemiologie - BIPS, Germany)<br>Antje Timmer, MD, MSc<br>(University of Oldenburg, Germany)<br>Gero von Gersdorff, MD; Mathias Schaller PhD; Katherine Rascher, PhD<br>(University Hospital of Cologne, Department II of Internal Medicine – QiN-group in collaboration with Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme [KfH QiN], Germany)<br>Jetty Overbeek, PhD; Lisa Smits, MSc; Fernie Penning-van Beest, PhD; Ron Herings, PharmD, PhD<br>(PHARMO Institute for Drug Outcomes Research, the Netherlands)<br>Jochen Dreß, MD<br>(Information system for health care data (data transparency) of the German Institute of Medical Documentation and Information) (DIMDI-DaTraV), Germany<br>Helle Kieler, MD, PhD, Professor, Marie Linder, MSc, PhD, Zoltan Thinsz, BSc, Ingvild Odsbu, MScPharm PhD<br>(Centre for Pharmacoepidemiology, Karolinska Institutet)<br><br>**The members of the IV Iron Consortium and Michael Forstner as Coordinator of the Consortium have reviewed this report** |
| Version and date: | Final Report Version 1.3, 20 November 2020 |

On behalf of the IV Iron MAH Consortium

20-Nov-2020

Michael Forstner, MSc, PhD
Managing Director
Mesama Consulting, Switzerland.

*Date*

# 2 List of Abbreviations

| | |
|---|---|
| ATC | Anatomical Therapeutic Chemical (classification system) |
| BIPS | Leibniz Institute for Prevention Research and Epidemiology - BIPS |
| BP | blood pressure |
| CI | confidence interval |
| CIP | French pharmacy dispensing coding system |
| CNAM-TS | French health care insurance system for salaried workers |
| DDD | defined daily dose |
| DIMDI-DaTraV | Information system for health care data (data transparency) of the German Institute of Medical Documentation and Information |
| DNPR | Danish National Patient Registry |
| EMA | European Medicines Agency |
| EMA-PRAC | European Medicines Agency, Pharmacovigilance Risk Assessment Committee |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| ER | emergency room |
| EU PAS Register | European Union electronic register of postauthorisation studies |
| FMM | finite mixture model |
| GePaRD | German Pharmacoepidemiological Research Database |
| GP | general practitioner |
| GVP | Good Pharmacovigilance Practices |
| HSR | hypersensitivity reaction |
| IBD | irritable bowel disease |
| ICD | International Classification of Diseases |
| ICD-10 | International Statistical Classification of Diseases and Related Health Problems, 10th Revision |
| ICD10-GM | International Classification of Diseases, 10$^{th}$ revision German modification |
| ICPC | International Classification of Primary Care |
| IM | intramuscular |
| IP | incidence proportion |
| ISPE | International Society for Pharmacoepidemiology |
| IV | intravenous |
| KfH QiN | KfH - Kuratorium für Dialyse und Nierentransplantation e.V. (Board of Trustees for Dialysis and Kidney Transplantation) and its Qualität in der Nephrologie (Quality in Nephrology) programme, Germany |
| MAH | marketing authorisation holder |
| Max | maximum |
| Min | minimum |
| NA | not applicable |
| NE | not estimable |

| | |
|---|---|
| PASS | postauthorisation safety study |
| PEF | peak expiratory flow |
| PHARMO | PHARMO Database Network or PHARMO Institute for Drug Outcomes Research |
| PHARMO-NL | PHARMO Database Network in the Netherlands |
| PPV | positive predictive value |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PZN | Pharmazentralnummer, nationwide german identification number for pharmaceuticals |
| RD | risk difference |
| REF CAT | reference category |
| RMP | risk management plan |
| RR | risk ratio |
| RTI-HS | RTI Health Solutions |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SHI | German statutory health insurance provider |
| SNDS | Système National des Données de Santé (French National health care insurance system database, previously named French National Health Insurance Inter Plans Information System Database [SNIIRAM]) |
| US | United States |

# 3 Investigators

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At Aarhus University Hospital: Henriette Kristoffersen, research nurse, for medical record review, Christian Fynbo Christiansen, MD, PhD for clinical advice, and Lisbeth Munksgård Baggesen, PhD for statistical support.

At PHARMO-NL: Irene Bezemer (Senior Research Manager for this project until April 2019) and health care providers contributing information to the PHARMO Database Network.

At BIPS: Alina Ludewig, Inga Schaffer and Federica Pisa (Senior Epidemiologist for this project until August 2019).

At the Carl von Ossietzky University Oldenburg: Constanze Kathan-Selck (liaison coordinator at Oldenburg Hospital), Lara Disselhoff (project student), Jan Thies Soller (data manager until April 2019) and, all clinical directors participating at Oldenburg Hospital.

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At the Centre for Pharmacoepidemiology, Karolinska Institutet: Camilla Byström for project administration and editorial review.

# 4 Other Responsible Parties

## External Scientific Advisory Board

The study oversight was conducted by a scientific steering committee, and an external scientific advisory board set up between the research partners, both data sources, the coordinating centre (RTI-HS), and the sponsor. The members of the external scientific advisory board were as follows:

- Prof. Edeltraut Garbe, MD, pharmacoepidemiologist, Germany
- Prof. David Rampton, MD, gastroenterologist, Royal London Hospital, London-United Kingdom
- Prof. Andreas Bircher, MD, allergologist, Dermatology Department, University Hospital, Basel, Switzerland
- Prof. Jacques Benichou, MD, biostatistician, Medical Department, Rouen University, France

- Ad hoc external consultant:

  Dr. Kathleen Walsh, principal investigator for the United States (US) Sentinel study, also advised on methodological aspects with a focus on the case-identification algorithm

## Study Sponsor

**IV Iron Consortium**

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- Michael Forstner, MSc, PhD, Managing Director, Mesama Consulting, Switzerland; on behalf of IV Iron MAH Consortium
- For a list of Marketing Authorisation Holders, Consortium member names and contact details, see Table 2 1 Annex 2

# 5 Milestones

| Milestone | Estimated/Actual Date Protocol V1.1, May 4, 2017 | Revised Timeline Protocol V2.1, 26 September 2019 | Actual |
|---|---|---|---|
| Protocol submission to EMA-PRAC: 3 months after receipt of the final assessment of the extended feasibility study report | 21 December 2016 | 21 December 2016 | 21 December 2016 |
| EMA-PRAC protocol endorsement | Anticipated by 3Q 2017 | 01 September 2017 | 01 September 2017 |
| Registration in the EU PAS Register including the protocol (following regulatory endorsement) | 3Q 2017 | 30 November 2017 | 30 November 2017 |
| Ethics or other relevant approvals and data source-specific adaptation of study materials | 3Q-4Q 2017 | 20 September 2017- 23 May 2019 | 20 September-23 May 2019 |
| Start of data collection[a] i.e., retrieval (first data source) | 1Q 2018 | 09 March 2018 | 09 March 2018 |
| Start of outcome validation studies | To be determined | 01 December 2018- 30 April 2019 | 01 December 2018-30 April 2019 |

| Milestone | Estimated/Actual Date Protocol V1.1, May 4, 2017 | Revised Timeline Protocol V2.1, 26 September 2019 | Actual |
|---|---|---|---|
| End of data collection[b] i.e., complete analytical data set (last data source for main analyses) | 4Q 2018-1Q 2019 | 4Q 2019 (including validation but not including DaTraV data) | 12 March 2020 |
| Data source analysis | 1Q-2Q 2019 | November 2018-4Q 2019 (including validation results but not DaTraV) | November 2018-February 2020 (including validation results but not DaTraV) |
| Pooled analysis | 2Q-3Q 2019 | 4Q 2019 | 22 February 2020 |
| Final report of study results | 3Q 2019-1Q 2020 (an additional report may be needed for the re-analysis after source record validation has been completed) | 1Q 2020 (including validation results) | 24 March 2020 (including PHARMO validation results) |
| Final report of study results V.1.1 | NA | NA | 6 May 2020 (updated including Danish validation results). |
| Final report of study results V.1.2 | NA | NA | 10 September 2020 (revised conclusion following PRAC review) |
| Final report of study results V.1.3 | NA | NA | 20 November 2020 (revised conclusion following PRAC review) |
| Final report of study results including DaTraV data | TBD | TBD | Will not be available |

EMA-PRAC = European Medicines Agency Pharmacovigilance Risk Assessment Committee; EU PAS Register = European Union electronic register of postauthorisation studies; *n*Q = *n*th quarter of the year
NA = not applicable.

Note: Contracts between the sponsor and research organisation(s) and approvals by data protection, data custodian, ethics, and scientific review bodies are completed. Timelines may be affected by approvals of these bodies, duration of contract reviews, and availability of data and staff at research institutions once contracts and approvals are finalised.

[a] Start of data collection is "the date from which information on the first study subject is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts" (EMA, 2017a).

[b] End of data collection is "the date from which the analytical data set is completely available" (EMA, 2017a).

# 6 Rationale and Background

## 6.1 Rationale

Intravenous (IV) iron therapy was introduced in the 1950s for the treatment of severe anaemia (Auerbach and Ballard, 2010). In the last decades, the use of IV iron has been growing worldwide due to a better understanding of the management of moderate and severe anaemia related to numerous conditions such as chronic kidney disease, heavy uterine bleeding, pregnancy and postpartum anaemia, chemotherapy-induced anaemia, elective surgery, and chronic heart failure (Bailie and Verhoef, 2012). Studies evaluating hypersensitivity reactions (HSRs) in association with IV iron preparations have been previously reported (Bailie et al., 2005; Bailie and Verhoef, 2012; Chertow et al., 2004; Chertow et al., 2006; Walsh et al., 2016; Wang et al., 2015).

The benefit-risk relationship of iron-containing IV medicinal products was evaluated by the European Medicines Agency (EMA) in the context of a referral under Article 31 of Directive 2001/83/EC completed in September 2013. The iron complexes involved in the EMA's referral procedure were ferric carboxymaltose, iron dextran, sodium ferric gluconate, iron isomaltoside, and iron sucrose, which are authorised in European Union Member States (EMA, 2013).

As a result of this evaluation, the EMA imposed a labelling update reinforcing risk information on HSRs and formulated a series of "conditions to marketing authorisation", which included the recommendation by the EMA Pharmacovigilance Risk Assessment Committee (PRAC) for the "*MAHs to conduct a post-authorisation safety study (PASS) to further characterise the safety concerns on the hypersensitivity reactions. The study will also have to be reflected in the updated/new RMP submission*" (EMA, 2017a).

To address the EMA request, a consortium of IV iron manufacturers was created to conduct a non-interventional pharmacoepidemiology safety study in multiple European Union countries.

## 6.2 Background

The occurrence of anaphylactic shock from any cause (food, medications, insect bites, and other) in the general population was reported to be 0.2 to 1.2 per 10,000 person-years in a study conducted across several European health databases within the context of the European initiative "Exploring and understanding adverse drug reactions by integrative mining of clinical records and biomedical knowledge" (EU-ADR) (Avillach et al., 2013). Rates of hospitalisation with anaphylaxis from any cause in the general population from the Danish National Health Databases averaged 0.65 per 10,000 person-years between 1995 through 2012 (Jeppesen et al., 2016).

Hypersensitivity reactions in association with IV iron preparations have been reported in the scientific literature (Bailie et al., 2005; Bailie and Verhoef, 2012; Chertow et al., 2004; Chertow et al., 2006; Durup et al., 2020; Ehlken et al., 2019; Nathell et al., 2020; Walsh et al., 2016; Wang et al., 2015).

Studies based on spontaneous reports have reported rates of serious allergic reactions, per gram of IV iron per million inhabitants between 0.1 per $10^3$ and 10.5 per $10^3$ for sodium ferric gluconate, between 0.9 per $10^3$ and 47 per $10^3$ for iron dextran, between 0.2 per $10^3$ and 2.7 per $10^3$ for iron sucrose (Bailie and Verhoef, 2012). Ehlken et al. (2019) reported rates of severe HSRs in Europe between 0.3 and 0.5 per 100 mg dose-equivalents of iron for ferric carboxymaltose, and between 2.4 and 5.0 per 100 mg dose equivalents of iron for iron (III) isomaltoside 1000. Nathell et al. (2020) reported rates of severe HSRs in European countries per 100 mg dose-equivalents of iron for iron sucrose from 0.03 to 0.20, for ferric gluconate from 0.02 to 0.14, for ferric carboxymaltose from 0.18 to 1.47 , for iron dextran from 0.22 to 2.80 and for iron (III) isomaltoside 1000 from 0 to 7.94. Durup et al. (2020) reported global annual rates for eight categories of HSRs ranging from 0.59 to 1.00 per 100,000 defined daily dose for iron dextran and from 2.77 to 12.2 for iron carboxymaltose.

Wang et al. (2015) conducted a cohort study of new users of IV iron products (n = 688,183) enrolled in the US fee-for-service Medicare programme from January 2003 through December 2013 and found that the risk for anaphylaxis assessed on the same date of a first exposure was 68 per 100,000 persons for iron dextran (95% CI, 57.8-78.7 per 100 000 persons) and 24 per 100,000 persons for all non-dextran IV iron products combined (iron sucrose, gluconate, and ferumoxytol) (95% CI, 20.0-29.5 per 100,000 persons), with an adjusted odds ratio of 2.6 (95% CI, 2.0-3.3). The estimated cumulative risk of anaphylaxis following total iron repletion of 1,000 mg administered over a 12-week period was highest with iron dextran (82 per 100,000 persons; 95% CI, 70.5-93.1) and lowest with iron sucrose (21 per 100,000 persons; 95% CI, 15.3-26.4) (Wang et al., 2015). This study has been criticised on the basis of a potential misclassification of exposure due to the grouping of high- and low-molecular-weight dextrans together, as well as potential misclassification of the anaphylaxis outcome (DeLoughery and Auerbach, 2016). However, the authors have argued that the low use of high-molecular-weight iron dextran ascertained during a study interval period suggests that the results likely represent the risk of the low-molecular-weight dextran.

In the US, a large multisite database study was conducted under the Food and Drug Administration's Sentinel programme to evaluate the risk of anaphylactoid/anaphylaxis reactions on the day of or the day after exposure among IV iron users, in which health plan members with a first administration of a parenteral iron preparation were identified from January 2000 through June 2013 (Walsh et al., 2014; Walsh et al., 2016). Results from this study, based on a cohort of 70,866 new users of IV iron not undergoing dialysis, are consistent with those published in the Medicare study by Wang et al. (2015). The study reports crude incidence rates of 4 per 10,000 new users of iron dextran (95% CI, 2-8) and 2 per 10,000 new users of other iron products (95% CI, 1-3), with a 2.6-fold greater risk of anaphylaxis among IV iron dextran new users than among new users of non-dextran IV irons (Walsh et al., 2016). Walsh and colleagues had previously reported on the validation of an algorithm developed to identify anaphylaxis using health plan administrative and claims data within the Mini-Sentinel programme (Walsh et al., 2013). Using the clinical criteria by Sampson et al. (2006) as the gold standard, the positive predictive value (PPV) for the algorithm based on International

Statistical Classification of Diseases, 9th Revision, Clinical Modification codes was 63.1% (95% CI, 53.9%-71.7%).

Akhuemonkhan et al. (2018) conducted a cohort study to examine adverse reactions after IV iron infusion among patients diagnosed with irritable bowel disease (IBD) and ulcerative colitis using the US Truven Health MarketScan Commercial Claims and Encounters database from 2010 to 2014. This database collects data from service-level claims for inpatient and outpatient services and outpatient prescription drugs. The risk of anaphylactic reactions within 7 days of any IV iron administration was calculated using Poisson regression after adjusting for type of IBD, type of IV iron, sex, age at first IBD encounter, and receiving a biologic infusion on the same day as IV iron. Risk and 95% CI per 10,000 infusions was 4.4 (1.4-13.8) for ferric gluconate users, 1.7 (0.2-12.3) for iron dextran users and 1.4 (0.4-4.3) for iron sucrose users. Ferric carboxymaltose users experienced no anaphylactic events (Akhuemonkhan et al., 2018). Adjusted incidence rate per 10,000 infusions in Crohn's disease patients ranged from 2.4 (0.6-9.7) for iron sucrose users to 16.3 (4.1-65.9) in ferumoxytol users. Ulcerative colitis incidence rate per 10,000 infusions were 1.2 (0.2-8.7) for iron sucrose and 91.3 (9.5-879) for ferric gluconate. There were six infusions of ferric carboxymaltose and none of them led to an anaphylaxis event.

Pollock and Biggar (2020) compared the occurrence of serious or severe HSRs for three IV iron formulations by pooling data from 21 published, prospective clinical studies including over 8,500 patients treated with IV iron. By using various meta-analytic techniques, the odds ratio of any serious or severe HSRs of isomaltose relative to iron carboxymaltose or iron sucrose ranged from 0.39 to 0.56.

# 7 Research Question and Objectives

The primary objective of the study was to assess the risk of anaphylactic or severe immediate hypersensitivity reactions (hereafter, "anaphylactic reactions" or "anaphylaxis"), overall and by groups and types of IV iron, among patients with any indication for IV iron, including patients undergoing dialysis, in routine clinical practice in European populations.

The following parameters were estimated:

- Incidence proportion (IP; risk) of anaphylactic reactions occurring on the day of or the day after exposure to the first (new users), second, and third or subsequent, and overall dispensing/administration of any IV iron, by group of IV iron product (iron(III)-hydroxide dextran complex vs. other IV irons), and by the individual IV iron types listed below:
  - Iron(III)-hydroxide dextran complex
  - Iron sucrose complex/iron(III)-hydroxide sucrose complex
  - Ferric carboxymaltose complex
  - Iron(III) isomaltoside complex
  - Sodium ferric gluconate complex

- Risk ratios (RRs) were estimated to compare the risk of anaphylactic reactions between IV iron groups (i.e., iron dextran vs. iron non-dextrans) and among the various IV iron types (iron sucrose, the IV iron type with longest time since marketing authorisation and the largest expected number of users, was used as the comparison reference group) at the first, second and third or subsequent and overall exposure.
- The IP of anaphylactic reactions in patients dispensed or administered IV penicillins, the selected anaphylaxis marker compound, were calculated to provide context for the incidence of anaphylactic reactions from a medication group with a well-recognised risk of anaphylaxis.

As part of good research practices, the protocol and European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) checklist were registered in the EU PAS Register (ENCePP, 2016) before the start of data collection (30 November 2017). The study was designed and implemented in line with the International Society for Pharmacoepidemiology *Guidelines for Good Pharmacoepidemiology Practices* (ISPE, 2015); EMA *Guidelines on Good Pharmacovigilance Practices (GVP), Module VIII Postauthorization Safety Studies* (EMA, 2017a); ENCePP *Guide on Methodological Standards in Pharmacoepidemiology* (ENCePP, 2018); and Food and Drug Administration *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Guidance* (FDA, 2013). The contract for the implementation of the study between RTI-HS and Vifor (Vifor acting on behalf of the Iron Consortium) included independent publication rights.

On 20 September 2017, the RTI-HS study team received the determination made by the RTI International institutional review board of the study as research not involving human subjects (RTI-HS will have no interaction with human subjects). Registration into EU PAS Register and ENCePP Study Seal application was completed on 30 November 2017 - EU PAS 20720.

Researchers at the University of Aarhus Epidemiology Department notified the Danish Data Protection Agency about the study on 13 December 2017. The study was listed on the University's overview of research projects covered by the notification, the Data Inspectorate's record number 2015-57-0002, and Aarhus University's journal number 2016-051-000001, serial number 810. On 10 October 2019, the Patient Safety Board granted approval for the study validation component.

Approvals for accessing the Système National des Données de Santé (SNDS, French National Health Care Insurance System Database) were obtained from the Comité d'Expertise pour les Recherches les Études et les Évaluations dans le domaine de la Santé on 18 January 2018, the Commission Nationale de l'Informatique et des Libertés on 11 June 2018, and on 23 May 2019 from the French health care insurance system for salaried workers.

Approvals for accessing the German Pharmacoepidemiological Research Database (GePaRD) health data from the Statutory Health Insurances (SHIs) in Germany were obtained for the first SHI on 14 November 2017 and for the two additional SHIs on 16 April 2018.

No ethics committee approval was required for access to the KfH QiN dialysis registry data in Germany. Researchers from the University of Cologne in Germany received a letter from the Ethics Board agreeing to the use of the data for this study.

Ethics approval from the Oldenburg University Hospital for the indirect validation activities was obtained on 15 March 2018.

Ethics approval is not required for anonymised database research in the Netherlands. However, this study fulfilled the requirements, as checked by the PHARMO Compliance Commission on 7 October 2011, to use data from PHARMO-NL for this specific study. Approvals from four hospitals were obtained for accessing patient records where case validation of PHARMO-NL data was performed.

The Centre for Pharmacoepidemiology at Karolinska Institutet received ethics approval for the study on 28 February 2018, and approval to use data from the Swedish registers from the National Board of Health and Welfare on 7 November 2018.

# 8 Amendments and Updates

The protocol version 1.1, dated 4 May 2017, was the protocol endorsed by the EMA and first posted in the EU PAS Register, EUPAS20720. The protocol version 2.1, dated 26 September 2019, was the protocol amended to reflect substantial changes proposed after the start of data collection and before the final implementation of the IV iron PASS. This amended protocol version 2.1, was endorsed by the EMA on 4 October 2019. Listed below are the specific amendments reflected in the protocol version 2.1.

| Version Number | Date | Section(s) of Study Protocol | Amendment | Reason |
|---|---|---|---|---|
| 2.1 | 26 Sep 2019 | PASS Information, Approval pages and Section 4, Abstract | Updated protocol version and date | Reflect updates in amended protocol version 2.1 |
| 2.1 | 26 Sep 2019 | Section 4, Abstract; Section 6, Milestones and Timeline | Updated timelines with actual and revised timelines for some milestones | Reflect actual dates for achieved milestones; delays in completion of outcome validation |
| 2.1 | 26 Sep 2019 | Section 5, Amendments and Updates | Added specifications on the revisions incorporated in the amended protocol | Reflect updates in amended protocol 2.1 |
| 2.1 | 26 Sep 2019 | Section 7.2, Background | Added published estimates on the occurrence of | Address requests from the EMA-PRAC preliminary |

| Version Number | Date | Section(s) of Study Protocol | Amendment | Reason |
|---|---|---|---|---|
| | | | anaphylaxis in the general population<br>Clarified meaning of estimates from Bailie and Verhoef (2012) and corrected figure | assessment report (PAR) |
| 2.1 | 26 Sep 2019 | Section 9.3.3, Other Variables, Table 8 | Added column to indicate availability of study covariates across data sources | Address EMA-PRAC PAR request |
| 2.1 | 26 Sep 2019 | Section 9.4, Data Sources | Clarified generalisability of PHARMO-NL data to the Dutch population and added population size for the French SNDS database | Address EMA-PRAC PAR request |
| 2.1 | 26 Sep 2019 | Section 9.7, Data Analysis | Added text to clarify that the study aims to evaluate risk of anaphylactic reactions at first, second, third or subsequent and any IV iron exposure and at first and any IV penicillins exposure | Address EMA-PRAC PAR request |
| 2.1 | 26 Sep 2019 | Section 9.7.2, Crude Incidence Proportions and Crude Comparative Analyses | Added text to clarify propensity score methodology and highlight the impact of potential zero events in some IV iron subtypes | Address EMA-PRAC PAR request |
| 2.1 | 26 Sep 2019 | Section 9.7.4.7, Sensitivity Analyses: Worst-Case Scenario Assessment | Corrected error | Address EMA-PRAC PAR request |
| 2.1 | 26 Sep 2019 | Section 9.7.5, Pooled Analyses | Added text to clarify pooling methods in relation to heterogeneity | Address EMA-PRAC PAR request |

| Version Number | Date | Section(s) of Study Protocol | Amendment | Reason |
|---|---|---|---|---|
| 2.1 | 26 Sep 2019 | Section 9.9, Limitations of Research Methods | Added text to acknowledge capture of a single type of IV iron in France | Address EMA-PRAC PAR request |
| 2.1 | 26 Sep 2019 | Section 10, Protection of Human Subjects and Good Research Practice, and Section 11, Management and Reporting of Adverse Events/Adverse Reactions | Added mention to updated versions of EMA GPV guidelines | Address EMA-PRAC PAR request |
| 2.0 | 04 Jul 2019 | PASS Information | Added EU PAS Register number, updated MAH list and MAH contact person | Protocol has been registered in the EU PAS Register; change in MAH members of the IV Iron Consortium; changes in contact information for MAH contact person |
| 2.0 | 04 Jul 2019 | Approval pages | Updated authors and reviewers and affiliation of MAH contact person | Change in research team members; change in contact information of MAH contact person |
| 2.0 | 04 Jul 2019 | Section 3, Responsible Parties | Updated members for responsible parties | Changes in responsible parties |
| 2.0 | 04 Jul 2019 | Section 4, Abstract; Section 9.2.3, Study Cohort; 9.2.3.2, Cohort entry date; 9.2.3.3, Inclusion criteria | Clarified wording for inclusion of second and subsequent dispensing or administration of study drugs | Align text with original planned analysis |
| 2.0 | 04 Jul 2019 | Section 4, Abstract; Section 9.2.2, Study Period | Updated year for end of study period; change in name of French database | Change to reflect additional year of data available in one centre |
| 2.0 | 04 Jul 2019 | Section 4, Abstract; Section 6, Milestones and Timeline | Updated timelines with actual and revised timelines | Reflect actual dates for achieved milestones; |

| Version Number | Date | Section(s) of Study Protocol | Amendment | Reason |
|---|---|---|---|---|
| | | | for some milestones | delays in completion of some intermediate milestones |
| 2.0 | 04 Jul 2019 | Section 9.3.2, Outcomes | Updated Criterion B and Criterion C of the main outcome algorithm | Reflect input from external scientific advisory board June 2017 |
| 2.0 | 04 Jul 2019 | Section 9.3.3, Other Variables; Table 7 | Added new variables to the list of covariates of interest | Updates based on research team discussions and input from external advisers in June 2017 |
| 2.0 | 04 Jul 2019 | Section 9.5, Study Size; Table 9 | Modified cell-count reporting limits for Danish and Swedish data | Updated input from researchers |
| 2.0 | 04 Jul 2019 | Section 9.6, Data Collection and Management | Added text for use of secure file transfer protocol site as a method to transfer study data between the research data centres and the coordinating centre | To comply with data-protection requirements of some centres |
| 2.0 | 04 Jul 2019 | Section 9.7.2, Crude Incidence Proportions and Comparative Analyses | Re-ordered section to indicate higher priority of crude incidence and crude comparative analyses.<br>Added text to clarify definition of "risk windows" | Crude incidence analyses will be performed as part of the main analyses due to low number of events in preliminary descriptive results.<br>Time-at-risk definitions vary according to type of exposure data |
| 2.0 | 04 Jul 2019 | Section 4, Abstract; Section 9.7.3, Propensity Score Analyses | Revised text to highlight that the conduct of all propensity score-adjusted analyses will be dependent | Based on low number of events in preliminary descriptive results, the |

| Version Number | Date | Section(s) of Study Protocol | Amendment | Reason |
|---|---|---|---|---|
| | | | on the number of events. | propensity score-adjusted analyses do not seem feasible |
| 2.0 | 04 Jul 2019 | Section 4, Abstract; Section 9.7.4, Sensitivity Analyses | Added text on new planned sensitivity analyses for the expanded outcome algorithm, IV iron switchers, and dialysis patients. In addition, new text was added to describe timing of events up to 21 days after the risk window and listing of causes of death. | Additional analyses were triggered by the low number of events in the preliminary descriptive analyses and the research team agreements to perform further explorations of the available data |
| 2.0 | 04 Jul 2019 | Section 9.7.4.3, Sensitivity Analyses: Alternative Risk Window | Removed text for alternative risk window analysis based on "same day" of dispensing of the study drug. | Analysis dropped due to low number of events |

EMA = European Medicines Agency; EMA-PRAC = Pharmacovigilance Risk Assessment Committee; EU PAS Register = European Union electronic register of postauthorisation studies; GPV = Good pharmacovigilance; IV = intravenous; MAH = marketing authorisation holder; PAR = Preliminary assessment report; PASS = postauthorisation safety study; PHARMO-NL = PHARMO Database Network in the Netherlands; SNDS = Système National des Données de Santé (French National health care insurance system database).

# 9 Research Methods

## 9.1 Study Design

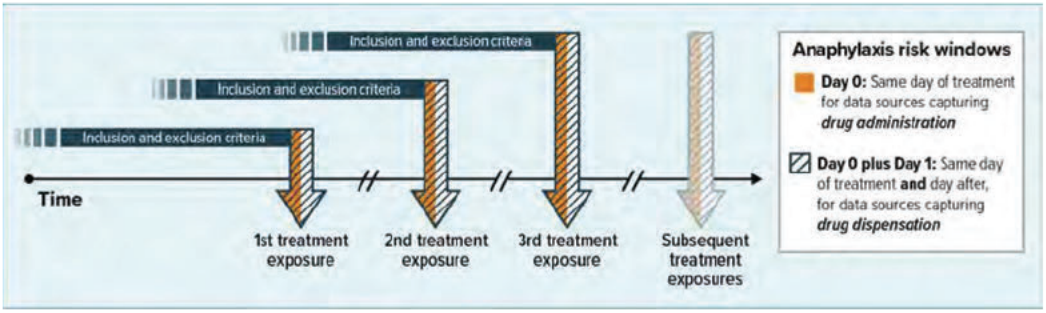
This was a multinational cohort study of patients initiating IV iron treatment, conducted in populations covered by sources of routinely collected health and administrative data in Europe. To obtain a sufficient number of IV iron new users to address the study objectives given the low risk of anaphylactic reactions, the study included national- or regional-level data from five countries: Denmark, the Netherlands, France, Germany, and Sweden.

Given that the risk of anaphylactic reactions rapidly decreases after the first administration of the drug, the study used a "new-user" design (main analysis) which allowed for more comparable study groups. However, prevalent users (i.e., users with a second and third or subsequent IV iron exposure), were also included to assess the evolution of risk beyond the first exposure as part of the sensitivity analyses.

The study aimed to estimate the risk of anaphylactic reactions occurring on the day of or the day after a first dispensing/administration of an IV iron medication. Risk was estimated using the IP among patients receiving any IV iron medication overall, by defined groups and individual types. Risk ratios and 95% CIs were calculated to compare the risk of anaphylactic reactions at the first (main analysis), second, and third or subsequent IV iron exposure overall and by the defined IV iron groups and individual types of IV iron.

To provide context to the estimated risk of anaphylactic reactions associated with exposure to IV iron, we estimated the risk of anaphylactic reactions in patients initiating treatment with IV penicillins, in the data sources where it was feasible. Penicillins have a well-characterised anaphylaxis risk that can help to validate the methodology.

**Figure 1. Study Design**

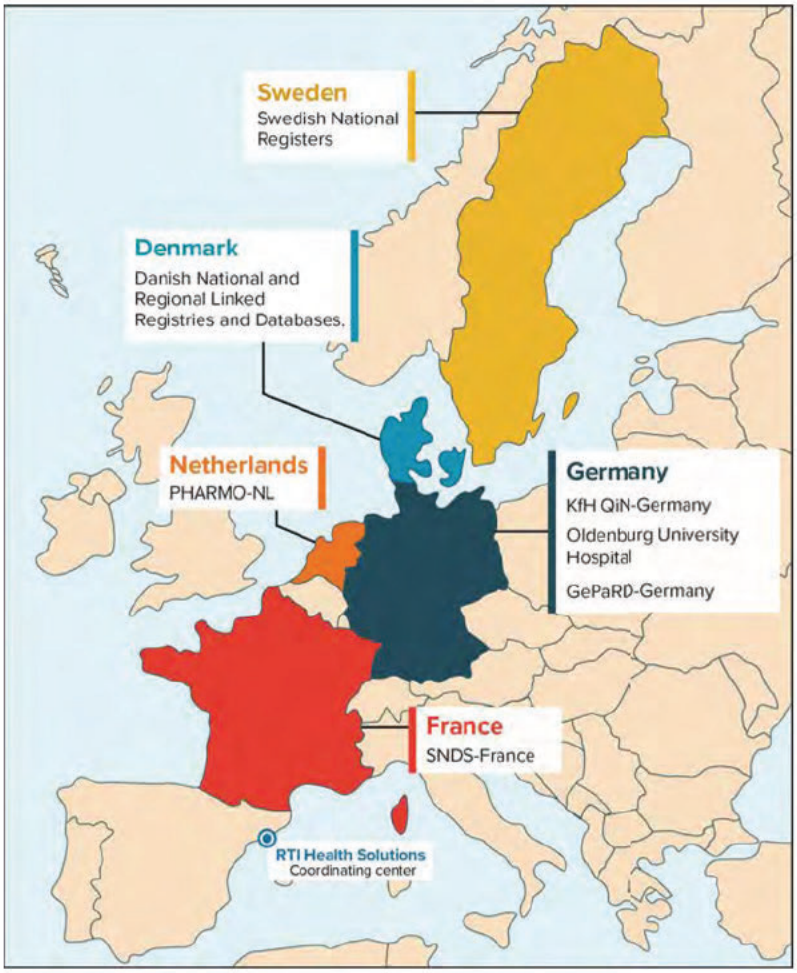



## 9.2 Setting

The study was conducted following a common core protocol in population-based health databases and registries in five countries in Europe that are available for research and that provide access to health-related data, including drug dispensing or administration data. RTI-HS was the coordinating centre also responsible for the conduct of the meta-analyses of aggregate data from all data sources. Figure 2 displays the data sources and countries participating in this study.

- Data from the German Institute of Medical Documentation and Information (DIMDI-DaTraV), Germany were originally planned to be included in the study. However, multiple issues were encountered that precluded contribution of data from DIMDI-DaTraV to this study. Details are provided in Section 9.9.5.

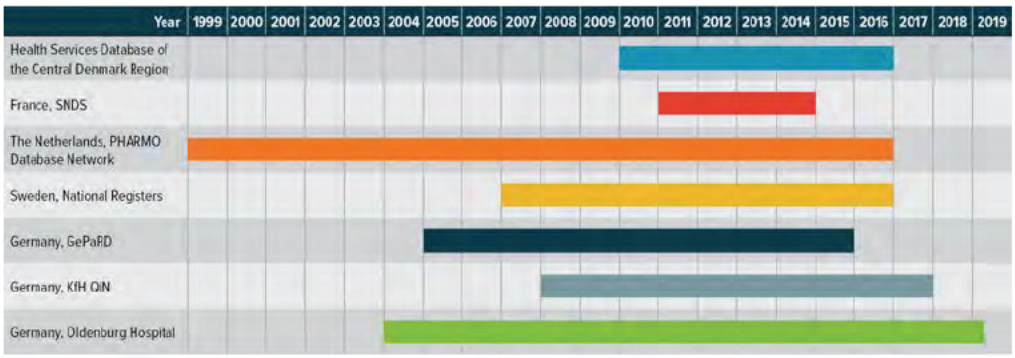
**Figure 2. Study Countries and Data Sources**




GePaRD = German Pharmacoepidemiological Research Database; SNDS = Système National des Données de Santé (French National Health Care Insurance System Database); KfH QiN = Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme; PHARMO-NL = PHARMO Database Network in the Netherlands.

The study period was defined in each data source as the time between the date of the first-eligible recorded code for dispensing or administration of IV iron (i.e., first-recorded code for dispensing or administration of IV iron after 1 year of continuous enrolment in the database) and the latest date of data availability (see Figure 3). The start date in each data source in Figure 3 reflects the time of "first IV iron/IV penicillin use" after the minimum 12-month lookback period required before cohort entry. In the French SNDS database, IV iron was removed from the list of reimbursed medications in 2014; therefore, data on IV iron were not available after this date.

**Figure 3. IV Iron PASS: Study Period for Each Data Source**




GePaRD = German Pharmacoepidemiological Research Database; IV = intravenous; KfH QiN = Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme; PASS = postauthorisation safety study; SNDS = Système National des Données de Santé (French National Health Care Insurance System Database).

## 9.3 Subjects

The study cohort comprised all adults from the source population who had a first-recorded dispensing/administration of IV iron during the study period, were continuously enrolled or registered in the data source for at least 12 months before the first recorded iron treatment and were at least 18 years of age on the date of the first dispensing/administration of IV iron (see Figure 4). Second or subsequent dispensing/administration of the same type of IV iron meeting the inclusion criteria were also considered for the corresponding analyses (see Figure 4). For the KfH QiN dialysis registry in Germany, the eligibility requirement for a minimum continuous enrolment of 12 months before the first IV iron administration was not applied because medical information is captured only from the date patients' initiate dialysis.

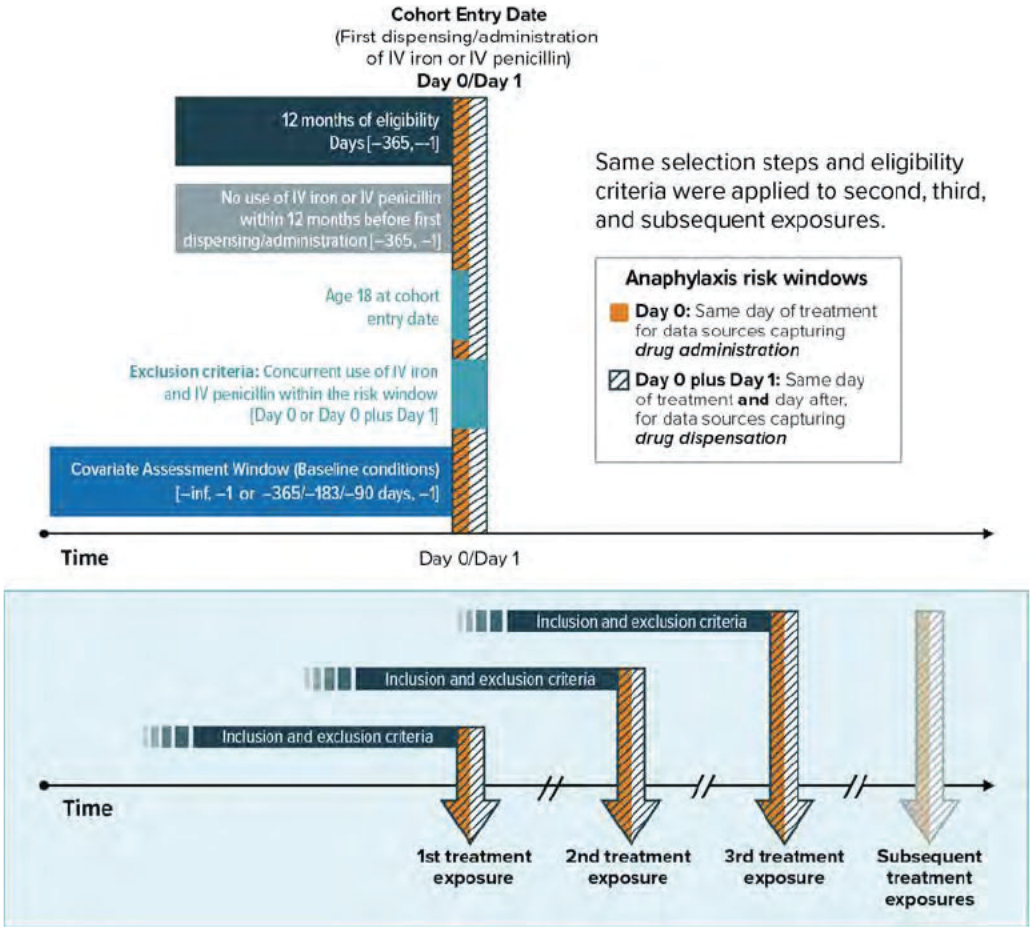
The same selection criteria were applied to the IV penicillins cohort in the data sources where IV penicillins use was captured (i.e., Danish national and regional linked registries and databases, PHARMO-NL, SNDS in France, and GePaRD in Germany).

### *9.3.1 New Users*

New users were defined as individuals initiating treatment with IV iron or IV penicillins without a recorded code for dispensing/administration of these drugs within at least 12 months before entry date (defined in Section 9.3.2).

Due to the idiosyncratic nature of hypersensitivity reactions, patients were allowed to enter the study only once. No switches between IV iron groups or individual types were allowed for the main analysis. However, prior use of IV penicillins compounds did not affect the eligibility status as a new-user of IV iron and vice versa, as cross-reactivity between IV iron and IV penicillins is considered to be highly unlikely.

**Figure 4. Study Inclusion and Exclusion Criteria**




IV = intravenous.

### *9.3.2 Follow-up*

The follow-up of eligible patients for identification of anaphylaxis in the main analysis is described below (see also Figure 5):

The cohort entry date (Day 0) was defined as the date of a record for a first qualifying dispensing/administration of IV iron or IV penicillins in the study data sources.

Patients were followed from the cohort entry date until the first occurrence of any of the following censoring events:

- Occurrence of the study outcome (event date)
- Death
- End of study period
- Switch between types of IV iron

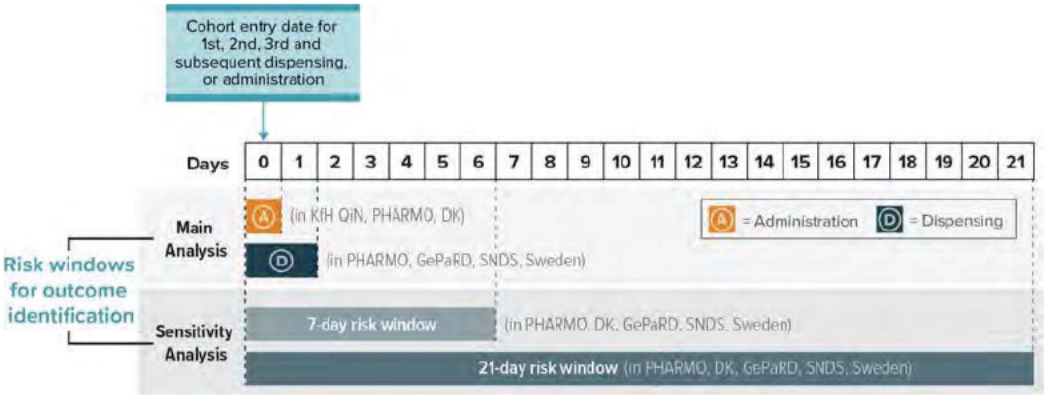
- Concurrent use (i.e., within Day 0 ["same day"] or Day 0 and Day 1 ["same day and day after"] of a recorded exposure) of IV iron and IV penicillins
- Day 0 (same day) for data sources capturing drug administration data or Day 0 and Day 1 (main analysis) after dispensing/administration of IV iron for data sources capturing drug-dispensing data
- Disenrollment from the data source

Drug administration data were captured in the KfH QiN dialysis registry in Germany, the Health Services Database of the Central Denmark Region, and the PHARMO-NL inpatient Pharmacy Database.

Drug-dispensing data were available (i.e., no data on dates of actual treatment administration were available) in the SNDS in France, PHARMO-NL Outpatient Pharmacy and General Practitioner (GP) Database, GePaRD in Germany, and the Swedish national registers (see Figure 5).

Alternative risk windows (i.e., 7-day and 21-day risk window) were also considered for sensitivity analyses as shown in Figure 5 (see Section 9.9.4).

**Figure 5. Study Follow-up**




DK = Denmark; GePaRD = German Pharmacoepidemiological Research Database; SNDS = Système National des Données de Santé (French National Health Care Insurance System Database); KfH QiN = Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme; PHARMO = PHARMO Database Network.

## 9.4 Variables

### *9.4.1 Outcome Variable*

The outcome of interest was anaphylactic reaction or severe immediate hypersensitivity reaction following exposure to a study drug. The definition of anaphylactic reactions followed the definition by the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network symposium as a "serious allergic reaction that is rapid in onset and may cause death" (Sampson et al., 2006). The clinical criteria proposed by these organisations are displayed in Figure 6.

## Figure 6. Clinical Criteria for Diagnosing Anaphylaxis

**Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:**

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   *AND AT LEAST ONE OF THE FOLLOWING*
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

*PEF*, Peak expiratory flow; *BP*, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

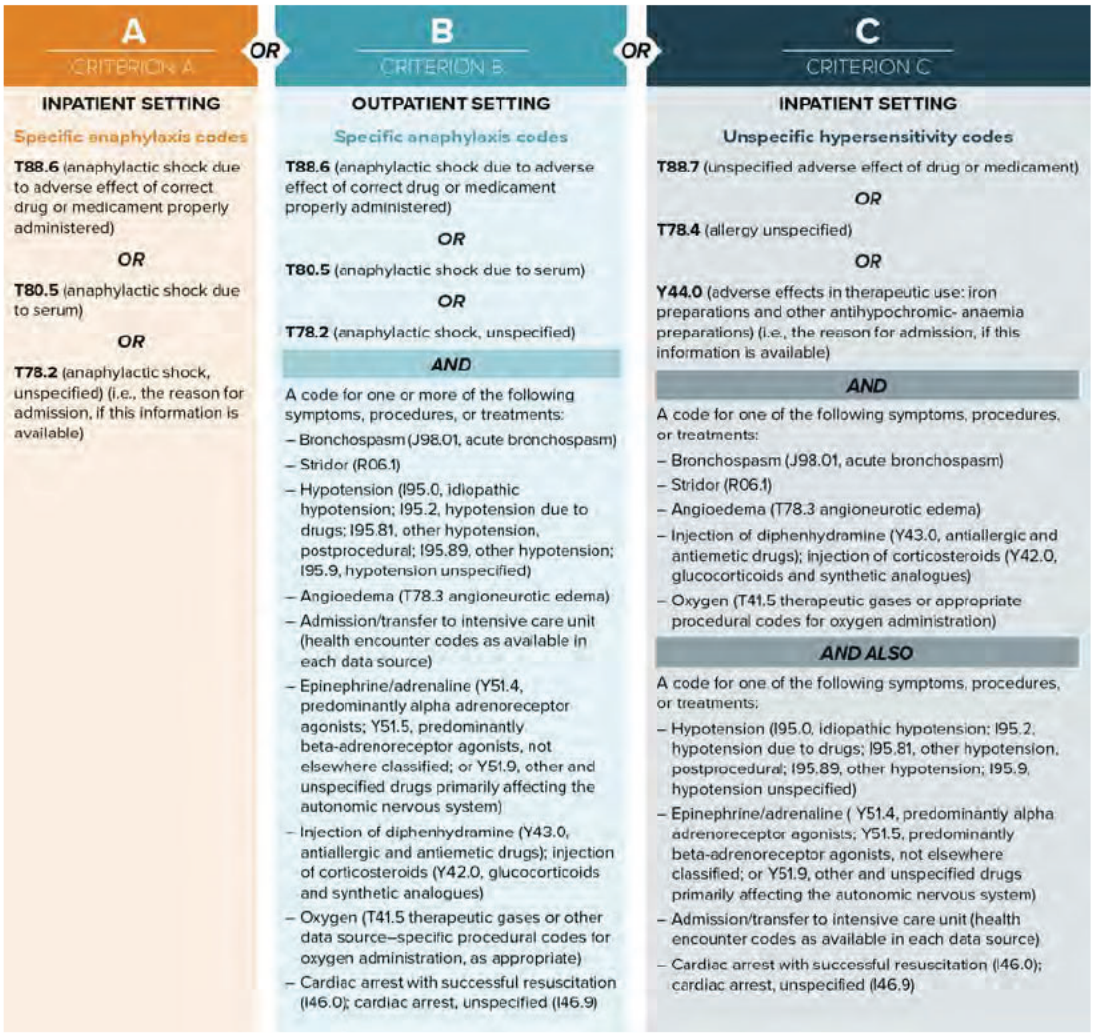
Source: Table I from Sampson et al. (2006).

### 9.4.1.1 Outcome Identification

#### Main Anaphylaxis Algorithm

Anaphylactic reactions were identified using an algorithm created using International Classification of Diseases, 10th Revision (ICD-10) codes based on the algorithm developed and validated by investigators from the US Mini-Sentinel project based on International Classification of Diseases, 9th Revision codes (Walsh et al., 2014). The algorithm was adapted to each data source. Fatal events occurring during the defined time-at-risk windows for the outcome were also captured. Note that cause of death was not available in all data sources. The event-finding algorithm used for further data-source adaptations for the main analysis is presented in Figure 7.

**Figure 7. Main Anaphylaxis Algorithm**




### Expanded Anaphylactic Reactions Algorithm

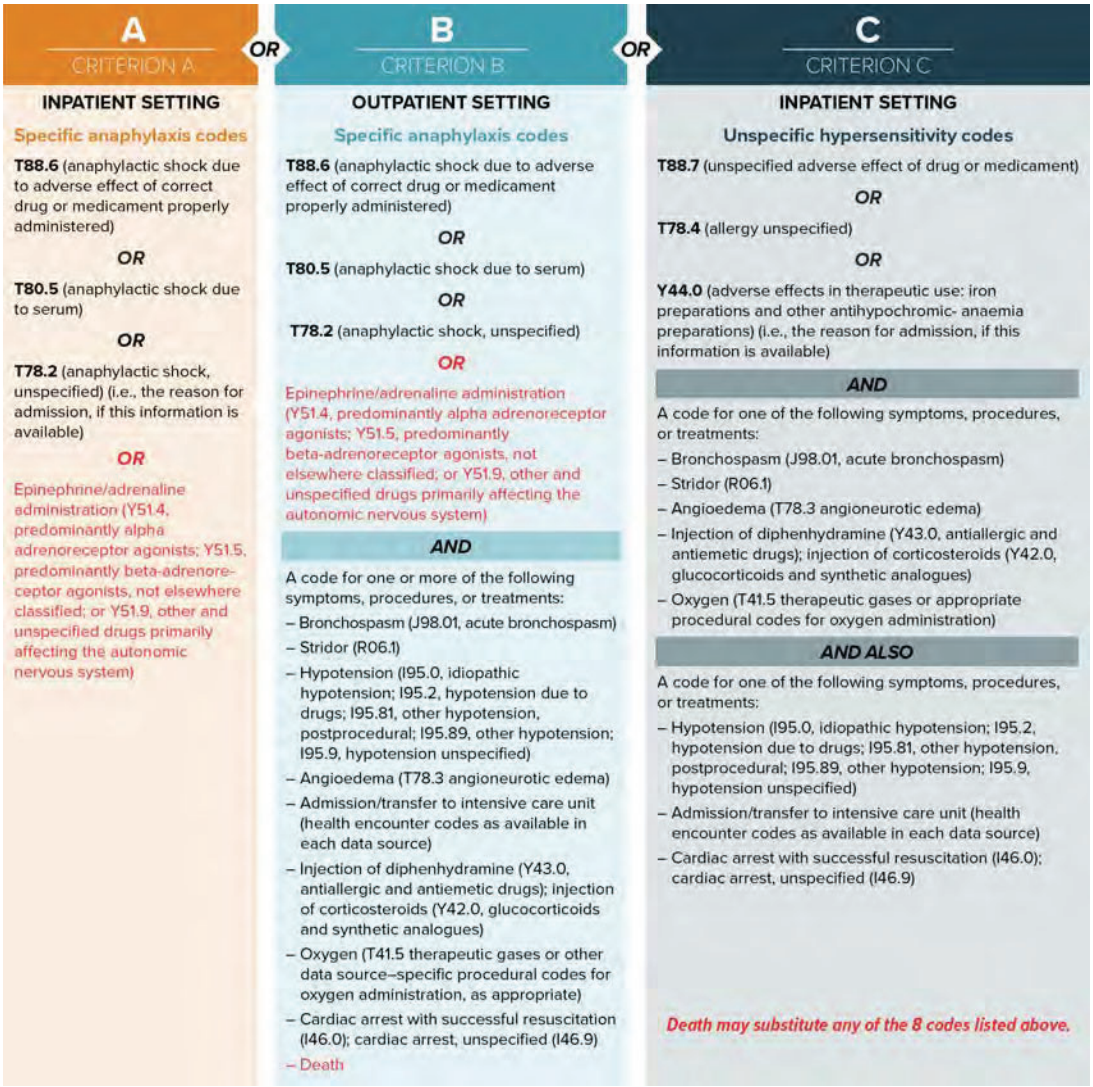
An expanded algorithm was developed for a sensitivity analysis including the following modifications to the main algorithm (Figure 8):

- Adrenaline administration within the defined risk window, in data sources capturing "actual" administration of adrenaline, was considered indicative of anaphylaxis in an inpatient setting. Consequently, adrenaline administration was removed from the list of additional clinical information for Criterion C. For Criterion B (outpatient setting), adrenaline was removed from the list of additional clinical information, and at least one of the remaining clinical items was required for ascertainment of an anaphylaxis.

- Death occurring within 72 hours after IV iron or IV penicillins treatment and allergic urticaria were added as equivalent to the additional clinical information required for Criterion B and Criterion C.

These modifications to the algorithm were agreed by the research team and endorsed by the external scientific advisory board in March 2019. The addition of the expanded algorithm was also documented in the amended protocol of 26 September 2019 (Section 9.7.4.1).

**Figure 8. Expanded Anaphylaxis Algorithm**



#### 9.4.1.2 Outcome Validation

Direct validation i.e., confirmation of potential cases in the study cohort by examining the source record was feasible only in the Danish national and regional linked registries and databases and in PHARMO-NL. We also conducted indirect validation i.e., confirmation of potential anaphylaxis reaction events of any origin using source records in the Oldenburg Hospital in Germany with no possibility to establish a link to the potential study cases identified in the GePaRD database. These potential anaphylaxis events were identified using algorithms approximating the case-identification algorithms applied to the GePaRD data in Germany.

**Direct Case Validation in Denmark and The Netherlands**

In Denmark, it was possible to conduct direct validation of all potential cases of anaphylactic reactions identified through linked data sources through review of medical records. The Danish Patient Safety Board granted permission to perform validation of all potential cases identified through the main and expanded algorithms among users of IV iron and potential cases identified through the main algorithm only among users of IV penicillins.

The PHARMO Institute performed direct case validation of all potential cases identified through the main and expanded algorithms among users of IV iron and IV penicillins in the PHARMO-NL. PHARMO-NL worked with a third-party organisation, Stichting Informatievoorziening voor Zorg en Onderzoek, to de-anonymise the potential cases and request local ethics committees' approvals at the individual hospitals for access to patient medical records. Only cases from the hospitals that granted approval were included in the validation analysis.

**Indirect Validation of Case-Identification Algorithm in Germany**

Owing to data-protection rules, no linkage of individual patients between the Oldenburg Hospital and GePaRD was possible. Therefore, we validated the case-identification algorithm. This indirect validation of the case-identification algorithm used in the GePaRD was conducted using the Hospital Information System (digitalised inpatient/emergency room discharge diagnoses coded using the German modification International Classification of Diseases, 10$^{th}$ revision (ICD10-GM) codes and outpatient clinic visit diagnoses) and electronic medical record data (clinical data) at the Oldenburg University Hospital in Germany, which is part of the area covered by the GePaRD. All potential cases identified through the anaphylaxis-identification algorithm, regardless of exposure/trigger, among patients aged 18 years or older discharged between 01 January 2004 up until 30 April 2019 from the departments that agreed to contribute data (i.e., cardiology, nephrology, dermatology, and emergency medicine) were eligible for validation. The estimated PPV and 95% CIs of the algorithms used to identify anaphylaxis events were calculated.

### *9.4.2 Study Exposures*

The Anatomical Therapeutic Chemical (ATC) classification system code B03AC (parenteral iron preparations) was used to identify IV iron exposure in each data source. Additional country and data source-specific coding nomenclatures were also used for

identifying substance- or product-specific information including recording of prescription, dispensing, and procedural treatment administration codes for IV drugs, as available.

The selected study IV iron products and corresponding ATC codes captured in the study data sources are presented in Table 1.

**Table 1. Study IV Iron Compounds**

| Type of Intravenous Iron Product [Naming convention*] | ATC Drug Class/ Substance Code | Country |
|---|---|---|
| Iron sucrose complex [iron sucrose] | B03AC/B03AC02 | Denmark, Germany, Netherlands, Sweden |
| Ferric carboxymaltose complex [iron carboxymaltose] | B03AC/B03AC01 | Denmark, France, Germany, Netherlands, Sweden |
| Iron(III)-hydroxide dextran complex [iron dextran] | B03AC/B03AC06 | Denmark, Germany, Netherlands, Sweden |
| Iron(III) isomaltoside complex [iron isomaltoside] | B03AC/B03AC06 | Denmark, Germany, Netherlands, Sweden |
| Sodium ferric gluconate complex [iron gluconate] | B03AC/B03AC07 | Germany |

ATC = Anatomical Therapeutic Chemical (classification system); IV = intravenous.

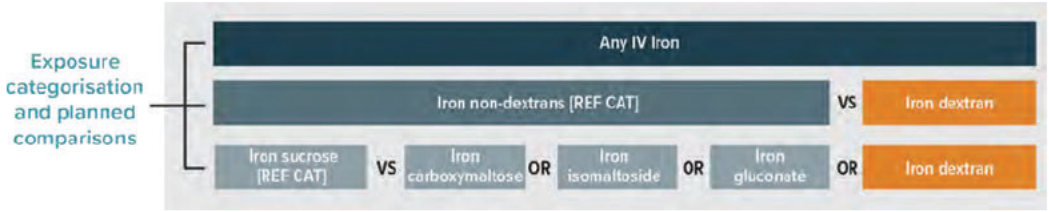
*The IV iron naming convention terminology is used throughout this document to refer to individual types of IV iron products using a simplified name.

Note: The ATC classification version of January 2014 classified all "Iron, parenteral preparations" on the ATC 4th level only (B03AC), and the 5th-level ATC codes (e.g., B03AC01, B03AC02) were deleted. This means that the 4th-level ATC codes can be used only in combination with product names.

To address the study objectives, IV iron exposure data were categorised by group of IV iron and where feasible, by individual IV iron types as shown in Figure 9.

For comparative analyses, iron dextran was compared with iron non-dextrans. In addition, the individual IV iron types listed in Figure 9 below were each compared with iron sucrose, the IV iron type with longest time since marketing authorisation and the largest expected number of users.

**Figure 9. IV Iron Exposure Categorisation**




IV = intravenous; REF CAT = reference category for the comparison by iron group (iron dextran vs. iron non-dextran) and by individual iron types.

### *9.4.3 Covariates*

The following variables were assessed through descriptive analyses as risk factors or potential confounding variables for potential adjustment of incidence estimates:

- Demographic/other variables: age, sex, year of new use of IV iron.
- History of medical conditions considered to be proxies of prior history of hypersensitivity reactions, severity of anaemia, possible indications of IV iron treatment and other relevant comorbidities. Prior use of selected medications was also considered. Diagnosis codes for medical conditions were evaluated from outpatient, inpatient, or emergency department encounters, depending on data available in each data source using International Classification of Diseases (ICD), 9th or ICD-10 Revision, or International Classification of Primary Care codes among others. Medications were identified using ATC codes and data source-specific codes/variables. Note that some variables were not available in all data sources, were underrecorded, or available only for a subset of the study population.

The evaluation period for each variable was set according to the chronicity of the conditions/medications and relevance as confounding variables. In general, the research team used all information available before the cohort entry date on conditions related to prior history of hypersensitivity reactions, relevant comorbidities, and specific chronic conditions that could be potential confounders. For more acute conditions (e.g., GI bleeding and peptic ulcer) a shorter lookback period was assessed. Data on prior use of medications, including use of other medications for anaemia, were generally based on information available during the 6 months before cohort entry.

## 9.5 Data Sources and Measurement

The study was conducted following a common core protocol and a core statistical analysis plan in populations covered in the six population-based health databases and registries in Europe listed in Section 9.2. The DIMDI-DaTraV database was unable to contribute data to the study (see Section 9.9.5). Summary information on main characteristics of the data sources and availability of health information relevant to this PASS is presented in Table 2.

**Table 2. Selected Characteristics and Outcome and Variable Assessment in Study Data Sources**

| Characteristic | Danish National and Regional Linked Registries and Databases | SNDS, France | PHARMO-NL | GePaRD, Germany | KfH QiN, Germany | DIMDI-DaTraV, Germany* | Swedish National Registers |
|---|---|---|---|---|---|---|---|
| Database population | 1,295,584 (adult population 1,021 908 as of 2016) of the Central Denmark region | 66,600,000 | 3,200,000 | ~25,000,000 | 18,000 dialysis patients annually | 70,000,000 | 9,995,153** (as of 2016) |
| Database type | Administrative routinely collected data linked from several databases and restricted to the catchment population of the area served by the hospitals in the Central Denmark Region, as data on hospital based IV iron administration were complete | Contains information from all out of hospital claims linked to the national hospital discharge summaries database system and the national death registry. Covers the three main health care insurance | PHARMO NL holds several databases, linked on patient level. For this study, GP data, outpatient pharmacy data and inpatient pharmacy, and hospitalisation data, were used. | Contains claims data for reimbursement of diagnostic and therapeutic services from four Statutory Health Insurance providers (SHIs). Population represents approximately 17% of the German population. | KfH is the largest provider of haemodialysis in Germany. Comprises more than 200 dialysis clinics. Data for adult patients undergoing dialysis are collected electronically through the QiN registry system. | Contains claims data from Statutory Health Insurance providers (SHIs) approximately representing 90% of German population. | Prescribed Drug Register since 1 Jul 2005<br>Patient registers: hospital admissions and hospital outpatient visits<br>Register of the total population<br>Cancer register |

| Characteristic | Danish National and Regional Linked Registries and Databases | SNDS, France | PHARMO-NL | GePaRD, Germany | KfH QiN, Germany | DIMDI-DaTraV, Germany* | Swedish National Registers |
|---|---|---|---|---|---|---|---|
| | | systems plus a majority of smaller ones, representing approximately 99% of the French population. | | | | | |
| **Drugs** | | | | | | | |
| Administered/Dispensed drugs | Prescribed and administered treatments (from inpatient hospitals' data and hospital outpatient specialists clinics as recorded in the Health Services Database of the Central Denmark Region). ATC code plus active substance name, strength, brand, route of administration, | Dispensed reimbursed drugs from outpatient pharmacy and inpatient pharmacy (only for a list of expensive drugs).<br>Date of treatment administration based on the date of the first outpatient nurse visit encounter | Out patient Pharmacy Database (dispensed drugs), Inpatient Pharmacy Database (administered treatments, date and route of administration), and partial GP Database (prescribed or dispensed).<br>ATC codes (drug class code, active substance code through free text searching on package label)<br>Brand name, dose, date of prescription/dispensing | Prescribed and dispensed treatments from outpatient pharmacies with date of prescription and dispensing, linkable via an identification code (PZN) to ATC codes, brand name, active substance name, strength, dosage form and dose dispensed | Administered reimbursed treatments in dialysis centres.<br>ATC codes<br>Brand name/compound type, dosage, route, and date of administration | Outpatient pharmacy data with date of prescription (date of dispensing not captured).<br>Brand name, dose and duration based on PZN number and DDD | Drugs dispensed by prescription in community pharmacies since July 1, 2005, (reimbursed and not reimbursed medications). For this study drug exposure data captured since Jan 1, 2007, (2006 as wash out)<br>ATC codes<br>Brand name/compound type; dosage and date of dispensing |

| Characteristic | Danish National and Regional Linked Registries and Databases | SNDS, France | PHARMO-NL | GePaRD, Germany | KfH QiN, Germany | DIMDI-DaTraV, Germany* | Swedish National Registers |
|---|---|---|---|---|---|---|---|
| | amount dispensed, date of dispensing, and administration | after drug dispensing (when available) ATC and CIP codes, brand name, dosage, quantity of packs dispensed | (Out patient Pharmacy and GP Databases), route of administration (partially from dosing details in the outpatient pharmacy data) | | | | |
| **Study outcome & other variables and outcome validation** | | | | | | | |
| Hospital diagnoses | Yes, ICD 10 codes for discharge diagnoses, through linkage with data from the Danish National Patient Registry (DNPR). ER, only if overnight stay | Yes, ICD 10 codes. Discharge diagnoses. ER diagnoses only if overnight stay | Yes, ICD 9 & ICD 10 codes. Discharge diagnoses. ER diagnoses, only if resulting in overnight stay | Yes, ICD 10 GM codes. Admission and discharge diagnoses including secondary and ancillary diagnoses and corresponding dates | Yes, ICD 10 GM codes | Yes, ICD 10 GM codes. Discharge diagnoses (month of discharge) | Yes, ICD 10 codes, admission and discharge. ER diagnoses captured*** |
| Outpatient diagnoses | Yes, ICD 10 codes from hospital outpatient | Not available | GP data (ICPC codes) for a subset population | Yes, ICD 10 GM codes. Outpatient care diagnoses (quarter of visit) | Not available | Yes, ICD 10 GM, date of visit as | Yes, hospital outpatient clinics diagnoses |

| Characteristic | Danish National and Regional Linked Registries and Databases | SNDS, France | PHARMO-NL | GePaRD, Germany | KfH QiN, Germany | DIMDI-DaTraV, Germany* | Swedish National Registers |
|---|---|---|---|---|---|---|---|
| | clinics diagnoses at DNPR | | | including primary care (GP) and specialists diagnoses. Procedures and prescriptions were used to derive the exact date for outpatient diagnoses | | quarter and year | |
| **Study outcome** | | | | | | | |
| Outcome validation | Yes, through review of medical records | No access to medical record data possible. | Yes, through clinical review of hospital medical records | No access to medical record allowed.<br>Clinical review of patient profiles (i.e., reconstructed patient medical record based on claims).<br>Indirect validation of anaphylaxis algorithm through Oldenburg University Hospital | No access to medical record allowed. | No access to medical record allowed. Indirect validation of anaphylaxis algorithm through Oldenburg University Hospital | No access to medical record allowed. |

ATC = Anatomical Therapeutic Chemical (classification system); CIP = French pharmacy dispensing coding system; DDD = Defined daily dose; DIMDI DaTraV = Information system for health care data (data transparency) of the German Institute of Medical Documentation and Information; DNPR = Danish National Patient Registry; ER = emergency room; GePaRD = German Pharmacoepidemiological Research Database; GP = general practitioner; ICD = International Classification of Diseases; ICPC = International Classification of Primary Care; IV = intravenous; KfH QiN = Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme; PHARMO NL = PHARMO Database Network in the Netherlands; PZN = Pharmazentralnummer, nationwide german identification number for pharmaceuticals; SHI = statutory health insurer; SNDS = Système National des Données de Santé (French National Health Care Insurance System Database).

* In the end, DIMDI DaTraV did not provide data for the study.

** In 2016, 6,530,258 individuals had had at least one drug dispensed out of a total of 9,995,153 people covered by the national registry.

*** In the Swedish National Patient Register, ER visits are captured by the use of information on "unplanned visits".

## 9.6 Bias

### *9.6.1 Confounding*

In this study, the initial plan was to control for confounding through propensity score stratification using relevant baseline covariates. However, the small number of events identified precluded this approach (see Section 9.9.5).

### *9.6.2 Outcome Misclassification*

In all data sources, the anaphylactic reactions outcome was identified through electronic algorithms (see Section 9.4.1.2). In data sources where medical record review was feasible (the Central Denmark Region and PHARMO-NL), validation via medical record review was performed for all identified potential cases for hospitals/departments where access to records was permitted. Indirect validation of the anaphylaxis algorithm applied to the GePaRD data in Germany was conducted through review of medical records of potential cases of anaphylaxis reactions in the Oldenburg University Hospital, in Germany.

## 9.7 Study Size

The study included all available patients fulfilling the inclusion criteria and none of the exclusion criteria. Preliminary data on IV iron use obtained from the 2014 and 2016 feasibility evaluations suggested that approximately 250,000 to 300,000 patients with IV iron dispensings or administrations would be available across all data sources. As detailed in the final endorsed study protocol, the focus was on the study precision calculations derived from the estimates of risk of anaphylactic reactions for IV iron dextran and non-dextrans reported by Wang et al. (2015). Table 3 shows the study precision calculations for two risk scenarios for IV iron dextran and non-dextrans. The PASS 14 software (NCSS, LLC. Kaysville, Utah; 2015. http://www.ncss.com/software/pass/) was used for the calculations.

**Table 3. Protocol Study Precision Calculations**

| Number of Patients | Dextrans 95% CI for Risk of 6.8 per 10,000 Persons | Non-dextrans 95% CI for Risk of 2.4 per 10,000 Persons |
|---|---|---|
| 10,000 | 2.69 to 14.15 | 0.38 to 7.85 |
| 8,000 | 2.34 to 15.35 | 0.27 to 8.87 |
| 6,000 | 1.88 to 17.25 | 0.16 to 10.52 |
| 4,000 | 1.25 to 20.84 | 0.05 to 13.75 |
| 3,000 | 0.85 to 24.27 | 0.02 to 16.91 |
| 2,000 | 0.39 to 30.88 | 0 to 23.16 |

CI = confidence interval.

Source of risk estimates: Wang et al. (2015).

## 9.8 Data Transformation

At each research centre, raw data were obtained and transformed and harmonised into a study specific common data model (minimal informative data sets for demographics, drugs, diagnoses and person characteristics). At each centre, analysis data sets were derived from these data.

The following transformations were made to the analytical data sets:

- Age was categorised according to 10-year age groups except for the groups aged 18 to 24 years and 85 years or older.
- IV iron exposure was categorised into iron dextran and iron non-dextrans (all other iron types). IV iron exposure was also categorised into individual IV iron types as described in the Section 7 (Research question and objectives).
- IV penicillins were categorised into subtypes i.e., natural penicillins, betalactamase-resistant penicillins, aminopenicillins, carboxypenicillins, ureidopenicillins and other penicillins.

## 9.9 Statistical Methods

Data analyses occurred in two stages: (1) an analysis conducted at each data source and (2) a combined analysis of aggregated data conducted by the coordinating centre, where summary data from each data source were integrated.

The objective of the study was to assess the risk of anaphylaxis among users of IV iron across all study data sources. Comparisons between data sources were not part of the objectives.

All analyses were conducted according to the originally endorsed study protocol dated 04 May 2017, the endorsed amended protocol of 26 September 2019, and the plan of analyses detailed in the statistical analysis plan (SAP) dated 19 December 2017, with documentation of data source-specific adaptations. Data specifications that varied between the data sources were documented and maintained by each data source. Amendments to and deviations from the SAP are described in Section 9.9.5.

Not all data sources captured data for all IV iron compounds targeted for analyses or for the IV penicillins cohort; therefore, each research centre performed the analyses that were applicable to their data.

Most research partners conducted analysis using SAS software (SAS Institute, Inc, Cary North Carolina), researchers from the KfH QiN dialysis registry in Germany conducted analysis using R software.

Analyses of data across data sources included estimates for IPs and RRs and risk differences (RDs) using iron sucrose as the common reference. Crude pooled analysis and beta-binomial meta-regression techniques were employed to integrate the data across sources.

### *9.9.1 Main Summary Measures*

Categorical variables were summarised by frequencies and proportions, and continuous variables were summarised by means and standard deviations, medians and interquartile ranges (first quartile to third quartile), and minimum and maximum values.

Crude IPs of anaphylactic reactions were calculated for each IV iron exposure group and the IV penicillins cohort expressed per 10,000 person-years with Wilson score 95% CIs.

Crude RRs and RDs with corresponding 95% confidence intervals (CIs) derived from the Miettinen-Nurminen method were estimated to compare the IP estimates of anaphylactic reactions between the pairs of IV iron groups.

For all analyses and for reporting purposes, country-specific data-protection rules were taken into consideration (see Table 4 for cell-count limit specifications).

### *9.9.2 Main Statistical Methods*

#### 9.9.2.1 Descriptive Statistics

Descriptive analyses were performed as a first step, to inform final decisions on the analytical approach.

At each data source, patients were identified after the application of each inclusion and exclusion criterion, beginning with the total number of registered patients in the data source and ending with the number of patients ultimately included in the IV iron cohort based on the first exposure. The process of cohort identification was repeated for users of IV iron compounds based on second exposure, third or subsequent exposure, and any exposure. For the IV penicillins cohort, the number of patients for each IV penicillins compound were identified where applicable. This process was repeated based on any treatment of an IV penicillins compound (regardless of the type) in which the number of patients and number of treatments were tabulated for each criterion.

Descriptive statistics were calculated to summarise baseline characteristics (e.g., demographic information, comorbidities, and medication use) of users of IV iron and new users of IV penicillins compounds. These baseline characteristics were presented only for the "any" dispensing/treatment of interest. Separate tables were generated for users of each exposure of interest, grouped as follows:

- Any IV iron product; iron dextran and iron non-dextrans
- Iron carboxymaltose, iron isomaltoside, iron gluconate, iron dextran, and iron sucrose
- Intravenous penicillins

Data source-specific limits on the minimum number of counts per cell that can be reported, which are driven by data-protection regulations, were considered given the expected low number of outcomes (Table 4).

**Table 4. Cell Counts Limits by Data Source**

| Data Source | Minimum Reportable Number of Individuals per Cell | Possibility of Reporting Smaller Cell Counts for Regulatory-Driven Research |
|---|---|---|
| Danish national and regional linked registries and databases | 5 individuals per cell | Limit applies to regulatory-driven studies and publications |
| PHARMO Database Network, the Netherlands (PHARMO-NL) | 5 individuals per cell | Does not apply to regulatory-driven reports; does apply to publications |
| French National Health Care Insurance System Database (SNDS, France) | 10 individuals per cell (applies only to descriptive data) | Does not apply to regulatory-driven reports and publications |
| German Pharmacoepi-demiological Research Database (GePaRD, Germany) | No established limits, data must be fully de-identified | |
| Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme (KfH QiN, Germany) | No established limits, data must be fully de-identified | |
| Swedish National Registers | No established limits, data must be fully de-identified | |

GePaRD = German Pharmacoepidemiological Research Database; PHARMO-NL = PHARMO Database Network in the Netherlands; KfH QiN = Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme; SNDS = Système National des Données de Santé (French National Health Care Insurance System Database).

#### 9.9.2.2 Crude Incidence Proportions and Crude Comparative Analyses

**Analysis Performed at Each Data Source**

The time window at risk for outcome events for the main analyses was the day of the administration (1-day risk window) for data sources capturing actual drug administration and the day of dispensing and the day after (2-day risk window) for data sources capturing drug dispensing.

Incidence proportions were calculated as the number of patients with an incident anaphylaxis event (E) that occur during the 1-day or 2-day risk window among IV iron users divided by the total number of patients or patient treatments at risk (N). In the results tables, the IP are expressed per 10,000 patients:

$$IP = \frac{E}{N} \qquad \text{[Equation 1]}$$

Given that the incidence of anaphylaxis was expected to be very small, the 95% CIs for IP estimates were calculated as follows using the Wilson score interval, which is recommended as the most robust for rare events (Brown et al., 2001):

$$IP_{95\%} = \frac{IP + \frac{z^2_{0.025}}{2N} \pm z_{0.025}\sqrt{\frac{IP(1-IP)}{N} + \frac{z^2_{0.025}}{4N^2}}}{1 + \frac{z^2_{0.025}}{N}} \qquad \text{[Equation 2]}$$

In the above equation, the term *z* represents the value of the standard normal distribution associated with the indicated level of confidence.

These unadjusted estimates served as an initial step in characterising risk and providing insight into the feasibility of conducting subsequent analyses. Among the crude IV penicillins compound populations, the total number of patients or patient treatments at risk and the number of anaphylaxis events were also calculated. Using equations 1 and 2, respectively, crude IP estimates and 95% CIs were calculated separately for initiators of IV penicillins compounds and for any dispensing/treatment of IV penicillins. The IP of anaphylactic reactions among those exposed to the IV penicillins compounds was used to gauge the performance of the case-identification algorithm which helped provide context to the results for IV iron products. The study was not designed for direct comparisons between the IV penicillins cohort and any of the IV iron groups (or types).

Incidence proportion estimates of anaphylaxis between the pairs of IV iron groups and types listed below were compared with RRs and RDs.

The RR is the IP of one type of IV iron compound (referred to using the subscript "*i*") divided by the IP of another type of IV iron compound that serves as a referent compound (subscript "*Ref*"). Thus, RR estimates of predicted compound initiators relative to referent compound initiators were computed as follows:

$$R = \frac{IP_i}{IP_{Ref}} = \frac{E_i/N_i}{E_{Ref}/N_{Ref}} \qquad \text{[Equation 3]}$$

The RD was also calculated to compare the occurrence of anaphylaxis between initiators of various types of IV iron compounds. The RD estimates were computed as follows:

$$RD = IP_i - IP_{Ref} \qquad \text{[Equation 4]}$$

The 95% CIs for RR and RD estimates were then calculated using the Miettinen-Nurminen method (Miettinen and Nurminen, 1985), which performs well in cases of rare events (Klingenberg, 2014). Miettinen-Nurminen CIs for RR and RD estimates are standard options implementable in the FREQ procedure in SAS version 9.4.

For users of each type of IV iron compound, unadjusted IP estimates and 95% CIs were calculated (using equations 1 and 2). Additionally, between IV iron compounds of interest, unadjusted RR and RD estimates and their 95% CIs were calculated and summarised. Because risk of anaphylaxis is highly dependent on the history of previous administrations of the studied drug, risks were assessed stratifying by first, second, and subsequent dispensings/administrations of the study drugs, as well as overall with all dispensings/administrations combined.

These estimates are presented for the following IV iron groups and IV iron subtypes:

- Any IV iron compound, iron dextran, and iron non-dextrans; RR and RD estimates comparing iron dextran to iron non-dextrans (referent compound)

  - New users or first dispensing or administration
  - Second dispensing or administration
  - Third or subsequent dispensing or administration
  - All dispensing or administration where the exposure and number of events for each patient are accumulated over the entire observation period
- Iron carboxymaltose, iron isomaltoside, iron gluconate, iron dextran, and iron sucrose; RR and RD estimates comparing each individual compound to iron sucrose (referent compound)
  - New users or first dispensing or administration
  - Second dispensing or administration
  - Third or subsequent dispensing or administration
  - All dispensing or administration where the exposure and number of events for each patient are accumulated over the entire observation period

**Meta-analyses Performed at the Coordinating Centre**

Meta-analyses of data across research centres focused on summarising IP, RR, and RD estimates. The coordinating centre compiled aggregated data from each research centre into integrated data sets for analysis. Summary data of IP, RR, and RD estimates specific to each research centre were combined into a single source for a comprehensive presentation alongside the meta-analysed estimates across data sources.

As an initial step, crude methods were applied to summarise data across research centres. For each IV iron compound and for IV penicillins, IP estimates were generated by summing the number of potential anaphylaxis events across research centres (numerator), summing the total number of treatments or patients across research centres (denominator), and dividing these two values (numerator divided by denominator). Crude RR and RD estimates were computed using equations 3 and 4, respectively, to compare IV iron dextran to IV iron non-dextrans and to compare each individual type of IV iron to IV iron sucrose. As in the analyses conducted by each individual research centre, 95% CIs were derived from the Wilson score method for the IP and from the Miettinen-Nurminen method for the RR and RD.

Crude methods, while insightful as an initial step, are susceptible to bias due to the assumption of the same underlying risk of anaphylaxis across research centres (Altman and Deeks, 2002; Lievre et al., 2002). Meta-analytic methods are typically applied to stem this potential bias. However, in situations where research centres have zero events, these traditional methods either ignore information from these research centres or apply continuity corrections, both of which have the potential to introduce error (Kuss, 2015).

In situations of rare events, particularly when some studies have zero events, simulation studies have recommended the use of beta-binomial regression (Kuss, 2015; Ma et al., 2016), which is a type of binary regression that accounts for overdispersion, to provide summary estimates across research centres. Beta-binomial regression was implemented

using the finite mixture model (FMM) procedure in SAS with default iteration and convergence parameters and the dual quasi-Newton optimisation technique to obtain maximum likelihood estimates. The logit link was used to estimate regression coefficients, and the inverse logit function was applied to these regression coefficients to derive IP point estimates for each compound of interest. For comparative analyses, RR point estimates were derived by dividing corresponding model-derived IP estimates (Equation 3), and RD point estimates were derived by subtracting corresponding model-derived IP estimates (Equation 4).

To avoid relying on assumptions of IP, RR, and RD distributions in this situation of very rare events, confidence intervals around these parameter point estimates were derived from Monte Carlo methods. From the results of each beta-binomial model, 10,000 random samples of the regression coefficients were drawn from the multivariate normal distribution while incorporating model-derived regression coefficient point estimates and their corresponding variance-covariance matrix. For each random sample of regression coefficients, the inverse logit function was applied to derive IP values for each compound, and RR and RD values were computed using equations 3 and 4, respectively, for comparative analyses. For each of these derived parameters, the 2.5th and 97.5th percentiles across all 10,000 random samples were computed to serve as the lower and upper bounds of the 95% CI.

**Validation Analysis**

As described in section 9.4.1.2, direct validation of potential anaphylaxis events through medical record review was only possible in the Central Denmark Region and PHARMO-NL database. The validity of the main and modified algorithms used to identify potential anaphylaxis events in these two study populations were assessed by calculating their positive predictive values. The PPVs for the algorithms are presented with 95% CIs for binomial proportions by the exact method.

The PPV was defined as the probability that a patient classified as a potential anaphylaxis event by the algorithm was a confirmed case of anaphylaxis. Positive predictive values were calculated among the total number of potential cases originally identified by the algorithm that were accessible for abstraction of medical records. In addition, PPVs were also calculated including in the denominator all potential events identified by the case-identification algorithm, irrespective of medical record accessibility.

Adjustments of the IPs based on the PPVs could be performed in PHARMO-NL data for IV penicillins. In the Central Denmark Region the adjustment of the IPs could ultimately not be performed due to data privacy rules aimed at preventing the identification of individual patients.

### *9.9.3 Missing Values*

Information on some covariates (e.g., laboratory test results) was not available in all the study data sources. When information on a variable was not available in a study data source, this variable was not evaluated in descriptive tables. For all other variables (both continuous and categorical), the number of non-missing observations were reported as part of the descriptive summary. No regression analyses were performed at the research partner level due to the rareness of the event. All meta-analyses were performed using only observed data of numerators (number of anaphylaxis events) and denominators

(number of patients exposed to, or dispensings of, the compound of interest) in applicable data sources. Thus, no imputation methods for missing data were performed as the potential for missing covariate data did not factor into any regression analyses.

### *9.9.4 Sensitivity Analyses*

Sensitivity analyses were focused on the calculation of IPs, RRs and RDs of anaphylactic reactions among the different types of IV iron compounds assuming different scenarios of risk. Estimates were derived using the same methods described in Section 9.9.2.2. The following risk scenarios were considered:

- *Expansion of the case-identification algorithm* (See Section 9.4.1.1): In this analysis, the criteria of the "Main Outcome Algorithm" were modified to assess the potential for missed study outcomes among IV iron first, second, third and subsequent and any users by group and individual types and for IV penicillins among first and any users and by IV penicillins (any) subtype.
- *Expansion of the risk window from day 0 to day 7*: The expansion of the risk window was conducted in all data sources except in the KfH QiN dialysis registry in Germany, where date of IV iron administration and date of anaphylaxis diagnoses were captured. In all sites except KfH QiN, all potential events were identified using the main case identification algorithm during a 7-day period after the date of exposure to a first, second, third or subsequent IV iron use by group and by type. The calculations of IPs and incidence RRs were based on all sites including KfH QiN that contributed data for day 0 only.
- *Risk among IV iron switchers:* This analysis assessed the occurrence of potential events among patients switching between different types of IV iron at the first and any switch by IV iron group and type.
- R*isk among IV iron users (any) before 01 January 2013 and after 31 December 2013:* This analysis assessed the potential effect of the EMA Referral Assessment Letter. Cases identified during 2013 were not accounted for.
- *Analysis removing data sources with no study cases from the pooling of the aggregate data (IV iron and IV penicillins)*: This analysis represented a "worst-case scenario" because the removal of these patients from the denominator would cause an increase in the observed IP which would result in an overestimation of the risk.
- *Analysis of any use of IV iron:* This analysis assessed the risk of anaphylaxis among new and prevalent users of IV iron.
- *Number of potential anaphylaxis reactions identified after the risk window (up to 21 days):* This analysis was intended to address the potential delayed administration of a dispensed IV iron among users (any) of IV iron by group and type and among IV penicillins users.
- *Listing of causes of death of fatal cases*: in data sources where these data were available.

- *Risk among IV iron users excluding dialysis patients:* Given the differences between the population of patients undergoing dialysis receiving IV iron treatment compared with patients treated for other indications, this analysis was of relevance. Applied to IV iron users at first, second, third or subsequent and any dispensing/treatment by group and by type.
- *Risk among IV iron dialysis patients only*: Applied to IV iron users (any) by group.

### *9.9.5 Amendments to the Statistical Analysis Plan*

The PRAC-endorsed amended protocol dated 26 September 2019 incorporated most deviations to the original analyses detailed in the SAP dated 19 December 2017. Listed below are the complete list of deviations to the SAP.

**SAP Section 2 (Study Design), Section 2.1 (Data Sources), Section 2.2 (Population)**

DIMDI-DaTraV Database: In spite of the highly engaged and motivated DIMDI principal investigator, the limited resources available at DIMDI to perform study-related activities precluded inclusion of this database in the study. Furthermore, the rules at DIMDI did not allow to fund additional resources for the study. This situation was further complicated by the ongoing merger between the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizineprodukte [BfArM]) and DIMDI. As of February 4, 2020, no data from DaTraV are available for the final report. It is worth noting that the critical limitation identified during the study feasibility assessment concerning the lack of date on hospital admission combined with the lack of the last year of data for patients who died remains unchanged.

**SAP Section 2.5.1 Descriptive Analyses (Crude Risk Ratios and Risk Differences)**

Due to the low number of events identified in the study, the planned Wald-based approach for calculation of the 95% CIs for the RRs could not be performed. Similarly, the planned calculations provided for the 95% CIs for the RD were modified accordingly. For both the RR and RD, the Miettinen-Nurminen method was used to calculate the 95% CIs of RRs.

**SAP Sections 2.5.2 and 2.5.3 Propensity Score Analyses and Adjusted Incidence Proportions and Comparative Analyses**

The PRAC-endorsed protocol of 04 May 2017 proposed the use of propensity scores to adjust the RR estimates, a method that was chosen because of its usefulness in situations where a small number of events is expected. Preliminary descriptive results reviewed by the study investigators in March 2019 indicated that the number of events identified through the main analyses were very low. Additional sensitivity analyses performed to address the potential for missing study outcomes provided similar results. Propensity score methods and other methods to address confounding are not able to deal with situations of extremely small numbers of study events, as encountered in this study. Therefore, the research team agreed that the low number of events did not allow

for the planned implementation of propensity scores and estimation of adjusted comparative analyses.

**SAP Section 2.5.5 Analysis of Validated Cases (Only Research Partners Performing Case Validation)**

The originally planned analyses considering only confirmed cases of anaphylactic reactions after validation among research partners, were not performed due to impossibility to validate all potential cases and also due to Danish data-protection rules in low count situations.

**SAP Section 2.5.4 Sensitivity Analyses**

The following additional sensitivity analyses were performed (see Section 9.9.4 for additional information):

- Expanded anaphylaxis-identification algorithm
- Incidence proportions by subtype of penicillins
- Description of events occurring up to 21 days after the risk window
- Exclusion of dialysis patients

The planned listing of causes of death among fatal cases was not possible due to lack of cause of death data most from data sources or absence of fatal cases when cause of death was available (i.e., no fatal cases identified in Sweden).

## 9.10 Quality Control

The standard operating procedures, internal process guidance, or routine practice at each research centre were used to guide the conduct of the study. These procedures included, among others, internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

All programming written by one study analyst was reviewed independently by a different analyst, with oversight by a senior statistician, if possible. All key study documents, such as the study protocol, SAP, validation plan, abstraction forms, and study reports, underwent quality-control review, senior scientific review, and editorial review. The quality and audit trails are centre specific, and each research partner followed its own quality and audit trail procedures. Individual patient-level data are available at the centres only. Selected data fields are not available to be viewed by pharmaceutical companies.

For work conducted at RTI-HS, an independent Office of Quality Assurance performed internal audits and assessments that involved various aspects of the project, including but not limited to education and training documentation, data transfer procedures and documentation, and institutional review board documentation.

# 10 Results

**Owing to the reporting restrictions for cell counts below five for Denmark, the number of events and incidence estimates for the Central Denmark Region and for some estimates from the meta-analyses are reported as minimum and maximum ranges. Also, when data source-specific estimates are presented, numerators and denominators for the Central Denmark Region data are rounded to the nearest 10 to comply with data-protection rules aimed at prevention of identification of individuals.**

Complete results for all the analyses conducted at each data source and for the meta-analyses are provided in Annex 3 and Annex 4.

## 10.1 Participants

The study population consisted of all eligible patients with a recorded first, second, and third or subsequent exposure to IV iron compounds meeting all inclusion criteria and none of the exclusion criteria during the study period in each participating data source. The participating data sources provided data on the use of IV iron products in the general population in each country and also from a network of dialysis centers in Germany. The main results of the final cohort selection across data sources are summarised in this section.

Complete results of the IV iron cohort attrition process for each data source are provided in Annex 3, Cohort Attrition excel file, Tabs IV Iron-1$^{st}$ (first users), IV iron-2$^{nd}$ (second users), and IV Iron-3$^{rd}$ Sub (third or subsequent users).

The same cohort selection criteria were applied to identify eligible patients for inclusion in the IV penicillins cohort. Complete results of the IV penicillins cohort attrition process for each data source are provided in Annex 3, Cohort Attrition excel file, Tabs Penicillin-1$^{st}$ (first users) and Penicillin-Any (any users).

### *10.1.1 IV Iron Cohort*

#### 10.1.1.1 Overall and by IV Iron Groups: Iron Dextran and Iron Non-Dextrans

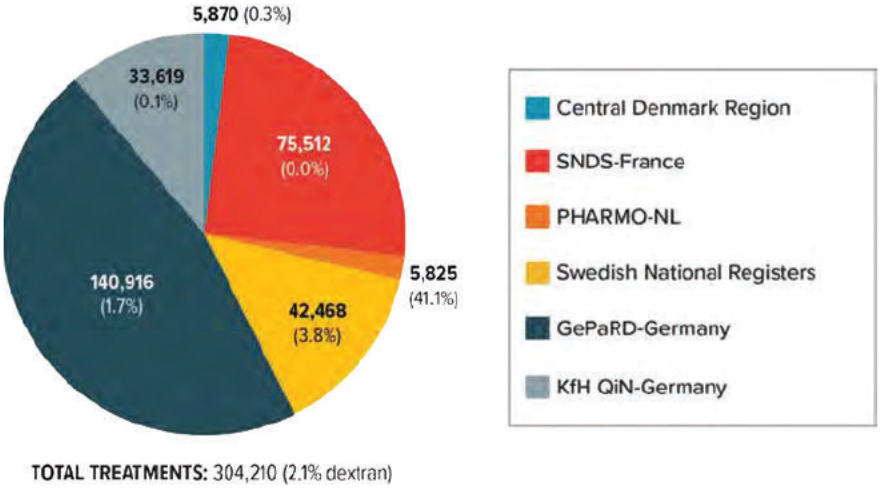
There was no comprehensive capture of all types of IV iron in any of the study data sources. Moreover, the IV iron exposure captured in this study is based on partial capture mostly reflecting IV iron treatment from ambulatory outpatient settings.

This section presents the final number of eligible IV iron exposures by ordinal number of the exposure to IV iron i.e., first exposure, second exposure, and third or subsequent exposure overall and for each data source. The percentage of IV iron dextran treatments over the total IV iron exposure is also provided.

### First Dispensing or Administration

Overall, 304,210 first IV iron treatments were identified during the study period across all data sources. The number of first IV iron exposures varied by data source from 5,825 in PHARMO-NL to 140,916 in GePaRD in Germany. Intravenous iron dextran treatments represented 2.1% of all first IV iron exposures with marked variability between data sources; notably IV iron dextran use represented 41.1% of the overall IV iron use captured in PHARMO-NL, while in the remaining data sources it ranged from 0.1% (KfH QiN, Germany) to 3.8% in the Swedish registers (Figure 10).

**Figure 10. Number of First IV Iron Treatments (Percentage of Iron Dextran)**



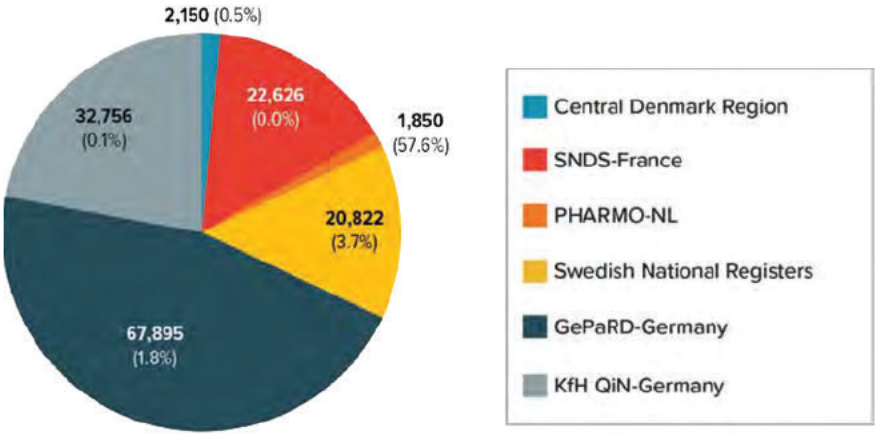

GePaRD = German Pharmacoepidemiological Research Database; IV = intravenous; KfH QiN = Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme; PHARMO-NL = PHARMO Database Network in the Netherlands; SNDS = Système National des Données de Santé (French National health care insurance system database, previously named SNIIRAM).

Note: Numbers for the Central Denmark Region data were rounded to the nearest 10 to comply with Danish data-protection and reporting requirements rules aimed at prevention of identification of individuals.

### Second Dispensing or Administration

There were 148,099 second IV iron exposures across data sources ranging from 1,850 treatments in PHARMO-NL to 67,895 treatments in GePaRD in Germany. The overall proportion of IV iron-dextran treatments was 2.1% of all IV iron treatments and in PHARMO-NL represented 57.6% of the total PHARMO-NL IV iron exposure (Figure 11).

**Figure 11. Number of Second IV Iron Treatments (Percentage of Iron Dextran)**



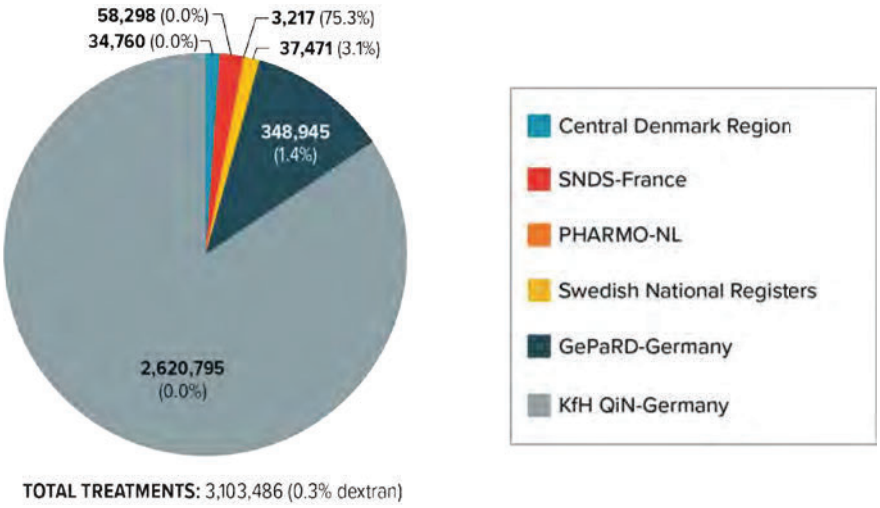

GePaRD = German Pharmacoepidemiological Research Database; IV = intravenous; KfH QiN = Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme; PHARMO-NL = PHARMO Database Network in the Netherlands; SNDS = Système National des Données de Santé (French National health care insurance system database, previously named SNIIRAM).

Note: Numbers for the Central Denmark Region data were rounded to the nearest 10 to comply with Danish data-protection and reporting requirements rules aimed at prevention of identification of individuals.

### Third or Subsequent Dispensing or Administration

For the third or subsequent IV iron exposures, a total of 3,103,486 exposures in 105,634 patients were identified of which 2,620,795 (84.4%) IV iron treatments were contributed by the KfH QiN dialysis registry and 348,945 (11.2%) IV iron treatments came from the GePaRD, both located in Germany. The average number of IV iron treatments per patient in the KfH QiN was 80 treatments per patient whereas in the general population data sources ranged from 2 to 8 treatments per patient. IV iron dextran accounted for 0.3% of third or subsequent IV iron exposures across all data sources, however, in PHARMO-NL IV iron dextran accounted for 75.3% of third or subsequent IV iron treatments (Figure 12).

**Figure 12. Number of Third or Subsequent IV Iron Treatments (Percentage of Iron Dextran)**




GePaRD = German Pharmacoepidemiological Research Database; IV = intravenous; KfH QiN = Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme; PHARMO-NL = PHARMO Database Network in the Netherlands; SNDS = Système National des Données de Santé (French National health care insurance system database, previously named SNIIRAM).

Note: Numbers for the Danish data were rounded to the nearest 10 to comply with Danish data-protection and reporting requirements rules aimed at prevention of identification of individuals.

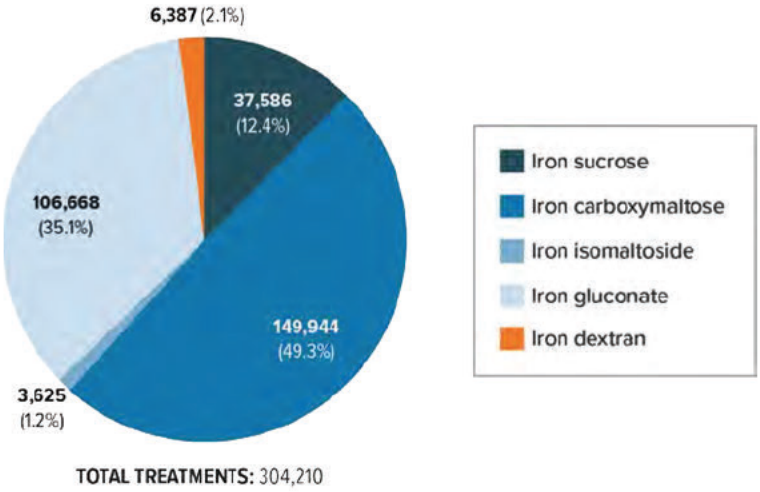
#### 10.1.1.2 Individual IV Iron Types

The distribution of the individual IV iron types differed across data sources. Iron carboxymaltose was the only IV iron product available across all data sources. Iron gluconate was available only in the GePaRD and the KfH QiN registry both located in Germany. The SNDS database in France contributed data only for iron carboxymaltose.

**First Dispensing or Administration**

Among first exposures to IV iron, iron carboxymaltose was the most frequent IV iron type (49.3% of patients) followed by iron gluconate (35.1% of patients) and iron sucrose (12.4%). The use of iron dextran and iron isomaltoside was low (Figure 13).

**Figure 13. Number of First IV Iron Treatments by Individual IV Iron Type: All Data Sources**



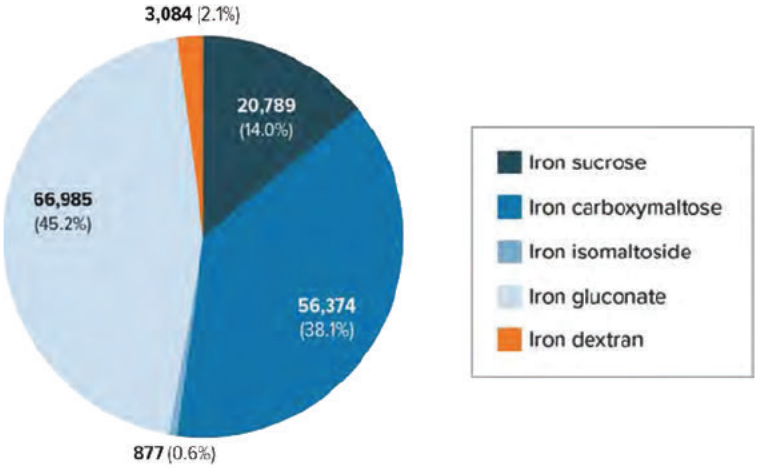

IV = intravenous.

Note: Percentages were calculated from the total number of patients with a first IV iron treatment.

**Second Dispensing or Administration**

For second IV iron exposures, iron gluconate was the product most frequently used (45.2% of treatments) followed by iron carboxymaltose in 38.1% of treatments and iron sucrose in 14.0% of all treatments. Iron dextran and iron isomaltoside were used in 2.1% and 0.6% of treatments, respectively (Figure 14).

**Figure 14. Number of Second IV Iron Treatments by Individual IV Iron Type: All Data Sources**




TOTAL TREATMENTS: 148,109

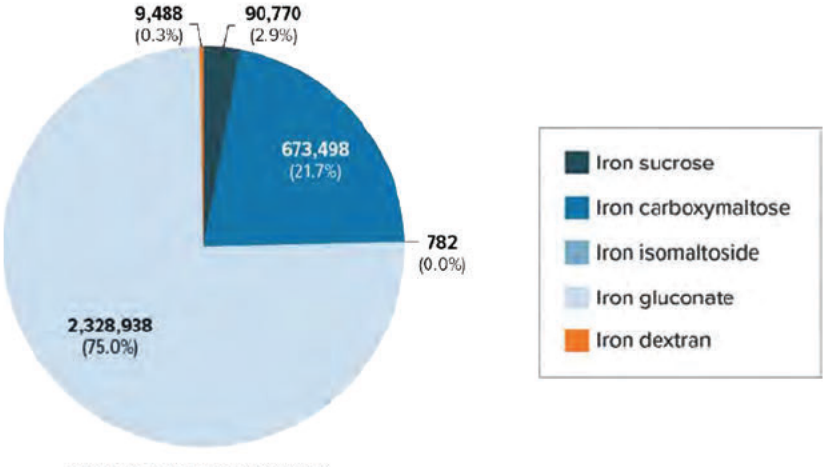
Iv = intravenous.

Note: Percentages were calculated from the total number of patients with a second IV iron treatment.

### Third or Subsequent Dispensing or Administration

For the third or subsequent IV iron treatments, 75% were iron gluconate followed by iron carboxymaltose representing 21.7% of all third or subsequent treatments and iron sucrose 2.9% (Figure 15). As previously highlighted, the KfH QiN registry in Germany contributed the largest number of all third and subsequent treatments (N = 2,620,795 [75%]).

**Figure 15. Number of Third and Subsequent Treatments by Individual IV Iron Type: All Data Sources**




TOTAL TREATMENTS: 3,103,476

IV = intravenous.

Note: Percentages were calculated from the total number of third or subsequent IV iron treatments.

### *10.1.2 IV Penicillin Cohort*

Data for the IV penicillins cohort was contributed by the Health Services Database of the Central Denmark Region, the SNDS in France, the PHARMO-NL, and the GePaRD in Germany databases.

Table 5 displays the final number of first exposures to parenteral penicillins (IV or intramuscular [IM]) and the number of treatments for any parenteral penicillins exposure, overall and by data source.

Overall, 231,294 first exposures to penicillins and 984,000 penicillins treatments were identified during the study period from the data sources contributing to the penicillins cohort. The Health Services Database of the Central Denmark Region contributed the largest number of first parenteral penicillins treatments (50.6%) and of any penicillins treatments (74.8%). Relevant numbers of IV penicillins treatments were also contributed by the three data sources where information on IV penicillins use was available.

**Table 5. Final Cohort Selection: IV Penicillins Cohort**

| IV Penicillins Treatments (n) | Central Denmark Region | SNDS, France | PHARMO-NL | GePaRD, Germany | Overall |
|---|---|---|---|---|---|
| Number of **first** IV penicillins treatments | 116,980[a] | 57,200 | 39,002 | 18,112 | 231,294 |
| Number of **any** IV penicillins treatments | 736,070[a] | 78,292 | 114,639 | 54,999 | 984,000 |

GePaRD = German Pharmacoepidemiological Research Database; IV = intravenous; KfH QiN = Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme; PHARMO-NL = PHARMO Database Network in the Netherlands; SNDS = Système National des Données de Santé (French National Health Insurance System database, previously named SNIIRAM).

[a] Numbers were rounded to the nearest 10 to comply with data-protection rules aimed at prevention of identification of individuals.

Note: IV penicillins use is not available in the Swedish registers and the KfH QiN dialysis registry in Germany.

## 10.2 Descriptive Data

### *10.2.1 Baseline Characteristics of Users*

The full results of the distribution of the baseline characteristics of users in each data source are included in Annex 3, Baseline Characteristics excel file, Tabs IV iron Any by Group and IV Penicillin Any.

#### 10.2.1.1 IV Iron Cohort

- The distributions by age and sex were similar in all study populations. The overall mean age (standard deviation [SD]) was 57 (19.3) years. For iron dextran the mean age (SD) was 58.8 (20.2) years and for non-dextrans 56.9 (19.3) years.

Across data sources, the mean (SD) age of patients among the iron-dextran group ranged from 58.5 (20.2) years in the Swedish registers to 63 (22.0) years in the Central Denmark Region. Among the iron non-dextran group, the mean (SD) age ranged from 54.2 (20.8) years in the Swedish registers to 67.5 (14.9) years in the KfH QiN dialysis registry in Germany.

- IV iron users were more frequently females, with differences across data sources by iron group; among the iron-dextran group, the proportion of females ranged from 52% in the KfH QiN dialysis registry in Germany to 78% in PHARMO-NL. For the iron non-dextran group females comprised 37% in the KfH QiN registry and 75% in the Swedish registers.

- In the general population data sources, IV iron treatment at cohort entry was mostly captured from outpatient ambulatory drug-dispensing data (ambulatory IV iron dispensings were 100% in SNDS in France, GePaRD in Germany, and the Swedish registers, and in the PHARMO-NL, 78% of iron dextran and 5% iron non-dextrans). Hospital treatment administration data were captured in the PHARMO-NL in 22% of iron dextran and 95% of iron non-dextrans and for most iron treatments in the Central Denmark Region.

- Chronic kidney disease, iron-deficiency anaemia, and gastrointestinal bleeding were among the conditions assessed as potential IV iron indications. Their prevalence varied greatly across study populations, dependent on the type of available data, i.e., outpatient diagnosis and primary care diagnoses as opposed to hospital discharge diagnoses. Overall, the highest prevalences were those from the GePaRD in Germany where diagnoses were captured from all health care settings. The following results were found in the general population data sources (not including KfH QiN dialysis registry in Germany):

  - Chronic kidney disease: among the iron-dextran group ranged from 0% in the Central Denmark Region to 45% in the GePaRD in Germany, and in the iron non-dextran group from 15% in the Swedish registers to 37% in the Health Services Database of the Central Denmark Region.

  - Iron-deficiency anaemia: among iron dextran users ranged from 2% in the Swedish registers to 40% in the GePaRD in Germany, and among iron non-dextran users from 3% in the Central Denmark Region and the Swedish registers to 47% in the GePaRD.

  - Gastrointestinal bleeding: among iron dextran users ranged from 3% in PHARMO-NL and the Swedish registers to 22% in GePaRD in Germany, and among iron non-dextrans from 4% in the Swedish registers to 20% in the GePaRD.

- The prevalence of conditions that are risk factors for hypersensitivity reactions also varied across data sources, mainly because of type of available data: the prevalence of history of anaphylaxis was low, ranging from 0% to 1%; history of asthma ranged from 0% to 11% in the iron dextran group and from 1% to 14% in the iron non-dextran group; and history of any allergies ranged from 2% in PHARMO-NL to 51% in GePaRD in Germany in the iron-dextran group and 3% in PHARMO-NL to 56% in GePaRD in the iron non-dextran group.

- The prevalence of use of antibacterials ranged from 32% to 52% (in the iron-dextran group) and from 30% to 42% (in the iron non-dextran group), with the lower ranges referring to the Swedish national registers and the highest range to the Central Denmark Region, respectively.

#### 10.2.1.2 IV Penicillins

- The mean (SD) age of patients in the IV penicillins cohort overall was 60.2 (19.6) years and ranged from 51.3 (18.0) years in the GePaRD in Germany to 61.9 (19.9) years in the SNDS in France.
- Females comprised from 39% of users in the GePaRD in Germany to 58.3% in the SNDS in France.
- History of anaphylaxis at baseline was low (0%-1%) and history of any allergies ranged from 2.0% in PHARMO-NL to 54% in the GePaRD in Germany.
- The Health Services Database of the Central Denmark Region captured the largest number of any IV penicillins treatments of which 96% where administered in hospital. In the SNDS in France and GePaRD in Germany, all penicillins use was captured through outpatient dispensing data. In the PHARMO-NL, 65% of IV penicillins treatments were captured as in-hospital treatments.

## 10.3 Outcome Data

### *10.3.1 Main Analysis*

#### 10.3.1.1 IV Iron

The following sections present the number of potential anaphylaxis events identified in the main analysis using the main case-identification algorithm and the same day or the same day and day after risk windows overall and for first, second, and third or subsequent IV iron exposure across all data sources by IV iron dextran group and by IV iron types.

Table 6 summarises the data source-specific results for the number of anaphylaxis events identified as potential study cases through the main case-identification algorithm recorded on the same day or same day and day after IV iron exposure, among patients receiving first, second, and third or subsequent IV iron treatment.

**Table 6. IV Iron Treatment and Number of Potential Anaphylaxis Events: Overall and Data Source-specific Results**

| IV Iron Treatment and Potential Anaphylaxis Events (n) | Central Denmark Region | SNDS, France | PHARMO-NL | Swedish National Registers | GePaRD, Germany | KfH QiN, Germany | Overall |
|---|---|---|---|---|---|---|---|
| **First IV iron treatment** | | | | | | | |
| Patients | 5,870[a] | 75,512 | 5,825 | 42,468 | 140,916 | 33,619 | 304,210 |
| Events[b] | Min, 1; max, 4 | 0 | 0 | 3 | 9 | 0 | Min, 13; max, 16 |
| **Second IV iron treatment** | | | | | | | |
| Patients | 2,150 | 22,626 | 1,850 | 20,822 | 67,895 | 32,756 | 148,099 |
| Events | 0 | 0 | 0 | 1 | 2 | 0 | 3 |
| **Third or subsequent IV iron treatment** | | | | | | | |
| Patients (treatments) | 1,420 (34,760)[a] | 11,597 (58,298) | 913 (3,217) | 11,771 (37,471) | 47,789 (348,945) | 32,144 (2,620,795) | 105,634 (3,103,486) |
| Events | 0 | 0 | 0 | 0 | 10 | 0 | 10 |

GePaRD = German Pharmacoepidemiological Research Database; IV = intravenous; KfH QiN = Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme; PHARMO-NL = PHARMO Database Network in the Netherlands; SNDS = Système National des Données de Santé (French National Health Insurance System database, previously named SNIIRAM).

[a] Numbers were rounded to the nearest 10 because of data-protection rules aimed at prevention of identification of individuals.

[b] Number of potential anaphylaxis events reported as ranges to comply with data-protection rules aimed at prevention of identification of individuals.

**Overall and IV Iron Groups: Iron Dextran and Iron Non-dextrans**

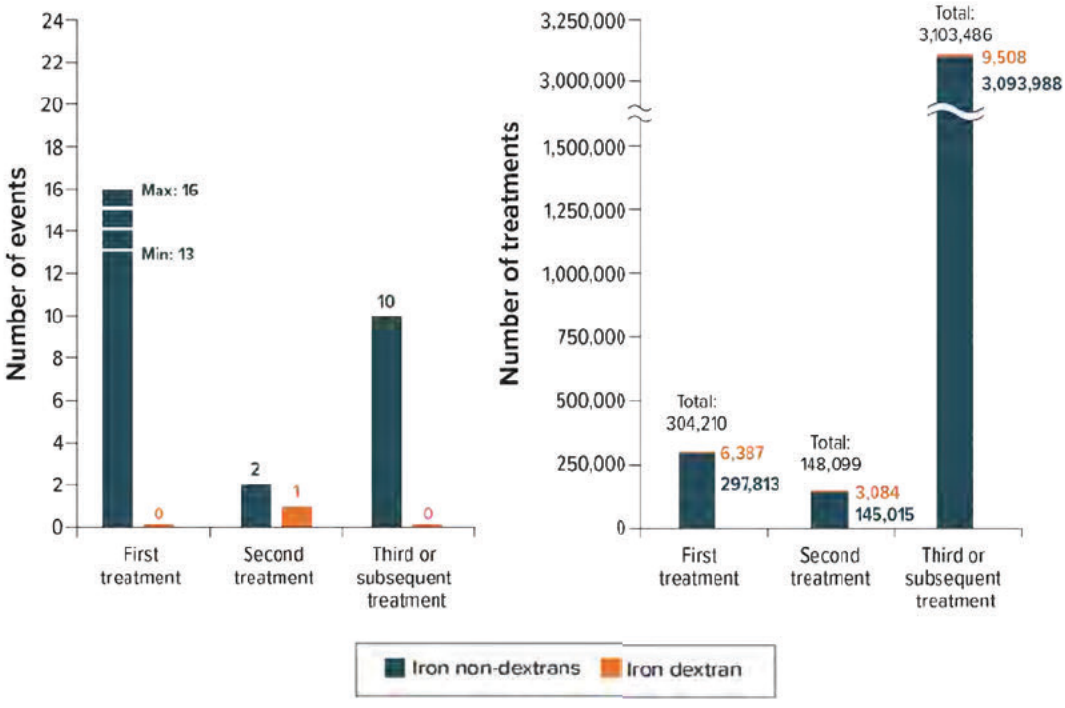
Figure 16 displays the pooled number of potential anaphylaxis events identified through the main case-identification algorithm, overall and by iron group (iron dextran and iron non-dextran) for first, second, and third or subsequent IV iron exposures across all data sources.

The number of potential anaphylaxis events among patients that had a first exposure to IV iron (N = 304,210 patients) ranged from 13 to 16 events across all data sources (numbers are reported as ranges to comply with Danish data-protection rules aimed at the prevention of identification of individuals). All events were identified in the iron non-dextran group.

Among patients with second IV iron exposures, there were three potential anaphylaxis events identified (N = 148,099 patients) across all data sources. One event was identified among the iron-dextran group and two events among the iron non-dextran group.

For third or subsequent IV iron treatments, 10 potential events were identified from a total of 3,103,486 treatments. All events were found among the iron non-dextran group. It is worth noting that in the KfH QiN dialysis registry in Germany contributing 84.4% of all third or subsequent treatments, no events were identified.

**Figure 16. Number of Potential Anaphylaxis Events and Treatments by Iron Dextran and Iron Non-dextran: First, Second, and Third or Subsequent IV Iron Treatments (Main Algorithm)**




IV = intravenous.

### By IV Iron Individual Type

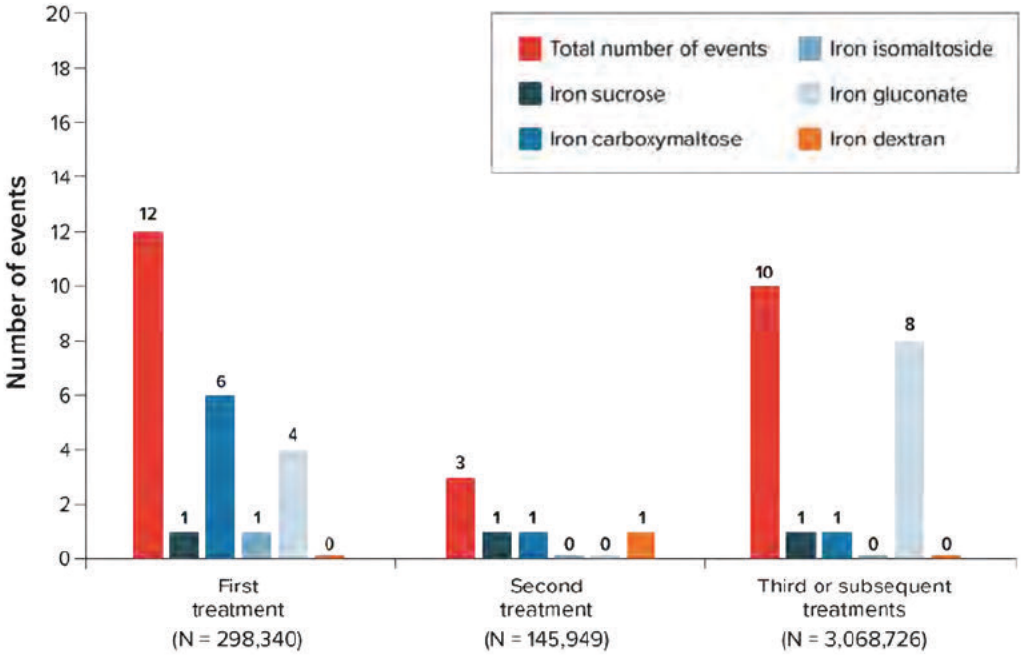
Figure 17 displays the number of potential anaphylaxis events, overall and by IV iron type in relation to IV iron at first, second, and third or subsequent exposures across all data sources but not including the Central Denmark Region. Data by individual IV iron types were not available from Denmark because of the low cell-count limits and data-protection rules aimed at prevention of identification of individuals. Therefore, the denominators and number of events by IV iron type shown here are different from those by IV iron group (iron dextran and iron non-dextran) for the first, second, and third or subsequent exposures.

Among patients with a first exposure (N = 298,340 patients), 12 potential anaphylaxis events were identified after excluding the Health Services Database of the Central Denmark Region; 6 following exposure to iron carboxymaltose, 4 for iron gluconate, and one each among those exposed to iron sucrose and to iron isomaltoside.

Among patients with a second exposure (N = 145,949), three potential events were identified: one following exposure to iron carboxymaltose, one among the iron sucrose type, and one among iron dextran.

Among the third or subsequent IV iron treatments (N = 3,068,726), 10 potential events were identified: one following exposure to iron carboxymaltose, 8 for iron gluconate, and one following exposure to iron sucrose.

**Figure 17. Number of Potential Anaphylaxis Events by IV Iron Type: First, Second, and Third or Subsequent IV Iron Treatments (Main Algorithm)**




IV = intravenous.

Note: Number of events and denominators do not match the numbers by IV iron group (iron dextran and iron non-dextran) because Danish data by individual IV iron type were not included because of Danish data-protection reporting restrictions aimed at protection of identification of individuals.

#### 10.3.1.2 IV Penicillins

In the main analysis (cases identified through the main case-identification algorithm within the "same day" or "same day and day after" IV penicillins treatment), 30 potential anaphylaxis events were identified among patients who had a first IV penicillins treatment (N = 231,294 patients) across the four data sources contributing data to the IV penicillins cohort. There were 44 potential anaphylaxis events from all 984,000 penicillins treatments (see Table 7).

**Table 7. IV Penicillins Treatment and Number of Potential Anaphylaxis Events: Overall and Data Source-specific Results**

| IV Penicillins Treatment (n) | Central Denmark Region | SNDS, France | PHARMO-NL | GePaRD, Germany | Overall |
|---|---|---|---|---|---|
| Number of **first** IV penicillins treatments | 116,980[a] | 57,200 | 39,002 | 18,112 | 231,294 |
| Events | 20[a] | 1 | 3 | 6 | 30 |
| Number of **any** IV penicillins treatments | 736,070[a] | 78,292 | 114,639 | 54,999 | 984,000 |
| Events | 30[a] | 2 | 4 | 8 | 44 |

GePaRD = German Pharmacoepidemiological Research Database; IV = intravenous; KfH QiN = Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme; PHARMO-NL = PHARMO Database Network in the Netherlands; SNDS = Système National des Données de Santé (French National Health Insurance System database, previously named SNIIRAM).

[a] Numbers were rounded up to the nearest 10 because of data-protection rules aimed at prevention of identification of individuals.

Note: Data on IV penicillins use are not available in Sweden and the KfH QiN registry in Germany.

### *10.3.2 Expanded Algorithm (Sensitivity Analyses)*

#### 10.3.2.1 IV Iron

The expanded case-identification algorithm (see Section 9.4.1.1) identified nine additional potential anaphylaxis events following an IV iron exposure.

**Overall and by IV Iron Group: Iron Dextran and Iron Non-dextrans**

Figure 18 displays the pooled number of potential anaphylaxis events identified through the expanded case-identification algorithm, overall and by iron group (iron dextran and iron non-dextran) for first, second, and third or subsequent IV iron exposures across all data sources.

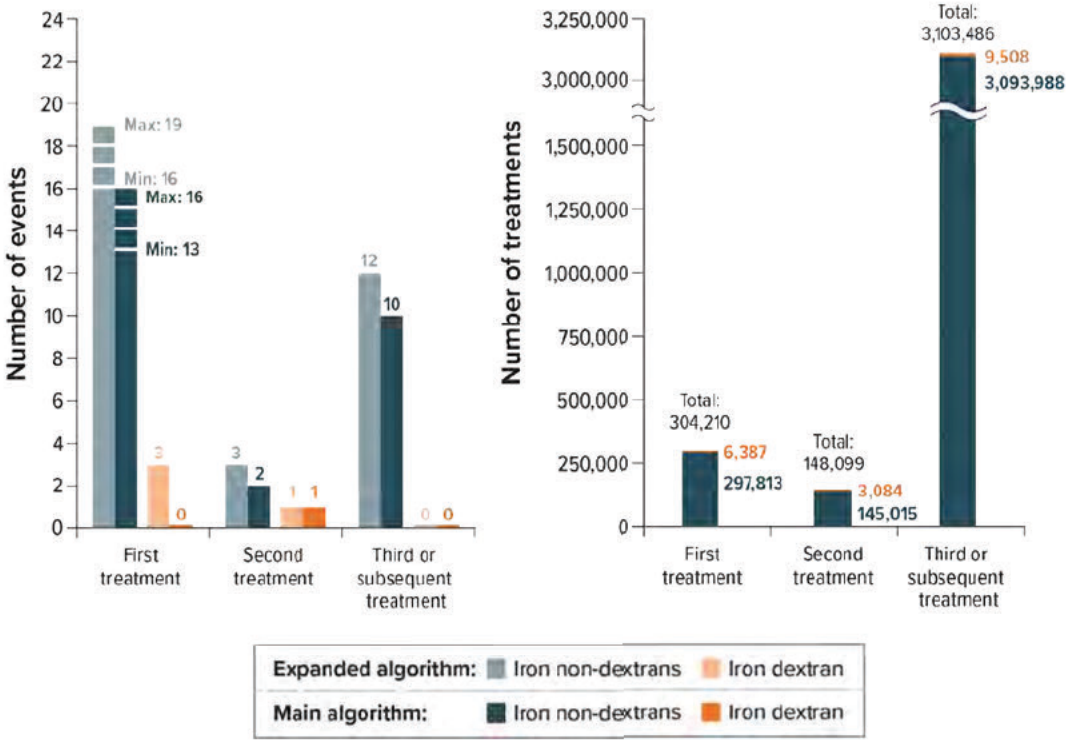
Among patients with a first exposure to IV iron (N = 304,210 patients), six additional potential events were identified through the expanded case-identification algorithm (three for iron dextran and three for iron non-dextrans) for a total number of potential anaphylaxis events ranging from 19 to 22 events across all data sources (numbers are reported as ranges to comply with Danish data-protection rules aimed at prevention of

identification of individuals). Three events were identified in the iron-dextran group and between 16 and 19 events among the iron non-dextran group.

Among patients with second IV iron exposures (148,099 patients), one additional potential event was identified among iron non-dextran users for a total of four potential anaphylaxis events (one event among the iron-dextran group and three events among the iron non-dextran group).

For third or subsequent IV iron treatments, two additional potential anaphylaxis events were identified from 3,103,486 treatments for 12 potential events. All events were found among the iron non-dextran group. As previously highlighted, in the KfH QiN dialysis registry in Germany contributing 84.4% of all third or subsequent treatments, no events were identified

**Figure 18. Number of Potential Anaphylaxis Events and Number of Treatments by Iron Dextran and Iron Non-dextran: First, Second, and Third or Subsequent IV Iron Treatments (Expanded Algorithm Compared With Main Algorithm)**




IV = intravenous.

### By IV Iron Individual Type

Figure 19 shows the results by IV iron type in relation to exposure to IV iron at first, second, and third or subsequent exposure. As previously highlighted, because of the Danish data-protection rules aimed at prevention of identification of individuals, Danish data by individual iron types could not be reported. Therefore, the denominators and

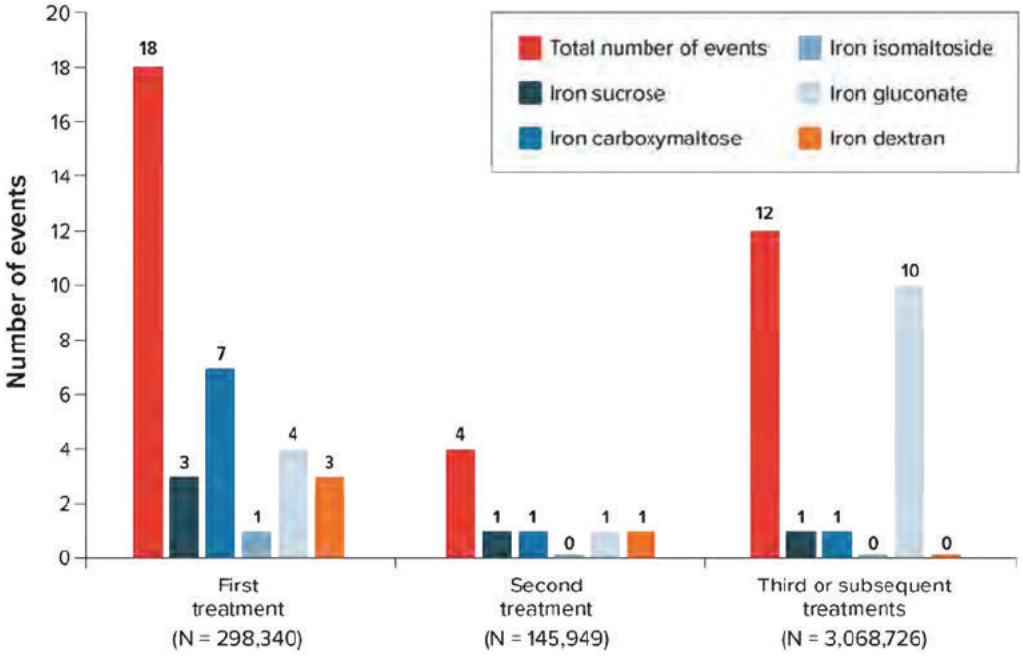
potential anaphylaxis events for the individual IV iron types in this section do not include the Danish data.

Overall, 34 potential events were identified for all ordinal IV iron exposures across all IV iron types. Among patients with a first exposure (N = 298,340 patients), 18 potential anaphylaxis events were identified through the expanded algorithm; seven following exposure to iron carboxymaltose, four for iron gluconate, three among those exposed to iron sucrose, one among an iron isomaltoside-exposed patient, and three among patients exposed to iron dextran.

Among patients with a second exposure (N = 145,949), four potential anaphylaxis events were identified: one patient each following exposure to iron carboxymaltose, iron gluconate, iron sucrose, and iron dextran.

Among the third and subsequent IV iron treatments (N = 3,068,726), 12 potential anaphylaxis events were identified: 1 following exposure to iron carboxymaltose, 10 to iron gluconate, and 1 following exposure to iron sucrose.

**Figure 19. Number of Potential Anaphylaxis Events by IV Iron Type: First, Second, and Third or Subsequent IV Iron Treatments (Expanded Algorithm)**




IV = intravenous

Note: Number of events and denominators do not match the numbers by IV iron group (iron dextran and iron non-dextran) because of Danish data-protection reporting restrictions aimed at prevention of identification of individuals.

For comparison purposes refer to number of events from the main analysis reported in Figure 17.

#### 10.3.2.2 IV Penicillins

The expanded algorithm identified 259 potential anaphylaxis events among patients that had a first IV penicillins treatment (N = 231,294 patients) across the four data sources

contributing data to the IV penicillins cohort. Overall, there were 471 potential anaphylaxis events from a total of 984,000 penicillins treatments.

### *10.3.3 Seven-day Risk Window (Sensitivity Analyses)*

#### 10.3.3.1 IV Iron Cohort

**Overall and by IV Iron Group: Iron Dextran and Iron Non-dextrans**

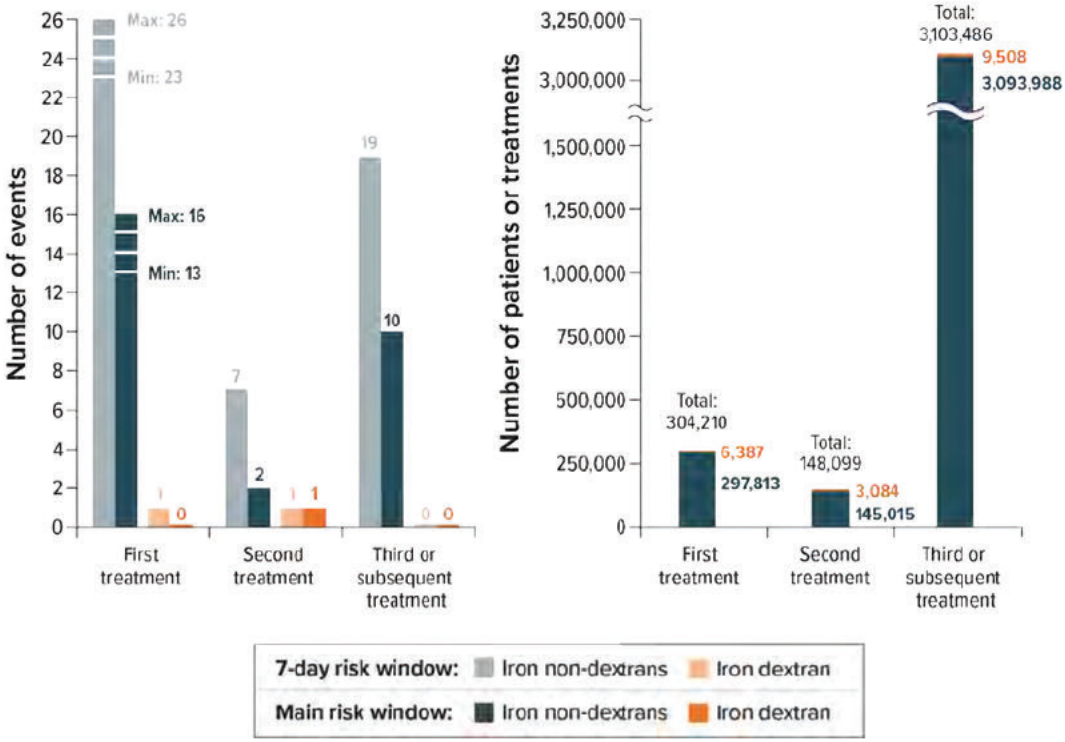
The overall number of potential anaphylaxis events identified through the main case-identification algorithm and the 7-days risk window in relation to exposure to IV iron at first, second, and third or subsequent exposure by iron-dextran group across all data sources are presented in Figure 20.

Among patients with a first exposure to IV iron (N = 304,210 patients), 11 additional potential anaphylactic events were identified through the 7-days risk window for a total number of potential events ranging from 24 to 27 events across all data sources (numbers are reported as ranges to comply with Danish data-protection rules). One event was identified among the iron-dextran group and between 23 and 26 potential events among the iron non-dextran group.

Among patients with second IV iron exposures, five additional potential events were identified for a total of eight potential anaphylaxis events identified among 148,099 patients across data sources. One event was identified among the iron-dextran group and seven events among the iron non-dextran group.

For third or subsequent IV iron treatments, 9 additional potential anaphylaxis events were identified from a total of 3,103,486 treatments for 19 potential events. All events were found among the iron non-dextran group. As previously highlighted, in the KfH QiN dialysis registry in Germany contributing 84.4% of all third or subsequent treatments, no events were sought beyond day 0 as both administration date and event date were available.

**Figure 20. Number of Potential Anaphylaxis Events and Treatments by Iron Dextran and Iron Non-dextran: First, Second, and Third or Subsequent IV Iron Treatments, Main Algorithm in 7-days Risk Window and Main Algorithm in Main Risk Window**




IV = intravenous.

### By IV Iron Individual Type

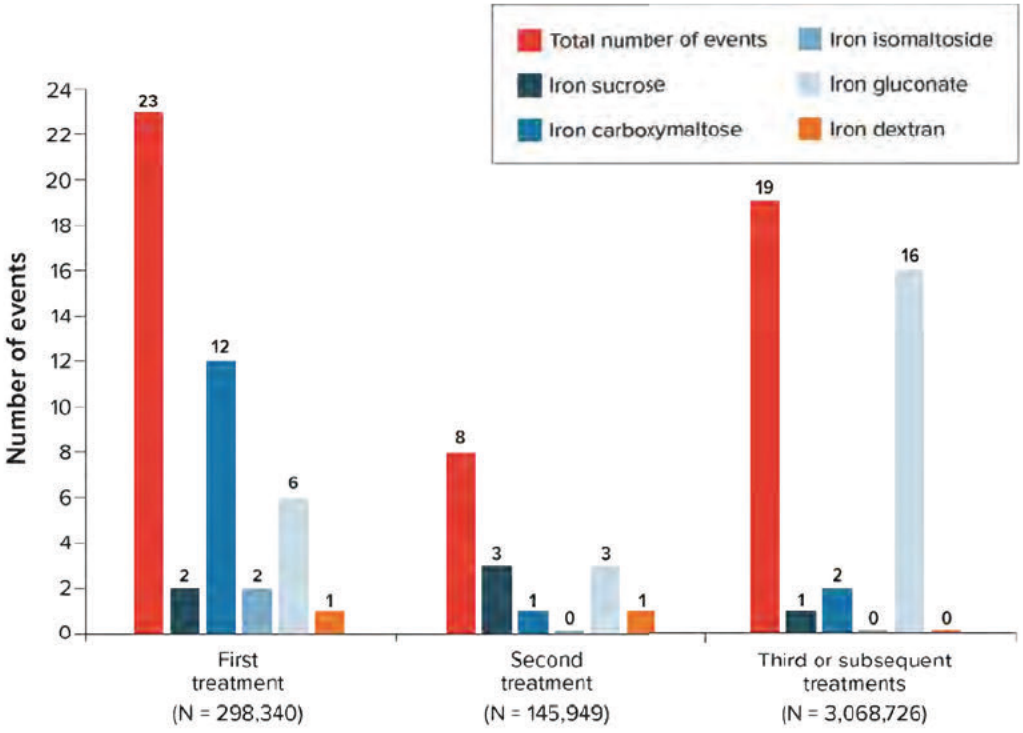
Results are shown overall and by IV iron type in relation to exposure to IV iron at first, second, and third or subsequent exposures (Figure 21). As previously highlighted, because of the Danish data-protection rules, no data by individual iron types were available from the Central Denmark Region data. Therefore, the denominators and potential anaphylaxis events for the individual IV iron types reflect numbers from all data sources except the Health Services Database of the Central Denmark Region.

Overall, 50 potential events were identified in all IV iron exposures across all IV iron types. Among patients with a first exposure (N = 298,340 patients), 23 potential anaphylaxis events were identified through the 7-days risk window across all data sources (not including Danish data); 12 following exposure to iron carboxymaltose, 6 to iron gluconate, 2 to iron sucrose, 2 to iron isomaltoside, and 1 to iron dextran.

Among patients with a second exposure (N = 145,949), eight potential anaphylaxis events were identified: one event following exposure to iron carboxymaltose, three following iron gluconate, three among the iron sucrose type, and one in the iron dextran type.

Among the third or subsequent IV iron treatments (N = 3,068,726), 19 potential anaphylaxis events were identified: 2 following exposure to iron carboxymaltose, 16 among the iron gluconate type, and 1 following exposure to iron sucrose.

**Figure 21. Number of Potential Anaphylaxis Events by IV Iron Type: First, Second, and Third or Subsequent IV Iron Treatments (7-days Risk Window)**




IV = intravenous.

Note: Number of events and denominators do not match the numbers by IV iron group (iron dextran and iron non-dextrans) because of Danish data-protection reporting restrictions aimed at prevention of identification of individuals.

For comparison purposes refer to number of events from the main analysis reported in Figure 17.

### *10.3.4 Outcome Validation*

#### 10.3.4.1 Direct Validation

**Health Services Database of the Central Denmark Region**

All potential anaphylaxis cases identified in the Central Denmark Region among IV iron-treated patients were considered for validation (N = 1-4, data-protection range). For the IV penicillins cohort, a sample of potential cases identified through the main algorithm was selected for validation.

Case validation was performed through review of medical records of potential cases in the hospital departments that granted permission to access patient records.

A total of 42 potential anaphylaxis events were targeted for validation:

- Between 1 and 4 in the IV iron cohort, identified through the main and expanded algorithms (range owing to data-protection rules aimed at preventing identification of individual patients)
- The remainder in the IV penicillin cohort, identified through the main algorithm.

Access was obtained for all 42 medical records and all underwent clinical adjudication. The PPV (95% CI) for the case-identification algorithms used to identify potential events among IV iron users is presented combined with the potential events identified among IV penicillin users because of the data-protection rules. Accordingly, the number of potential cases excluded because of insufficient information cannot be reported.

Table 8 reports an estimated PPV (95% CI) for the IV iron and IV penicillin potential cases combined of 70% (50%-86%). This PPV was calculated based on the potential cases identified through the main and expanded algorithms for the IV iron cohort and from the main algorithm for the IV penicillin cohort, while excluding potential cases with insufficient information.

When potential cases among IV penicillin users were analysed separately, the estimated PPV of the main case-identification algorithm ranged from 43%, when all potential cases for which there was insufficient information to establish case status were classified as non-cases, to 81%, when all potential cases with insufficient information were classified as cases.

The PPV for IV penicillin users excluding potential cases with insufficient information cannot be provided because of data-protection rules to prevent the back calculation of cells with less than five cases.

**Table 8. Positive Predictive Value for IV Iron and IV Penicillin (Denmark)**

| | Positive Predictive Value % (95% CI) |
|---|---|
| **IV iron (main and expanded algorithm) plus IV penicillin (main algorithm)** | |
| Excluding potential cases with insufficient information | 70 (50-86) |
| **IV penicillin (main algorithm only)** | |
| Potential cases with insufficient information classified as non-cases | 43 (27-61) |
| Potential cases with insufficient information classified as cases | 81 (65-92) |

CI = confidence interval; IV = intravenous; PPV = positive predictive value.

### PHARMO Database Network

All potential events of anaphylaxis (N = 26) identified through the main and expanded algorithms among IV iron users (N = 6) and IV penicillins users (N = 20) were targeted for validation. There were no additional potential events identified through the 7-days risk window analysis.

Out of 10 hospitals where the potential anaphylaxis events were identified, 4 hospitals did not find the patients in their systems (N = 11 potential events) and 2 additional hospitals (N = 2 potential events) did not grant approval.

- The main difficulty for not finding the patient records in the hospital systems was because the hospitals switched to a different system several years previously. Not all information was transferred into the new system because this was no longer required (i.e., retention of information was expired) or patients had passed away.
- The main reason for not granting approval for access to the medical records were concerns around recent changes in patient data-protection rules (GDPR).

Four hospitals granted approval for access to the medical records of 13 potential events. The records of 13 potential events were abstracted for case adjudication (3 were captured through the main algorithm and 10 additional cases identified through the expanded algorithm). The case adjudication resulted in 9 non-cases, 3 non-evaluable cases, and 1 confirmed case.

Table 9 presents the number of potential anaphylaxis events and confirmed cases for the main algorithm and for the expanded algorithm for IV iron dextran, IV iron non-dextran, and IV penicillin treatments.

**Table 9. Positive Predictive Value by IV Iron Group and IV Penicillin: Main and Expanded Algorithm (PHARMO-NL)**

| | Main Algorithm | | | | Expanded Algorithm | | | |
|---|---|---|---|---|---|---|---|---|
| | **Potential Events (N)** | **Records Obtained (N)** | **Patients Evaluable (N)** | **Confirmed Cases (N)** | **Potential Events (N)** | **Records Obtained (N)** | **Patients Evaluable (N)** | **Confirmed Cases (N)** |
| **IV iron** | | | | | | | | |
| IV iron dextran | 0 | NA | NA | NA | 3 | 0 | NA | NA |
| IV iron non-dextrans | 0 | NA | NA | NA | 3 | 0 | NA | NA |
| IV iron (any) | 0 | NA | NA | NA | 6 | 0 | NA | NA |
| PPV (95% CI) | | | | NE | | | | NE |
| **IV penicillin** | | | | | | | | |
| IV penicillin (any) | 4 | 3 | 1 | 1 | 20 | 13 | 10 | 1 |
| PPV (%) (95% CI) | | | | 100 (2.50-100) | | | | 10 (0.25-44.5) |

CI = confidence interval; IV = intravenous; NA = not applicable; NE = not estimable; PHARMO-NL = PHARMO Database Network in the Netherlands; PPV = positive predictive value.

For the IV iron cohort, as no potential cases were identified through the main algorithm and no medical records were obtained for potential cases identified through the expanded algorithm, the IV iron-specific PPV could not be calculated. For the IV penicillin cohort the PPV of the main case-identification algorithm, based on one confirmed case, was 100.0% (95% CI, 25.0-100.0) and the PPV for the expanded algorithm was 10.0% (95% CI, 2.5-44.5).

The adjusted IPs by the PPVs are not presented due to the small number of evaluable patients identified through the main algorithm.

#### 10.3.4.2 Indirect Validation

**Validation of GePaRD, Germany, Case-Identification Algorithm Through Oldenburg Hospital**

The anaphylaxis algorithm searched the Hospital Information System data for potential anaphylaxis events recorded as admission diagnoses and primary and secondary discharge diagnoses. On the basis of 78 patients with potential anaphylaxis events identified through the algorithm Criterion A (inpatient-specific ICD codes for anaphylaxis) and 43 confirmed events, the estimated PPV was 62.3% (95% CI, 49.8%-73.7%) based on all codes in Criterion A. When non-evaluable patients with an anaphylaxis diagnosis were considered as confirmed events the PPV was 68.1% (95% CI, 55.8%-78.8%).

One potential anaphylaxis event was identified though Criterion C (inpatient ICD codes of unspecific hypersensitivity reactions) which was not confirmed by validation. For the Criterion B of the algorithm no potential events were identified in this hospital-based setting.

#### 10.3.4.3 Other Validation Activities

**KfH QiN, Germany, Medical Record Review**

In KfH QiN no events of anaphylaxis were identified during the main analysis risk window ("same day" of IV iron administration). However, there were 5 patients who had a code for angioneurotic oedema during the risk window but lacked other necessary criteria to be considered study events. The medical records of these 5 patients were accessed and their non-case status was further confirmed either by recorded evidence of continued use of IV iron after the angioneurotic event (n = 4) or by explicit confirmation by the treating doctor in 1 patient who died after the angioneurotic event.

## 10.4 Main Results

**The results presented in this section are based on the beta-binomial regression analyses since these are more appropriate for studies involving very low number of events (see Methods Section 9.9.2.2). In the tables of results in Annex 4, results based on the traditional meta-analysis approach are also presented.**

### *10.4.1 IV Iron*

Complete overall and data source-specific results for IV iron can be found by IV iron group in Tables 1.1 to 1.3 and by IV iron types in Tables 2.1a to 2.3c in Annex 4 Final Results 20Feb2020. In Annex 4 and throughout the following sections in this report, estimates are presented rounded to three digits i.e., rounding estimates to the nearest decimal place, the nearest unit, or the nearest 10. Values less than 999 are reported to three digits on the indicated scale; values greater than 999 are reported to three informative digits.

Table 10 shows, by ordinal number of IV iron treatment (i.e., first, second, and third or subsequent), the IPs (95% CI) of potential anaphylaxis events per 10,000 IV iron treatments, overall for all IV irons and for iron dextran and non-dextrans separately.

The resulting RRs and RDs (iron dextran vs. iron non-dextrans), with the corresponding 95% CIs are also displayed.

Table 10 displays results from the main analyses (i.e., main case-identification algorithm applied during the exposure risk window defined by "same day" or "same day and day after" after IV iron treatment).

**Table 10. Risk of Anaphylaxis After Treatment With IV Iron, Overall, by IV Iron Dextran and Iron Non-dextran Groups and Incidence by IV Iron Types. Main Analysis**

| | First Treatments | Second Treatments | Third and Subsequent Treatments |
|---|---|---|---|
| **Overall IV iron** | | | |
| Anaphylaxis events (n) | Min, 13; max, 16* | 3 | 10 |
| Patients (n)** | 304,210 | 148,099 | 3,103,486 |
| IP (95% CI)* | Min, 0.38 (0.17-0.88); max, 0.51 (0.28-0.97) | 0.25 (0.07-0.94) | 0.02 (0.00-0.13) |
| **Iron dextran** | | | |
| Anaphylaxis events (n) | 0 | 1 | 0 |
| Patients (n)** | 6,387 | 3,084 | 9,508 |
| IP (95% CI) | 0 (0-> 9,995) | 3.33 (0.48-23.3) | 0 (0-> 9,995) |
| **Iron non-dextran** | | | |
| Anaphylaxis events (n) | Min, 13; max, 16 | 2 | 10 |
| Patients (n)** | 297,813 | 145,015 | 3,093,988 |
| IP (95% CI) | Min, 0.44 (0.16-1.24); max, 0.55 (0.23-1.34) | 0.25 (0.06-1.06) | 0.03 (0.00-0.19) |
| RR (95% CI)*** | Min, 0 (0.00-> 9,995); max, 0 (0.00-> 9,995) | 13.1 (1.26-146) | 0 (0-> 9,995) |

| | First Treatments | Second Treatments | Third and Subsequent Treatments |
|---|---|---|---|
| RD (95% CI)*** | Min, −0.44 (−1.02 to > 9,995); max, −0.55, (−1.14 to > 9,995) | 3.08 (0.12-23.1) | -0.03 (−0.13-> 9,995) |
| **Iron types** | | | |
| *Iron sucrose* | | | |
| Anaphylaxis events (n) | 1 | 1 | 1 |
| Patients (n) | 36,306 | 19,669 | 56,840 |
| IP (95% CI) | 0.43 (0.06-3.10) | 0.59 (0.08-4.25) | 0.21 (0.03-1.50) |
| *Iron carboxymaltose* | | | |
| Anaphylaxis events (n) | 6 | 1 | 1 |
| Patients (n) | 146,674 | 55,684 | 672,948 |
| IP (95% CI) | 0.45 (0.12-1.69) | 0.22 (0.03-1.62) | 0.05 (0.01-0.33) |
| *Iron gluconate* | | | |
| Anaphylaxis events (n) | 4 | 0 | 8 |
| Patients (n) | 106,668 | 66,985 | 2,328,938 |
| IP (95% CI) | 0.46 (0.08-2.79) | 0 (0-NE) | 0.05 (0.01-0.34) |
| *Iron isomaltoside* | | | |
| Anaphylaxis events (n) | 1 | 0 | 0 |
| Patients (n) | 2,325 | 537 | 512 |
| IP (95% CI) | 4.44 (0.62-31.5) | 0 (0-NE) | 0 (0-> 9,995) |
| *Iron dextran* | | | |
| Anaphylaxis events (n) | 0 | 1 | 0 |
| Patients (n) | 6,367 | 3,074 | 9,488 |
| IP (95% CI) | 0 (0-> 9,995) | 3.31 (0.48-23.7) | 0 (0-> 9,995) |

CI = confidence interval; IP = incidence proportion; IV = intravenous; Max = maximum; Min = minimum; NE = not estimable; RR = risk ratio; RD = risk difference.

*The number of events identified in Denmark was between 1 and 4, the exact number cannot be disclosed because of data-protection rules aimed at prevention of identification of individuals. Therefore, IPs per 10,000 first treatments are reported as minimum and maximum range.

** Treatments included the Danish data which were rounded to the nearest 10 to comply with data-protection rules aimed at prevention of identification of individuals.

***RRs calculated for iron dextran vs. non-dextrans; RDs calculated for iron dextran minus iron non-dextrans.

#### 10.4.1.1 Overall IV Iron

**First Dispensing or Administration**

Overall, between 13 and 16 potential anaphylaxis events were identified in all data sources after a first treatment with IV iron which translated into an IP of anaphylaxis ranging between 0.38 and 0.51 per 10,000 first IV iron treatments (reported as range

because of Danish data-protection reporting restrictions that do not allow reporting counts between 1 and 4) (see Table 10).

**Second Dispensing or Administration**

Overall, three potential anaphylaxis events were identified in all data sources after a second treatment with IV iron, which translated into an IP of anaphylaxis of 0.25 per 10,000 second IV iron treatments (see Table 10).

**Third or Subsequent Dispensing or Administration**

Overall, 10 potential anaphylaxis events were identified in all data sources after a third or subsequent treatment with IV iron, which translated into an IP of anaphylaxis of 0.02 per 10,000 third or subsequent IV iron treatments (see Table 10).

#### 10.4.1.2 IV Iron Groups: Iron Dextran and Iron Non-dextran

**First Dispensing or Administration**

No potential anaphylaxis events were identified among first treatments with iron dextran and, consequently, the RR comparing the IP of anaphylaxis between iron dextran and non-dextrans was estimated to be 0. The RD of anaphylaxis between iron dextran and non-dextrans ranged from 0.44 to 0.55 per 10,000 treatments, favouring the iron dextran. See Table 10.

**Second Dispensing or Administration**

Of the three potential anaphylaxis events identified in all data sources after a second treatment with IV iron, one was identified among iron dextran and two among iron non-dextrans. The estimated RR comparing the IP of anaphylaxis between iron dextran and non-dextrans was 13.1 and the corresponding RD was 3.08 per 10,000 treatments, favouring the iron non-dextran group. See Table 10.

**Third or Subsequent Dispensing or Administration**

Ten potential anaphylaxis events were identified in the iron non-dextran group and no cases were identified among iron dextran. Consequently, the RR comparing the IP of anaphylaxis between iron dextran and non-dextrans was estimated to be 0. The corresponding RD was 0.03 per 10,000 treatments, favouring the iron dextran. See Table 10.

#### 10.4.1.3 IV Iron Types

The main results for the individual types of IV iron are described in this section and the corresponding complete tabulated results can be found in Tab 2.1, Tab 2.2, and Tab 2.3 of the excel file Annex 3 Main Results 18Dec2919. Overall, results for individual types of IV iron are based on very small numbers.

**First Dispensing or Administration**

At first treatment, the IP of anaphylaxis ranged from 0.43 per 10,000 treatments for iron sucrose (based on one potential event of anaphylaxis) to 4.44 per 10,000 treatments for iron isomaltoside (based on one event of anaphylaxis). No events were identified for first

treatments with iron dextran. The RR and RD of anaphylaxis using iron sucrose as the common reference was highest for iron isomaltoside (RR, 10.3; 95% CI, 0.62-158; RD, 4.01; 95% CI, 0.67 to 30.6, favouring iron sucrose).

**Second Dispensing or Administration**

At second treatment, IPs ranged from 0.22 per 10,000 second treatments of iron carboxymaltose (based on one event of anaphylaxis) to 3.31 per 10,000 second treatments of iron dextran (based on one event of anaphylaxis). No events were identified for iron isomaltoside or iron gluconate second treatments. The RR and RD of anaphylaxis using iron sucrose as the common reference was highest for iron dextran (RR, 5.60; 95% CI, 0.35-86.6; RD, 2.72; 95% CI, 1.84 to 22.8, favouring iron sucrose).

**Third or Subsequent Dispensing or Administration**

At third or subsequent treatments, IPs ranged from 0.05 per 10,000 third or subsequent treatments of iron carboxymaltose and iron gluconate, respectively to 0.21 per 10,000 third treatments of iron sucrose (based on one event of anaphylaxis for iron carboxymaltose, eight events of anaphylaxis for iron gluconate and one event of anaphylaxis for iron sucrose). No events were identified for iron dextran and iron isomaltoside. The RR of anaphylaxis using iron sucrose as the common reference was highest for iron gluconate (RR, 0.24; 95% CI, 0.02-3.54) whereas the RD of anaphylaxis using iron sucrose as the common reference were highest for iron dextran (RD, 0.21; 95% CI, 1.08 to > 9,995) and iron isomaltose (RD, 0.21; 95% CI, 1.11 to > 9,995), favouring iron dextran and iron isomaltose respectively.

### *10.4.2 IV Penicillins*

Table 11 shows the risk of anaphylaxis among users of IV penicillins at first treatment and at any treatment, based on the data sources that contributed data to the IV penicillins cohort (i.e., Health Services Database of the Central Denmark Region, PHARMO-NL and the GePaRD in Germany). Complete results for IV penicillins can be found in Tables 1.1 and 1.4 in Annex 4 Final Results 20Feb2020.

At first treatment with IV penicillins, the IP of anaphylaxis, based on 30 potential events, was 1.16 per 10,000 first treatments, whereas at any treatment, the IP was 0.45 per 10,000 treatments.

**Table 11. Risk of Anaphylaxis at First Treatment and at any Treatment With IV Penicillins. Main Analysis**

| | First Treatment With IV Penicillins | Any Treatment With IV Penicillins |
|---|---|---|
| **Any IV penicillins** | | |
| Anaphylaxis events (n) | 30 | 44 |
| Treatments (n) | 231,294* | 984,000* |
| IP (95% CI) | 1.16 (0.78-1.73) | 0.45 (0.32-0.63) |

CI = confidence interval; IP = incidence proportion; IV = intravenous.

* Treatments included the Danish data which were rounded to the nearest 10 to comply with data-protection rules aimed at prevention of identification of individuals.

## 10.5 Other Analyses

**All sensitivity analyses were conducted using the main case-identification algorithm (see Figure 7) and the risk window defined as "same day" or "same day and day after" IV iron exposure as described in the methods Section 9.3.2 and Figure 5. Exceptions were the analyses that used the expanded case-identification algorithm and the expanded 7-day exposure risk window. For the IV penicillin exposure, sensitivity analyses focused on the expanded case-identification algorithm, the modified exposure windows, and the penicillin subtypes.**

This section presents the results of all sensitivity analyses listed in the methods Section 9.9.4. The estimated IPs per 10,000 IV iron treatments, RRs (iron dextran vs. iron non-dextrans) and RDs per 10,000 (iron dextran minus iron non-dextrans), and the corresponding 95% CIs described in this section were calculated using beta-binomial regression meta-analysis (see Section 9.9.2.2) to account for between-site variability because of the very low number of events.

For some analyses, the estimated IPs, RRs, and RDs by iron type using iron sucrose as the common reference for the individual comparisons are also presented. The analyses by IV iron type did not include data from the Health Services Database of the Central Denmark Region because of data-protection rules, aimed at prevention of identification of individuals.

Annex 4 displays the detailed results for the sensitivity analyses by order of IV iron treatments and by IV iron groups and types, including the data source-specific data as follows: Tables 3.1, 3.2, 3.3, 3.4, and 4.1, 4.2, 4.3, 4.4 (expanded algorithm by IV iron groups and types, respectively); Table 5 (penicillin subtype); Tables 6.1, 6.2, 6.3, 6.4, and 7.1, 7.2, 7.3, 7.4 (7-days risk window analysis by IV iron groups and types, respectively); Table 8 (dialysis patients only by IV iron groups), Tables 9.1, 9.2, 9.3, 9.4, and 10.1, 10.2, 10.3, 10.4 (excluding dialysis patients by IV iron groups and types, respectively), Tables 11.1, 11.2, 11.3, 11.4, and 12.1, 12.2, 12.3, 12.4 (excluding sites with zero events by IV iron groups and types, respectively), Tables 13.1 and 13.2 (any IV iron before and after 2013, respectively), and Tables 14.1, 14.2, and 15.1, 15.2 (IV iron after first switch and any switch, by IV iron groups and types, respectively). The data source and overall results for IV penicillin exposure are included in Tables 3.1 and 3.4 (expanded algorithm for first and any IV penicillin exposure) and Table 6.4 for the 7-days risk window for any IV penicillin exposure.

### *10.5.1 Expanded Case-Identification Algorithm*

#### 10.5.1.1 Overall IV Iron, IV Iron Groups, and IV Iron Types

Table 12 shows, by ordinal number of IV iron treatment (i.e., first, second, and third or subsequent), the IPs of potential anaphylaxis events per 10,000 IV iron treatments, overall for all IV irons and for iron dextran and non-dextrans separately using the expanded case-identification algorithm applied during the exposure risk window defined by "same day" or "same day and day after" IV iron dispensing/administration).

**Table 12. Risk of Anaphylaxis After Treatment with IV Iron, Overall and by IV Iron Dextran and Iron Non-dextran Groups. Expanded Case-Identification Algorithm**

| | First Treatments | Second Treatments | Third or Subsequent Treatments |
|---|---|---|---|
| **Overall IV irons** | | | |
| Anaphylaxis events (n) | Min, 19; max, 22* | 4 | 12 |
| Treatments (n)** | 304,210 | 148,099 | 3,103,486 |
| IP (95% CI)* | Min, 0.63 (0.38-1.05); max, 2.81 (0.60-13.8) | 0.30 (0.08-1.09) | 0.03 (0.01-0.14) |
| **IV iron dextran** | | | |
| Anaphylaxis events (n) | 3 | 1 | 0 |
| Treatments (n)** | 6,387 | 3,084 | 9,508 |
| IP (95% CI) | Min, 4.59 (1.43-14.8); max, 4.62 (1.46-14.7) | 3.35 (0.48-23.4) | 0 (0-> 9,995) |
| **IV iron non-dextrans** | | | |
| Anaphylaxis events (n) | Min, 16; max, 19 | 3 | 12 |
| Treatments (n)** | 297,813 | 145,015 | 3,093,988 |
| IP (95% CI) | Min, 0.58 (0.28-1.22); max, 0.70 (0.38-1.31) | 0.32 (0.08-1.27) | 0.03 (0.00-0.20) |
| RR (95% CI)*** | Min, 7.95 (2.05-31.8); max, 6.61 (1.83-24.6) | 10.6 (1.03-115) | 0 (0-> 9,995) |
| RD (95% CI)*** | Min, 4.02 (0.77-14.3); max, 3.92 (0.68-14.0) | 3.03 (0.02-23.1) | -0.03 (−0.14 to > 9,995) |

CI = confidence interval; IP = incidence proportion; IV = intravenous; Max = maximum; Min = minimum; RR = risk ratio; RD = risk difference.

Note: Because the IV iron non-dextrans have a different number of events in the minimum and maximum scenarios, the data going into these two models are different. Thus, all regression coefficients may be affected, and IP estimates for IV iron dextran can vary slightly between scenarios even in situations where the numerators and denominators are the same in both scenarios.

*The number of events identified in Denmark was between 1 and 4, the exact number cannot be disclosed due to data-protection rules aimed at prevention of identification of individuals. Therefore, IPs per 10,000 first treatments are reported as minimum and maximum range.

** Treatments included the Danish data which were rounded to the nearest 10 to comply with data-protection rules aimed at prevention of identification of individuals.

***RRs calculated for iron dextran vs. non-dextrans; RDs calculated for iron dextran minus iron non-dextrans.

### First Dispensing or Administration

When the expanded case-identification algorithm was used, between 19 and 22 potential anaphylaxis events were identified (i.e., 6 additional events compared with the number from the main algorithm), for an IP ranging from 0.63 (95% CI, 0.38-1.05) to 2.81 (95% CI, 0.60-13.8) per 10,000 first iron treatments. Of these, 3 events occurred in iron dextran and between 16 and 19 in iron non-dextrans first treatments, for a resulting RR ranging from 7.95 (95% CI, 2.05-31.8) to 6.61 (95% CI, 1.83-24.6) and a resulting RD ranging from 4.02 (95% CI, 0.77-14.3) to 3.92 (95% CI, 0.68-14.0), per 10,000 first iron treatments favouring iron non-dextrans.

When assessing IV iron types, the RR of anaphylaxis using iron sucrose as the common reference after a first IV iron treatment was highest for iron dextran, based on three potential events (RR, 4.70; 95% CI, 0.83-26.1) and iron isomaltoside, based on one potential event (RR, 4.52; 95% CI, 0.44-45.8). The largest RD using iron sucrose as the common reference was observed for iron dextran (RD, 3.58; 95% CI, 0.38 to 14.3), and iron isomaltoside (RD, 3.40; 95% CI, 1.19 to 29.7), favouring iron sucrose in both cases.

### Second Dispensing or Administration

When the expanded case-identification algorithm was used, four potential anaphylaxis events were identified (i.e., one additional event compared with the number from the main algorithm) for an IP of 0.30 (95% CI, 0.08-1.09) per 10,000 second IV iron treatments. Of these, one event occurred in iron dextran and three in iron non-dextrans, for a resulting RR of 10.6 (95% CI, 1.03-115) and a corresponding RD of 3.03 (95% CI, 0.02-23.1) per 10,000 second IV iron treatments favouring iron non-dextrans. When assessing IV iron types, the RR and RD of anaphylaxis using iron sucrose as the common reference after a second treatment with IV iron was largest for iron dextran (RR, 6.32; 95% CI, 0.39-97.8; RD, 2.74; 95% CI, 1.45 to 22.5), favouring iron sucrose.

### Third or Subsequent Dispensing or Administration

When the expanded case-identification algorithm was used, 12 potential anaphylaxis events were identified (i.e., 2 additional events compared with the number from the main algorithm) for an IP of 0.03 (95% CI, 0.01-0.14) per 10,000 third or subsequent IV iron treatments. No potential anaphylaxis events were identified among third or subsequent treatments with iron dextran and, consequently, the RR comparing the IP of anaphylaxis between iron dextran and non-dextrans was estimated to be 0. The corresponding RD was 0.03 (95% CI, 0.14 to > 9,995) per 10,000 treatments, favouring the iron dextran. When assessing IV iron types, the RR of anaphylaxis using iron sucrose as the common reference after a third or subsequent treatment with IV iron was highest for iron gluconate (RR, 0.27; 95% CI, 0.02-3.83), whereas the RD using iron sucrose as the common reference after a third or subsequent treatment with IV iron

was largest for iron dextran (RD, 0.21; 95% CI, 1.09 to > 9,995) and iron isomaltoside (RD, 0.21; 95% CI, 1.12 to > 9,995), per 10,000 third or subsequent treatments with IV iron, favouring iron dextran and iron isomaltoside, respectively.

#### 10.5.1.2 IV Penicillin, First and Any Exposure

When the expanded case-identification algorithm was used, 259 potential anaphylaxis events were identified (i.e., 229 additional events) among first IV penicillin treatments and 471 potential events were identified (i.e., 427 additional potential events) among first and subsequent IV penicillin treatments. Table 13 shows, the IPs of potential anaphylaxis events per 10,000 IV penicillin treatments, for first and any treatment using the expanded case-identification algorithm applied during the exposure risk window defined by "same day" or "same day and day after" IV penicillin dispensing/administration).

**Table 13. Risk of Anaphylaxis at First Treatment and at any Treatment With IV Penicillins. Expanded Algorithm**

| | First Treatment With IV Penicillins | Any Treatment With IV Penicillins |
|---|---|---|
| **Any IV penicillins** | | |
| Anaphylaxis events (n) | 259 | 471 |
| Treatments (n) | 231,294* | 984,000* |
| IP (95% CI) | 6.45 (4.98-8.42) | 3.38 (2.81-4.09) |

CI = confidence interval; IP = incidence proportion; IV = intravenous.

* Treatments included the Danish data which were rounded to the nearest 10 to comply with data-protection rules aimed at prevention of identification of individuals.

### *10.5.2 Seven-day Risk Window*

#### 10.5.2.1 Overall IV Iron, IV Iron Groups, and IV Iron Types

Table 14 shows, by ordinal number of IV iron treatment (i.e., first, second, and third or subsequent), the IPs of potential anaphylaxis events per 10,000 IV iron treatments, overall for all IV irons and for iron dextran and iron non-dextrans separately using the main case-identification algorithm applied during the expanded exposure risk window including up to 7 days after IV iron treatment) (see Section 9.9.4).

These analyses were performed in all data sources, however, KfH QiN, Germany, contributed data to the risk window expansion analysis based on administration data and events identified during the same day (day 0) risk window applicable to this data source.

The resulting RRs and RDs (iron dextran vs. iron non-dextrans), with the corresponding 95% CIs, are also displayed.

**Table 14. Risk of Anaphylaxis After Treatment With IV Iron, Overall and by IV Iron Dextran and Iron Non-dextran Groups. 7-days Risk Window**

| | First Treatments | Second Treatments | Third or Subsequent Treatments |
|---|---|---|---|
| **Overall IV irons** | | | |
| Anaphylaxis events (n) | Min, 24; max, 27* | 8 | 19 |
| Treatments (n)** | 304,210 | 148,099 | 3,103,486 |
| IP (95% CI)* | Min, 0.74 (0.43-1.29); max, 0.88 (0.56-1.39) | 0.46 (0.15-1.45) | 0.05 (0.02-0.15) |
| **IV iron dextran** | | | |
| Anaphylaxis events (n) | 1 | 1 | 0 |
| Treatments (n)** | 6,387 | 3,084 | 9,508 |
| IP (95% CI) | Min, 1.62 (0.23-11.3); max, 1.61 (0.23-11.2) | 3.39 (0.49-23.6) | 0 (0-> 9,995) |
| **IV iron non-dextrans** | | | |
| Anaphylaxis events (n) | Min, 23; max, 26 | 7 | 19 |
| Treatments (n)** | 297,813 | 145,015 | 3,093,988 |
| IP (95% CI) | Min, 0.77 (0.37-1.62); max, 0.93 (0.50-1.75) | 0.50 (0.14-1.86) | 0.06 (0.02-0.22) |
| RR (95% CI)*** | Min, 2.11 (0.27-17.0); max, 1.74 (0.23-13.4) | 6.76 (0.69-70.1) | 0 (0-> 9,995) |
| RD (95% CI)*** | Min, 0.85 (−0.80 to 10.6); max, 0.68 (−0.95 to 10.4) | 2.88 (−0.30 to 23.2) | −0.06(−0.17 to > 9,995) |

CI = confidence interval; IP = incidence proportion; IV = intravenous; Max = maximum; Min = minimum; RR = risk ratio; RD = risk difference.

Note: Because the IV iron non-dextrans have a different number of events in the minimum and maximum scenarios, the data going into these two models are different. Thus, all regression coefficients may be affected, and IP estimates for IV iron dextran can vary slightly between scenarios even in situations where the numerators and denominators are the same in both scenarios.

*The number of events identified in Denmark was between 1 and 4, the exact number cannot be disclosed due to data-protection rules aimed at the prevention of identification of individuals. Therefore, IPs per 10,000 first treatments are reported as minimum and maximum range.

** Treatments included the Danish data which were rounded to the nearest 10 to comply with data-protection rules aimed at the prevention of identification of individuals.

***RRs calculated for iron dextran vs. non-dextrans; RDs calculated for iron dextran minus iron non-dextrans.

### First Dispensing or Administration

When the main algorithm was used in conjunction with the 7-day risk window in all data sources except KfH QiN dialysis registry in Germany, where dates of IV iron administration and anaphylaxis diagnoses were captured, between 24 and 27 anaphylaxis events were identified (i.e., 11 additional events compared with the number from the main algorithm) for an IP ranging from 0.74 (95% CI, 0.43-1.29) to 0.88 (95% CI, 0.56-1.39) per 10,000 first iron treatments. Of these, 1 event occurred in iron

dextran and between 23 and 26 in iron non-dextrans first treatments, for a resulting RR ranging from 2.11 (95% CI, 0.27-17.0) to 1.74 (95% CI, 0.23-13.4) and a resulting RD ranging from 0.85 (95% CI, 0.80 to 10.6) to 0.68 (95% CI, 0.95 to 10.4), per 10,000 first iron treatments favouring iron non-dextrans. When assessing IV iron types, the RR and RD of anaphylaxis using iron sucrose as the common reference after a first treatment with IV iron were highest for iron isomaltoside (RR, 15.2; 95% CI, 1.63-133; RD, 8.18; 95% CI, 1.07-33.8, favouring iron sucrose).

**Second Dispensing or Administration**

In the 7-day risk window sensitivity analysis conducted using all data sources, except the KfH QiN dialysis registry in Germany, eight potential anaphylaxis events were identified (i.e., five additional events), for an IP of 0.46 (95% CI, 0.15-1.45) per 10,000 second IV iron treatments. Of these, one event occurred in iron dextran and seven in iron non-dextrans, for a resulting RR of 6.76 (95% CI, 0.69-70.1) and a corresponding RD of 2.88 (95% CI, 0.30 to 23.2) per 10,000 second IV iron treatments favouring IV iron non-dextrans. The RR and RD of anaphylaxis using IV iron sucrose as the common reference was highest for iron dextran (RR, 2.04; 95% CI, 0.20-19.7; RD, 1.67; 95% CI, 3.02 to 21.7), favouring iron sucrose.

**Third or Subsequent Dispensing or Administration**

In the 7-day risk window sensitivity analysis conducted using all data sources except the KfH QiN dialysis registry in Germany, 19 potential anaphylaxis events were identified (i.e., 9 additional events), for an IP of 0.05 (95% CI, 0.02-0.15) per 10,000 third or subsequent IV iron treatments. No potential events of anaphylaxis were identified among iron dextran and, consequently, the RR comparing the IP of anaphylaxis between iron dextran and non-dextrans was estimated to be 0. The corresponding RD was 0.06 (95% CI, 0.17 to > 9,995) per 10,000 treatments, favouring the iron dextran. The RR of anaphylaxis using iron sucrose as the common reference was highest for iron carboxymaltose (RR, 0.45; 95% CI, 0.04-4.99). The largest RD using iron sucrose as the common reference was seen for iron dextran (RD, 0.21; 95% CI, 1.09 to > 9,995) and iron isomaltoside (RD, 0.21; 95% CI, 1.12 to > 9,995), favouring iron dextran and iron isomaltoside, respectively.

#### 10.5.2.2 IV Penicillin, any Exposure

Table 15 shows the IPs of potential anaphylaxis events per 10,000 IV penicillin treatments, for any treatment using the main case-identification algorithm applied during the 7-days exposure risk window. This analysis was conducted in the data sources that contributed data to the IV penicillins cohort (i.e., Central Denmark Region, the SNDS in France, PHARMO-NL, and the GePaRD in Germany).

**Table 15. Risk of Anaphylaxis at First Treatment and at any Treatment With IV Penicillins. 7-days Risk Window**

| | Any Treatment With IV Penicillins |
|---|---|
| **Any IV penicillins** | |
| Anaphylaxis events (n) | 48 |
| Treatments (n) | 984,000* |
| IP (95% CI) | 0.53 (0.40-0.71) |

CI = confidence interval; IP = incidence proportion; IV = intravenous.

* Treatments included the Danish data which were rounded to the nearest 10 to comply with data-protection rules aimed at prevention of identification of individuals.

### *10.5.3 Before 1 January 2013 and After 31 December 2013*

Owing to the low number of events, this stratified analysis was conducted among users of IV iron irrespective of the number of exposures (i.e., first, second, and third or subsequent exposures confounded). Only GePaRD in Germany and the Swedish National Registers contributed events to this analysis. The Central Denmark Region did not contribute data to this analysis. Data from 2013 were not included.

This analysis was conducted using the main case-identification algorithm applied during the exposure risk window defined by "same day" or "same day and day after" IV iron treatment.

Table 16 shows, for both periods of interest, the IPs of potential anaphylaxis events per 10,000 IV iron treatments, overall for all IV irons and for iron dextran and non-dextrans, separately. The resulting RRs and RDs (iron dextran vs. iron non-dextrans), with the corresponding 95% CIs, are also displayed.

**Table 16. Risk of Anaphylaxis at any Treatment With IV Irons, Before and After 2013. Main Analysis**

| | Before 2013 | After 2013 |
|---|---|---|
| **Any IV iron** | | |
| Anaphylaxis events (n) | 12 | 10 |
| Treatments (n)* | 1,775,379 | 1,331,988 |
| IP (95% CI) | 0.06 (0.03-0.17) | 0.09 (0.04-0.24) |
| **IV iron dextran** | | |
| Anaphylaxis events (n) | 0 | 1 |
| Treatments (n)* | 14,908 | 2,753 |
| IP (95% CI) | 0 (0.00 to > 9,995) | 3.64 (0.53-25.4) |
| **IV iron non-dextrans** | | |
| Anaphylaxis events (n) | 12 | 9 |
| Treatments (n)* | 1,760,471 | 1,329,235 |
| IP (95% CI) | 0.07 (0.02-0.24) | 0.11 (0.04-0.34) |
| RR (95% CI)** | 0 (0.00 to > 9,995)) | 33.2 (3.76-317) |
| RD (95% CI)** | −0.07 (−0.19 to > 9,995) | 3.53 (0.39-25.4) |

CI = confidence interval; IP = incidence proportion; IV = intravenous; RR = risk ratio; RD = risk difference.

*Treatments included the Danish data which were rounded to the nearest 10 to comply with data-protection rules aimed at prevention of identification of individuals.

**RRs calculated for iron dextran vs. iron non-dextrans; RDs calculated for iron dextran minus iron non-dextrans.

On the basis of a comparable number of IV iron treatments in both periods, the IP of anaphylaxis remained similar at 0.06 per 10,000 IV iron treatments and 0.09 per 10,000 IV iron treatments from the period before 2013 to the period after 2013. No events of anaphylaxis were observed for iron dextran in the period before 2013. The RD changed from slightly favouring iron dextran in the before 2013 period (RD, 0.07; 95% CI, 0.19 to > 9,995 per 10,000 iron treatments) to favouring iron non-dextrans in the after 2013 period (RD, 3.53; 95% CI, 0.39-25.4 per 10,000 iron treatments).

### *10.5.4 Exclusion of Data Sources with Zero Events*

#### 10.5.4.1 Overall IV Iron, IV Iron Groups, and IV Iron Types

This section presents the resulting estimates after excluding data sources with zero events for each ordinal IV iron exposure i.e., first, second, and third or subsequent events.

**First Dispensing or Administration**

There were zero events identified among patients with a first IV iron dispensing/administration in three data sources: the SNDS in France, PHARMO-NL, and

the KfH QiN dialysis registry in Germany. After excluding these data sources, based on 189,254 first IV iron users and between 13 and 16 anaphylaxis events, the overall IPs ranged from 0.69 (95% CI, 0.40-1.19) to 1.92 (95% CI, 0.79-4.77) per 10,000 first iron treatments. There were no events in the iron dextran group and, thus, the resulting RRs (min, max) were 0 (95% CI, 0.00 to > 9,995). Risk differences ranged from 0.85 (95% CI, 1.63 to > 9,995) to 1.03 (95% CI, 1.70 to > 9,995) per 10,000 first iron treatments favouring iron dextran.

When assessing IV iron types, the RRs and RDs of anaphylaxis using iron sucrose as the common reference were highest for iron isomaltoside, based on one potential event (RR, 16.2; 95% CI, 0.97-248; RD, 5.11; 95% CI, 0.04 to 37.9, favouring iron sucrose).

**Second Dispensing or Administration**

There were no anaphylaxis events among patients with a second IV iron treatment in the Health Services Database of the Central Denmark Region, SNDS in France, PHARMO-NL, and the KfH QiN dialysis registry in Germany. Exclusion of these data sources resulted in 88,717 patients with a second IV iron treatment for an overall IP of 0.34 (95% CI, 0.11-1.07) per 10,000 second IV iron treatments. On the basis of one potential anaphylaxis event among iron dextran and two events in the iron non-dextrans, the estimated RR was 21.9 (95% CI, 2.09-243) corresponding to a RD of 4.81 (95% CI, 0.41-35.1) per 10,000 second IV iron treatments favouring the iron non-dextrans.

Results by IV iron types showed highest IPs (5.17; 95% CI, 0.75-36.9), highest RRs (8.02; 95% CI, 0.50-124) and RDs (4.53; 95% CI, 51.35 to 36.0, favouring iron sucrose) for the iron dextran type.

**Third or Subsequent Dispensing or Administration**

The GePaRD database in Germany was the only data source identifying potential cases among 348,945 third or subsequent IV iron treatments. The beta-binomial meta-analysis IPs, RRs, and RDs were not estimable because the model failed to converge when there was only one data point.

### *10.5.5 Exclusion of Dialysis Patients*

The patterns of IV iron treatment among dialysis patients differ from those among patients with other conditions. Therefore, an analysis excluding patients undergoing dialysis, in data sources where these patients could be identified, was considered of relevance. Furthermore, in the US studies assessing the risk of anaphylaxis associated with IV iron treatment, dialysis patients were excluded.

#### 10.5.5.1 Overall IV Iron, IV Iron Groups and IV Iron Types

Table 17 summarises the IPs, RRs, and RDs estimates for each ordinal IV iron exposure i.e., first, second, and third or subsequent overall and by iron group after excluding dialysis patients in each data source except in the SNDS in France, where dialysis patients could not be identified.

**Table 17. Risk of Anaphylaxis After Treatment With IV Iron Excluding Dialysis Patients, Overall, and by IV Iron-dextran and Non-dextran Groups**

| | First Treatments | Second Treatments | Third and Subsequent Treatments |
|---|---|---|---|
| **Overall IV iron** | | | |
| Anaphylaxis events (n) | Min, 13; max, 16* | 3 | 6 |
| Treatments (n)** | 176,261 | 76,224 | 144,717 |
| IPs per 10,000 (95% CI) | Min, 0.77 (0.41-1.47); max, 1.75 (0.71-4.46) | 0.46 (0.14-1.59) | 0.34 (0.08-1.63) |
| **Iron dextran** | | | |
| Anaphylaxis events (n) | 0 | 1 | 0 |
| Treatments (n)** | 5,804 | 2,604 | 4,915 |
| IPs per 10,000 (95% CI) | 0 (0.00 to > 9,995) | 3.91 (0.56-27.3) | 0.0 (0.00-NE) |
| **Iron non-dextrans** | | | |
| Anaphylaxis events (n) | Min, 13; max, 16* | 2 | 6 |
| Treatments (n)** | 170,457 | 73,620 | 139,802 |
| IPs per 10,000 (95% CI) | Min, 1.00 (0.42-2.42); max, 1.24 (0.62-2.53) | 0.45 (0.11-1.87) | 0.38 (0.10-1.42) |
| RRs (95% CI)*** | Min, 0.00 (0.00-NE); max, 0 (0.00 to > 9,995) | 8.72 (0.83-96.8) | 0 (0.00-NE) |
| RDs (95% CI)*** | Min, −1.00 (NE52-NE); max, −1.24 (−2.22 to > 9,995) | 3.46 (−0.15 to 27.0) | −0.38 (NE-NE) |

CI = confidence interval; IP = incidence proportion; IV = intravenous; Max = maximum; Min = minimum; NE = not estimable; RR = risk ratio; RD = risk difference.

*The number of events identified in Denmark was between 1 and 4, the exact number cannot be disclosed due to data-protection rules aimed at prevention of identification of individuals. Therefore, IPs per 10,000 first treatments are reported as minimum and maximum range.

** Treatments included the Danish data which were rounded to the nearest 10 to comply with data-protection rules aimed at prevention of identification of individuals.

***RRs calculated for iron dextran vs. non-dextrans; RDs calculated for iron dextran minus iron non-dextrans.

### First Dispensing or Administration

After excluding dialysis patients, based on 176,261 patients with a first IV iron treatment and between 13 and 16 potential anaphylaxis events (all occurring among the iron non-dextran group), the overall IPs ranged from 0.77 (95% CI, 0.41-1.47) to 1.75 (95% CI, 0.71-4.46) per 10,000 first iron treatments. The RD ranged from 1.00 (95% CI, NE-NE) to 1.24 (95% CI, 2.22 to > 9,995), favouring iron dextran in both scenarios.

Results by IV iron type (using iron sucrose as the common reference) showed the highest RR and the largest RD of anaphylaxis after a first treatment for iron isomaltoside although based on one potential event each for iron sucrose and iron isomaltoside (RR, 13.2; 95% CI, 0.79-202; RD, 4.21; 95% CI, 0.27 to 31.6).

**Second Dispensing or Administration**

There were 76,224 non-dialysis patients with second IV iron treatments; one potential anaphylaxis event in the iron-dextran and two potential events in the iron non-dextran group. The IP of anaphylaxis per 10,000 second treatments was higher in the iron-dextran group than in the iron non-dextran group. The resulting RR of 8.72 (95% CI, 0.83-96.8) and RD of 3.46 (95% CI, 0.15 to 27.0) favoured the iron non-dextran group.

Results by IV iron type (using iron sucrose as the common reference) showed the highest RR and largest RD of anaphylaxis after second treatments for iron dextran, although based on one potential event (RR, 6.37; 95% CI, 0.40-98.5; RD, 3.25; 95% CI, 1.69 to 26.7).

**Third or Subsequent Dispensing or Administration**

There were 144,717 third or subsequent IV iron treatments and six potential anaphylaxis events (all among the iron non-dextran group).

Results by IV iron type showed that all potential anaphylaxis events occurred among the iron gluconate type, thus resulting in a RR of 0; 95% CI, 0-NE, and a RD, 0.38; 95% CI, NE-NE.

### *10.5.6 Risk in Patients Switching Between IV Iron Types*

We conducted an analysis on the risk of anaphylaxis after switching from an iron non-dextran to an iron dextran (and vice versa). The analysis was conducted after a first switch and after any switch. Results are shown in Table 18.

**Table 18. Risk of Anaphylaxis After Switching Between IV Iron Groups, After a First Switch and After any Subsequent Switch**

| | Anaphylaxis After a First Switch | | Anaphylaxis After any Switch | |
|---|---|---|---|---|
| | From Dextrans to Non-dextrans | From Non-dextrans to Dextrans | From Dextrans to Non-dextrans | From Non-dextrans to Dextrans |
| Anaphylaxis events (n) | 0 | 2 | 0 | 2 |
| Switches (n) | 332 | 608 | 619 | 702 |
| IPs per 10,000 (95% CI) | 0 (0-0) | 32.9 (8.26-136) | 0 (NE-NE) | 29.0 (NE-NE) |

CI = confidence interval; IP = incidence proportion, IV = intravenous; NE = not estimable.

Overall, no anaphylaxis occurred after a switch from an iron dextran to an iron non-dextran.

However, two potential anaphylaxis events occurred after a first switch from an iron non-dextran to an iron dextran for an IP of 32.9 per 10,000 first switches. No additional events occurred in subsequent switches from an iron dextran to an iron non-dextran.

### *10.5.7 All First and Subsequent Treatments With IV Iron Combined*

The risk estimates for anaphylaxis (identified through the main case-identification algorithm and the same day and day after exposure risk window) among all users of IV iron captured by the study, are presented in Table 19. Similar to the analyses focusing on third or subsequent treatments, the low IPs found in this analysis can be largely attributed to the high number of IV iron treatments in the KfH QiN dialysis registry network in Germany.

Overall, between 26 and 29 potential anaphylaxis events were identified that resulted in a range of IPs from 0.07 to 0.09 per 10,000 IV iron treatments. The IP for iron dextran was 0.53 per 10,000 iron-dextran treatments (based on one event). For iron non-dextrans the IPs ranged from 0.08 to 0.10 per 10,000 iron non-dextrans treatments. The RR for iron dextran versus iron non-dextrans ranged from 5.45 to 7.03 and the RD ranged from 0.44 to 0.45 anaphylaxis per 10,000 iron treatments, favouring iron non-dextrans.

**Table 19. Risk of Anaphylaxis After Treatment With IV Iron Irrespective of Number of Treatments, Overall, and by IV Iron-dextran and Iron Non-dextran Groups**

| | Any Treatments |
|---|---|
| **Overall IV iron** | |
| Anaphylaxis events (n) | Min, 26; max, 29* |
| Treatments (n)** | 3,555,795 |
| IPs per 10,000 (95% CI) | Min, 0.07 (0.04-0.15); max, 0.09 (0.05-0.16) |
| **Iron dextran** | |
| Anaphylaxis events (n) | 1 |
| Treatments (n)** | 18,979 |
| IPs per 10,000 (95% CI)*** | 0.53 (0.08-3.74) |
| **Iron non-dextrans** | |
| Anaphylaxis events (n) | Min, 25; max, 28* |
| Treatments (n)** | 3,536,816 |
| IPs per 10,000 (95% CI) | Min, 0.08 (0.03-0.19); max, 0.10 (0.05-0.21) |
| RRs (95% CI)**** | Min, 5.45 (0.70-44.2); max, 7.03 (0.85-59.9) |
| RDs (95% CI)**** | Min, 0.44 (−0.04 to 3.65); max, 0.45 (−0.01 to 2.91) |

CI = confidence interval; IP = incidence proportion; IV = intravenous; Max = maximum; Min = minimum; RD = risk difference; RR = risk ratio.

*The number of events identified in Denmark was between 1 and 4, the exact number cannot be disclosed due to data-protection rules aimed at prevention of identification of individuals. Therefore, IPs per 10,000 first treatments are reported as minimum and maximum range.

** Treatments included the Danish data which were rounded to the nearest 10 to comply with data-protection rules aimed at prevention of identification of individuals.

*** The IP for iron dextran was calculated using a pooled crude approach because the beta-binomial model did not converge due to the sparsity of data.

****RRs calculated for iron dextran vs. iron non-dextrans; RDs calculated for iron dextran minus iron non-dextrans.

### *10.5.8 Description of Number of Potential Events Outside the Main Risk Window up to 21 Days After Treatment*

#### 10.5.8.1 IV Iron

To evaluate the possibility of a delayed administration of a dispensed IV iron, the occurrence of potential anaphylaxis events from day 2 to 21 days after treatment was assessed. This analysis was performed in data sources not capturing the date of administration of IV iron or the precise date of diagnosis of anaphylaxis.

Table 20 shows the additional potential events identified from day 2 up to 21 days after IV iron exposure. Overall, 70 additional potential events were identified of which 46% occurred during the 2 to 7 days after IV iron treatment.

**Table 20. Number of Potential Anaphylaxis Occurrences (Main Algorithm) Identified After the Risk Window Among New Users of Intravenous Iron Compounds at any Treatment**

| Number of Days After IV Iron Treatment | SNDS, France | PHARMO-NL | Swedish National Registers | GePaRD, Germany |
|---|---|---|---|---|
| 2-4 | 2 | 0 | 2 | 7 |
| 5-7 | 2 | 0 | 1 | 18 |
| 8-10 | 1 | 0 | 2 | 5 |
| 11-13 | 2 | 0 | 0 | 9 |
| 14-16 | 1 | 0 | 1 | 6 |
| 17-19 | 2 | 0 | 0 | 1 |
| 20-21 | 2 | 0 | 0 | 6* |

GePaRD = German Pharmacoepidemiological Research Database; IV = intravenous; PHARMO NL = PHARMO Database Network in the Netherlands; SNDS = Système National des Données de Santé (French National health care insurance system database, previously named SNIIRAM).

*In GePaRD the number refers to potential occurrences of anaphylaxis from day 20 to day 22 after IV iron treatment.

This analysis was not performed in the Central Denmark Region due to data-protection rules aimed at preventing identification of individuals.

#### 10.5.8.2 IV Penicillin

Overall, there were 15 additional potential anaphylaxis events among IV penicillin users identified in GePaRD in Germany and SNDS in France outside the risk window. Overall, 33% of all potential events occurred from day 2 to day 7 after IV penicillin treatment.

### *10.5.9 Risk of Anaphylaxis by IV Penicillins Subtypes*

We conducted an analysis of the risk of anaphylaxis among penicillins users by subtype of penicillins. The groups considered a priori were natural penicillins, betalactamase-resistant penicillins, aminopenicillins, carboxypenicillins, ureidopenicillins, and other penicillins.

Ureidopenicillins were associated with a higher IP of anaphylaxis, ranging from 3.40 to 3.48 per 10,000 first treatments. Aminopenicillins were associated with a lower risk of anaphylaxis; IP ranged from 0.43 to 0.49 per 10,000 first treatments based on one event.

#### *10.5.10 Risk Among Dialysis Patients*

The analysis among patients undergoing dialysis was performed in patients receiving any first or subsequent IV iron treatment. Two potential anaphylaxis events were identified, both among IV iron non-dextrans treated patients. The resulting IP was 0.01 (95% CI, 0.00-0.09) per 10,000 IV iron exposures. Table 8 in Annex 4 presents data source-specific results.

## 10.6 Adverse Events/Adverse Reactions

This study followed the EMA guideline on the requirements for reporting of adverse events, *"EMA's GVP Module VI Management and Reporting of Adverse Reactions to Medicinal Products (Rev 2)"* (EMA, 2014; EMA, 2017b) and the ISPE guideline (ISPE, 2015) The guideline indicates that the reporting of suspected adverse reactions in the form of individual case safety reports is not required for non-interventional, postauthorisation studies such as the study described here that is based on secondary use of data.

# 11 Discussion

## 11.1 Key Results

### *11.1.1 Main Analyses*

#### 11.1.1.1 IV Iron

- The study identified 304,210 patients with a first-recorded IV iron dispensing/administration of whom 6,367 (2.1%) were for iron dextran. For the second IV iron treatments, there were 148,099 patients of whom iron dextran users represented 2.1%; for the third and subsequent treatments, 3,103,486 treatments in 105,634 patients were captured with iron dextran accounting for 0.3% of all third or subsequent treatments. Eighty-four percent of all third or subsequent IV iron treatments were driven by treatments from the KfH QiN dialysis registry in Germany. This finding reflects the repeated treatments required for the management of dialysis patients.
- IV iron treatment in this study reflects only partial use in each country, mostly from ambulatory drug-dispensing data. The study only captures hospital use in the Central Denmark Region (full capture) and the Netherlands (partial capture). Likewise, the study captures IV iron types as used in each of the settings covered in each country.

- Chronic kidney disease, iron-deficiency anaemia, and gastrointestinal bleeding were the most frequent conditions related to potential IV iron indications. The prevalence of these conditions varied greatly across study populations dependent on the type of available data i.e., outpatient diagnosis, primary care diagnoses versus hospital discharge diagnoses. The prevalence of conditions that are risk factors for hypersensitivity reactions also varied across data sources: history of anaphylaxis ranged from 0% to 1% and history of any allergies ranged from 2% to 51%.
- At first IV iron treatment, between 13 and 16 potential cases of anaphylaxis were identified. The resulting IP ranged from 0.38 (95% CI, 0.17-0.88) to 0.51 (95% CI, 0.28-0.97) per 10,000 first treatments. No events among iron dextran users were identified in this group. Therefore, the RR of iron dextran versus iron non-dextrans was 0. The corresponding risk difference ranged from -0.44 to -0.55 events per 10,000 first treatments. IPs and RDs estimates presented as ranges owing to the data protection rules aimed at preventing the identification of individual patients.
- The IPs of anaphylaxis were generally higher for the first treatment. Among second IV iron treatments, from a total of three potential anaphylaxis cases, a single case was identified in the iron-dextran group.
- There were no anaphylaxis events identified in three populations i.e., the SNDS in France, PHARMO-NL, and KfH QiN dialysis registry in Germany.
- Risk estimates by groups and types of IV iron were estimated but are based on a very small number of events.
- No adjusted analyses could be performed because of the small number of events.
- The study case-identification algorithm as used in GePaRD in Germany has been validated in the Oldenburg University Hospital showing a PPV of 62.3% (95% CI, 49.8-73.7).
- There were no potential anaphylaxis events among IV iron users in PHARMO-NL. In the Central Denmark Region, owing to the data-protection rules aimed at preventing identification of individual patients, the results of the validation of potential events among IV iron users (1-4 events) could only be reported as a combined PPV for potential anaphylaxis events among the IV iron users and IV penicillin users (PPV 70; 95% CI, 50-86).

#### 11.1.1.2 IV Penicillins

- The study identified 231,294 first treatments and 984,000 total treatments of IV penicillins overall.
- At first IV penicillins treatment, 30 potential cases of anaphylaxis were identified. The resulting IP was 1.16 (95% CI, 0.78-1.73) per 10,000 treatments.
- The Central Denmark Region contributed the majority of parenteral penicillins patients (50.6%) and treatments (74.8%) because it was the only study data source that comprehensively captured in-hospital administration of drugs.

- Two data sources did not contribute data for IV penicillins i.e., KfH QiN dialysis registry in Germany, and the Swedish registers.
- The only evaluable case identified through the main algorithm in PHARMO-NL was confirmed resulting in a PPV of 100%. In the Central Denmark Region, the estimated PPV combining the potential events from IV iron and IV penicillin users was 70% based on potential cases with sufficient information.

### *11.1.2 Sensitivity Analyses*

#### 11.1.2.1 IV Iron

The sensitivity analyses conducted were intended to assess whether the main case-identification algorithm and the exposure risk window applied in the main analysis were adequately identifying the study outcome.

- Expanding the case-identification algorithm to include adrenaline administration as a proxy of anaphylaxis, six additional potential events were identified among first IV iron treatment in PHARMO-NL. However, direct validation of these potential events suggested that most adrenaline use in these patients was not intended to treat an anaphylactic reaction. In the Central Denmark Region, the data were too sparse to evaluate meaningfully the impact of this algorithm expansion.
- Expanding the exposure risk window up to 7 days to identify events in data sources using dispensing data or where the exact date of the potential event was not known identified 11 additional potential events. All these additional events were identified in data sources where case validation was not possible. The analysis of potential events occurring from day 2 up to day 21 did not provide strong evidence of delayed administration of IV iron.
- Dialysis patients were excluded based on the different pattern (i.e., chronic) of use of IV iron among these patients and the impossibility of ascertaining new-user status (especially in the KfH QiN dialysis registry in Germany). This analysis showed an increase in the IP of anaphylaxis among first IV iron treatments (IPs ranged from 0.77 to 1.75 per 10,000 first treatments).
- When anaphylaxis occurring after a switch from iron non-dextrans to iron dextran was assessed, two additional potential anaphylaxis events were identified after a first switch from an iron non-dextran to an iron dextran. No additional potential events were identified after further switches between the iron non-dextran and iron-dextran groups.
- Similar to the analyses focusing on third or subsequent treatments, the results assessing all treatments with IV iron combined were largely driven by the large number of IV iron treatments in the KfH QiN dialysis registry in Germany.

#### 11.1.2.2 IV Penicillin

- Expanding the case-identification algorithm to include adrenaline administration as a proxy of anaphylaxis, 427 additional potential events were identified among

first and subsequent IV penicillin treatments across all sites with IV penicillin data.

- Direct validation of the additional potential events in PHARMO-NL suggested that most adrenaline use in these patients was not intended to treat an anaphylactic reaction.
- Expanding the exposure risk window up to 7 days to identify events in data sources using dispensing data or where the exact date of the potential event was not known identified four additional potential events. Since there were no cases identified in PHARMO-NL or the Central Denmark Region direct validation was not possible.

## 11.2 Limitations

The 2014 and 2016 feasibility evaluations identified a large number of important challenges that have been confirmed upon conduct of the study (the study feasibility reports are included in Annex 5).

The following are the main limitations encountered:

- A very low number of potential anaphylaxis events has been identified despite the use of multiple, large, population-based data sources. This low number of events was identified in the descriptive analysis (March 2019). This prompted a modification of the methods as reflected in the amended protocol endorsed by EMA-PRAC on September 2019. Among others, this precluded the conduct of the originally planned propensity score-adjusted analyses. Estimates from beta-binomial regression meta-analyses have been provided. While they take into account site variability, estimates may be subject to confounding. Section 9.4.3 shows the variables initially considered for the propensity score models.
- Assessment of a differential risk of anaphylaxis by groups or types of IV iron has been limited by the very small number of users of some types of IV iron and its variability across countries. There is substantial capture only for iron sucrose, iron gluconate, and iron carboxymaltose. However, capture of iron dextran and iron isomaltoside in this study was marginal. This limited the comparison of iron dextran with iron non-dextrans and of individual IV iron types based on an appropriate number of exposures and events. Of interest, iron dextran represented a large proportion of all IV iron treatments captured in the PHARMO-NL. This finding was further assessed by verifying that all treatments originally identified as iron dextran from all PHARMO-NL sources (Outpatient Pharmacy, Inpatient Pharmacy and GP Database) contained the description "Cosmofer", the brand name for iron dextran.
- Full validation was not possible in any data source and therefore the degree of outcome misclassification is unknown. Validation of potential events was conducted in PHARMO-NL and the Central Denmark Region for hospitals that allowed access to the medical records. The approvals and access requests took longer than originally envisioned. Some hospitals did not grant access to their records. In Denmark, the data-protection rules compounded by lack of sufficient

information available from the reviewed records precluded detailed analysis of the validation data.

- There was important heterogeneity in the type of information available across data sources, notably only the Health Services Database of the Central Denmark Region captured in-hospital use of the medications of interest comprehensively and the PHARMO-NL captured partial in-hospital use. In France, only one IV iron preparation (iron carboxymaltose) was available for outpatients and captured in the SNDS, while all other IV iron preparations were available in hospital and included in the Diagnosis Related Group cost and were not identifiable. In addition, some data sources have relied on dispensed drug data rather than on actual administration of the drugs. This introduced a degree of uncertainty around the actual date of exposure and some degree of exposure misclassification may exist.

- New-user status has also been challenging to determine because of the limited capture of in-hospital use, likely the most common setting where the study drugs are administered often for the first time. According to whole-sales statistics from the Swedish eHealth Agency (Swedish Pharmaceutical Statistics, 2020), approximately 50% to 80% of IV iron treatments were administered in the inpatient setting (i.e., recorded as requisitions for IV iron treatments bought by hospitals and administered directly to the patient) during the study period. The same limitation applies to the ascertainment of second and third or subsequent treatments and analysis in all countries.

- Patients diagnosed with chronic kidney disease are likely to have received IV iron treatment before registration into the KfH QiN dialysis registry in Germany. Therefore, this may have introduced a depletion of susceptible patients because patients who had experienced a prior hypersensitivity reaction after treatment with IV iron would be less likely to be treated again.

- In most data sources it has been difficult to distinguish between IV and IM iron administration, which is of relevance for iron dextran, the IV iron compound that can be administered IV or IM. The lack of data on route of administration is expected to apply mainly to treatment dispensing/administration capture in outpatient settings because in the inpatient settings, data mostly refers to IV use. This may also have applied to IV penicillins.

- Although beta-binomial regression was recommended for meta-analyses of rare events, the model was not able to estimate CIs in certain situations where at least one treatment group had zero events. In other situations, variance estimates were orders of magnitude larger than regression coefficient estimates, yielding CIs bounded by minimum and maximum possible values. Additionally, model convergence was not always stable. When beta-binomial regression was implemented using the non-linear mixed (NLMIXED) procedure in SAS, the model would converge to slightly different parameter estimates or not converge at all depending on the user-specified initial starting values. To standardise regression models, the FMM procedure in SAS was implemented, which does not depend on user-specified initial starting values. However, within the FMM procedure, slightly different parameter estimates could be obtained by changing the default convergence criteria, maximum number of iterations, or optimisation technique.

- Despite all efforts and the commitment and engagement of the principal investigator at DIMDI, the DIMDI-DaTraV data source was not able to contribute data to the study because of the lack of resources at DIMDI to perform the study activities. DIMDI-DaTraV would have likely been the database with the largest contribution of IV iron exposure data to the study because of its coverage of the whole German population. However, the major limitations identified during feasibility evaluation have persisted. Most relevant is the lack of a recorded exact date for all diagnoses (only one quarter is available) which would have jeopardised the establishment of a plausible temporal relationship between the exposure to IV iron and the diagnosis of a potential anaphylaxis event. Also, the systematic lack of data for the year before a patient's death would have effectively excluded all fatal cases from the study.

## 11.3 Interpretation

This study found an IP of anaphylaxis ranging from 0.38 (95% CI, 0.17-0.88) to 0.51 (95% CI, 0.28-0.97) per 10,000 first IV iron treatments (IP, 0.77-1.75 per 10,000 first IV iron treatment in the non-dialysis populations). These estimates are lower than the estimates of 2.4 to 6.8 per 10,000 first treatments (IV iron non-dextrans and iron dextran, respectively) reported in Wang et al. (2015) or those reported by Walsh et al. (2016): 2 to 4 per 10,000 first treatments (IV iron non-dextrans and iron dextran, respectively). For the resulting RRs and RDs by IV iron groups and types the interpretation was limited due to the small number of events underlying these estimates.

The following potential reasons for the differences in the incidence of anaphylaxis between our study and the US studies exist:

- Potential underascertainment of anaphylaxis events.
  - This study adapted the case-identification algorithm from the US study by Walsh et al. (2016) that used ICD, ATC, procedure and other types of codes to identify anaphylaxis events. Had the case-identification algorithm not been adapted to the type of data available in the participating data sources, an underascertainment of events would have occurred. The inclusion in the study of a cohort of new users of penicillins was intended to assess the performance of the algorithm and address this potential limitation. The IP of anaphylaxis among new users of penicillins was 1.16 per 10,000 first treatments which is in the lower range of published estimates (ranging from 0.1 to 5 per 10,000). This provides evidence supporting the adequateness of the case-identification algorithm used in the study.
- The validation of potential events in Denmark and PHARMO-NL.

  Although based on a single confirmed case (PHARMO-NL), direct validation of the main algorithm suggests that the PPV is in line with other studies. The direct validation of the expanded algorithm in PHARMO-NL suggests that the addition of adrenaline to the algorithm was not helpful; a similar finding was suggested by the validation in the Central Denmark Region. In Denmark, the direct validation of the case-identification algorithms, despite the limitations imposed by compliance with data-protection rules, resulted in a PPV of 70% for the combined potential events among IV iron and IV penicillin users.

The validation of the study case-identification algorithm used in GePaRD in Germany in the Oldenburg University Hospital also supports that the case-identification algorithm can detect cases of anaphylaxis. The estimated PPV of the case-identification algorithm was similar to that of the algorithm used in the US Sentinel study (Walsh et al., 2013).

Therefore, even if a certain degree of misclassification of the outcomes is likely to exist, the study has provided evidence supporting the notion that the results are unlikely to have been driven by a major misclassification of the outcome status of participating patients.

- Underascertainment of exposure to IV iron.

  This study captured limited data on in-hospital use of IV iron, the setting where most use of this drug is likely to happen. Moreover, the data sources capturing inpatient use, Health Services Database of the Central Denmark Region, and PHARMO-NL, covered only a subset of the countries' population: about 25% of the total Danish population in the Health Services Database of the Central Denmark Region and 20% of the Dutch population in PHARMO-NL. In contrast, the US studies captured use of IV iron drugs comprehensively irrespective of administration setting.

  Nevertheless, this study was able to capture a substantial amount of IV iron treatments (i.e., 304,210 first treatments) thanks to the use of multiple large data sources. This use of IV iron was in line with that observed in the US Sentinel study by Walsh et al. (2016) (70,866 first treatments) and the US Medicare study by Wang et al. (2015) (688,183 first treatments).

  Therefore, the small number of events identified in the study does not appear driven by a poor capture of the use of IV iron in Europe.

- Misclassification of IV iron new-user status.

  The correct ascertainment of first use of IV iron may have been limited by the lack of data on in-hospital (or specialty clinics) use of IV iron. For instance, it is conceivable that a patient may have received the first doses of IV iron while in hospital and later received follow-up doses in an outpatient setting. The former treatments will have been missed by our study (except in the Central Denmark Region and PHARMO-NL) and the latter will have been captured but incorrectly considered as initial treatments. Indeed, data from Sweden suggests that between 50% and 80% of IV iron treatments occur in an in-hospital setting. A similar situation may have occurred with IV penicillins.

  In contrast, the US studies by Walsh et al. (2016) and Wang et al. (2015) had ascertainment of exposure to IV iron, irrespective of administration setting, and could therefore determine new-user status more precisely. Interestingly, both US studies excluded dialysis patients.

  It is known that the risk of anaphylaxis decreases with the increasing number of exposures to a drug because of the nature of anaphylactic reactions and to the depletion of susceptible patients. Therefore, the lower than expected number of events observed may, at least in part, be due to a misclassification of the new-user status of patients in our study. The sensitivity analysis excluding dialysis

patients is consistent with this hypothesis. Indeed, patients undergoing dialysis are regularly treated with IV iron to compensate for the increased losses of iron during dialysis and a decreased production of red blood cells. The main contributor of IV treatments in dialysis patients in this study, the KfH QiN in Germany, was unable to ascertain use of IV iron before registration in the registry network. It is likely that patients who undergo dialysis will have received IV iron doses before joining the dialysis speciality clinics in the KfH QiN registry network. Therefore, the misclassification of the new-user status of IV iron may be particularly important among dialysis patients. The analysis excluding dialysis patients was intended to reduce the new-user status misclassification and, as expected, showed an increase of the IP of anaphylaxis, from 0.38 to 0.51 per 10,000 first IV iron treatments when dialysis patients were included to 0.77 to 1.75 per 10,000 first IV iron treatments when dialysis patients were excluded.

- Results by group and type of IV iron.

  The main aim of this study was to compare the risk of anaphylaxis among iron dextran users with iron non-dextrans users. This analysis has been jeopardised by the small number of users of iron dextran and only one event in the second iron-dextran treatment. In contrast, iron-dextran use was common in the US studies.

  The evaluation of type of IV iron was targeted to identify anaphylaxis among users of the first type of IV iron, irrespective of the number of treatments with the specific IV iron type. However, the sensitivity analyses looking at the risk of anaphylaxis after a switch between IV iron groups identified two events after a first switch from an iron non-dextran to an iron dextran, for a high IP of anaphylaxis after such switches (i.e., IP, 32.9; 95% CI, 8.26-136 per 10,000 first switches). This finding is based on a low number of events.

## 11.4 Generalisability

The study provided a wide array of patient characteristics, health systems, drug use, and medical practice patterns, most of which were from outpatient settings across populations in different European countries. Generalisations from these findings depend on the category of the finding (Rothman et al., 2013; Rothman, 2014). Findings that relate to drug use and patient characterisation, or to risk minimisation evaluation apply to the specific patient population in the participating countries (i.e., Denmark, France, Germany, The Netherlands, and Sweden). The results that relate to endpoint validation should be generalisable to database or medical record systems using data collection and data linkage approaches similar to those used in Denmark and The Netherlands. The risk of events among those using IV iron products should be generalisable to all patients using this medication, apart from the effect of any as yet unidentified biological mediators.

# 12 Other Information

None.

# 13 Conclusion

This study was based on 304,210 patients with a first-recorded IV iron treatment in five European countries. However, there were only 6,387 first treatments of iron dextran.

Overall, the study found an overall IP of anaphylaxis, ranging from 0.38 (95% CI, 0.17-0.88) to 0.51 (95% CI, 0.28-0.97) per 10,000 first treatments; for iron non-dextrans from 0.44 to 0.55 and not assessable for iron dextran. The range stemmed from the masking of the exact number of events mandated by current data-protection Danish regulations to prevent identification of individual patients. These IPs were lower than the estimates of 2 and 6.8 per 10,000 first treatments (IV iron non-dextrans and iron dextran, respectively) reported in the US studies by Walsh et al. (2016) and Wang et al. (2015).

The low number of events precluded the conduct of the originally planned adjusted analyses and thus limits the interpretation of the results based on groups and types of IV iron.

The risk of anaphylaxis among IV penicillins users was within the expected range of IPs based on the literature, suggesting that the main case-identification algorithm used by the study was adequate. The results from the sensitivity analyses and from the available data of validation of cases, and the study case-identifying algorithm also supported this view.

The limitations of the study were identified by the feasibility evaluations conducted in 2014 and 2016 and reflected in the submitted reports. Most notably, the likely misclassification of repeated users of IV iron as first users, due to the impossibility of capturing use in hospital and specialty clinics in most data sources, may have resulted in an underestimation of the IPs of anaphylaxis.

Due to methodological limitations, the study cannot exclude the possibility of a high risk of anaphylaxis associated with the administration of injectable iron and whether there are differences in the risk between the different types of IV iron. Some sensitivity analyses yielded risk ratios above the unity when comparing the risk of anaphylaxis for iron dextran versus iron non-dextrans; however, these analyses were based on very few cases, all of which had important validity concerns, and therefore conclusions cannot be drawn.

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# Appendices

# Annex 1.
# List of Stand-alone Documents

None.

# Annex 2
# IV Iron Marketing Authorisation Holders Consortium

**Table 2 1. List of Participants in the IV Iron Marketing Authorisation Holders Consortium**

| Name | Address | Contact Details |
|---|---|---|
| Accord Healthcare Limited | [redacted] | [redacted] |
| Acino AG | [redacted] | [redacted] |
| Arrow Génériques | [redacted] | [redacted] |
| Baxter | [redacted] | [redacted] |
| Generis Farmacéutica SA | [redacted] | [redacted] |
| Altan Pharmaceuticals SAU | [redacted] | [redacted] |
| Laboratoires Sterop SA | [redacted] | [redacted] |
| Medice Arzneimittel Pütter GmbH & Co. KG | [redacted] | [redacted] |
| Mylan SAS | [redacted] | [redacted] |
| Orifarm Generics A/S | [redacted] | [redacted] |
| Panmedica (Panpharma SA), | [redacted] | [redacted] |
| Pharmachemie BV (Teva) | [redacted] | [redacted] |
| Pharmacosmos A/S | [redacted] | [redacted] |
| Rafarm SA | [redacted] | [redacted] |

| Name | Address | Contact Details |
|---|---|---|
| Sandoz SAS | [redacted] | [redacted] |
| Sanofi Aventis Groupe | [redacted] | [redacted] |
| Vifor France | [redacted] | [redacted] |

# Annex 3. Cohort Attrition and Baseline Characteristics: Data Source-specific Tables of Results

Annex 3_Cohorts Attrition.xlsx

Annex 3_Baseline Characteristics.xlsx

# Annex 4.
# Main and Sensitivity Analysis: Tables of Results

**Table 1.1 Combined Analysis Across Research Partner Databases By Dextran Category - Main Algorithm - First Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database (Min) | Estimate | 1.71 (20 / 116,980) | 1.71 (1 / 5,870) | 0 (0 / 20) | 1.71 (1 / 5,840) | 0 | 1.71 |
| | 95% CI | 1.11, 2.64 | 0.30, 9.65 | 0, 1430 | 0.30, 9.69 | 0, 943 | 5.07, 1.64 |
| Danish Central Region EMR Database (Max) | Estimate | 1.71 (20 / 116,980) | 6.82 (4 / 5,870) | 0 (0 / 20) | 6.85 (4 / 5,840) | 0 | 6.85 |
| | 95% CI | 1.11, 2.64 | 2.65, 17.5 | 0, 1430 | 2.66, 17.6 | 0, 225 | 13.6, 0.14 |
| SNDS Database, France | Estimate | 0.17 (1 / 57,200) | 0 (0 / 75,512) | NE | 0 (0 / 75,512) | NE | NE |
| | 95% CI | 0.03, 0.99 | 0, 0.51 | NE, NE | 0, 0.51 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0.77 (3 / 39,002) | 0 (0 / 5,825) | 0 (0 / 2,393) | 0 (0 / 3,432) | NE | 0 |
| | 95% CI | 0.26, 2.26 | 0, 6.59 | 0, 16.0 | 0, 11.2 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NA | 0.71 (3 / 42,468) | 0 (0 / 1,599) | 0.73 (3 / 40,869) | 0 | 0.73 |
| | 95% CI | NA | 0.24, 2.08 | 0, 24.0 | 0.25, 2.16 | 0, 32.7 | 1.56, 0.10 |
| GePaRD, Germany | Estimate | 3.31 (6 / 18,112) | 0.64 (9 / 140,916) | 0 (0 / 2,346) | 0.65 (9 / 138,570) | 0 | 0.65 |
| | 95% CI | 1.52, 7.23 | 0.34, 1.21 | 0, 16.3 | 0.34, 1.23 | 0, 25.2 | 1.07, 0.23 |
| KfH QiN, Germany | Estimate | NA | 0 (0 / 33,619) | 0 (0 / 29) | 0 (0 / 33,590) | NE | 0 |
| | 95% CI | NA | 0, 1.14 | 0, 1170 | 0, 1.14 | NE, NE | NE, NE |
| Pooled (Crude) Analysis (Min) | Estimate | 1.17 (30 / 231,294) | 0.43 (13 / 304,210) | 0 (0 / 6,387) | 0.44 (13 / 297,813) | 0 | 0.44 |
| | 95% CI | 0.80, 1.70 | 0.25, 0.73 | 0, 6.01 | 0.26, 0.75 | 0, 13.8 | 0.75, 5.57 |
| Beta Binomial Meta Analysis (Min) | Estimate | 1.16 | 0.38 | 0 | 0.44 | 0 | 0.44 |
| | 95% CI | 0.78, 1.73 | 0.17, 0.88 | 0, >9995 | 0.16, 1.24 | 0, >9995 | 1.02, >9995 |
| Pooled (Crude) Analysis (Max) | Estimate | 1.17 (30 / 231,294) | 0.53 (16 / 304,210) | 0 (0 / 6,387) | 0.54 (16 / 297,813) | 0 | 0.54 |
| | 95% CI | 0.80, 1.70 | 0.32, 0.85 | 0, 6.01 | 0.33, 0.87 | 0, 11.2 | 0.87, 5.47 |

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Beta Binomial Meta Analysis (Max) | Estimate | 1.16 | 0.51 | 0 | 0.55 | 0 | 0.55 |
| | 95% CI | 0.78, 1.73 | 0.28, 0.97 | 0, >9995 | 0.23, 1.34 | 0, >9995 | 1.14, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 1.2 Combined Analysis Across Research Partner Databases By Dextran Category - Main Algorithm - Second Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | NA | 0 (0 / 2,150) | 0 (0 / 10) | 0 (0 / 2,140) | NE | 0 |
| | 95% CI | NA | 0, 17.8 | 0, 3540 | 0, 17.9 | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NA | 0 (0 / 22,626) | NE | 0 (0 / 22,626) | NE | NE |
| | 95% CI | NA | 0, 1.70 | NE, NE | 0, 1.70 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NA | 0 (0 / 1,850) | 0 (0 / 1,066) | 0 (0 / 784) | NE | 0 |
| | 95% CI | NA | 0, 20.7 | 0, 35.9 | 0, 48.8 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NA | 0.48 (1 / 20,822) | 0 (0 / 760) | 0.50 (1 / 20,062) | 0 | 0.50 |
| | 95% CI | NA | 0.08, 2.72 | 0, 50.3 | 0.09, 2.82 | 0, 101 | 1.48, 0.48 |
| GePaRD, Germany | Estimate | NA | 0.29 (2 / 67,895) | 8.18 (1 / 1,223) | 0.15 (1 / 66,672) | 54.5 | 8.03 |
| | 95% CI | NA | 0.08, 1.07 | 1.44, 46.2 | 0.03, 0.85 | 5.69, 522 | 8.00, 24.0 |
| KfH QiN, Germany | Estimate | NA | 0 (0 / 32,756) | 0 (0 / 25) | 0 (0 / 32,731) | NE | 0 |
| | 95% CI | NA | 0, 1.17 | 0, 1330 | 0, 1.17 | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | NA | 0.20 (3 / 148,099) | 3.25 (1 / 3,084) | 0.14 (2 / 145,015) | 23.5 | 3.11 |
| | 95% CI | NA | 0.07, 0.60 | 0.57, 18.4 | 0.04, 0.50 | 3.08, 180 | 0.42, 18.2 |
| Beta Binomial Meta Analysis | Estimate | NA | 0.25 | 3.33 | 0.25 | 13.1 | 3.08 |
| | 95% CI | NA | 0.07, 0.94 | 0.48, 23.3 | 0.06, 1.06 | 1.26, 146 | 0.12, 23.1 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 1.3 Combined Analysis Across Research Partner Databases By Dextran Category - Main Algorithm - Third or Subsequent Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | NA | 0 (0 / 34,760) | 0 (0 / 20) | 0 (0 / 34,750) | NE | 0 |
| | 95% CI | NA | 0, 1.10 | 0, 2040 | 0, 1.11 | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NA | 0 (0 / 58,298) | NE | 0 (0 / 58,298) | NE | NE |
| | 95% CI | NA | 0, 0.66 | NE, NE | 0, 0.66 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NA | 0 (0 / 3,217) | 0 (0 / 2,421) | 0 (0 / 796) | NE | 0 |
| | 95% CI | NA | 0, 11.9 | 0, 15.8 | 0, 48.0 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NA | 0 (0 / 37,471) | 0 (0 / 1,148) | 0 (0 / 36,323) | NE | 0 |
| | 95% CI | NA | 0, 1.03 | 0, 33.4 | 0, 1.06 | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | NA | 0.29 (10 / 348,945) | 0 (0 / 5,015) | 0.29 (10 / 343,930) | 0 | 0.29 |
| | 95% CI | NA | 0.16, 0.53 | 0, 7.65 | 0.16, 0.54 | 0, 26.3 | 0.47, 0.11 |
| KfH QiN, Germany | Estimate | NA | 0 (0 / 2,620,795) | 0 (0 / 904) | 0 (0 / 2,619,891) | NE | 0 |
| | 95% CI | NA | 0, 0.01 | 0, 42.3 | 0, 0.01 | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | NA | 0.03 (10 / 3,103,486) | 0 (0 / 9,508) | 0.03 (10 / 3,093,988) | 0 | 0.03 |
| | 95% CI | NA | 0.02, 0.06 | 0, 4.04 | 0.02, 0.06 | 0, 125 | 0.06, 4.01 |
| Beta Binomial Meta Analysis | Estimate | NA | 0.02 | 0 | 0.03 | 0 | 0.03 |
| | 95% CI | NA | 0.00, 0.13 | 0, >9995 | 0.00, 0.19 | 0, >9995 | 0.13, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 1.4 Combined Analysis Across Research Partner Databases By Dextran Category - Main Algorithm - Any Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database (Min) | Estimate | 0.41 (30 / 736,070) | 0.23 (1 / 42,780) | 0 (0 / 50) | 0.23 (1 / 42,730) | 0 | 0.23 |
| | 95% CI | 0.29, 0.58 | 0.04, 1.32 | 0, 787 | 0.04, 1.33 | 0, 3580 | 0.69, 0.22 |
| Danish Central Region EMR Database (Max) | Estimate | 0.41 (30 / 736,070) | 0.94 (4 / 42,780) | 0 (0 / 50) | 0.94 (4 / 42,730) | 0 | 0.94 |
| | 95% CI | 0.29, 0.58 | 0.36, 2.40 | 0, 787 | 0.36, 2.41 | 0, 874 | 1.85, 0.02 |
| SNDS Database, France | Estimate | 0.26 (2 / 78,292) | 0 (0 / 156,436) | NE | 0 (0 / 156,436) | NE | NE |
| | 95% CI | 0.07, 0.93 | 0, 0.25 | NE, NE | 0, 0.25 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0.35 (4 / 114,639) | 0 (0 / 10,892) | 0 (0 / 5,880) | 0 (0 / 5,012) | NE | 0 |
| | 95% CI | 0.14, 0.90 | 0, 3.53 | 0, 6.53 | 0, 7.66 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NA | 0.40 (4 / 100,761) | 0 (0 / 3,507) | 0.41 (4 / 97,254) | 0 | 0.41 |
| | 95% CI | NA | 0.15, 1.02 | 0, 10.9 | 0.16, 1.06 | 0, 26.6 | 0.81, 0.01 |
| GePaRD, Germany | Estimate | 1.45 (8 / 54,999) | 0.38 (21 / 557,756) | 1.16 (1 / 8,584) | 0.36 (20 / 549,172) | 3.20 | 0.80 |
| | 95% CI | 0.74, 2.87 | 0.25, 0.58 | 0.21, 6.60 | 0.24, 0.56 | 0.55, 18.7 | 1.49, 3.09 |
| KfH QiN, Germany | Estimate | NA | 0 (0 / 2,687,170) | 0 (0 / 958) | 0 (0 / 2,686,212) | NE | 0 |
| | 95% CI | NA | 0, 0.01 | 0, 39.9 | 0, 0.01 | NE, NE | NE, NE |
| Pooled (Crude) Analysis (Min) | Estimate | 0.44 (44 / 984,000) | 0.07 (26 / 3,555,795) | 0.53 (1 / 18,979) | 0.07 (25 / 3,536,816) | 7.46 | 0.46 |
| | 95% CI | 0.32, 0.59 | 0.05, 0.11 | 0.09, 2.99 | 0.05, 0.10 | 1.28, 43.4 | 0.02, 2.91 |
| Beta Binomial Meta Analysis (Min) | Estimate | 0.45 | 0.07 | 0.53 | 0.08 | 7.03 | 0.46 |
| | 95% CI | 0.32, 0.63 | 0.04, 0.15 | 0.08, 3.74 | 0.03, 0.19 | 0.85, 59.9 | 0.01, 3.68 |
| Pooled (Crude) Analysis (Max) | Estimate | 0.44 (44 / 984,000) | 0.08 (29 / 3,555,795) | 0.53 (1 / 18,979) | 0.08 (28 / 3,536,816) | 6.66 | 0.45 |
| | 95% CI | 0.32, 0.59 | 0.06, 0.12 | 0.09, 2.99 | 0.05, 0.11 | 1.15, 38.6 | 0.01, 2.91 |
| Beta Binomial Meta Analysis (Max) | Estimate | 0.45 | 0.09 | 0.53 | 0.10 | 5.45 | 0.44 |

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| | 95% CI | 0.32, 0.63 | 0.05, 0.16 | 0.08, 3.73 | 0.05, 0.21 | 0.70, 44.2 | 0.04, 3.65 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 2.1a Combined Analysis Across Research Partner Databases By Individual Category - Main Algorithm - First Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0 (0 / 75,512) | NE | NE | NE | NE |
| | 95% CI | 0, 0.51 | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 1,594) | 0 (0 / 456) | NE | 0 (0 / 2,393) | 0 (0 / 1,382) |
| | 95% CI | 0, 24.0 | 0, 83.5 | NE, NE | 0, 16.0 | 0, 27.7 |
| Swedish National Registries | Estimate | 0.51 (1 / 19,485) | 9.36 (1 / 1,068) | NE | 0 (0 / 1,599) | 0.49 (1 / 20,316) |
| | 95% CI | 0.09, 2.91 | 1.65, 52.8 | NE, NE | 0, 24.0 | 0.09, 2.79 |
| GePaRD, Germany | Estimate | 1.31 (5 / 38,101) | 0 (0 / 784) | 0.47 (4 / 85,282) | 0 (0 / 2,346) | 0 (0 / 14,403) |
| | 95% CI | 0.56, 3.07 | 0, 48.8 | 0.18, 1.21 | 0, 16.3 | 0, 2.67 |
| KfH QiN, Germany | Estimate | 0 (0 / 11,982) | 0 (0 / 17) | 0 (0 / 21,386) | 0 (0 / 29) | 0 (0 / 205) |
| | 95% CI | 0, 3.20 | 0, 1840 | 0, 1.80 | 0, 1170 | 0, 184 |
| Pooled (Crude) Analysis | Estimate | 0.41 (6 / 146,674) | 4.30 (1 / 2,325) | 0.37 (4 / 106,668) | 0 (0 / 6,367) | 0.28 (1 / 36,306) |
| | 95% CI | 0.19, 0.89 | 0.76, 24.3 | 0.15, 0.96 | 0, 6.03 | 0.05, 1.56 |
| Beta Binomial Meta Analysis | Estimate | 0.45 | 4.44 | 0.46 | 0 | 0.43 |
| | 95% CI | 0.12, 1.69 | 0.62, 31.5 | 0.08, 2.79 | 0, >9995 | 0.06, 3.10 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 2.1b Combined Analysis Across Research Partner Databases By Individual Category - Main Algorithm - First Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 1.04 | 19.0 | NE | 0 |
| | 95% CI | 0.11, 9.99 | 1.99, 182 | NE, NE | 0, 48.8 |
| GePaRD, Germany | Estimate | Inf | NE | Inf | NE |
| | 95% CI | 0.49, Inf | NE, NE | 0.18, Inf | NE, NE |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 1.49 | 15.6 | 1.36 | 0 |
| | 95% CI | 0.23, 9.39 | 1.63, 150 | 0.20, 9.06 | 0, 21.9 |
| Beta Binomial Meta Analysis | Estimate | 1.04 | 10.3 | 1.06 | 0 |
| | 95% CI | 0.10, 11.1 | 0.62, 158 | 0.08, 14.7 | 0, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

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- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 2.1c Combined Analysis Across Research Partner Databases By Individual Category - Main Algorithm - First Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.02 | 8.87 | NE | 0.49 |
| | 95% CI | 1.37, 1.41 | 9.50, 27.2 | NE, NE | 1.46, 0.47 |
| GePaRD, Germany | Estimate | 1.31 | 0 | 0.47 | 0 |
| | 95% CI | 0.16, 2.46 | NE, NE | 0.01, 0.93 | NE, NE |
| KfH QiN, Germany | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.13 | 4.03 | 0.10 | 0.28 |
| | 95% CI | 1.16, 0.68 | 0.39, 24.1 | 1.20, 0.74 | 1.56, 5.75 |
| Beta Binomial Meta Analysis | Estimate | 0.02 | 4.01 | 0.03 | 0.43 |
| | 95% CI | 2.55, 1.26 | 0.67, 30.6 | 2.52, 2.24 | 2.23, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 2.2a Combined Analysis Across Research Partner Databases By Individual Category - Main Algorithm - Second Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0 (0 / 22,626) | NE | NE | NE | NE |
| | 95% CI | 0, 1.70 | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 364) | 0 (0 / 82) | NE | 0 (0 / 1,066) | 0 (0 / 338) |
| | 95% CI | 0, 104 | 0, 448 | NE, NE | 0, 35.9 | 0, 112 |
| Swedish National Registries | Estimate | 1.28 (1 / 7,842) | 0 (0 / 248) | NE | 0 (0 / 760) | 0 (0 / 11,972) |
| | 95% CI | 0.23, 7.22 | 0, 153 | NE, NE | 0, 50.3 | 0, 3.21 |
| GePaRD, Germany | Estimate | 0 (0 / 13,236) | 0 (0 / 194) | 0 (0 / 46,021) | 8.18 (1 / 1,223) | 1.38 (1 / 7,221) |
| | 95% CI | 0, 2.90 | 0, 194 | 0, 0.83 | 1.44, 46.2 | 0.24, 7.84 |
| KfH QiN, Germany | Estimate | 0 (0 / 11,616) | 0 (0 / 13) | 0 (0 / 20,964) | 0 (0 / 25) | 0 (0 / 138) |
| | 95% CI | 0, 3.31 | 0, 2280 | 0, 1.83 | 0, 1330 | 0, 271 |
| Pooled (Crude) Analysis | Estimate | 0.18 (1 / 55,684) | 0 (0 / 537) | 0 (0 / 66,985) | 3.25 (1 / 3,074) | 0.51 (1 / 19,669) |
| | 95% CI | 0.03, 1.02 | 0, 71.0 | 0, 0.57 | 0.57, 18.4 | 0.09, 2.88 |
| Beta Binomial Meta Analysis | Estimate | 0.22 | 0 | 0 | 3.31 | 0.59 |
| | 95% CI | 0.03, 1.62 | 0, NE | 0, NE | 0.48, 23.7 | 0.08, 4.25 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

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- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 2.2b Combined Analysis Across Research Partner Databases By Individual Category - Main Algorithm - Second Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | Inf | NE | NE | NE |
| | 95% CI | 0.40, Inf | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 0 | 0 | 0 | 5.90 |
| | 95% CI | 0, 2.10 | 0, 142 | 0, 0.60 | 0.62, 56.5 |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.35 | 0 | 0 | 6.40 |
| | 95% CI | 0.04, 3.38 | 0, 141 | 0, 1.13 | 0.67, 61.3 |
| Beta Binomial Meta Analysis | Estimate | 0.38 | 0 | 0 | 5.60 |
| | 95% CI | 0.03, 6.03 | 0, NE | 0, NE | 0.35, 86.6 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 2.2c Combined Analysis Across Research Partner Databases By Individual Category - Main Algorithm - Second Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 1.28 | 0 | NE | 0 |
| | 95% CI | 1.22, 3.77 | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 1.38 | 1.38 | 1.38 | 6.79 |
| | 95% CI | 4.10, 1.33 | 4.10, 1.33 | 4.10, 1.33 | 9.46, 23.0 |
| KfH QiN, Germany | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.33 | 0.51 | 0.51 | 2.74 |
| | 95% CI | 2.71, 0.58 | 2.88, 70.5 | 2.88, 0.07 | 0.56, 17.9 |
| Beta Binomial Meta Analysis | Estimate | 0.37 | 0.59 | 0.59 | 2.72 |
| | 95% CI | 3.87, 1.03 | NE, NE | NE, NE | 1.84, 22.8 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 2.3a Combined Analysis Across Research Partner Databases By Individual Category - Main Algorithm - Third or Subsequent Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0 (0 / 58,298) | NE | NE | NE | NE |
| | 95% CI | 0, 0.66 | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 353) | 0 (0 / 31) | NE | 0 (0 / 2,421) | 0 (0 / 412) |
| | 95% CI | 0, 108 | 0, 1100 | NE, NE | 0, 15.8 | 0, 92.4 |
| Swedish National Registries | Estimate | 0 (0 / 8,562) | 0 (0 / 149) | NE | 0 (0 / 1,148) | 0 (0 / 27,612) |
| | 95% CI | 0, 4.48 | 0, 251 | NE, NE | 0, 33.4 | 0, 1.39 |
| GePaRD, Germany | Estimate | 0.59 (1 / 16,895) | 0 (0 / 248) | 0.27 (8 / 299,533) | 0 (0 / 5,015) | 0.37 (1 / 27,254) |
| | 95% CI | 0.10, 3.35 | 0, 153 | 0.14, 0.53 | 0, 7.65 | 0.06, 2.08 |
| KfH QiN, Germany | Estimate | 0 (0 / 588,840) | 0 (0 / 84) | 0 (0 / 2,029,405) | 0 (0 / 904) | 0 (0 / 1,562) |
| | 95% CI | 0, 0.07 | 0, 437 | 0, 0.02 | 0, 42.3 | 0, 24.5 |
| Pooled (Crude) Analysis | Estimate | 0.01 (1 / 672,948) | 0 (0 / 512) | 0.03 (8 / 2,328,938) | 0 (0 / 9,488) | 0.18 (1 / 56,840) |
| | 95% CI | 0.00, 0.08 | 0, 74.5 | 0.02, 0.07 | 0, 4.05 | 0.03, 1.00 |
| Beta Binomial Meta Analysis | Estimate | 0.05 | 0 | 0.05 | 0 | 0.21 |
| | 95% CI | 0.01, 0.33 | 0, >9995 | 0.01, 0.34 | 0, >9995 | 0.03, 1.50 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 2.3b Combined Analysis Across Research Partner Databases By Individual Category - Main Algorithm - Third or Subsequent Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 1.61 | 0 | 0.73 | 0 |
| | 95% CI | 0.17, 15.5 | 0, 421 | 0.12, 4.48 | 0, 20.9 |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.08 | 0 | 0.20 | 0 |
| | 95% CI | 0.01, 0.81 | 0, 426 | 0.03, 1.20 | 0, 23.0 |
| Beta Binomial Meta Analysis | Estimate | 0.22 | 0 | 0.24 | 0 |
| | 95% CI | 0.01, 3.53 | 0, >9995 | 0.02, 3.54 | 0, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 2.3c Combined Analysis Across Research Partner Databases By Individual Category - Main Algorithm - Third or Subsequent Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 0.22 | 0.37 | 0.10 | 0.37 |
| | 95% CI | 1.14, 1.59 | 1.09, 0.35 | 0.84, 0.64 | 1.09, 0.35 |
| KfH QiN, Germany | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.16 | 0.18 | 0.14 | 0.18 |
| | 95% CI | 0.98, 0.01 | 1.00, 74.3 | 0.96, 0.01 | 1.00, 3.87 |
| Beta Binomial Meta Analysis | Estimate | 0.16 | 0.21 | 0.16 | 0.21 |
| | 95% CI | 1.44, 0.17 | 1.11, >9995 | 1.41, 0.16 | 1.08, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 2.4a Combined Analysis Across Research Partner Databases By Individual Category - Main Algorithm - Any Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0 (0 / 156,436) | NE | NE | NE | NE |
| | 95% CI | 0, 0.25 | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 2,311) | 0 (0 / 569) | NE | 0 (0 / 5,880) | 0 (0 / 2,132) |
| | 95% CI | 0, 16.6 | 0, 67.1 | NE, NE | 0, 6.53 | 0, 18.0 |
| Swedish National Registries | Estimate | 0.56 (2 / 35,889) | 6.83 (1 / 1,465) | NE | 0 (0 / 3,507) | 0.17 (1 / 59,900) |
| | 95% CI | 0.15, 2.03 | 1.21, 38.6 | NE, NE | 0, 10.9 | 0.03, 0.95 |
| GePaRD, Germany | Estimate | 0.88 (6 / 68,232) | 0 (0 / 1,226) | 0.28 (12 / 430,836) | 1.16 (1 / 8,584) | 0.41 (2 / 48,878) |
| | 95% CI | 0.40, 1.92 | 0, 31.2 | 0.16, 0.49 | 0.21, 6.60 | 0.11, 1.49 |
| KfH QiN, Germany | Estimate | 0 (0 / 612,438) | 0 (0 / 114) | 0 (0 / 2,071,755) | 0 (0 / 958) | 0 (0 / 1,905) |
| | 95% CI | 0, 0.06 | 0, 326 | 0, 0.02 | 0, 39.9 | 0, 20.1 |
| Pooled (Crude) Analysis | Estimate | 0.09 (8 / 875,306) | 2.96 (1 / 3,374) | 0.05 (12 / 2,502,591) | 0.53 (1 / 18,929) | 0.27 (3 / 112,815) |
| | 95% CI | 0.05, 0.18 | 0.52, 16.8 | 0.03, 0.08 | 0.09, 2.99 | 0.09, 0.78 |
| Beta Binomial Meta Analysis | Estimate | 0.10 | 2.97 | 0.04 | 0.54 | 0.29 |
| | 95% CI | 0.03, 0.31 | 0.41, 21.1 | 0.01, 0.23 | 0.08, 3.86 | 0.09, 0.98 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 2.4b Combined Analysis Across Research Partner Databases By Individual Category - Main Algorithm - Any Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 3.34 | 40.9 | NE | 0 |
| | 95% CI | 0.44, 25.5 | 4.27, 391 | NE, NE | 0, 65.6 |
| GePaRD, Germany | Estimate | 2.15 | 0 | 0.68 | 2.85 |
| | 95% CI | 0.50, 9.31 | 0, 76.5 | 0.17, 2.72 | 0.37, 21.7 |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.34 | 11.1 | 0.18 | 1.99 |
| | 95% CI | 0.10, 1.19 | 1.60, 77.7 | 0.05, 0.59 | 0.28, 13.9 |
| Beta Binomial Meta Analysis | Estimate | 0.35 | 10.2 | 0.14 | 1.85 |
| | 95% CI | 0.07, 1.77 | 1.02, 102 | 0.02, 1.10 | 0.18, 18.2 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 2.4c Combined Analysis Across Research Partner Databases By Individual Category - Main Algorithm - Any Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.39 | 6.66 | NE | 0.17 |
| | 95% CI | 0.45, 1.23 | 6.72, 20.0 | NE, NE | 0.49, 0.16 |
| GePaRD, Germany | Estimate | 0.47 | 0.41 | 0.13 | 0.76 |
| | 95% CI | 0.43, 1.37 | 0.98, 0.16 | 0.72, 0.46 | 1.60, 3.11 |
| KfH QiN, Germany | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.17 | 2.70 | 0.22 | 0.26 |
| | 95% CI | 0.69, 0.02 | 0.22, 16.5 | 0.73, 0.04 | 0.41, 2.73 |
| Beta Binomial Meta Analysis | Estimate | 0.19 | 2.68 | 0.25 | 0.25 |
| | 95% CI | 0.86, 0.10 | 0.01, 20.7 | 0.91, 0.01 | 0.59, 3.53 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 3.1 Combined Analysis Across Research Partner Databases By Dextran Category - Expanded Algorithm - First Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database (Min) | Estimate | 20.5 (240 / 116,980) | 1.71 (1 / 5,870) | 0 (0 / 20) | 1.71 (1 / 5,840) | 0 | 1.71 |
| | 95% CI | 18.1, 23.3 | 0.30, 9.65 | 0, 1430 | 0.30, 9.69 | 0, 943 | 5.07, 1.64 |
| Danish Central Region EMR Database (Max) | Estimate | 20.5 (240 / 116,980) | 6.82 (4 / 5,870) | 0 (0 / 20) | 6.85 (4 / 5,840) | 0 | 6.85 |
| | 95% CI | 18.1, 23.3 | 2.65, 17.5 | 0, 1430 | 2.66, 17.6 | 0, 225 | 13.6, 0.14 |
| SNDS Database, France | Estimate | 0.35 (2 / 57,200) | 0 (0 / 75,512) | NE | 0 (0 / 75,512) | NE | NE |
| | 95% CI | 0.10, 1.27 | 0, 0.51 | NE, NE | 0, 0.51 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 2.82 (11 / 39,002) | 10.3 (6 / 5,825) | 12.5 (3 / 2,393) | 8.74 (3 / 3,432) | 1.43 | 3.80 |
| | 95% CI | 1.57, 5.05 | 4.72, 22.5 | 4.26, 36.8 | 2.97, 25.7 | 0.33, 6.21 | 13.5, 21.1 |
| Swedish National Registries | Estimate | NA | 0.71 (3 / 42,468) | 0 (0 / 1,599) | 0.73 (3 / 40,869) | 0 | 0.73 |
| | 95% CI | NA | 0.24, 2.08 | 0, 24.0 | 0.25, 2.16 | 0, 32.7 | 1.56, 0.10 |
| GePaRD, Germany | Estimate | 3.31 (6 / 18,112) | 0.64 (9 / 140,916) | 0 (0 / 2,346) | 0.65 (9 / 138,570) | 0 | 0.65 |
| | 95% CI | 1.52, 7.23 | 0.34, 1.21 | 0, 16.3 | 0.34, 1.23 | 0, 25.2 | 1.07, 0.23 |
| KfH QiN, Germany | Estimate | NA | 0 (0 / 33,619) | 0 (0 / 29) | 0 (0 / 33,590) | NE | 0 |
| | 95% CI | NA | 0, 1.14 | 0, 1170 | 0, 1.14 | NE, NE | NE, NE |
| Pooled (Crude) Analysis (Min) | Estimate | 11.2 (259 / 231,294) | 0.62 (19 / 304,210) | 4.69 (3 / 6,387) | 0.54 (16 / 297,813) | 8.74 | 4.16 |
| | 95% CI | 9.92, 12.6 | 0.40, 0.98 | 1.60, 13.8 | 0.33, 0.87 | 2.72, 28.0 | 1.04, 13.3 |
| Beta Binomial Meta Analysis (Min) | Estimate | 6.45 | 0.63 | 4.59 | 0.58 | 7.95 | 4.02 |
| | 95% CI | 4.98, 8.42 | 0.38, 1.05 | 1.43, 14.8 | 0.28, 1.22 | 2.05, 31.8 | 0.77, 14.3 |
| Pooled (Crude) Analysis (Max) | Estimate | 11.2 (259 / 231,294) | 0.72 (22 / 304,210) | 4.69 (3 / 6,387) | 0.64 (19 / 297,813) | 7.36 | 4.06 |
| | 95% CI | 9.92, 12.6 | 0.48, 1.10 | 1.60, 13.8 | 0.41, 1.00 | 2.32, 23.3 | 0.94, 13.2 |
| Beta Binomial Meta Analysis (Max) | Estimate | 6.45 | 2.81 | 4.62 | 0.70 | 6.61 | 3.92 |

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| | 95% CI | 4.98, 8.42 | 0.60, 13.8 | 1.46, 14.7 | 0.38, 1.31 | 1.83, 24.6 | 0.68, 14.0 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 3.2: Combined Analysis Across Research Partner Databases By Dextran Category - Expanded Algorithm - Second Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | NA | 0 (0 / 2,150) | 0 (0 / 10) | 0 (0 / 2,140) | NE | 0 |
| | 95% CI | NA | 0, 17.8 | 0, 3540 | 0, 17.9 | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NA | 0 (0 / 22,626) | NE | 0 (0 / 22,626) | NE | NE |
| | 95% CI | NA | 0, 1.70 | NE, NE | 0, 1.70 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NA | 0 (0 / 1,850) | 0 (0 / 1,066) | 0 (0 / 784) | NE | 0 |
| | 95% CI | NA | 0, 20.7 | 0, 35.9 | 0, 48.8 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NA | 0.48 (1 / 20,822) | 0 (0 / 760) | 0.50 (1 / 20,062) | 0 | 0.50 |
| | 95% CI | NA | 0.08, 2.72 | 0, 50.3 | 0.09, 2.82 | 0, 101 | 1.48, 0.48 |
| GePaRD, Germany | Estimate | NA | 0.44 (3 / 67,895) | 8.18 (1 / 1,223) | 0.30 (2 / 66,672) | 27.3 | 7.88 |
| | 95% CI | NA | 0.15, 1.30 | 1.44, 46.2 | 0.08, 1.09 | 3.57, 208 | 8.15, 23.9 |
| KfH QiN, Germany | Estimate | NA | 0 (0 / 32,756) | 0 (0 / 25) | 0 (0 / 32,731) | NE | 0 |
| | 95% CI | NA | 0, 1.17 | 0, 1330 | 0, 1.17 | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | NA | 0.27 (4 / 148,099) | 3.25 (1 / 3,084) | 0.21 (3 / 145,015) | 15.7 | 3.04 |
| | 95% CI | NA | 0.11, 0.69 | 0.57, 18.4 | 0.07, 0.61 | 2.25, 109 | 0.35, 18.2 |
| Beta Binomial Meta Analysis | Estimate | NA | 0.30 | 3.35 | 0.32 | 10.6 | 3.03 |
| | 95% CI | NA | 0.08, 1.09 | 0.48, 23.4 | 0.08, 1.27 | 1.03, 115 | 0.02, 23.1 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 3.3: Combined Analysis Across Research Partner Databases By Dextran Category - Expanded Algorithm - Third or Subsequent Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | NA | 0 (0 / 34,760) | 0 (0 / 20) | 0 (0 / 34,750) | NE | 0 |
| | 95% CI | NA | 0, 1.10 | 0, 2040 | 0, 1.11 | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NA | 0 (0 / 58,298) | NE | 0 (0 / 58,298) | NE | NE |
| | 95% CI | NA | 0, 0.66 | NE, NE | 0, 0.66 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NA | 0 (0 / 3,217) | 0 (0 / 2,421) | 0 (0 / 796) | NE | 0 |
| | 95% CI | NA | 0, 11.9 | 0, 15.8 | 0, 48.0 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NA | 0 (0 / 37,471) | 0 (0 / 1,148) | 0 (0 / 36,323) | NE | 0 |
| | 95% CI | NA | 0, 1.03 | 0, 33.4 | 0, 1.06 | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | NA | 0.34 (12 / 348,945) | 0 (0 / 5,015) | 0.35 (12 / 343,930) | 0 | 0.35 |
| | 95% CI | NA | 0.20, 0.60 | 0, 7.65 | 0.20, 0.61 | 0, 21.9 | 0.55, 0.15 |
| KfH QiN, Germany | Estimate | NA | 0 (0 / 2,620,795) | 0 (0 / 904) | 0 (0 / 2,619,891) | NE | 0 |
| | 95% CI | NA | 0, 0.01 | 0, 42.3 | 0, 0.01 | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | NA | 0.04 (12 / 3,103,486) | 0 (0 / 9,508) | 0.04 (12 / 3,093,988) | 0 | 0.04 |
| | 95% CI | NA | 0.02, 0.07 | 0, 4.04 | 0.02, 0.07 | 0, 104 | 0.07, 4.00 |
| Beta Binomial Meta Analysis | Estimate | NA | 0.03 | 0 | 0.03 | 0 | 0.03 |
| | 95% CI | NA | 0.01, 0.14 | 0, >9995 | 0.00, 0.20 | 0, >9995 | 0.14, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 3.4: Combined Analysis Across Research Partner Databases By Dextran Category - Expanded Algorithm - Any Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database (Min) | Estimate | 5.98 (440 / 736,070) | 0.23 (1 / 42,780) | 0 (0 / 50) | 0.23 (1 / 42,730) | 0 | 0.23 |
| | 95% CI | 5.44, 6.56 | 0.04, 1.32 | 0, 787 | 0.04, 1.33 | 0, 3580 | 0.69, 0.22 |
| Danish Central Region EMR Database (Max) | Estimate | 5.98 (440 / 736,070) | 0.94 (4 / 42,780) | 0 (0 / 50) | 0.94 (4 / 42,730) | 0 | 0.94 |
| | 95% CI | 5.44, 6.56 | 0.36, 2.40 | 0, 787 | 0.36, 2.41 | 0, 874 | 1.85, 0.02 |
| SNDS Database, France | Estimate | 0.38 (3 / 78,292) | 0 (0 / 156,436) | NE | 0 (0 / 156,436) | NE | NE |
| | 95% CI | 0.13, 1.13 | 0, 0.25 | NE, NE | 0, 0.25 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 1.74 (20 / 114,639) | 5.51 (6 / 10,892) | 5.10 (3 / 5,880) | 5.99 (3 / 5,012) | 0.85 | 0.88 |
| | 95% CI | 1.13, 2.69 | 2.52, 12.0 | 1.74, 15.0 | 2.04, 17.6 | 0.20, 3.69 | 9.78, 8.01 |
| Swedish National Registries | Estimate | NA | 0.40 (4 / 100,761) | 0 (0 / 3,507) | 0.41 (4 / 97,254) | 0 | 0.41 |
| | 95% CI | NA | 0.15, 1.02 | 0, 10.9 | 0.16, 1.06 | 0, 26.6 | 0.81, 0.01 |
| GePaRD, Germany | Estimate | 1.45 (8 / 54,999) | 0.43 (24 / 557,756) | 1.16 (1 / 8,584) | 0.42 (23 / 549,172) | 2.78 | 0.75 |
| | 95% CI | 0.74, 2.87 | 0.29, 0.64 | 0.21, 6.60 | 0.28, 0.63 | 0.48, 16.2 | 1.54, 3.04 |
| KfH QiN, Germany | Estimate | NA | 0 (0 / 2,687,170) | 0 (0 / 958) | 0 (0 / 2,686,212) | NE | 0 |
| | 95% CI | NA | 0, 0.01 | 0, 39.9 | 0, 0.01 | NE, NE | NE, NE |
| Pooled (Crude) Analysis (Min) | Estimate | 4.79 (471 / 984,000) | 0.10 (35 / 3,555,795) | 2.11 (4 / 18,979) | 0.09 (31 / 3,536,816) | 24.1 | 2.02 |
| | 95% CI | 4.37, 5.24 | 0.07, 0.14 | 0.82, 5.42 | 0.06, 0.12 | 8.86, 65.3 | 0.73, 5.33 |
| Beta Binomial Meta Analysis (Min) | Estimate | 3.38 | 0.11 | 2.11 | 0.11 | 19.5 | 2.00 |
| | 95% CI | 2.81, 4.09 | 0.07, 0.18 | 0.79, 5.63 | 0.06, 0.22 | 6.06, 65.1 | 0.67, 5.54 |
| Pooled (Crude) Analysis (Max) | Estimate | 4.79 (471 / 984,000) | 0.11 (38 / 3,555,795) | 2.11 (4 / 18,979) | 0.10 (34 / 3,536,816) | 21.9 | 2.01 |
| | 95% CI | 4.37, 5.24 | 0.08, 0.15 | 0.82, 5.42 | 0.07, 0.13 | 8.11, 59.3 | 0.72, 5.32 |

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Beta Binomial Meta Analysis (Max) | Estimate | 3.38 | 0.12 | 2.11 | 0.13 | 16.3 | 1.98 |
| | 95% CI | 2.81, 4.09 | 0.08, 0.19 | 0.79, 5.62 | 0.07, 0.23 | 5.34, 51.5 | 0.65, 5.51 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 4.1a: Combined Analysis Across Research Partner Databases By Individual Category - Expanded Algorithm - First Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0 (0 / 75,512) | NE | NE | NE | NE |
| | 95% CI | 0, 0.51 | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 6.27 (1 / 1,594) | 0 (0 / 456) | NE | 12.5 (3 / 2,393) | 14.5 (2 / 1,382) |
| | 95% CI | 1.11, 35.5 | 0, 83.5 | NE, NE | 4.26, 36.8 | 3.97, 52.6 |
| Swedish National Registries | Estimate | 0.51 (1 / 19,485) | 9.36 (1 / 1,068) | NE | 0 (0 / 1,599) | 0.49 (1 / 20,316) |
| | 95% CI | 0.09, 2.91 | 1.65, 52.8 | NE, NE | 0, 24.0 | 0.09, 2.79 |
| GePaRD, Germany | Estimate | 1.31 (5 / 38,101) | 0 (0 / 784) | 0.47 (4 / 85,282) | 0 (0 / 2,346) | 0 (0 / 14,403) |
| | 95% CI | 0.56, 3.07 | 0, 48.8 | 0.18, 1.21 | 0, 16.3 | 0, 2.67 |
| KfH QiN, Germany | Estimate | 0 (0 / 11,982) | 0 (0 / 17) | 0 (0 / 21,386) | 0 (0 / 29) | 0 (0 / 205) |
| | 95% CI | 0, 3.20 | 0, 1840 | 0, 1.80 | 0, 1170 | 0, 184 |
| Pooled (Crude) Analysis | Estimate | 0.48 (7 / 146,674) | 4.30 (1 / 2,325) | 0.37 (4 / 106,668) | 4.71 (3 / 6,367) | 0.83 (3 / 36,306) |
| | 95% CI | 0.23, 0.99 | 0.76, 24.3 | 0.15, 0.96 | 1.60, 13.8 | 0.28, 2.43 |
| Beta Binomial Meta Analysis | Estimate | 0.54 | 4.37 | 0.39 | 4.54 | 0.97 |
| | 95% CI | 0.20, 1.50 | 0.60, 31.0 | 0.08, 2.05 | 1.37, 15.4 | 0.28, 3.35 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 4.1b: Combined Analysis Across Research Partner Databases By Individual Category - Expanded Algorithm - First Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0.43 | 0 | NE | 0.87 |
| | 95% CI | 0.06, 3.31 | 0, 5.81 | NE, NE | 0.17, 4.33 |
| Swedish National Registries | Estimate | 1.04 | 19.0 | NE | 0 |
| | 95% CI | 0.11, 9.99 | 1.99, 182 | NE, NE | 0, 48.8 |
| GePaRD, Germany | Estimate | Inf | NE | Inf | NE |
| | 95% CI | 0.49, Inf | NE, NE | 0.18, Inf | NE, NE |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.58 | 5.21 | 0.45 | 5.70 |
| | 95% CI | 0.16, 2.05 | 0.75, 36.3 | 0.11, 1.81 | 1.32, 24.7 |
| Beta Binomial Meta Analysis | Estimate | 0.56 | 4.52 | 0.41 | 4.70 |
| | 95% CI | 0.12, 2.76 | 0.44, 45.8 | 0.05, 3.10 | 0.83, 26.1 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 4.1c: Combined Analysis Across Research Partner Databases By Individual Category - Expanded Algorithm - First Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 8.20 | 14.5 | NE | 1.94 |
| | 95% CI | 31.7, 15.3 | 34.5, 5.57 | NE, NE | 26.5, 22.6 |
| Swedish National Registries | Estimate | 0.02 | 8.87 | NE | 0.49 |
| | 95% CI | 1.37, 1.41 | 9.50, 27.2 | NE, NE | 1.46, 0.47 |
| GePaRD, Germany | Estimate | 1.31 | 0 | 0.47 | 0 |
| | 95% CI | 0.16, 2.46 | NE, NE | 0.01, 0.93 | NE, NE |
| KfH QiN, Germany | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.35 | 3.47 | 0.45 | 3.89 |
| | 95% CI | 1.97, 0.40 | 0.34, 23.5 | 2.07, 0.34 | 0.49, 13.0 |
| Beta Binomial Meta Analysis | Estimate | 0.43 | 3.40 | 0.57 | 3.58 |
| | 95% CI | 2.75, 0.74 | 1.19, 29.7 | 2.88, 1.12 | 0.38, 14.3 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 4.2a: Combined Analysis Across Research Partner Databases By Individual Category - Expanded Algorithm - Second Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0 (0 / 22,626) | NE | NE | NE | NE |
| | 95% CI | 0, 1.70 | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 364) | 0 (0 / 82) | NE | 0 (0 / 1,066) | 0 (0 / 338) |
| | 95% CI | 0, 104 | 0, 448 | NE, NE | 0, 35.9 | 0, 112 |
| Swedish National Registries | Estimate | 1.28 (1 / 7,842) | 0 (0 / 248) | NE | 0 (0 / 760) | 0 (0 / 11,972) |
| | 95% CI | 0.23, 7.22 | 0, 153 | NE, NE | 0, 50.3 | 0, 3.21 |
| GePaRD, Germany | Estimate | 0 (0 / 13,236) | 0 (0 / 194) | 0.22 (1 / 46,021) | 8.18 (1 / 1,223) | 1.38 (1 / 7,221) |
| | 95% CI | 0, 2.90 | 0, 194 | 0.04, 1.23 | 1.44, 46.2 | 0.24, 7.84 |
| KfH QiN, Germany | Estimate | 0 (0 / 11,616) | 0 (0 / 13) | 0 (0 / 20,964) | 0 (0 / 25) | 0 (0 / 138) |
| | 95% CI | 0, 3.31 | 0, 2280 | 0, 1.83 | 0, 1330 | 0, 271 |
| Pooled (Crude) Analysis | Estimate | 0.18 (1 / 55,684) | 0 (0 / 537) | 0.15 (1 / 66,985) | 3.25 (1 / 3,074) | 0.51 (1 / 19,669) |
| | 95% CI | 0.03, 1.02 | 0, 71.0 | 0.03, 0.85 | 0.57, 18.4 | 0.09, 2.88 |
| Beta Binomial Meta Analysis | Estimate | 0.18 | 0 | 0.16 | 3.26 | 0.52 |
| | 95% CI | 0.03, 1.32 | 0, NE | 0.02, 1.15 | 0.47, 23.3 | 0.07, 3.70 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 4.2b: Combined Analysis Across Research Partner Databases By Individual Category - Expanded Algorithm - Second Dispensing or Administration - Relative Risk**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 1.28 | 0 | NE | 0 |
| | 95% CI | 1.22, 3.77 | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 1.38 | 1.38 | 1.17 | 6.79 |
| | 95% CI | 4.10, 1.33 | 4.10, 1.33 | 3.91, 1.58 | 9.46, 23.0 |
| KfH QiN, Germany | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.33 | 0.51 | 0.36 | 2.74 |
| | 95% CI | 2.71, 0.58 | 2.88, 70.5 | 2.73, 0.42 | 0.56, 17.9 |
| Beta Binomial Meta Analysis | Estimate | 0.33 | 0.52 | 0.36 | 2.74 |
| | 95% CI | 3.40, 0.82 | NE, NE | 3.40, 0.64 | 1.45, 22.5 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 4.2c: Combined Analysis Across Research Partner Databases By Individual Category - Expanded Algorithm - Second Dispensing or Administration - Risk Difference**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | Inf | NE | NE | NE |
| | 95% CI | 0.40, Inf | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 0 | 0 | 0.16 | 5.90 |
| | 95% CI | 0, 2.10 | 0, 142 | 0.02, 1.50 | 0.62, 56.5 |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.35 | 0 | 0.29 | 6.40 |
| | 95% CI | 0.04, 3.38 | 0, 141 | 0.03, 2.81 | 0.67, 61.3 |
| Beta Binomial Meta Analysis | Estimate | 0.36 | 0 | 0.30 | 6.32 |
| | 95% CI | 0.02, 5.66 | 0, NE | 0.02, 4.72 | 0.39, 97.8 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 4.3a: Combined Analysis Across Research Partner Databases By Individual Category - Expanded Algorithm - Third or Subsequent Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0 (0 / 58,298) | NE | NE | NE | NE |
| | 95% CI | 0, 0.66 | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 353) | 0 (0 / 31) | NE | 0 (0 / 2,421) | 0 (0 / 412) |
| | 95% CI | 0, 108 | 0, 1100 | NE, NE | 0, 15.8 | 0, 92.4 |
| Swedish National Registries | Estimate | 0 (0 / 8,562) | 0 (0 / 149) | NE | 0 (0 / 1,148) | 0 (0 / 27,612) |
| | 95% CI | 0, 4.48 | 0, 251 | NE, NE | 0, 33.4 | 0, 1.39 |
| GePaRD, Germany | Estimate | 0.59 (1 / 16,895) | 0 (0 / 248) | 0.33 (10 / 299,533) | 0 (0 / 5,015) | 0.37 (1 / 27,254) |
| | 95% CI | 0.10, 3.35 | 0, 153 | 0.18, 0.61 | 0, 7.65 | 0.06, 2.08 |
| KfH QiN, Germany | Estimate | 0 (0 / 588,840) | 0 (0 / 84) | 0 (0 / 2,029,405) | 0 (0 / 904) | 0 (0 / 1,562) |
| | 95% CI | 0, 0.07 | 0, 437 | 0, 0.02 | 0, 42.3 | 0, 24.5 |
| Pooled (Crude) Analysis | Estimate | 0.01 (1 / 672,948) | 0 (0 / 512) | 0.04 (10 / 2,328,938) | 0 (0 / 9,488) | 0.18 (1 / 56,840) |
| | 95% CI | 0.00, 0.08 | 0, 74.5 | 0.02, 0.08 | 0, 4.05 | 0.03, 1.00 |
| Beta Binomial Meta Analysis | Estimate | 0.05 | 0 | 0.06 | 0 | 0.21 |
| | 95% CI | 0.01, 0.34 | 0, >9995 | 0.01, 0.37 | 0, >9995 | 0.03, 1.52 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 4.3b: Combined Analysis Across Research Partner Databases By Individual Category - Expanded Algorithm - Third or Subsequent Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 1.61 | 0 | 0.91 | 0 |
| | 95% CI | 0.17, 15.5 | 0, 421 | 0.15, 5.51 | 0, 20.9 |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.08 | 0 | 0.24 | 0 |
| | 95% CI | 0.01, 0.81 | 0, 426 | 0.04, 1.48 | 0, 23.0 |
| Beta Binomial Meta Analysis | Estimate | 0.23 | 0 | 0.27 | 0 |
| | 95% CI | 0.02, 3.59 | 0, >9995 | 0.02, 3.83 | 0, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 4.3c: Combined Analysis Across Research Partner Databases By Individual Category - Expanded Algorithm - Third or Subsequent Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 0.22 | 0.37 | 0.03 | 0.37 |
| | 95% CI | 1.14, 1.59 | 1.09, 0.35 | 0.78, 0.72 | 1.09, 0.35 |
| KfH QiN, Germany | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.16 | 0.18 | 0.13 | 0.18 |
| | 95% CI | 0.98, 0.01 | 1.00, 74.3 | 0.95, 0.02 | 1.00, 3.87 |
| Beta Binomial Meta Analysis | Estimate | 0.16 | 0.21 | 0.16 | 0.21 |
| | 95% CI | 1.45, 0.17 | 1.12, >9995 | 1.41, 0.18 | 1.09, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 4.4a: Combined Analysis Across Research Partner Databases By Individual Category - Expanded Algorithm - Any Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0 (0 / 156,436) | NE | NE | NE | NE |
| | 95% CI | 0, 0.25 | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 4.33 (1 / 2,311) | 0 (0 / 569) | NE | 5.10 (3 / 5,880) | 9.38 (2 / 2,132) |
| | 95% CI | 0.76, 24.5 | 0, 67.1 | NE, NE | 1.74, 15.0 | 2.57, 34.1 |
| Swedish National Registries | Estimate | 0.56 (2 / 35,889) | 6.83 (1 / 1,465) | NE | 0 (0 / 3,507) | 0.17 (1 / 59,900) |
| | 95% CI | 0.15, 2.03 | 1.21, 38.6 | NE, NE | 0, 10.9 | 0.03, 0.95 |
| GePaRD, Germany | Estimate | 0.88 (6 / 68,232) | 0 (0 / 1,226) | 0.35 (15 / 430,836) | 1.16 (1 / 8,584) | 0.41 (2 / 48,878) |
| | 95% CI | 0.40, 1.92 | 0, 31.2 | 0.21, 0.57 | 0.21, 6.60 | 0.11, 1.49 |
| KfH QiN, Germany | Estimate | 0 (0 / 612,438) | 0 (0 / 114) | 0 (0 / 2,071,755) | 0 (0 / 958) | 0 (0 / 1,905) |
| | 95% CI | 0, 0.06 | 0, 326 | 0, 0.02 | 0, 39.9 | 0, 20.1 |
| Pooled (Crude) Analysis | Estimate | 0.10 (9 / 875,306) | 2.96 (1 / 3,374) | 0.06 (15 / 2,502,591) | 2.11 (4 / 18,929) | 0.44 (5 / 112,815) |
| | 95% CI | 0.05, 0.20 | 0.52, 16.8 | 0.04, 0.10 | 0.82, 5.43 | 0.19, 1.04 |
| Beta Binomial Meta Analysis | Estimate | 0.13 | 2.97 | 0.04 | 2.11 | 0.48 |
| | 95% CI | 0.05, 0.31 | 0.41, 21.1 | 0.01, 0.23 | 0.79, 5.74 | 0.19, 1.21 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 4.4b: Combined Analysis Across Research Partner Databases By Individual Category - Expanded Algorithm - Any Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0.46 | 0 | NE | 0.54 |
| | 95% CI | 0.06, 3.52 | 0, 7.18 | NE, NE | 0.11, 2.72 |
| Swedish National Registries | Estimate | 3.34 | 40.9 | NE | 0 |
| | 95% CI | 0.44, 25.5 | 4.27, 391 | NE, NE | 0, 65.6 |
| GePaRD, Germany | Estimate | 2.15 | 0 | 0.85 | 2.85 |
| | 95% CI | 0.50, 9.31 | 0, 76.5 | 0.22, 3.34 | 0.37, 21.7 |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.23 | 6.69 | 0.14 | 4.77 |
| | 95% CI | 0.08, 0.66 | 1.04, 43.1 | 0.05, 0.36 | 1.39, 16.4 |
| Beta Binomial Meta Analysis | Estimate | 0.26 | 6.16 | 0.09 | 4.37 |
| | 95% CI | 0.07, 0.94 | 0.70, 53.0 | 0.01, 0.56 | 1.13, 16.6 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 4.4c: Combined Analysis Across Research Partner Databases By Individual Category - Expanded Algorithm - Any Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 5.05 | 9.38 | NE | 4.28 |
| | 95% CI | 20.6, 10.5 | 22.4, 3.61 | NE, NE | 18.5, 9.94 |
| Swedish National Registries | Estimate | 0.39 | 6.66 | NE | 0.17 |
| | 95% CI | 0.45, 1.23 | 6.72, 20.0 | NE, NE | 0.49, 0.16 |
| GePaRD, Germany | Estimate | 0.47 | 0.41 | 0.06 | 0.76 |
| | 95% CI | 0.43, 1.37 | 0.98, 0.16 | 0.65, 0.53 | 1.60, 3.11 |
| KfH QiN, Germany | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.34 | 2.52 | 0.38 | 1.67 |
| | 95% CI | 0.94, 0.07 | 0.02, 16.3 | 0.98, 0.13 | 0.27, 5.00 |
| Beta Binomial Meta Analysis | Estimate | 0.36 | 2.49 | 0.44 | 1.63 |
| | 95% CI | 1.07, 0.01 | 0.20, 20.5 | 1.14, 0.11 | 0.11, 5.21 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 5: Combined Analysis Across Research Partner Databases By IV Penicillin Subtype - Main Algorithm - First Dispensing or Administration**

| Database | Statistic | IP per 10,000 Natural Penicillins | IP per 10,000 Betalactamase Resistant Penicillins | IP per 10,000 Aminopenicillins | IP per 10,000 Carboxypenicillins | IP per 10,000 Ureidopenicillins | IP per 10,000 Other Penicillins |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database (Min) | Estimate | 0.27 (1 / 36,510) | 0.26 (1 / 38,730) | 0 (0 / 6,220) | 0 (0 / 4) | 3.50 (10 / 28,560) | 1.44 (1 / 6,970) |
| | 95% CI | 0.05, 1.55 | 0.05, 1.46 | 0, 6.17 | 0, 4900 | 1.90, 6.45 | 0.25, 8.13 |
| Danish Central Region EMR Database (Max) | Estimate | 1.10 (4 / 36,510) | 1.03 (4 / 38,730) | 0 (0 / 6,220) | 0 (0 / 1) | 3.50 (10 / 28,560) | 5.74 (4 / 6,970) |
| | 95% CI | 0.43, 2.82 | 0.40, 2.66 | 0, 6.17 | 0, 7930 | 1.90, 6.45 | 2.23, 14.8 |
| SNDS Database, France | Estimate | NE | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 11,739) | 2.35 (2 / 8,508) | 0.64 (1 / 15,583) | NE | 0 (0 / 2,935) | NE |
| | 95% CI | 0, 3.27 | 0.64, 8.57 | 0.11, 3.63 | NE, NE | 0, 13.1 | NE, NE |
| Swedish National Registries | Estimate | NE | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 4.18 (5 / 11,950) | 0 (0 / 310) | 0 (0 / 4,581) | NE | 8.05 (1 / 1,243) | NE |
| | 95% CI | 1.79, 9.79 | 0, 122 | 0, 8.38 | NE, NE | 1.42, 45.4 | NE, NE |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis (Min) | Estimate | 1.00 (6 / 60,199) | 0.63 (3 / 47,548) | 0.38 (1 / 26,384) | 0 (0 / 4) | 3.36 (11 / 32,738) | 1.44 (1 / 6,970) |
| | 95% CI | 0.46, 2.17 | 0.21, 1.86 | 0.07, 2.15 | 0, 4900 | 1.88, 6.02 | 0.25, 8.13 |
| Beta Binomial Meta Analysis (Min) | Estimate | 1.00 | 0.97 | 0.49 | NE | 3.48 | NE |
| | 95% CI | 0.32, 3.30 | 0.27, 3.49 | 0.07, 3.49 | NE, NE | 1.44, 8.37 | NE, NE |
| Pooled (Crude) Analysis (Max) | Estimate | 1.50 (9 / 60,199) | 1.26 (6 / 47,548) | 0.38 (1 / 26,384) | 0 (0 / 1) | 3.36 (11 / 32,738) | 5.74 (4 / 6,970) |
| | 95% CI | 0.79, 2.84 | 0.58, 2.75 | 0.07, 2.15 | 0, 7930 | 1.88, 6.02 | 2.23, 14.8 |

| Database | Statistic | IP per 10,000 Natural Penicillins | IP per 10,000 Betalactamase Resistant Penicillins | IP per 10,000 Aminopenicillins | IP per 10,000 Carboxypenicillins | IP per 10,000 Ureidopenicillins | IP per 10,000 Other Penicillins |
|---|---|---|---|---|---|---|---|
| Beta Binomial Meta Analysis (Max) | Estimate | 1.54 | 1.46 | 0.43 | NE | 3.40 | NE |
| | 95% CI | 0.69, 3.50 | 0.58, 3.74 | 0.06, 3.04 | NE, NE | 1.61, 7.17 | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 6.1: Combined Analysis Across Research Partner Databases By Dextran Category - 7 Day Risk Window - First Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database (Min) | Estimate | NA | 1.71 (1 / 5,870) | 0 (0 / 20) | 1.71 (1 / 5,840) | 0 | 1.71 |
| | 95% CI | NA | 0.30, 9.65 | 0, 1430 | 0.30, 9.69 | 0, 943 | 5.07, 1.64 |
| Danish Central Region EMR Database (Max) | Estimate | NA | 6.82 (4 / 5,870) | 0 (0 / 20) | 6.85 (4 / 5,840) | 0 | 6.85 |
| | 95% CI | NA | 2.65, 17.5 | 0, 1430 | 2.66, 17.6 | 0, 225 | 13.6, 0.14 |
| SNDS Database, France | Estimate | NA | 0.40 (3 / 75,512) | NE | 0.40 (3 / 75,512) | NE | NE |
| | 95% CI | NA | 0.14, 1.17 | NE, NE | 0.14, 1.17 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NA | 0 (0 / 5,825) | 0 (0 / 2,393) | 0 (0 / 3,432) | NE | 0 |
| | 95% CI | NA | 0, 6.59 | 0, 16.0 | 0, 11.2 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NA | 1.18 (5 / 42,468) | 0 (0 / 1,599) | 1.22 (5 / 40,869) | 0 | 1.22 |
| | 95% CI | NA | 0.50, 2.76 | 0, 24.0 | 0.52, 2.86 | 0, 19.6 | 2.30, 0.15 |
| GePaRD, Germany | Estimate | NA | 1.06 (15 / 140,916) | 4.26 (1 / 2,346) | 1.01 (14 / 138,570) | 4.22 | 3.25 |
| | 95% CI | NA | 0.65, 1.76 | 0.75, 24.1 | 0.60, 1.70 | 0.71, 25.1 | 5.12, 11.6 |
| KfH QiN, Germany | Estimate | NA | 0 (0 / 33,619) | 0 (0 / 29) | 0 (0 / 33,590) | NE | 0 |
| | 95% CI | NA | 0, 1.14 | 0, 1170 | 0, 1.14 | NE, NE | NE, NE |
| Pooled (Crude) Analysis (Min) | Estimate | NA | 0.79 (24 / 304,210) | 1.56 (1 / 6,387) | 0.77 (23 / 297,813) | 2.03 | 0.79 |
| | 95% CI | NA | 0.53, 1.17 | 0.28, 8.86 | 0.51, 1.16 | 0.35, 11.8 | 0.57, 8.09 |
| Beta Binomial Meta Analysis (Min) | Estimate | NA | 0.74 | 1.62 | 0.77 | 2.11 | 0.85 |
| | 95% CI | NA | 0.43, 1.29 | 0.23, 11.3 | 0.37, 1.62 | 0.27, 17.0 | 0.80, 10.6 |
| Pooled (Crude) Analysis (Max) | Estimate | NA | 0.89 (27 / 304,210) | 1.56 (1 / 6,387) | 0.87 (26 / 297,813) | 1.79 | 0.69 |
| | 95% CI | NA | 0.61, 1.29 | 0.28, 8.86 | 0.60, 1.28 | 0.31, 10.4 | 0.67, 7.99 |
| Beta Binomial Meta Analysis (Max) | Estimate | NA | 0.88 | 1.61 | 0.93 | 1.74 | 0.68 |

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| | 95% CI | NA | 0.56, 1.39 | 0.23, 11.2 | 0.50, 1.75 | 0.23, 13.4 | 0.95, 10.4 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 6.2: Combined Analysis Across Research Partner Databases By Dextran Category - 7 Day Risk Window - Second Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | NA | 0 (0 / 2,150) | 0 (0 / 10) | 0 (0 / 2,140) | NE | 0 |
| | 95% CI | NA | 0, 17.8 | 0, 3540 | 0, 17.9 | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NA | 0 (0 / 22,626) | NE | 0 (0 / 22,626) | NE | NE |
| | 95% CI | NA | 0, 1.70 | NE, NE | 0, 1.70 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NA | 0 (0 / 1,850) | 0 (0 / 1,066) | 0 (0 / 784) | NE | 0 |
| | 95% CI | NA | 0, 20.7 | 0, 35.9 | 0, 48.8 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NA | 0.96 (2 / 20,822) | 0 (0 / 760) | 1.00 (2 / 20,062) | 0 | 1.00 |
| | 95% CI | NA | 0.26, 3.50 | 0, 50.3 | 0.27, 3.63 | 0, 50.6 | 2.38, 0.38 |
| GePaRD, Germany | Estimate | NA | 0.88 (6 / 67,895) | 8.18 (1 / 1,223) | 0.75 (5 / 66,672) | 10.9 | 7.43 |
| | 95% CI | NA | 0.41, 1.93 | 1.44, 46.2 | 0.32, 1.76 | 1.69, 70.3 | 8.61, 23.5 |
| KfH QiN, Germany | Estimate | NA | 0 (0 / 32,756) | 0 (0 / 25) | 0 (0 / 32,731) | NE | 0 |
| | 95% CI | NA | 0, 1.17 | 0, 1330 | 0, 1.17 | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | NA | 0.54 (8 / 148,099) | 3.25 (1 / 3,084) | 0.48 (7 / 145,015) | 6.72 | 2.76 |
| | 95% CI | NA | 0.27, 1.07 | 0.57, 18.4 | 0.23, 1.00 | 1.08, 41.9 | 0.05, 17.9 |
| Beta Binomial Meta Analysis | Estimate | NA | 0.46 | 3.39 | 0.50 | 6.76 | 2.88 |
| | 95% CI | NA | 0.15, 1.45 | 0.49, 23.6 | 0.14, 1.86 | 0.69, 70.1 | 0.30, 23.2 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 6.3: Combined Analysis Across Research Partner Databases By Dextran Category - 7 Day Risk Window - Third or Subsequent Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | NA | 0 (0 / 34,760) | 0 (0 / 20) | 0 (0 / 34,750) | NE | 0 |
| | 95% CI | NA | 0, 1.10 | 0, 2040 | 0, 1.11 | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NA | 0.17 (1 / 58,298) | NE | 0.17 (1 / 58,298) | NE | NE |
| | 95% CI | NA | 0.03, 0.97 | NE, NE | 0.03, 0.97 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NA | 0 (0 / 3,217) | 0 (0 / 2,421) | 0 (0 / 796) | NE | 0 |
| | 95% CI | NA | 0, 11.9 | 0, 15.8 | 0, 48.0 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NA | 0 (0 / 37,471) | 0 (0 / 1,148) | 0 (0 / 36,323) | NE | 0 |
| | 95% CI | NA | 0, 1.03 | 0, 33.4 | 0, 1.06 | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | NA | 0.52 (18 / 348,945) | 0 (0 / 5,015) | 0.52 (18 / 343,930) | 0 | 0.52 |
| | 95% CI | NA | 0.33, 0.82 | 0, 7.65 | 0.33, 0.83 | 0, 14.6 | 0.77, 0.28 |
| KfH QiN, Germany | Estimate | NA | 0 (0 / 2,620,795) | 0 (0 / 904) | 0 (0 / 2,619,891) | NE | 0 |
| | 95% CI | NA | 0, 0.01 | 0, 42.3 | 0, 0.01 | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | NA | 0.06 (19 / 3,103,486) | 0 (0 / 9,508) | 0.06 (19 / 3,093,988) | 0 | 0.06 |
| | 95% CI | NA | 0.04, 0.10 | 0, 4.04 | 0.04, 0.10 | 0, 65.8 | 0.10, 3.98 |
| Beta Binomial Meta Analysis | Estimate | NA | 0.05 | 0 | 0.06 | 0 | 0.06 |
| | 95% CI | NA | 0.02, 0.15 | 0, >9995 | 0.02, 0.22 | 0, >9995 | 0.17, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 6.4: Combined Analysis Across Research Partner Databases By Dextran Category - 7 Day Risk Window - Any Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database (Min) | Estimate | 0.41 (30 / 736,070) | 0.23 (1 / 42,780) | 0 (0 / 50) | 0.23 (1 / 42,730) | 0 | 0.23 |
| | 95% CI | 0.29, 0.58 | 0.04, 1.32 | 0, 787 | 0.04, 1.33 | 0, 3580 | 0.69, 0.22 |
| Danish Central Region EMR Database (Max) | Estimate | 0.41 (30 / 736,070) | 0.94 (4 / 42,780) | 0 (0 / 50) | 0.94 (4 / 42,730) | 0 | 0.94 |
| | 95% CI | 0.29, 0.58 | 0.36, 2.40 | 0, 787 | 0.36, 2.41 | 0, 874 | 1.85, 0.02 |
| SNDS Database, France | Estimate | 0.77 (6 / 78,292) | 0.26 (4 / 156,436) | NE | 0.26 (4 / 156,436) | NE | NE |
| | 95% CI | 0.35, 1.67 | 0.10, 0.66 | NE, NE | 0.10, 0.66 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0.35 (4 / 114,639) | 0 (0 / 10,892) | 0 (0 / 5,880) | 0 (0 / 5,012) | NE | 0 |
| | 95% CI | 0.14, 0.90 | 0, 3.53 | 0, 6.53 | 0, 7.66 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NE | 0.69 (7 / 100,761) | 0 (0 / 3,507) | 0.72 (7 / 97,254) | 0 | 0.72 |
| | 95% CI | NE, NE | 0.34, 1.43 | 0, 10.9 | 0.35, 1.49 | 0, 15.2 | 1.25, 0.19 |
| GePaRD, Germany | Estimate | 1.45 (8 / 54,999) | 0.70 (39 / 557,756) | 2.33 (2 / 8,584) | 0.67 (37 / 549,172) | 3.46 | 1.66 |
| | 95% CI | 0.74, 2.87 | 0.51, 0.96 | 0.64, 8.49 | 0.49, 0.93 | 0.92, 13.0 | 1.58, 4.89 |
| KfH QiN, Germany | Estimate | NE | 0 (0 / 2,687,170) | 0 (0 / 958) | 0 (0 / 2,686,212) | NE | 0 |
| | 95% CI | NE, NE | 0, 0.01 | 0, 39.9 | 0, 0.01 | NE, NE | NE, NE |
| Pooled (Crude) Analysis (Min) | Estimate | 0.52 (48 / 984,000) | 0.14 (51 / 3,555,795) | 1.05 (2 / 18,979) | 0.14 (49 / 3,536,816) | 7.61 | 0.92 |
| | 95% CI | 0.39, 0.68 | 0.11, 0.19 | 0.29, 3.84 | 0.10, 0.18 | 2.04, 28.4 | 0.15, 3.70 |
| Beta Binomial Meta Analysis (Min) | Estimate | 0.53 | 0.15 | 1.05 | 0.16 | 6.68 | 0.89 |
| | 95% CI | 0.40, 0.71 | 0.09, 0.24 | 0.26, 4.26 | 0.08, 0.30 | 1.47, 31.0 | 0.09, 4.11 |
| Pooled (Crude) Analysis (Max) | Estimate | 0.52 (48 / 984,000) | 0.15 (54 / 3,555,795) | 1.05 (2 / 18,979) | 0.15 (52 / 3,536,816) | 7.17 | 0.91 |
| | 95% CI | 0.39, 0.68 | 0.12, 0.20 | 0.29, 3.84 | 0.11, 0.19 | 1.92, 26.7 | 0.14, 3.70 |
| Beta Binomial Meta Analysis (Max) | Estimate | 0.53 | 0.17 | 1.05 | 0.19 | 5.66 | 0.86 |

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| | 95% CI | 0.40, 0.71 | 0.11, 0.25 | 0.26, 4.25 | 0.11, 0.32 | 1.29, 25.5 | 0.06, 4.07 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 7.1a: Combined Analysis Across Research Partner Databases By Individual Category - 7 Day Risk Window - First Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0.40 (3 / 75,512) | NE | NE | NE | NE |
| | 95% CI | 0.14, 1.17 | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 1,594) | 0 (0 / 456) | NE | 0 (0 / 2,393) | 0 (0 / 1,382) |
| | 95% CI | 0, 24.0 | 0, 83.5 | NE, NE | 0, 16.0 | 0, 27.7 |
| Swedish National Registries | Estimate | 1.03 (2 / 19,485) | 9.36 (1 / 1,068) | NE | 0 (0 / 1,599) | 0.98 (2 / 20,316) |
| | 95% CI | 0.28, 3.74 | 1.65, 52.8 | NE, NE | 0, 24.0 | 0.27, 3.59 |
| GePaRD, Germany | Estimate | 1.84 (7 / 38,101) | 12.8 (1 / 784) | 0.70 (6 / 85,282) | 4.26 (1 / 2,346) | 0 (0 / 14,403) |
| | 95% CI | 0.89, 3.79 | 2.25, 71.9 | 0.32, 1.54 | 0.75, 24.1 | 0, 2.67 |
| KfH QiN, Germany | Estimate | 0 (0 / 11,982) | 0 (0 / 17) | 0 (0 / 21,386) | 0 (0 / 29) | 0 (0 / 205) |
| | 95% CI | 0, 3.20 | 0, 1840 | 0, 1.80 | 0, 1170 | 0, 184 |
| Pooled (Crude) Analysis | Estimate | 0.82 (12 / 146,674) | 8.60 (2 / 2,325) | 0.56 (6 / 106,668) | 1.57 (1 / 6,367) | 0.55 (2 / 36,306) |
| | 95% CI | 0.47, 1.43 | 2.36, 31.3 | 0.26, 1.23 | 0.28, 8.89 | 0.15, 2.01 |
| Beta Binomial Meta Analysis | Estimate | 0.91 | 8.76 | 0.52 | 1.65 | 0.58 |
| | 95% CI | 0.39, 2.15 | 2.17, 35.0 | 0.11, 2.52 | 0.24, 11.8 | 0.10, 3.22 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 7.1b: Combined Analysis Across Research Partner Databases By Individual Category - 7 Day Risk Window - First Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 1.04 | 9.51 | NE | 0 |
| | 95% CI | 0.18, 5.91 | 1.25, 72.5 | NE, NE | 0, 24.4 |
| GePaRD, Germany | Estimate | Inf | Inf | Inf | Inf |
| | 95% CI | 0.69, Inf | 4.78, Inf | 0.26, Inf | 1.60, Inf |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 1.49 | 15.6 | 1.02 | 2.85 |
| | 95% CI | 0.37, 5.93 | 2.76, 88.4 | 0.24, 4.42 | 0.37, 21.8 |
| Beta Binomial Meta Analysis | Estimate | 1.58 | 15.2 | 0.90 | 2.85 |
| | 95% CI | 0.24, 10.6 | 1.63, 133 | 0.09, 8.89 | 0.21, 37.0 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 7.1c: Combined Analysis Across Research Partner Databases By Individual Category - 7 Day Risk Window - First Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.04 | 8.38 | NE | 0.98 |
| | 95% CI | 1.93, 2.01 | 10.0, 26.8 | NE, NE | 2.35, 0.38 |
| GePaRD, Germany | Estimate | 1.84 | 12.8 | 0.70 | 4.26 |
| | 95% CI | 0.48, 3.20 | 12.2, 37.7 | 0.14, 1.27 | 4.09, 12.6 |
| KfH QiN, Germany | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.27 | 8.05 | 0.01 | 1.02 |
| | 95% CI | 1.22, 1.02 | 1.72, 30.8 | 1.47, 0.80 | 0.87, 8.35 |
| Beta Binomial Meta Analysis | Estimate | 0.33 | 8.18 | 0.06 | 1.07 |
| | 95% CI | 2.25, 1.64 | 1.07, 33.8 | 2.61, 1.86 | 1.86, 11.0 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 7.2a: Combined Analysis Across Research Partner Databases By Individual Category - 7 Day Risk Window - Second Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0 (0 / 22,626) | NE | NE | NE | NE |
| | 95% CI | 0, 1.70 | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 364) | 0 (0 / 82) | NE | 0 (0 / 1,066) | 0 (0 / 338) |
| | 95% CI | 0, 104 | 0, 448 | NE, NE | 0, 35.9 | 0, 112 |
| Swedish National Registries | Estimate | 1.28 (1 / 7,842) | 0 (0 / 248) | NE | 0 (0 / 760) | 0.84 (1 / 11,972) |
| | 95% CI | 0.23, 7.22 | 0, 153 | NE, NE | 0, 50.3 | 0.15, 4.73 |
| GePaRD, Germany | Estimate | 0 (0 / 13,236) | 0 (0 / 194) | 0.65 (3 / 46,021) | 8.18 (1 / 1,223) | 2.77 (2 / 7,221) |
| | 95% CI | 0, 2.90 | 0, 194 | 0.22, 1.92 | 1.44, 46.2 | 0.76, 10.1 |
| KfH QiN, Germany | Estimate | 0 (0 / 11,616) | 0 (0 / 13) | 0 (0 / 20,964) | 0 (0 / 25) | 0 (0 / 138) |
| | 95% CI | 0, 3.31 | 0, 2280 | 0, 1.83 | 0, 1330 | 0, 271 |
| Pooled (Crude) Analysis | Estimate | 0.18 (1 / 55,684) | 0 (0 / 537) | 0.45 (3 / 66,985) | 3.25 (1 / 3,074) | 1.53 (3 / 19,669) |
| | 95% CI | 0.03, 1.02 | 0, 71.0 | 0.15, 1.32 | 0.57, 18.4 | 0.52, 4.48 |
| Beta Binomial Meta Analysis | Estimate | 0.21 | 0 | 0.44 | 3.29 | 1.61 |
| | 95% CI | 0.03, 1.50 | 0, NE | 0.10, 2.02 | 0.48, 23.5 | 0.50, 5.26 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 7.2b: Combined Analysis Across Research Partner Databases By Individual Category - 7 Day Risk Window - Second Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 1.53 | 0 | NE | 0 |
| | 95% CI | 0.16, 14.6 | 0, 185 | NE, NE | 0, 60.5 |
| GePaRD, Germany | Estimate | 0 | 0 | 0.24 | 2.95 |
| | 95% CI | 0, 1.05 | 0, 71.0 | 0.05, 1.18 | 0.39, 22.5 |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.12 | 0 | 0.29 | 2.13 |
| | 95% CI | 0.02, 0.82 | 0, 46.8 | 0.07, 1.27 | 0.31, 14.9 |
| Beta Binomial Meta Analysis | Estimate | 0.13 | 0 | 0.27 | 2.04 |
| | 95% CI | 0.01, 1.28 | 0, NE | 0.04, 1.81 | 0.20, 19.7 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 7.2c: Combined Analysis Across Research Partner Databases By Individual Category - 7 Day Risk Window - Second Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.44 | 0.84 | NE | 0.84 |
| | 95% CI | 2.55, 3.43 | 2.47, 0.80 | NE, NE | 2.47, 0.80 |
| GePaRD, Germany | Estimate | 2.77 | 2.77 | 2.12 | 5.41 |
| | 95% CI | 6.61, 1.07 | 6.61, 1.07 | 6.03, 1.79 | 11.1, 21.9 |
| KfH QiN, Germany | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 1.35 | 1.53 | 1.08 | 1.73 |
| | 95% CI | 4.31, 0.15 | 4.48, 69.5 | 4.05, 0.21 | 2.23, 16.9 |
| Beta Binomial Meta Analysis | Estimate | 1.41 | 1.61 | 1.17 | 1.67 |
| | 95% CI | 4.92, 0.24 | NE, NE | 4.69, 0.65 | 3.02, 21.7 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 7.3a: Combined Analysis Across Research Partner Databases By Individual Category - 7 Day Risk Window - Third or Subsequent Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0.17 (1 / 58,298) | NE | NE | NE | NE |
| | 95% CI | 0.03, 0.97 | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 353) | 0 (0 / 31) | NE | 0 (0 / 2,421) | 0 (0 / 412) |
| | 95% CI | 0, 108 | 0, 1100 | NE, NE | 0, 15.8 | 0, 92.4 |
| Swedish National Registries | Estimate | 0 (0 / 8,562) | 0 (0 / 149) | NE | 0 (0 / 1,148) | 0 (0 / 27,612) |
| | 95% CI | 0, 4.48 | 0, 251 | NE, NE | 0, 33.4 | 0, 1.39 |
| GePaRD, Germany | Estimate | 0.59 (1 / 16,895) | 0 (0 / 248) | 0.53 (16 / 299,533) | 0 (0 / 5,015) | 0.37 (1 / 27,254) |
| | 95% CI | 0.10, 3.35 | 0, 153 | 0.33, 0.87 | 0, 7.65 | 0.06, 2.08 |
| KfH QiN, Germany | Estimate | 0 (0 / 588,840) | 0 (0 / 84) | 0 (0 / 2,029,405) | 0 (0 / 904) | 0 (0 / 1,562) |
| | 95% CI | 0, 0.07 | 0, 437 | 0, 0.02 | 0, 42.3 | 0, 24.5 |
| Pooled (Crude) Analysis | Estimate | 0.03 (2 / 672,948) | 0 (0 / 512) | 0.07 (16 / 2,328,938) | 0 (0 / 9,488) | 0.18 (1 / 56,840) |
| | 95% CI | 0.01, 0.11 | 0, 74.5 | 0.04, 0.11 | 0, 4.05 | 0.03, 1.00 |
| Beta Binomial Meta Analysis | Estimate | 0.10 | 0 | 0.07 | 0 | 0.21 |
| | 95% CI | 0.02, 0.39 | 0, >9995 | 0.01, 0.42 | 0, >9995 | 0.03, 1.52 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 7.3b: Combined Analysis Across Research Partner Databases By Individual Category - 7 Day Risk Window - Third or Subsequent Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 1.61 | 0 | 1.46 | 0 |
| | 95% CI | 0.17, 15.5 | 0, 421 | 0.25, 8.61 | 0, 20.9 |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.17 | 0 | 0.39 | 0 |
| | 95% CI | 0.02, 1.29 | 0, 426 | 0.07, 2.31 | 0, 23.0 |
| Beta Binomial Meta Analysis | Estimate | 0.45 | 0 | 0.31 | 0 |
| | 95% CI | 0.04, 4.99 | 0, >9995 | 0.02, 4.43 | 0, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 7.3c: Combined Analysis Across Research Partner Databases By Individual Category - 7 Day Risk Window - Third or Subsequent Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 0.22 | 0.37 | 0.17 | 0.37 |
| | 95% CI | 1.14, 1.59 | 1.09, 0.35 | 0.60, 0.93 | 1.09, 0.35 |
| KfH QiN, Germany | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.15 | 0.18 | 0.11 | 0.18 |
| | 95% CI | 0.97, 0.01 | 1.00, 74.3 | 0.93, 0.04 | 1.00, 3.87 |
| Beta Binomial Meta Analysis | Estimate | 0.12 | 0.21 | 0.15 | 0.21 |
| | 95% CI | 1.41, 0.23 | 1.12, >9995 | 1.40, 0.23 | 1.09, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 7.4a: Combined Analysis Across Research Partner Databases By Individual Category - 7 Day Risk Window - Any Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0.26 (4 / 156,436) | NE | NE | NE | NE |
| | 95% CI | 0.10, 0.66 | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 2,311) | 0 (0 / 569) | NE | 0 (0 / 5,880) | 0 (0 / 2,132) |
| | 95% CI | 0, 16.6 | 0, 67.1 | NE, NE | 0, 6.53 | 0, 18.0 |
| Swedish National Registries | Estimate | 0.84 (3 / 35,889) | 6.83 (1 / 1,465) | NE | 0 (0 / 3,507) | 0.50 (3 / 59,900) |
| | 95% CI | 0.28, 2.46 | 1.21, 38.6 | NE, NE | 0, 10.9 | 0.17, 1.47 |
| GePaRD, Germany | Estimate | 1.17 (8 / 68,232) | 8.16 (1 / 1,226) | 0.58 (25 / 430,836) | 2.33 (2 / 8,584) | 0.61 (3 / 48,878) |
| | 95% CI | 0.59, 2.31 | 1.44, 46.1 | 0.39, 0.86 | 0.64, 8.49 | 0.21, 1.80 |
| KfH QiN, Germany | Estimate | 0 (0 / 612,438) | 0 (0 / 114) | 0 (0 / 2,071,755) | 0 (0 / 958) | 0 (0 / 1,905) |
| | 95% CI | 0, 0.06 | 0, 326 | 0, 0.02 | 0, 39.9 | 0, 20.1 |
| Pooled (Crude) Analysis | Estimate | 0.17 (15 / 875,306) | 5.93 (2 / 3,374) | 0.10 (25 / 2,502,591) | 1.06 (2 / 18,929) | 0.53 (6 / 112,815) |
| | 95% CI | 0.10, 0.28 | 1.63, 21.6 | 0.07, 0.15 | 0.29, 3.85 | 0.24, 1.16 |
| Beta Binomial Meta Analysis | Estimate | 0.22 | 5.95 | 0.06 | 1.05 | 0.56 |
| | 95% CI | 0.11, 0.46 | 1.47, 23.8 | 0.01, 0.29 | 0.26, 4.39 | 0.23, 1.36 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 7.4b: Combined Analysis Across Research Partner Databases By Individual Category - 7 Day Risk Window - Any Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 1.67 | 13.6 | NE | 0 |
| | 95% CI | 0.39, 7.23 | 1.95, 95.0 | NE, NE | 0, 21.9 |
| GePaRD, Germany | Estimate | 1.91 | 13.3 | 0.95 | 3.80 |
| | 95% CI | 0.55, 6.63 | 1.90, 92.6 | 0.30, 2.94 | 0.76, 19.0 |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.32 | 11.1 | 0.19 | 1.99 |
| | 95% CI | 0.13, 0.80 | 2.57, 48.2 | 0.08, 0.45 | 0.46, 8.60 |
| Beta Binomial Meta Analysis | Estimate | 0.39 | 10.7 | 0.10 | 1.88 |
| | 95% CI | 0.13, 1.25 | 2.04, 55.2 | 0.02, 0.62 | 0.35, 9.94 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 7.4c: Combined Analysis Across Research Partner Databases By Individual Category - 7 Day Risk Window - Any Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.34 | 6.33 | NE | 0.50 |
| | 95% CI | 0.77, 1.44 | 7.06, 19.7 | NE, NE | 1.07, 0.07 |
| GePaRD, Germany | Estimate | 0.56 | 7.54 | 0.03 | 1.72 |
| | 95% CI | 0.51, 1.63 | 8.45, 23.5 | 0.76, 0.70 | 1.59, 5.02 |
| KfH QiN, Germany | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.36 | 5.40 | 0.43 | 0.52 |
| | 95% CI | 0.99, 0.05 | 1.06, 21.1 | 1.06, 0.14 | 0.46, 3.33 |
| Beta Binomial Meta Analysis | Estimate | 0.34 | 5.39 | 0.50 | 0.49 |
| | 95% CI | 1.12, 0.07 | 0.81, 23.1 | 1.27, 0.11 | 0.65, 3.77 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 8: Combined Analysis Across Research Partner Databases By Dextran Category - Dialysis Patients Only - Any Dispensing or Administration**

| Database | Statistic | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | 0 (0 / 34,700) | NE | 0 (0 / 34,700) | NE | NE |
| | 95% CI | 0, 1.11 | NE, NE | 0, 1.11 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 303) | 0 (0 / 89) | 0 (0 / 214) | NE | 0 |
| | 95% CI | 0, 125 | 0, 414 | 0, 176 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0 (0 / 6,041) | 0 (0 / 185) | 0 (0 / 5,856) | NE | 0 |
| | 95% CI | 0, 6.35 | 0, 203 | 0, 6.56 | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 0.20 (2 / 101,808) | 0 (0 / 1,573) | 0.20 (2 / 100,235) | 0 | 0.20 |
| | 95% CI | 0.05, 0.72 | 0, 24.4 | 0.05, 0.73 | 0, 122 | 0.48, 0.08 |
| KfH QiN, Germany | Estimate | 0 (0 / 2,687,170) | 0 (0 / 958) | 0 (0 / 2,686,212) | NE | 0 |
| | 95% CI | 0, 0.01 | 0, 39.9 | 0, 0.01 | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.01 (2 / 2,830,022) | 0 (0 / 2,805) | 0.01 (2 / 2,827,217) | 0 | 0.01 |
| | 95% CI | 0.00, 0.03 | 0, 13.7 | 0.00, 0.03 | 0, 1940 | 0.03, 13.7 |
| Beta Binomial Meta Analysis | Estimate | 0.01 | 0 | 0.02 | 0 | 0.02 |
| | 95% CI | 0.00, 0.09 | 0, >9995 | 0.00, 0.16 | 0, >9995 | 0.11, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 9.1: Combined Analysis Across Research Partner Databases By Dextran Category - Excluding Dialysis - First Dispensing or Administration**

| Database | Statistic | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|
| Danish Central Region EMR Database (Min) | Estimate | 1.96 (1 / 5,090) | 0 (0 / 20) | 1.97 (1 / 5,070) | 0 | 1.97 |
| | 95% CI | 0.35, 11.1 | 0, 1430 | 0.35, 11.2 | 0, 819 | 5.84, 1.89 |
| Danish Central Region EMR Database (Max) | Estimate | 7.86 (4 / 5,090) | 0 (0 / 20) | 7.89 (4 / 5,070) | 0 | 7.89 |
| | 95% CI | 3.06, 20.2 | 0, 1430 | 3.07, 20.3 | 0, 195 | 15.6, 0.16 |
| SNDS Database, France | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 5,689) | 0 (0 / 2,366) | 0 (0 / 3,323) | NE | 0 |
| | 95% CI | 0, 6.75 | 0, 16.2 | 0, 11.5 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.73 (3 / 41,196) | 0 (0 / 1,533) | 0.76 (3 / 39,663) | 0 | 0.76 |
| | 95% CI | 0.25, 2.14 | 0, 25.0 | 0.26, 2.22 | 0, 33.1 | 1.61, 0.10 |
| GePaRD, Germany | Estimate | 0.72 (9 / 124,286) | 0 (0 / 1,885) | 0.74 (9 / 122,401) | 0 | 0.74 |
| | 95% CI | 0.38, 1.38 | 0, 20.3 | 0.39, 1.40 | 0, 27.7 | 1.22, 0.25 |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis (Min) | Estimate | 0.74 (13 / 176,261) | 0 (0 / 5,804) | 0.76 (13 / 170,457) | 0 | 0.76 |
| | 95% CI | 0.43, 1.26 | 0, 6.61 | 0.45, 1.30 | 0, 8.67 | 1.30, 5.85 |
| Beta Binomial Meta Analysis (Min) | Estimate | 0.77 | 0 | 1.00 | 0 | 1.00 |
| | 95% CI | 0.41, 1.47 | 0, NE | 0.42, 2.42 | 0, NE | NE, NE |
| Pooled (Crude) Analysis (Max) | Estimate | 0.91 (16 / 176,261) | 0 (0 / 5,804) | 0.94 (16 / 170,457) | 0 | 0.94 |
| | 95% CI | 0.56, 1.47 | 0, 6.61 | 0.58, 1.52 | 0, 7.04 | 1.52, 5.67 |
| Beta Binomial Meta Analysis (Max) | Estimate | 1.75 | 0 | 1.24 | 0 | 1.24 |
| | 95% CI | 0.71, 4.46 | 0, >9995 | 0.62, 2.53 | 0, >9995 | 2.22, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 9.2: Combined Analysis Across Research Partner Databases By Dextran Category - Excluding Dialysis - Second Dispensing or Administration**

| Database | Statistic | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | 0 (0 / 1,390) | 0 (0 / 10) | 0 (0 / 1,380) | NE | 0 |
| | 95% CI | 0, 27.7 | 0, 3540 | 0, 27.8 | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 1,802) | 0 (0 / 1,054) | 0 (0 / 748) | NE | 0 |
| | 95% CI | 0, 21.3 | 0, 36.3 | 0, 51.1 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.50 (1 / 20,023) | 0 (0 / 724) | 0.52 (1 / 19,299) | 0 | 0.52 |
| | 95% CI | 0.09, 2.83 | 0, 52.8 | 0.09, 2.93 | 0, 102 | 1.53, 0.50 |
| GePaRD, Germany | Estimate | 0.38 (2 / 53,009) | 12.3 (1 / 816) | 0.19 (1 / 52,193) | 64.0 | 12.1 |
| | 95% CI | 0.10, 1.38 | 2.16, 69.1 | 0.03, 1.09 | 6.68, 612 | 11.9, 36.1 |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.39 (3 / 76,224) | 3.84 (1 / 2,604) | 0.27 (2 / 73,620) | 14.2 | 3.57 |
| | 95% CI | 0.13, 1.16 | 0.68, 21.7 | 0.07, 0.99 | 1.85, 108 | 0.36, 21.5 |
| Beta Binomial Meta Analysis | Estimate | 0.46 | 3.91 | 0.45 | 8.72 | 3.46 |
| | 95% CI | 0.14, 1.59 | 0.56, 27.3 | 0.11, 1.87 | 0.83, 96.8 | 0.15, 27.0 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 9.3: Combined Analysis Across Research Partner Databases By Dextran Category - Excluding Dialysis - Third or Subsequent Dispensing or Administration**

| Database | Statistic | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | 0 (0 / 1,600) | 0 (0 / 20) | 0 (0 / 1,580) | NE | 0 |
| | 95% CI | 0, 24.0 | 0, 2040 | 0, 24.2 | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 3,098) | 0 (0 / 2,371) | 0 (0 / 727) | NE | 0 |
| | 95% CI | 0, 12.4 | 0, 16.2 | 0, 52.6 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0 (0 / 33,501) | 0 (0 / 1,065) | 0 (0 / 32,436) | NE | 0 |
| | 95% CI | 0, 1.15 | 0, 35.9 | 0, 1.18 | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 0.56 (6 / 106,518) | 0 (0 / 1,459) | 0.57 (6 / 105,059) | 0 | 0.57 |
| | 95% CI | 0.26, 1.23 | 0, 26.3 | 0.26, 1.25 | 0, 46.0 | 1.03, 0.11 |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.41 (6 / 144,717) | 0 (0 / 4,915) | 0.43 (6 / 139,802) | 0 | 0.43 |
| | 95% CI | 0.19, 0.90 | 0, 7.82 | 0.20, 0.94 | 0, 18.2 | 0.94, 7.39 |
| Beta Binomial Meta Analysis | Estimate | 0.34 | 0 | 0.38 | 0 | 0.38 |
| | 95% CI | 0.08, 1.63 | 0, NE | 0.10, 1.42 | 0, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 9.4: Combined Analysis Across Research Partner Databases By Dextran Category - Excluding Dialysis - Any Dispensing or Administration**

| Database | Statistic | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|
| Danish Central Region EMR Database (Min) | Estimate | 1.24 (1 / 8,080) | 0 (0 / 50) | 1.25 (1 / 8,030) | 0 | 1.25 |
| | 95% CI | 0.22, 7.01 | 0, 787 | 0.22, 7.05 | 0, 674 | 3.69, 1.20 |
| Danish Central Region EMR Database (Max) | Estimate | 4.95 (4 / 8,080) | 0 (0 / 50) | 4.98 (4 / 8,030) | 0 | 4.98 |
| | 95% CI | 1.93, 12.7 | 0, 787 | 1.94, 12.8 | 0, 164 | 9.86, 0.10 |
| SNDS Database, France | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 10,589) | 0 (0 / 5,791) | 0 (0 / 4,798) | NE | 0 |
| | 95% CI | 0, 3.63 | 0, 6.63 | 0, 8.00 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.42 (4 / 94,720) | 0 (0 / 3,322) | 0.44 (4 / 91,398) | 0 | 0.44 |
| | 95% CI | 0.16, 1.09 | 0, 11.6 | 0.17, 1.13 | 0, 26.4 | 0.87, 0.01 |
| GePaRD, Germany | Estimate | 0.60 (17 / 283,813) | 2.40 (1 / 4,160) | 0.57 (16 / 279,653) | 4.20 | 1.83 |
| | 95% CI | 0.37, 0.96 | 0.42, 13.6 | 0.35, 0.93 | 0.71, 24.8 | 2.89, 6.55 |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis (Min) | Estimate | 0.55 (22 / 397,202) | 0.75 (1 / 13,323) | 0.55 (21 / 383,879) | 1.37 | 0.20 |
| | 95% CI | 0.37, 0.84 | 0.13, 4.25 | 0.36, 0.84 | 0.23, 8.03 | 0.49, 3.71 |
| Beta Binomial Meta Analysis (Min) | Estimate | 0.56 | 0.79 | 0.64 | 1.24 | 0.15 |
| | 95% CI | 0.32, 0.99 | 0.11, 5.49 | 0.29, 1.41 | 0.16, 10.2 | 0.88, 4.88 |
| Pooled (Crude) Analysis (Max) | Estimate | 0.63 (25 / 397,202) | 0.75 (1 / 13,323) | 0.63 (24 / 383,879) | 1.20 | 0.13 |
| | 95% CI | 0.43, 0.93 | 0.13, 4.25 | 0.42, 0.93 | 0.21, 7.00 | 0.58, 3.63 |
| Beta Binomial Meta Analysis (Max) | Estimate | 0.65 | 0.78 | 0.79 | 0.99 | 0.01 |
| | 95% CI | 0.42, 1.03 | 0.11, 5.43 | 0.42, 1.51 | 0.13, 7.64 | 1.01, 4.68 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 10.1a: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Dialysis - First Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 1,567) | 0 (0 / 451) | NE | 0 (0 / 2,366) | 0 (0 / 1,305) |
| | 95% CI | 0, 24.5 | 0, 84.5 | NE, NE | 0, 16.2 | 0, 29.4 |
| Swedish National Registries | Estimate | 0.52 (1 / 19,126) | 9.61 (1 / 1,041) | NE | 0 (0 / 1,533) | 0.51 (1 / 19,496) |
| | 95% CI | 0.09, 2.96 | 1.70, 54.2 | NE, NE | 0, 25.0 | 0.09, 2.91 |
| GePaRD, Germany | Estimate | 1.35 (5 / 36,991) | 0 (0 / 718) | 0.55 (4 / 73,007) | 0 (0 / 1,885) | 0 (0 / 11,685) |
| | 95% CI | 0.58, 3.16 | 0, 53.2 | 0.21, 1.41 | 0, 20.3 | 0, 3.29 |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 1.04 (6 / 57,684) | 4.52 (1 / 2,210) | 0.55 (4 / 73,007) | 0 (0 / 5,784) | 0.31 (1 / 32,486) |
| | 95% CI | 0.48, 2.27 | 0.80, 25.6 | 0.21, 1.41 | 0, 6.64 | 0.05, 1.74 |
| Beta Binomial Meta Analysis | Estimate | 1.04 | 4.55 | 0.63 | 0 | 0.35 |
| | 95% CI | 0.41, 2.74 | 0.63, 32.3 | 0.18, 2.26 | 0, NE | 0.05, 2.48 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 10.1b: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Dialysis - First Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 1.02 | 18.7 | NE | 0 |
| | 95% CI | 0.11, 9.76 | 1.96, 179 | NE, NE | 0, 48.8 |
| GePaRD, Germany | Estimate | Inf | NE | Inf | NE |
| | 95% CI | 0.41, Inf | NE, NE | 0.17, Inf | NE, NE |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 3.38 | 14.7 | 1.78 | 0 |
| | 95% CI | 0.53, 21.4 | 1.53, 141 | 0.27, 11.8 | 0, 21.6 |
| Beta Binomial Meta Analysis | Estimate | 3.02 | 13.2 | 1.81 | 0 |
| | 95% CI | 0.35, 26.5 | 0.79, 202 | 0.18, 18.7 | 0, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 10.1c: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Dialysis - First Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.01 | 9.09 | NE | 0.51 |
| | 95% CI | 1.43, 1.45 | 9.75, 27.9 | NE, NE | 1.52, 0.49 |
| GePaRD, Germany | Estimate | 1.35 | 0 | 0.55 | 0 |
| | 95% CI | 0.17, 2.54 | NE, NE | 0.01, 1.08 | NE, NE |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.73 | 4.22 | 0.24 | 0.31 |
| | 95% CI | 0.76, 2.01 | 0.37, 25.3 | 1.22, 1.16 | 1.74, 6.33 |
| Beta Binomial Meta Analysis | Estimate | 0.70 | 4.21 | 0.28 | 0.35 |
| | 95% CI | 1.42, 2.33 | 0.27, 31.6 | 1.79, 1.84 | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 10.2a: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Dialysis - Second Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 353) | 0 (0 / 82) | NE | 0 (0 / 1,054) | 0 (0 / 313) |
| | 95% CI | 0, 108 | 0, 448 | NE, NE | 0, 36.3 | 0, 121 |
| Swedish National Registries | Estimate | 1.30 (1 / 7,705) | 0 (0 / 241) | NE | 0 (0 / 724) | 0 (0 / 11,353) |
| | 95% CI | 0.23, 7.35 | 0, 157 | NE, NE | 0, 52.8 | 0, 3.38 |
| GePaRD, Germany | Estimate | 0 (0 / 12,613) | 0 (0 / 156) | 0 (0 / 34,501) | 12.3 (1 / 816) | 2.03 (1 / 4,923) |
| | 95% CI | 0, 3.04 | 0, 240 | 0, 1.11 | 2.16, 69.1 | 0.36, 11.5 |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.48 (1 / 20,671) | 0 (0 / 479) | 0 (0 / 34,501) | 3.86 (1 / 2,594) | 0.60 (1 / 16,589) |
| | 95% CI | 0.09, 2.74 | 0, 79.6 | 0, 1.11 | 0.68, 21.8 | 0.11, 3.41 |
| Beta Binomial Meta Analysis | Estimate | 0.49 | 0 | 0 | 3.86 | 0.61 |
| | 95% CI | 0.07, 3.50 | 0, NE | 0, NE | 0.56, 27.5 | 0.08, 4.34 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 10.2b: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Dialysis - Second Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | Inf | NE | NE | NE |
| | 95% CI | 0.38, Inf | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 0 | 0 | 0 | 6.03 |
| | 95% CI | 0, 1.50 | 0, 121 | 0, 0.55 | 0.63, 57.7 |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.80 | 0 | 0 | 6.40 |
| | 95% CI | 0.08, 7.69 | 0, 133 | 0, 1.85 | 0.67, 61.2 |
| Beta Binomial Meta Analysis | Estimate | 0.80 | 0 | 0 | 6.37 |
| | 95% CI | 0.05, 12.8 | 0, NE | 0, NE | 0.40, 98.5 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 10.2c: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Dialysis - Second Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 1.30 | 0 | NE | 0 |
| | 95% CI | 1.25, 3.84 | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 2.03 | 2.03 | 2.03 | 10.2 |
| | 95% CI | 6.01, 1.95 | 6.01, 1.95 | 6.01, 1.95 | 14.1, 34.6 |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.12 | 0.60 | 0.60 | 3.25 |
| | 95% CI | 2.96, 2.19 | 3.41, 79.0 | 3.41, 0.51 | 0.67, 21.2 |
| Beta Binomial Meta Analysis | Estimate | 0.12 | 0.61 | 0.61 | 3.25 |
| | 95% CI | 3.68, 2.80 | NE, NE | NE, NE | 1.69, 26.7 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 10.3a: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Dialysis - Third or Subsequent Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 341) | 0 (0 / 31) | NE | 0 (0 / 2,371) | 0 (0 / 355) |
| | 95% CI | 0, 111 | 0, 1100 | NE, NE | 0, 16.2 | 0, 107 |
| Swedish National Registries | Estimate | 0 (0 / 8,393) | 0 (0 / 146) | NE | 0 (0 / 1,065) | 0 (0 / 23,897) |
| | 95% CI | 0, 4.57 | 0, 256 | NE, NE | 0, 35.9 | 0, 1.61 |
| GePaRD, Germany | Estimate | 0 (0 / 14,785) | 0 (0 / 98) | 0.73 (6 / 82,106) | 0 (0 / 1,459) | 0 (0 / 8,070) |
| | 95% CI | 0, 2.60 | 0, 377 | 0.33, 1.59 | 0, 26.3 | 0, 4.76 |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0 (0 / 23,519) | 0 (0 / 275) | 0.73 (6 / 82,106) | 0 (0 / 4,895) | 0 (0 / 32,322) |
| | 95% CI | 0, 1.63 | 0, 138 | 0.33, 1.59 | 0, 7.84 | 0, 1.19 |
| Beta Binomial Meta Analysis | Estimate | 0 | 0 | 1.02 | 0 | 0 |
| | 95% CI | 0, NE | 0, NE | 0.26, 4.06 | 0, NE | 0, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 10.3b: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Dialysis - Third or Subsequent Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | NE | NE | Inf | NE |
| | 95% CI | NE, NE | NE, NE | 0.15, Inf | NE, NE |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | NE | NE | Inf | NE |
| | 95% CI | NE, NE | NE, NE | 0.61, Inf | NE, NE |
| Beta Binomial Meta Analysis | Estimate | 0.56 | 3.82 | >9995 | 6.05 |
| | 95% CI | 0.56, 0.56 | 3.82, 3.82 | >9995, >9995 | 6.05, 6.05 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 10.3c: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Dialysis - Third or Subsequent Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 0 | 0 | 0.73 | 0 |
| | 95% CI | NE, NE | NE, NE | 0.15, 1.32 | NE, NE |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0 | 0 | 0.73 | 0 |
| | 95% CI | NE, NE | NE, NE | 0.46, 1.59 | NE, NE |
| Beta Binomial Meta Analysis | Estimate | 0 | 0 | 1.02 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 10.4a: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Dialysis - Any Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 2,261) | 0 (0 / 564) | NE | 0 (0 / 5,791) | 0 (0 / 1,973) |
| | 95% CI | 0, 17.0 | 0, 67.7 | NE, NE | 0, 6.63 | 0, 19.4 |
| Swedish National Registries | Estimate | 0.57 (2 / 35,224) | 7.00 (1 / 1,428) | NE | 0 (0 / 3,322) | 0.18 (1 / 54,746) |
| | 95% CI | 0.16, 2.07 | 1.24, 39.6 | NE, NE | 0, 11.6 | 0.03, 1.03 |
| GePaRD, Germany | Estimate | 0.78 (5 / 64,389) | 0 (0 / 972) | 0.53 (10 / 189,614) | 2.40 (1 / 4,160) | 0.41 (1 / 24,678) |
| | 95% CI | 0.33, 1.82 | 0, 39.4 | 0.29, 0.97 | 0.42, 13.6 | 0.07, 2.30 |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.69 (7 / 101,874) | 3.37 (1 / 2,964) | 0.53 (10 / 189,614) | 0.75 (1 / 13,273) | 0.25 (2 / 81,397) |
| | 95% CI | 0.33, 1.42 | 0.60, 19.1 | 0.29, 0.97 | 0.13, 4.27 | 0.07, 0.90 |
| Beta Binomial Meta Analysis | Estimate | 0.77 | 3.42 | 0.65 | 0.80 | 0.36 |
| | 95% CI | 0.29, 2.09 | 0.47, 24.3 | 0.20, 2.27 | 0.12, 5.71 | 0.09, 1.46 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 10.4b: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Dialysis - Any Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 3.11 | 38.3 | NE | 0 |
| | 95% CI | 0.41, 23.7 | 4.00, 367 | NE, NE | 0, 63.3 |
| GePaRD, Germany | Estimate | 1.92 | 0 | 1.30 | 5.93 |
| | 95% CI | 0.30, 12.4 | 0, 97.5 | 0.21, 7.89 | 0.62, 56.8 |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 2.80 | 13.7 | 2.15 | 3.07 |
| | 95% CI | 0.66, 11.8 | 1.80, 105 | 0.53, 8.71 | 0.40, 23.4 |
| Beta Binomial Meta Analysis | Estimate | 2.12 | 9.41 | 1.79 | 2.19 |
| | 95% CI | 0.40, 11.6 | 0.83, 103 | 0.30, 11.3 | 0.20, 23.3 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 10.4c: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Dialysis - Any Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.39 | 6.82 | NE | 0.18 |
| | 95% CI | 0.48, 1.25 | 6.90, 20.5 | NE, NE | 0.54, 0.18 |
| GePaRD, Germany | Estimate | 0.37 | 0.41 | 0.12 | 2.00 |
| | 95% CI | 0.67, 1.42 | 1.20, 0.39 | 0.74, 0.98 | 2.78, 6.78 |
| KfH QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.44 | 3.13 | 0.28 | 0.51 |
| | 95% CI | 0.27, 1.21 | 0.31, 18.8 | 0.40, 0.77 | 0.36, 4.03 |
| Beta Binomial Meta Analysis | Estimate | 0.41 | 3.06 | 0.29 | 0.43 |
| | 95% CI | 0.75, 1.70 | 0.12, 23.8 | 0.88, 1.85 | 0.86, 5.27 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 11.1: Combined Analysis Across Research Partner Databases By Dextran Category - Excluding Zero-Event Studies - First Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database (Min) | Estimate | 1.71 (20 / 116,980) | 1.71 (1 / 5,870) | 0 (0 / 20) | 1.71 (1 / 5,840) | 0 | 1.71 |
| | 95% CI | 1.11, 2.64 | 0.30, 9.65 | 0, 1430 | 0.30, 9.69 | 0, 943 | 5.07, 1.64 |
| Danish Central Region EMR Database (Max) | Estimate | 1.71 (20 / 116,980) | 6.82 (4 / 5,870) | 0 (0 / 20) | 6.85 (4 / 5,840) | 0 | 6.85 |
| | 95% CI | 1.11, 2.64 | 2.65, 17.5 | 0, 1430 | 2.66, 17.6 | 0, 225 | 13.6, 0.14 |
| SNDS Database, France | Estimate | 0.17 (1 / 57,200) | NA | NA | NA | NA | NA |
| | 95% CI | 0.03, 0.99 | NA | NA | NA | NA | NA |
| PHARMO, Netherlands | Estimate | 0.77 (3 / 39,002) | NA | NA | NA | NA | NA |
| | 95% CI | 0.26, 2.26 | NA | NA | NA | NA | NA |
| Swedish National Registries | Estimate | NA | 0.71 (3 / 42,468) | 0 (0 / 1,599) | 0.73 (3 / 40,869) | 0 | 0.73 |
| | 95% CI | NA | 0.24, 2.08 | 0, 24.0 | 0.25, 2.16 | 0, 32.7 | 1.56, 0.10 |
| GePaRD, Germany | Estimate | 3.31 (6 / 18,112) | 0.64 (9 / 140,916) | 0 (0 / 2,346) | 0.65 (9 / 138,570) | 0 | 0.65 |
| | 95% CI | 1.52, 7.23 | 0.34, 1.21 | 0, 16.3 | 0.34, 1.23 | 0, 25.2 | 1.07, 0.23 |
| KfH QiN, Germany | Estimate | NA | NA | NA | NA | NA | NA |
| | 95% CI | NA | NA | NA | NA | NA | NA |
| Pooled (Crude) Analysis (Min) | Estimate | 1.17 (30 / 231,294) | 0.69 (13 / 189,254) | 0 (0 / 3,965) | 0.70 (13 / 185,279) | 0 | 0.70 |
| | 95% CI | 0.80, 1.70 | 0.40, 1.18 | 0, 9.67 | 0.41, 1.20 | 0, 13.8 | 1.20, 8.97 |
| Beta Binomial Meta Analysis (Min) | Estimate | 1.16 | 0.69 | 0 | 0.85 | 0 | 0.85 |
| | 95% CI | 0.78, 1.73 | 0.40, 1.19 | 0, >9995 | 0.40, 1.89 | 0, >9995 | 1.63, >9995 |
| Pooled (Crude) Analysis (Max) | Estimate | 1.17 (30 / 231,294) | 0.85 (16 / 189,254) | 0 (0 / 3,965) | 0.86 (16 / 185,279) | 0 | 0.86 |
| | 95% CI | 0.80, 1.70 | 0.52, 1.37 | 0, 9.67 | 0.53, 1.40 | 0, 11.2 | 1.40, 8.81 |
| Beta Binomial Meta Analysis (Max) | Estimate | 1.16 | 1.92 | 0 | 1.03 | 0 | 1.03 |

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| | 95% CI | 0.78, 1.73 | 0.79, 4.77 | 0, >9995 | 0.57, 1.91 | 0, >9995 | 1.70, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 11.2: Combined Analysis Across Research Partner Databases By Dextran Category - Excluding Zero-Event Studies - Second Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | NA | NA | NA | NA | NA | NA |
| | 95% CI | NA | NA | NA | NA | NA | NA |
| SNDS Database, France | Estimate | NA | NA | NA | NA | NA | NA |
| | 95% CI | NA | NA | NA | NA | NA | NA |
| PHARMO, Netherlands | Estimate | NA | NA | NA | NA | NA | NA |
| | 95% CI | NA | NA | NA | NA | NA | NA |
| Swedish National Registries | Estimate | NA | 0.48 (1 / 20,822) | 0 (0 / 760) | 0.50 (1 / 20,062) | 0 | 0.50 |
| | 95% CI | NA | 0.08, 2.72 | 0, 50.3 | 0.09, 2.82 | 0, 101 | 1.48, 0.48 |
| GePaRD, Germany | Estimate | NA | 0.29 (2 / 67,895) | 8.18 (1 / 1,223) | 0.15 (1 / 66,672) | 54.5 | 8.03 |
| | 95% CI | NA | 0.08, 1.07 | 1.44, 46.2 | 0.03, 0.85 | 5.69, 522 | 8.00, 24.0 |
| KfH QiN, Germany | Estimate | NA | NA | NA | NA | NA | NA |
| | 95% CI | NA | NA | NA | NA | NA | NA |
| Pooled (Crude) Analysis | Estimate | NA | 0.34 (3 / 88,717) | 5.04 (1 / 1,983) | 0.23 (2 / 86,734) | 21.9 | 4.81 |
| | 95% CI | NA | 0.12, 0.99 | 0.89, 28.5 | 0.06, 0.84 | 2.87, 167 | 0.64, 28.3 |
| Beta Binomial Meta Analysis | Estimate | NA | 0.34 | 5.04 | 0.23 | 21.9 | 4.81 |
| | 95% CI | NA | 0.11, 1.07 | 0.73, 35.2 | 0.06, 0.96 | 2.09, 243 | 0.41, 35.1 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 11.3: Combined Analysis Across Research Partner Databases By Dextran Category - Excluding Zero-Event Studies - Third or Subsequent Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | NA | NA | NA | NA | NA | NA |
| | 95% CI | NA | NA | NA | NA | NA | NA |
| SNDS Database, France | Estimate | NA | NA | NA | NA | NA | NA |
| | 95% CI | NA | NA | NA | NA | NA | NA |
| PHARMO, Netherlands | Estimate | NA | NA | NA | NA | NA | NA |
| | 95% CI | NA | NA | NA | NA | NA | NA |
| Swedish National Registries | Estimate | NA | NA | NA | NA | NA | NA |
| | 95% CI | NA | NA | NA | NA | NA | NA |
| GePaRD, Germany | Estimate | NA | 0.29 (10 / 348,945) | 0 (0 / 5,015) | 0.29 (10 / 343,930) | 0 | 0.29 |
| | 95% CI | NA | 0.16, 0.53 | 0, 7.65 | 0.16, 0.54 | 0, 26.3 | 0.47, 0.11 |
| KfH QiN, Germany | Estimate | NA | NA | NA | NA | NA | NA |
| | 95% CI | NA | NA | NA | NA | NA | NA |
| Pooled (Crude) Analysis | Estimate | NA | 0.29 (10 / 348,945) | 0 (0 / 5,015) | 0.29 (10 / 343,930) | 0 | 0.29 |
| | 95% CI | NA | 0.16, 0.53 | 0, 7.65 | 0.16, 0.54 | 0, 26.3 | 0.54, 7.36 |
| Beta Binomial Meta Analysis | Estimate | NA | NE | NE | NE | NE | NE |
| | 95% CI | NA | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 11.4: Combined Analysis Across Research Partner Databases By Dextran Category - Excluding Zero-Event Studies - Any Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database (Min) | Estimate | 0.41 (30 / 736,070) | 0.23 (1 / 42,780) | 0 (0 / 50) | 0.23 (1 / 42,730) | 0 | 0.23 |
| | 95% CI | 0.29, 0.58 | 0.04, 1.32 | 0, 787 | 0.04, 1.33 | 0, 3580 | 0.69, 0.22 |
| Danish Central Region EMR Database (Max) | Estimate | 0.41 (30 / 736,070) | 0.94 (4 / 42,780) | 0 (0 / 50) | 0.94 (4 / 42,730) | 0 | 0.94 |
| | 95% CI | 0.29, 0.58 | 0.36, 2.40 | 0, 787 | 0.36, 2.41 | 0, 874 | 1.85, 0.02 |
| SNDS Database, France | Estimate | 0.26 (2 / 78,292) | NA | NA | NA | NA | NA |
| | 95% CI | 0.07, 0.93 | NA | NA | NA | NA | NA |
| PHARMO, Netherlands | Estimate | 0.35 (4 / 114,639) | NA | NA | NA | NA | NA |
| | 95% CI | 0.14, 0.90 | NA | NA | NA | NA | NA |
| Swedish National Registries | Estimate | NA | 0.40 (4 / 100,761) | 0 (0 / 3,507) | 0.41 (4 / 97,254) | 0 | 0.41 |
| | 95% CI | NA | 0.15, 1.02 | 0, 10.9 | 0.16, 1.06 | 0, 26.6 | 0.81, 0.01 |
| GePaRD, Germany | Estimate | 1.45 (8 / 54,999) | 0.38 (21 / 557,756) | 1.16 (1 / 8,584) | 0.36 (20 / 549,172) | 3.20 | 0.80 |
| | 95% CI | 0.74, 2.87 | 0.25, 0.58 | 0.21, 6.60 | 0.24, 0.56 | 0.55, 18.7 | 1.49, 3.09 |
| KfH QiN, Germany | Estimate | NA | NA | NA | NA | NA | NA |
| | 95% CI | NA | NA | NA | NA | NA | NA |
| Pooled (Crude) Analysis (Min) | Estimate | 0.44 (44 / 984,000) | 0.37 (26 / 701,297) | 0.82 (1 / 12,141) | 0.36 (25 / 689,156) | 2.27 | 0.46 |
| | 95% CI | 0.32, 0.59 | 0.25, 0.54 | 0.15, 4.67 | 0.25, 0.54 | 0.39, 13.2 | 0.24, 4.30 |
| Beta Binomial Meta Analysis (Min) | Estimate | 0.45 | 0.37 | 0.84 | 0.39 | 2.17 | 0.45 |
| | 95% CI | 0.32, 0.63 | 0.24, 0.60 | 0.12, 5.90 | 0.20, 0.77 | 0.28, 17.0 | 0.38, 5.54 |
| Pooled (Crude) Analysis (Max) | Estimate | 0.44 (44 / 984,000) | 0.41 (29 / 701,297) | 0.82 (1 / 12,141) | 0.41 (28 / 689,156) | 2.03 | 0.42 |
| | 95% CI | 0.32, 0.59 | 0.29, 0.59 | 0.15, 4.67 | 0.28, 0.59 | 0.35, 11.8 | 0.29, 4.26 |
| Beta Binomial Meta Analysis (Max) | Estimate | 0.45 | 0.41 | 0.84 | 0.47 | 1.77 | 0.37 |

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| | 95% CI | 0.32, 0.63 | 0.29, 0.60 | 0.12, 5.86 | 0.28, 0.83 | 0.24, 13.5 | 0.45, 5.42 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 12.1a: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Zero-Event Studies - First Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.51 (1 / 19,485) | 9.36 (1 / 1,068) | NE | 0 (0 / 1,599) | 0.49 (1 / 20,316) |
| | 95% CI | 0.09, 2.91 | 1.65, 52.8 | NE, NE | 0, 24.0 | 0.09, 2.79 |
| GePaRD, Germany | Estimate | 1.31 (5 / 38,101) | 0 (0 / 784) | 0.47 (4 / 85,282) | 0 (0 / 2,346) | 0 (0 / 14,403) |
| | 95% CI | 0.56, 3.07 | 0, 48.8 | 0.18, 1.21 | 0, 16.3 | 0, 2.67 |
| Pooled (Crude) Analysis | Estimate | 1.04 (6 / 57,586) | 5.40 (1 / 1,852) | 0.47 (4 / 85,282) | 0 (0 / 3,945) | 0.29 (1 / 34,719) |
| | 95% CI | 0.48, 2.27 | 0.95, 30.5 | 0.18, 1.21 | 0, 9.73 | 0.05, 1.63 |
| Beta Binomial Meta Analysis | Estimate | 1.07 | 5.45 | 0.56 | 0 | 0.34 |
| | 95% CI | 0.41, 2.87 | 0.75, 38.6 | 0.15, 2.20 | 0, >9995 | 0.05, 2.41 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 12.1b: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Zero-Event Studies - First Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 1.04 | 19.0 | NE | 0 |
| | 95% CI | 0.11, 9.99 | 1.99, 182 | NE, NE | 0, 48.8 |
| GePaRD, Germany | Estimate | Inf | NE | Inf | NE |
| | 95% CI | 0.49, Inf | NE, NE | 0.18, Inf | NE, NE |
| Pooled (Crude) Analysis | Estimate | 3.62 | 18.7 | 1.63 | 0 |
| | 95% CI | 0.57, 22.9 | 1.96, 179 | 0.24, 10.8 | 0, 33.8 |
| Beta Binomial Meta Analysis | Estimate | 3.18 | 16.2 | 1.68 | 0 |
| | 95% CI | 0.36, 28.2 | 0.97, 248 | 0.16, 18.0 | 0, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 12.1c: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Zero-Event Studies - First Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.02 | 8.87 | NE | 0.49 |
| | 95% CI | 1.37, 1.41 | 9.50, 27.2 | NE, NE | 1.46, 0.47 |
| GePaRD, Germany | Estimate | 1.31 | 0 | 0.47 | 0 |
| | 95% CI | 0.16, 2.46 | NE, NE | 0.01, 0.93 | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.75 | 5.11 | 0.18 | 0.29 |
| | 95% CI | 0.65, 2.03 | 0.59, 30.2 | 1.18, 0.97 | 1.63, 9.44 |
| Beta Binomial Meta Analysis | Estimate | 0.73 | 5.11 | 0.23 | 0.34 |
| | 95% CI | 1.35, 2.47 | 0.04, 37.9 | 1.78, 1.78 | 1.74, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 12.2a: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Zero-Event Studies - Second Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Swedish National Registries | Estimate | 1.28 (1 / 7,842) | 0 (0 / 248) | NE | 0 (0 / 760) | 0 (0 / 11,972) |
| | 95% CI | 0.23, 7.22 | 0, 153 | NE, NE | 0, 50.3 | 0, 3.21 |
| GePaRD, Germany | Estimate | 0 (0 / 13,236) | 0 (0 / 194) | 0 (0 / 46,021) | 8.18 (1 / 1,223) | 1.38 (1 / 7,221) |
| | 95% CI | 0, 2.90 | 0, 194 | 0, 0.83 | 1.44, 46.2 | 0.24, 7.84 |
| Pooled (Crude) Analysis | Estimate | 0.47 (1 / 21,078) | 0 (0 / 442) | 0 (0 / 46,021) | 5.04 (1 / 1,983) | 0.52 (1 / 19,193) |
| | 95% CI | 0.08, 2.69 | 0, 86.2 | 0, 0.83 | 0.89, 28.5 | 0.09, 2.95 |
| Beta Binomial Meta Analysis | Estimate | 0.60 | 0 | 0 | 5.17 | 0.64 |
| | 95% CI | 0.09, 4.30 | 0, >9995 | 0, >9995 | 0.75, 36.9 | 0.09, 4.63 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 12.2b: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Zero-Event Studies - Second Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Swedish National Registries | Estimate | Inf | NE | NE | NE |
| | 95% CI | 0.40, Inf | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 0 | 0 | 0 | 5.90 |
| | 95% CI | 0, 2.10 | 0, 142 | 0, 0.60 | 0.62, 56.5 |
| Pooled (Crude) Analysis | Estimate | 0.91 | 0 | 0 | 9.68 |
| | 95% CI | 0.10, 8.72 | 0, 167 | 0, 1.60 | 1.01, 92.7 |
| Beta Binomial Meta Analysis | Estimate | 0.93 | 0 | 0 | 8.02 |
| | 95% CI | 0.06, 14.7 | 0, >9995 | 0, >9995 | 0.50, 124 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 12.2c: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Zero-Event Studies - Second Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Swedish National Registries | Estimate | 1.28 | 0 | NE | 0 |
| | 95% CI | 1.22, 3.77 | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 1.38 | 1.38 | 1.38 | 6.79 |
| | 95% CI | 4.10, 1.33 | 4.10, 1.33 | 4.10, 1.33 | 9.46, 23.0 |
| Pooled (Crude) Analysis | Estimate | 0.05 | 0.52 | 0.52 | 4.52 |
| | 95% CI | 2.51, 2.21 | 2.95, 85.6 | 2.95, 0.31 | 0.01, 28.0 |
| Beta Binomial Meta Analysis | Estimate | 0.05 | 0.64 | 0.64 | 4.53 |
| | 95% CI | 3.83, 3.52 | 3.41, >9995 | 3.27, >9995 | 1.35, 36.0 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 12.3a: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Zero-Event Studies - Third or Subsequent Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| GePaRD, Germany | Estimate | 0.59 (1 / 16,895) | 0 (0 / 248) | 0.27 (8 / 299,533) | 0 (0 / 5,015) | 0.37 (1 / 27,254) |
| | 95% CI | 0.10, 3.35 | 0, 153 | 0.14, 0.53 | 0, 7.65 | 0.06, 2.08 |
| Pooled (Crude) Analysis | Estimate | 0.59 (1 / 16,895) | 0 (0 / 248) | 0.27 (8 / 299,533) | 0 (0 / 5,015) | 0.37 (1 / 27,254) |
| | 95% CI | 0.10, 3.35 | 0, 153 | 0.14, 0.53 | 0, 7.65 | 0.06, 2.08 |
| Beta Binomial Meta Analysis | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 12.3b: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Zero-Event Studies - Third or Subsequent Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| GePaRD, Germany | Estimate | 1.61 | 0 | 0.73 | 0 |
| | 95% CI | 0.17, 15.5 | 0, 421 | 0.12, 4.48 | 0, 20.9 |
| Pooled (Crude) Analysis | Estimate | 1.61 | 0 | 0.73 | 0 |
| | 95% CI | 0.17, 15.5 | 0, 421 | 0.12, 4.48 | 0, 20.9 |
| Beta Binomial Meta Analysis | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 12.3c: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Zero-Event Studies - Third or Subsequent Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| GePaRD, Germany | Estimate | 0.22 | 0.37 | 0.10 | 0.37 |
| | 95% CI | 1.14, 1.59 | 1.09, 0.35 | 0.84, 0.64 | 1.09, 0.35 |
| Pooled (Crude) Analysis | Estimate | 0.22 | 0.37 | 0.10 | 0.37 |
| | 95% CI | 1.54, 3.00 | 2.08, 152 | 1.81, 0.31 | 2.08, 7.29 |
| Beta Binomial Meta Analysis | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 12.4a: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Zero-Event Studies - Any Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.56 (2 / 35,889) | 6.83 (1 / 1,465) | NE | 0 (0 / 3,507) | 0.17 (1 / 59,900) |
| | 95% CI | 0.15, 2.03 | 1.21, 38.6 | NE, NE | 0, 10.9 | 0.03, 0.95 |
| GePaRD, Germany | Estimate | 0.88 (6 / 68,232) | 0 (0 / 1,226) | 0.28 (12 / 430,836) | 1.16 (1 / 8,584) | 0.41 (2 / 48,878) |
| | 95% CI | 0.40, 1.92 | 0, 31.2 | 0.16, 0.49 | 0.21, 6.60 | 0.11, 1.49 |
| Pooled (Crude) Analysis | Estimate | 0.77 (8 / 104,121) | 3.72 (1 / 2,691) | 0.28 (12 / 430,836) | 0.83 (1 / 12,091) | 0.28 (3 / 108,778) |
| | 95% CI | 0.39, 1.52 | 0.66, 21.0 | 0.16, 0.49 | 0.15, 4.68 | 0.09, 0.81 |
| Beta Binomial Meta Analysis | Estimate | 0.78 | 3.73 | 0.31 | 0.84 | 0.30 |
| | 95% CI | 0.37, 1.71 | 0.52, 26.5 | 0.12, 0.80 | 0.12, 6.03 | 0.09, 0.99 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 12.4b: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Zero-Event Studies - Any Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 3.34 | 40.9 | NE | 0 |
| | 95% CI | 0.44, 25.5 | 4.27, 391 | NE, NE | 0, 65.6 |
| GePaRD, Germany | Estimate | 2.15 | 0 | 0.68 | 2.85 |
| | 95% CI | 0.50, 9.31 | 0, 76.5 | 0.17, 2.72 | 0.37, 21.7 |
| Pooled (Crude) Analysis | Estimate | 2.79 | 13.5 | 1.01 | 3.00 |
| | 95% CI | 0.80, 9.67 | 1.93, 94.0 | 0.31, 3.33 | 0.43, 20.9 |
| Beta Binomial Meta Analysis | Estimate | 2.61 | 12.5 | 1.02 | 2.82 |
| | 95% CI | 0.64, 10.8 | 1.25, 123 | 0.23, 4.66 | 0.28, 27.5 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 12.4c: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Zero-Event Studies - Any Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.39 | 6.66 | NE | 0.17 |
| | 95% CI | 0.45, 1.23 | 6.72, 20.0 | NE, NE | 0.49, 0.16 |
| GePaRD, Germany | Estimate | 0.47 | 0.41 | 0.13 | 0.76 |
| | 95% CI | 0.43, 1.37 | 0.98, 0.16 | 0.72, 0.46 | 1.60, 3.11 |
| Pooled (Crude) Analysis | Estimate | 0.49 | 3.44 | 0.00 | 0.55 |
| | 95% CI | 0.14, 1.27 | 0.35, 20.7 | 0.54, 0.28 | 0.30, 4.41 |
| Beta Binomial Meta Analysis | Estimate | 0.48 | 3.43 | 0.01 | 0.54 |
| | 95% CI | 0.29, 1.41 | 0.12, 26.1 | 0.69, 0.52 | 0.48, 5.69 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 13.1: Combined Analysis Across Research Partner Databases By Dextran Category - Before 2013 - Any Dispensing or Administration**

| Database | Statistic | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0 (0 / 80,883) | NE | 0 (0 / 80,883) | NE | NE |
| | 95% CI | 0, 0.47 | NE, NE | 0, 0.47 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 7,282) | 0 (0 / 4,771) | 0 (0 / 2,511) | NE | 0 |
| | 95% CI | 0, 5.27 | 0, 8.05 | 0, 15.3 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.32 (2 / 63,471) | 0 (0 / 2,604) | 0.33 (2 / 60,867) | 0 | 0.33 |
| | 95% CI | 0.09, 1.15 | 0, 14.7 | 0.09, 1.20 | 0, 44.9 | 0.78, 0.13 |
| GePaRD, Germany | Estimate | 0.27 (10 / 374,620) | 0 (0 / 6,939) | 0.27 (10 / 367,681) | 0 | 0.27 |
| | 95% CI | 0.15, 0.49 | 0, 5.53 | 0.15, 0.50 | 0, 20.3 | 0.44, 0.10 |
| KfH QiN, Germany | Estimate | 0 (0 / 1,249,123) | 0 (0 / 594) | 0 (0 / 1,248,529) | NE | 0 |
| | 95% CI | 0, 0.03 | 0, 64.3 | 0, 0.03 | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.07 (12 / 1,775,379) | 0 (0 / 14,908) | 0.07 (12 / 1,760,471) | 0 | 0.07 |
| | 95% CI | 0.04, 0.12 | 0, 2.58 | 0.04, 0.12 | 0, 37.8 | 0.12, 2.51 |
| Beta Binomial Meta Analysis | Estimate | 0.06 | 0 | 0.07 | 0 | 0.07 |
| | 95% CI | 0.03, 0.17 | 0, >9995 | 0.02, 0.24 | 0, >9995 | 0.19, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 13.2: Combined Analysis Across Research Partner Databases By Dextran Category - After 2013 - Any Dispensing or Administration**

| Database | Statistic | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0 (0 / 4,835) | NE | 0 (0 / 4,835) | NE | NE |
| | 95% CI | 0, 7.94 | NE, NE | 0, 7.94 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 3,034) | 0 (0 / 842) | 0 (0 / 2,192) | NE | 0 |
| | 95% CI | 0, 12.6 | 0, 45.4 | 0, 17.5 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.75 (2 / 26,601) | 0 (0 / 591) | 0.77 (2 / 26,010) | 0 | 0.77 |
| | 95% CI | 0.21, 2.74 | 0, 64.6 | 0.21, 2.80 | 0, 84.3 | 1.83, 0.30 |
| GePaRD, Germany | Estimate | 0.67 (8 / 119,650) | 10.1 (1 / 992) | 0.59 (7 / 118,658) | 17.1 | 9.49 |
| | 95% CI | 0.34, 1.32 | 1.78, 56.9 | 0.29, 1.22 | 2.74, 106 | 10.3, 29.2 |
| KfH QiN, Germany | Estimate | 0 (0 / 1,177,868) | 0 (0 / 328) | 0 (0 / 1,177,540) | NE | 0 |
| | 95% CI | 0, 0.03 | 0, 116 | 0, 0.03 | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.08 (10 / 1,331,988) | 3.63 (1 / 2,753) | 0.07 (9 / 1,329,235) | 53.6 | 3.56 |
| | 95% CI | 0.04, 0.14 | 0.64, 20.5 | 0.04, 0.13 | 8.79, 327 | 0.57, 20.5 |
| Beta Binomial Meta Analysis | Estimate | 0.09 | 3.64 | 0.11 | 33.2 | 3.53 |
| | 95% CI | 0.04, 0.24 | 0.53, 25.4 | 0.04, 0.34 | 3.76, 317 | 0.39, 25.4 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 14.1: Combined Analysis Across Research Partner Databases By Dextran Category - After First Switch**

| Database | Statistic | IP per 10,000 From: Dextrans To: Non-Dextrans | IP per 10,000 From: Non-Dextrans To: Dextrans |
|---|---|---|---|
| Danish Central Region EMR Database | Estimate | NE | NE |
| | 95% CI | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE |
| | 95% CI | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE |
| | 95% CI | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0 (0 / 318) | 36.1 (2 / 554) |
| | 95% CI | 0, 119 | 9.91, 131 |
| GePaRD, Germany | Estimate | 0 (0 / 1) | 0 (0 / 2) |
| | 95% CI | 0, 7930 | 0, 6580 |
| KfH QiN, Germany | Estimate | 0 (0 / 13) | 0 (0 / 52) |
| | 95% CI | 0, 2280 | 0, 688 |
| Pooled (Crude) Analysis | Estimate | 0 (0 / 332) | 32.9 (2 / 608) |
| | 95% CI | 0, 114 | 9.03, 119 |
| Beta Binomial Meta Analysis | Estimate | 0 | 32.9 |
| | 95% CI | 0, 0 | 8.26, 136 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 14.2: Combined Analysis Across Research Partner Databases By Dextran Category - After Any Switch**

| Database | Statistic | IP per 10,000 From: Dextrans To: Non-Dextrans | IP per 10,000 From: Non-Dextrans To: Dextrans |
|---|---|---|---|
| Danish Central Region EMR Database | Estimate | NE | NE |
| | 95% CI | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE |
| | 95% CI | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 3) | NE |
| | 95% CI | 0, 5610 | NE, NE |
| Swedish National Registries | Estimate | 0 (0 / 554) | 31.9 (2 / 627) |
| | 95% CI | 0, 68.9 | 8.75, 116 |
| GePaRD, Germany | Estimate | 0 (0 / 1) | 0 (0 / 2) |
| | 95% CI | 0, 7930 | 0, 6580 |
| KfH QiN, Germany | Estimate | 0 (0 / 61) | 0 (0 / 73) |
| | 95% CI | 0, 592 | 0, 500 |
| Pooled (Crude) Analysis | Estimate | 0 (0 / 619) | 28.5 (2 / 702) |
| | 95% CI | 0, 61.7 | 7.82, 103 |
| Beta Binomial Meta Analysis | Estimate | 0 | 29.0 |
| | 95% CI | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 15.1a: Combined Analysis Across Research Partner Databases By Individual Category - After First Switch From Ferric Carboxymaltose Complex**

| | | IP per 10,000<br>From: Ferric Carboxymaltose Complex | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **To: Iron(III) Isomaltoside Complex** | **To: Sodium Ferric Gluconate Complex** | **To: Iron(III)-Hydroxide Dextran Complex** | **To: Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | 0 (0 / 240) | NE | NE | 0 (0 / 100) |
| | 95% CI | 0, 161 | NE, NE | NE, NE | 0, 381 |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 4) | NE | 0 (0 / 5) | 0 (0 / 6) |
| | 95% CI | 0, 4900 | NE, NE | 0, 4340 | 0, 3900 |
| Swedish National Registries | Estimate | 60.6 (1 / 165) | NE | 0 (0 / 41) | 0 (0 / 364) |
| | 95% CI | 10.7, 335 | NE, NE | 0, 857 | 0, 104 |
| GePaRD, Germany | Estimate | 0 (0 / 1) | 0 (0 / 7) | NE | 0 (0 / 1) |
| | 95% CI | 0, 7930 | 0, 3540 | NE, NE | 0, 7930 |
| KfH QiN, Germany | Estimate | 0 (0 / 8) | 0 (0 / 911) | 0 (0 / 4) | 0 (0 / 59) |
| | 95% CI | 0, 3240 | 0, 42.0 | 0, 4900 | 0, 611 |
| Pooled (Crude) Analysis | Estimate | 24.2 (1 / 418) | 0 (0 / 918) | 0 (0 / 50) | 0 (0 / 530) |
| | 95% CI | 4.28, 136 | 0, 41.7 | 0, 713 | 0, 72.4 |
| Beta Binomial Meta Analysis | Estimate | 24.2 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 15.1b: Combined Analysis Across Research Partner Databases By Individual Category - After First Switch From Iron(III) Isomaltoside Complex**

| | | IP per 10,000 From: Iron(III) Isomaltoside Complex | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **To: Ferric Carboxymaltose Complex** | **To: Sodium Ferric Gluconate Complex** | **To: Iron(III)-Hydroxide Dextran Complex** | **To: Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | 0 (0 / 50) | NE | NE | 0 (0 / 70) |
| | 95% CI | 0, 787 | NE, NE | NE, NE | 0, 527 |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | 0 (0 / 1) |
| | 95% CI | NE, NE | NE, NE | NE, NE | 0, 7930 |
| Swedish National Registries | Estimate | 0 (0 / 29) | NE | 0 (0 / 2) | 0 (0 / 18) |
| | 95% CI | 0, 1170 | NE, NE | 0, 6580 | 0, 1760 |
| GePaRD, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| KfH QiN, Germany | Estimate | 0 (0 / 4) | NE | NE | 0 (0 / 3) |
| | 95% CI | 0, 4900 | NE, NE | NE, NE | 0, 5610 |
| Pooled (Crude) Analysis | Estimate | 0 (0 / 83) | NE | 0 (0 / 2) | 0 (0 / 92) |
| | 95% CI | 0, 469 | NE, NE | 0, 6580 | 0, 405 |
| Beta Binomial Meta Analysis | Estimate | 0 | NE | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 15.1c: Combined Analysis Across Research Partner Databases By Individual Category - After First Switch From Sodium Ferric Gluconate Complex**

| | | IP per 10,000<br>From: Sodium Ferric Gluconate Complex | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **To: Ferric Carboxymaltose Complex** | **To: Iron(III) Isomaltoside Complex** | **To: Iron(III)-Hydroxide Dextran Complex** | **To: Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 0 (0 / 12) | NE | 0 (0 / 2) | 0 (0 / 6) |
| | 95% CI | 0, 2420 | NE, NE | 0, 6580 | 0, 3900 |
| KfH QiN, Germany | Estimate | 0 (0 / 5,220) | 0 (0 / 3) | 0 (0 / 48) | 0 (0 / 192) |
| | 95% CI | 0, 7.35 | 0, 5610 | 0, 741 | 0, 196 |
| Pooled (Crude) Analysis | Estimate | 0 (0 / 5,232) | 0 (0 / 3) | 0 (0 / 50) | 0 (0 / 198) |
| | 95% CI | 0, 7.34 | 0, 5610 | 0, 713 | 0, 190 |
| Beta Binomial Meta Analysis | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 15.1d: Combined Analysis Across Research Partner Databases By Individual Category - After First Switch From Iron(III)-Hydroxide Dextran Complex**

| | | IP per 10,000<br>From: Iron(III)-Hydroxide Dextran Complex | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **To: Ferric Carboxymaltose Complex** | **To: Iron(III) Isomaltoside Complex** | **To: Sodium Ferric Gluconate Complex** | **To: Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 26) | 0 (0 / 1) | NE | 0 (0 / 12) |
| | 95% CI | 0, 1290 | 0, 7930 | NE, NE | 0, 2420 |
| Swedish National Registries | Estimate | 0 (0 / 173) | 0 (0 / 11) | NE | 0 (0 / 134) |
| | 95% CI | 0, 217 | 0, 2590 | NE, NE | 0, 279 |
| GePaRD, Germany | Estimate | 0 (0 / 1) | NE | NE | NE |
| | 95% CI | 0, 7930 | NE, NE | NE, NE | NE, NE |
| KfH QiN, Germany | Estimate | 0 (0 / 6) | NE | 0 (0 / 7) | NE |
| | 95% CI | 0, 3900 | NE, NE | 0, 3540 | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0 (0 / 206) | 0 (0 / 12) | 0 (0 / 7) | 0 (0 / 146) |
| | 95% CI | 0, 183 | 0, 2420 | 0, 3540 | 0, 256 |
| Beta Binomial Meta Analysis | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 15.1e: Combined Analysis Across Research Partner Databases By Individual Category - After First Switch**

| | | IP per 10,000<br>From: Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **To: Ferric Carboxymaltose Complex** | **To: Iron(III) Isomaltoside Complex** | **To: Sodium Ferric Gluconate Complex** | **To: Iron(III)-Hydroxide Dextran Complex** |
| Danish Central Region EMR Database | Estimate | 0 (0 / 120) | 0 (0 / 80) | NE | NE |
| | 95% CI | 0, 300 | 0, 442 | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 35) | 0 (0 / 6) | NE | 0 (0 / 18) |
| | 95% CI | 0, 989 | 0, 3900 | NE, NE | 0, 1760 |
| Swedish National Registries | Estimate | 0 (0 / 3,107) | 0 (0 / 200) | NE | 39.1 (2 / 511) |
| | 95% CI | 0, 12.3 | 0, 188 | NE, NE | 10.7, 142 |
| GePaRD, Germany | Estimate | NE | NE | 0 (0 / 3) | NE |
| | 95% CI | NE, NE | NE, NE | 0, 5610 | NE, NE |
| KfH QiN, Germany | Estimate | 0 (0 / 39) | NE | 0 (0 / 52) | NE |
| | 95% CI | 0, 897 | NE, NE | 0, 688 | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0 (0 / 3,301) | 0 (0 / 286) | 0 (0 / 55) | 37.8 (2 / 529) |
| | 95% CI | 0, 11.6 | 0, 131 | 0, 653 | 10.4, 137 |
| Beta Binomial Meta Analysis | Estimate | 0 | 0 | 0 | 37.9 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 15.2a: Combined Analysis Across Research Partner Databases By Individual Category - After Any Switch From Ferric Carboxymaltose Complex**

| | | IP per 10,000 From: Ferric Carboxymaltose Complex | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **To: Iron(III) Isomaltoside Complex** | **To: Sodium Ferric Gluconate Complex** | **To: Iron(III)-Hydroxide Dextran Complex** | **To: Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | 0 (0 / 300) | NE | NE | 0 (0 / 120) |
| | 95% CI | 0, 129 | NE, NE | NE, NE | 0, 318 |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 4) | NE | 0 (0 / 7) | 0 (0 / 9) |
| | 95% CI | 0, 4900 | NE, NE | 0, 3540 | 0, 2990 |
| Swedish National Registries | Estimate | 43.7 (1 / 229) | NE | 0 (0 / 76) | 0 (0 / 634) |
| | 95% CI | 7.71, 243 | NE, NE | 0, 481 | 0, 60.2 |
| GePaRD, Germany | Estimate | 0 (0 / 1) | 0 (0 / 2) | 0 (0 / 1) | 0 (0 / 2) |
| | 95% CI | 0, 7930 | 0, 6580 | 0, 7930 | 0, 6580 |
| KfH QiN, Germany | Estimate | 0 (0 / 15) | 0 (0 / 2,395) | 0 (0 / 10) | 0 (0 / 112) |
| | 95% CI | 0, 2040 | 0, 16.0 | 0, 2780 | 0, 332 |
| Pooled (Crude) Analysis | Estimate | 18.4 (1 / 549) | 0 (0 / 2,397) | 0 (0 / 94) | 0 (0 / 877) |
| | 95% CI | 3.25, 103 | 0, 16.0 | 0, 393 | 0, 43.8 |
| Beta Binomial Meta Analysis | Estimate | 20.3 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 15.2b: Combined Analysis Across Research Partner Databases By Individual Category - After Any Switch From Iron(III) Isomaltoside Complex**

| | | IP per 10,000<br>From: Iron(III) Isomaltoside Complex | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **To: Ferric Carboxymaltose Complex** | **To: Sodium Ferric Gluconate Complex** | **To: Iron(III)-Hydroxide Dextran Complex** | **To: Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | 0 (0 / 80) | NE | NE | 0 (0 / 110) |
| | 95% CI | 0, 437 | NE, NE | NE, NE | 0, 337 |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | 0 (0 / 1) |
| | 95% CI | NE, NE | NE, NE | NE, NE | 0, 7930 |
| Swedish National Registries | Estimate | 0 (0 / 63) | NE | 0 (0 / 4) | 0 (0 / 36) |
| | 95% CI | 0, 575 | NE, NE | 0, 4900 | 0, 964 |
| GePaRD, Germany | Estimate | 0 (0 / 1) | 0 (0 / 7) | NE | 0 (0 / 1) |
| | 95% CI | 0, 7930 | 0, 3540 | NE, NE | 0, 7930 |
| KfH QiN, Germany | Estimate | 0 (0 / 13) | 0 (0 / 3) | NE | 0 (0 / 4) |
| | 95% CI | 0, 2280 | 0, 5610 | NE, NE | 0, 4900 |
| Pooled (Crude) Analysis | Estimate | 0 (0 / 157) | 0 (0 / 10) | 0 (0 / 4) | 0 (0 / 152) |
| | 95% CI | 0, 233 | 0, 2780 | 0, 4900 | 0, 246 |
| Beta Binomial Meta Analysis | Estimate | 0 | NE | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 15.2c: Combined Analysis Across Research Partner Databases By Individual Category - After Any Switch From Sodium Ferric Gluconate Complex**

| | | IP per 10,000<br>From: Sodium Ferric Gluconate Complex | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **To: Ferric Carboxymaltose Complex** | **To: Iron(III) Isomaltoside Complex** | **To: Iron(III)-Hydroxide Dextran Complex** | **To: Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| KfH QiN, Germany | Estimate | 0 (0 / 6,895) | 0 (0 / 4) | 0 (0 / 61) | 0 (0 / 292) |
| | 95% CI | 0, 5.57 | 0, 4900 | 0, 592 | 0, 130 |
| Pooled (Crude) Analysis | Estimate | 0 (0 / 6,895) | 0 (0 / 4) | 0 (0 / 61) | 0 (0 / 292) |
| | 95% CI | 0, 5.57 | 0, 4900 | 0, 592 | 0, 130 |
| Beta Binomial Meta Analysis | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 15.2d: Combined Analysis Across Research Partner Databases By Individual Category - After Any Switch From Iron(III)-Hydroxide Dextran Complex**

| | | IP per 10,000<br>From: Iron(III)-Hydroxide Dextran Complex | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **To: Ferric Carboxymaltose Complex** | **To: Iron(III) Isomaltoside Complex** | **To: Sodium Ferric Gluconate Complex** | **To: Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 29) | 0 (0 / 1) | NE | 0 (0 / 12) |
| | 95% CI | 0, 1170 | 0, 7930 | NE, NE | 0, 2420 |
| Swedish National Registries | Estimate | 0 (0 / 292) | 0 (0 / 19) | NE | 0 (0 / 243) |
| | 95% CI | 0, 130 | 0, 1680 | NE, NE | 0, 156 |
| GePaRD, Germany | Estimate | 0 (0 / 12) | NE | 0 (0 / 2) | 0 (0 / 6) |
| | 95% CI | 0, 2420 | NE, NE | 0, 6580 | 0, 3900 |
| KfH QiN, Germany | Estimate | 0 (0 / 22) | NE | 0 (0 / 36) | 0 (0 / 3) |
| | 95% CI | 0, 1490 | NE, NE | 0, 964 | 0, 5610 |
| Pooled (Crude) Analysis | Estimate | 0 (0 / 355) | 0 (0 / 20) | 0 (0 / 38) | 0 (0 / 264) |
| | 95% CI | 0, 107 | 0, 1610 | 0, 918 | 0, 143 |
| Beta Binomial Meta Analysis | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 15.2e: Combined Analysis Across Research Partner Databases By Individual Category - After Any Switch From Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex**

| | | IP per 10,000<br>From: Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **To: Ferric Carboxymaltose Complex** | **To: Iron(III) Isomaltoside Complex** | **To: Sodium Ferric Gluconate Complex** | **To: Iron(III)-Hydroxide Dextran Complex** |
| Danish Central Region EMR Database | Estimate | 0 (0 / 140) | 0 (0 / 100) | NE | NE |
| | 95% CI | 0, 277 | 0, 366 | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 38) | 0 (0 / 7) | NE | 0 (0 / 21) |
| | 95% CI | 0, 918 | 0, 3540 | NE, NE | 0, 1550 |
| Swedish National Registries | Estimate | 0 (0 / 3,298) | 0 (0 / 215) | NE | 36.6 (2 / 547) |
| | 95% CI | 0, 11.6 | 0, 176 | NE, NE | 10.0, 132 |
| GePaRD, Germany | Estimate | 0 (0 / 1) | NE | NE | NE |
| | 95% CI | 0, 7930 | NE, NE | NE, NE | NE, NE |
| KfH QiN, Germany | Estimate | 0 (0 / 125) | 0 (0 / 3) | 0 (0 / 204) | 0 (0 / 2) |
| | 95% CI | 0, 298 | 0, 5610 | 0, 185 | 0, 6580 |
| Pooled (Crude) Analysis | Estimate | 0 (0 / 3,602) | 0 (0 / 325) | 0 (0 / 204) | 35.1 (2 / 570) |
| | 95% CI | 0, 10.7 | 0, 116 | 0, 185 | 9.63, 127 |
| Beta Binomial Meta Analysis | Estimate | 0 | 0 | 0 | 39.0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

# Annex 5.
# 2014 and 2016 Feasibility Assessment Report

Annex 5_RTI-HS_IV Iron_FeasibAssessm

## Annex 8 Summary of Changes to the Risk Management Plan Over Time

| Version | Approval Date Procedure | Change |
|---|---|---|
| 1.2 | N/A | • First DE RMP.<br>• The following important identified risks have been included: hypersensitivity/anaphylactoid reaction, iron overload or iron storage disease (e.g., haemochromatosis, haemosiderosis).<br>• The following potential risk has been included: medication error – necrosis due to paravenous injections.<br>• The following missing information of safety concerns has been included: use in paediatric population, use in elderly patients, use in patients with infectious diseases, use in pregnant or lactating women. |
| 2.0 | N/A | • SV Post-authorisation Experience.<br>• Part VII: Annex 4 Synopsis of Clinical Trial Programme. |
| 2.1 | N/A | • Part II Safety: Specification. SV Post-authorisation Experience<br>• Part II Safety: SVII Identified and Potential Risks<br>• Part II Safety: SVIII Summary of the Safety Concerns<br>• Part IV Plan for Post-authorisation Efficacy Studies<br>• Part VII Annexes: Annex 5 Synopsis of Pharmacoepidemiological Study Programme<br>• Part VII Annexes: Annex 6 Protocols for Proposed and Ongoing Studies in Part III<br>• Part VII Annexes: Annex 7 Specific Adverse Event Follow-up Forms<br>• Part VII Annexes: Annex 8 Protocols for Studies in Part IV<br>• Part VII Annexes: Annex 9 Synopsis of Newly Available Study Reports in Parts III-IV<br>• Part VII Annexes: Annex 10 Details of Proposed Additional Risk Minimisation Activities<br>• Part VII Annexes: Annex 11 Mock-up Examples |
| 2.2 | 04-Oct-2017 | • Part II Safety Specification: SI Epidemiology of the Indication and Target Population<br>• Part II Safety Specification: SII Nonclinical Part of the Safety Specification<br>• Part II Safety Specification: SVI Additional EU Requirements for the Safety Specification<br>• Part III Pharmacovigilance Plan<br>• Part V Risk Minimisation Measures<br>• Part VI Summary of RMP<br>• Part VII Annexes: Annex 2 Current SmPC/PL |
| 3.0 | N/A | • Removal of IIRs iron overload or iron storage disease (e.g., haemochromatosis, haemosiderosis).<br>• Removal of important potential risk medication error necrosis due to paravenous injections.<br>• Removal of risk minimisation measures educational material for IIR hypersensitivity/anaphylactoid reaction.<br>• Updated information regarding the Joint PASS.<br>• Updated the epidemiology of the disease.<br>• Alignment with Guidance on the format of the risk management plan (RMP) in the EU – in integrated format¸ EMA/164014/2018 Rev. 2.0.1 accompanying GVP Module V Rev. 2. |

| Version | Approval Date Procedure | Change |
|---|---|---|
| 3.1 | N/A | • Reintroduction of educational materials for the IIR hypersensitivity/anaphylactoid reaction |

Notes: GVP Good Pharmacovigilance Practice; IIR Important identified risk; N/A Not applicable; PASS Post authorisation Safety Study; PL Package Leaflet; RMP Risk Management Plan; SmPC Summary of Product Characteristics.

## Signature Page

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