

ENVIRONMENTAL SCAN

International Policies on Parenteral Iron

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Abbreviations

CKD	chronic kidney disease
EMA	European Medicines Agency
ESA	erythropoiesis-stimulating agents
FCM	ferric carboxymaltose
IBD	inflammatory bowel disease
IDA	iron deficiency anemia
IV	intravenous
NICE	National Institute for Health and Care Excellence
PBS	Pharmaceutical Benefits Scheme
PHARMAC	Pharmaceutical Management Agency
POAC	Primary Options for Acute Care

Summary

- For the countries of interest with universal drug coverage (pharmacare) programs, we identified various guidance and policy resources on intravenous (IV) iron, some specific to clinical indications or contexts.
- There was limited information about clinical criteria or reimbursement restrictions for IV iron. Countries with universal pharmacare programs provide reimbursement for IV iron on the condition that patients meet established criteria including a failed trial of oral iron — when appropriate — or other eligibility criteria based on clinical status or diagnoses.
- Preference for IV iron preparations varies by jurisdiction depending on context (length of hospital stay, urgency of repletion requirements) and which products are approved. There is a preference toward ferric carboxymaltose in jurisdictions where it is approved and available (Australia, France, New Zealand, the UK; however, this product is not yet available in Canada).
- Of the guidance and policies identified, none stated a preference for the IV iron preparations available in Canada. However, iron sucrose and iron isomaltoside were considered appropriate for use in certain contexts or for specific conditions. Neither iron dextran nor sodium ferric gluconate were mentioned as preferred products by other jurisdictions.
- There was limited information about the preferred preparation of IV iron in Canada. Iron sucrose, iron dextran, sodium ferric gluconate, and iron isomaltoside are available, but their use and reimbursement status may vary by jurisdiction and clinical indication.
- It was generally recommended that the administration and monitoring of IV iron treatment be carried out according to individual product information, and for there to be sufficient monitoring of the patient during and after administration, including access to resuscitation facilities because of the risk of hypersensitivity reactions.

Context

Clinical and Technology Background

The World Health Organization defines anemia as a circulating hemoglobin concentration of less than 13 g/dL for men and less than 12 g/dL for non-pregnant women.¹ In industrialized countries, the prevalence of iron deficiency anemia (IDA) has been estimated to be approximately 5% to 10%,² with more than 50% of cases of anemia caused by iron deficiency.^{1,3} Anemia can increase the risk of mortality, hospitalization, and prolonged hospital stays.⁴ Symptoms include fatigue and weakness, and often indicate an underlying health issue.⁴ Iron supplementation is necessary to treat IDA, but it can be challenging to identify the underlying cause of the condition and to select an appropriate iron replacement product.⁵

Iron deficiency can occur in two forms: absolute iron deficiency or functional iron deficiency.² Absolute iron deficiency is defined as a decrease in iron stores in the body,² often caused by sustained blood loss, insufficient iron intake, or inadequate iron absorption.^{1,6,7} Functional iron deficiency occurs because of reduced iron uptake at various sites,⁸ as a result of inflammation-driven disruption of iron transport. It is a core component of anemia of chronic disease (also called anemia of inflammation because of the association with sustained immune system activation).^{2,8-10} Conditions associated with functional iron deficiency include acute and chronic infections, cancer, auto-immune diseases such as rheumatoid arthritis and inflammatory bowel

disease (IBD), and chronic kidney disease (CKD).⁸ In certain conditions — such as inflammatory bowel disease and gastrointestinal malignancy — both forms can be present.²

The treatment for anemia aims to restore iron status, treat symptoms, and mitigate the risk of more serious sequelae (e.g., the progression of anemia, organ damage, ischemia).⁵ In most clinical cases of IDA, oral iron is the first treatment.^{1,6} It is inexpensive and easy to administer,^{1,6} but it can be associated with gastrointestinal side effects such as abdominal pain, diarrhea, constipation, and dyspepsia, which may impact adherence.⁶ It is estimated that more than half of patients who take oral iron report significant gastrointestinal adverse events, which lead to treatment discontinuation in 20% of patients.^{1,5} Switching from the daily administration of oral iron to every other day may reduce the gastrointestinal adverse events.¹¹

Individuals may be candidates for intravenous (IV) iron when side effects associated with oral iron are intolerable, patients are unresponsive to oral treatment, when rapid repletion is required, and if a patient has a condition that interferes with iron absorption or iron homeostasis.¹¹⁻¹⁴ Historically, IV iron was associated with a high risk of anaphylaxis and toxicity.¹⁵ Today, available formulations include features to slow the release of elemental iron to mitigate this risk, with newer treatment options allowing very high doses to be administered over short infusion periods. Despite these suggested advantages, the choice to use IV over oral iron and the selection of the appropriate IV preparation can be impacted by cost, the need for IV access and monitored infusion, the degree of blood loss, iron absorption capacity, the presence of malabsorptive and inflammatory conditions, and the risk of infusion reactions and other adverse effects. In response to an increased use of iron, some jurisdictions promote guidance from the European Medicines Agency (EMA) recommending measures to reduce the risk of hypersensitivity reactions.^{16,17}

Various formulations of IV iron are available in Canada (Appendix 1). Notably, ferric carboxymaltose (FCM) is not yet available, despite availability in Europe, the US, and several other jurisdictions. Iron dextran formulations are being phased out because of concern about adverse effects,¹⁵ and because of the availability of IV iron formulations with improved toxicity profiles⁵ and greater ease of administration. The efficacy and safety profiles of newer IV iron formulations is reported to be comparable,¹⁸ although product cost, purchasing agreements, and the requirements for treatment administration (e.g., duration of infusion, maximum dose and number of doses required) may differ and influence preference.⁵

Policy Issues

In discussion with a group of hospital pharmacy directors in Canada during the scoping phase of this project, it was noted that some hospitals across Canada are providing parenteral iron therapy to in-patients and outpatients as an open benefit to treat anemia. The product and administrative cost of IV iron is substantially higher than oral iron, and the cost to health systems is high.¹⁹ Attempts to encourage the judicious use of IV iron through the availability of a standardized order form have not yielded a decrease in utilization or cost. Thus, there is interest in determining the current best practices for the utilization of parenteral iron preparations in countries with universal pharmacare programs in order to assess whether such practices might be adopted in Canada (Appendix 2).

The purpose of this Environmental Scan is to gather evidence-based policies, guidelines, best practices, standard order sets, clinical criteria, and treatment protocols related to the appropriate utilization of parenteral iron in countries with a universal drug coverage (or pharmacare) program. Countries of interest include Australia, France, Germany, New

Zealand, and the UK. The scan summarizes clinical criteria and/or reimbursement restrictions, preferences for specific formulations, and approaches to administering and monitoring the administration of parenteral iron in these jurisdictions.

Methods

Objectives and Research Questions

The objective of this Environmental Scan was to identify the most appropriate circumstances in which to use parenteral iron over oral iron. To inform this policy question, the following research questions were addressed:

1. What are the evidence-based policies, guidelines, best practices, or standard order sets or protocols for the appropriate utilization of all forms of parenteral iron in countries with a universal pharmacare program?^a
2. What are the clinical criteria or reimbursement restrictions for the use of parenteral iron in countries with a universal pharmacare program?
3. Which parenteral iron preparation is preferred in various outpatient settings in countries with a universal pharmacare program?
4. How is parenteral iron administered and monitored in countries with a universal pharmacare program?

Scope

This Environmental Scan is based on a review of the literature. It does not include an assessment of the clinical or cost-effectiveness of IV iron formulations. Thus, conclusions or recommendations about the value and place in therapy of IV iron, or guidance for its use, are not within the scope of this report. This report serves to summarize the public policies and guidance available in the jurisdictions of interest. It does not serve to endorse or recommend the messaging in these documents or comment on their generalizability to the Canadian context.

Literature Search

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Scopus, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were IV iron and anemia. Search filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2009 and June 19, 2019. Alerts updated the search until July 18, 2019.

^aThis report was limited to the following jurisdictions with universal pharmacare programs: Australia, France, Germany, New Zealand, and the UK.

Screening and Selection

One author screened the results of the database and grey literature searches. Evidence-based policies, guidelines, best practices, standard order sets and protocols from the countries of interest (i.e., Australia, France, Germany, New Zealand, and the UK) were selected, as well as literature or resources addressing clinical criteria or reimbursement restrictions for parenteral iron, preferences for parenteral iron preparation, and modes of administration or monitoring in these regions. There were no restrictions by publication type. In addition to the formal literature search, targeted scoping searches were conducted to identify additional resources.

Synthesis

Information relating to the objectives of this Environmental Scan was extracted from the identified resources and grouped by research question. The findings were summarized narratively.

Findings

This Environmental Scan is informed by a review of the literature. Stakeholder surveys and direct stakeholder consultations were not conducted.

Literature Search

The database search identified 161 potentially relevant publications. After screening of titles and abstracts, 38 publications were selected for full-text review. An additional 26 resources were selected for full-text review from the grey literature search.

Of these 64 publications, 39 were selected and are summarized in this report. Seven publications were selected from the database search, including five studies on the current utilization of parenteral iron^{4,20-23} and two guidelines from the UK.^{24,25} The resources selected from the grey literature included 10 publications from the UK,^{24,26-34} nine from Australia,³⁵⁻⁴³ nine from New Zealand,⁴⁴⁻⁵² and four from France.⁵³⁻⁵⁶ No information from Germany was identified.

Parenteral Iron Guidance and Policies in Selected Countries With a Universal Pharmacare Program

Types of guidance and policy documents identified ranged from hospital-issued clinical guidance for specific conditions requiring iron supplementation to national policy documents with broad recommendations about the use of IV iron. Specific guidance for several clinical conditions was also reported (Appendix 3).

Common themes throughout the identified guidance were to use IV iron:

- when oral iron could not be tolerated, when adherence is poor, or when it is not effective
- for patients with functional iron deficiency or a history of malabsorptive or inflammatory conditions
- for patients requiring rapid repletion (e.g., due to extreme blood loss or non-deferrable surgery).

It was also commonly recommended to avoid the use of IV iron in the first trimester of pregnancy, in patients with known hypersensitivity, with anemia not caused by iron deficiency, or iron overload.

UK

In the UK, several evidence-based and clinical practice guidelines and protocols provide information on the use of IV iron.

The Greater Glasgow and Clyde Area Drug and Therapeutics Committee with the National Health Service (NHS),²⁴ the Royal College of Nursing,²⁷ and the Northern Ireland Transfusion Committee (Guidelines and Audit Implementation Network)²⁸ provide guidance for all adults with IDA.

The Greater Glasgow and Clyde Area Drug and Therapeutics Committee provides guidance on IV iron (i.e., FCM and iron isomaltoside) for patients with IDA (excluding pregnant and postpartum anemia, surgery and trauma, pediatrics, and patients with CKD [stages 4 and 5]).²⁴ It^b states that IV iron should be reserved as a last resort treatment and only be used in cases stated in the guidance.

IV iron is suggested by the Royal College of Nursing in the UK as a first-line treatment if surgery is planned less than six weeks after IDA is diagnosed, for pregnancy with severe IDA or for those who receive a diagnosis after 34 weeks' gestation, and for women with severe postpartum anemia.²⁷ IV iron is also recommended for patients who cannot tolerate or have poor adherence to oral iron — excluding patients with known hypersensitivity to IV iron, anemia not caused by iron deficiency, iron overload, and people in the first trimester of pregnancy.²⁷

The Northern Ireland Transfusion Committee suggests switching from oral to IV iron if there is no improvement in hemoglobin status after three months of treatment, if there is a history of malabsorption or chronic IBD, in cases of functional iron deficiency (e.g., patients with CKD on hemodialysis), or if major surgery must proceed in less than three weeks' time.²⁸

Blood Transfusions

The National Institute for Health and Care Excellence (NICE) issued guidance for patients undergoing blood transfusions in 2015.²⁹ It recommends consideration of IV iron before or after surgery in patients with IDA who cannot tolerate or absorb oral iron, are unable to comply with oral therapy, are diagnosed with functional iron deficiency, or in cases where the time interval between the diagnosis of anemia and surgery is predicted to be insufficient for oral iron to be effective.²⁹

Chronic Kidney Disease

The 2015 NICE guidelines for managing anemia in CKD⁵⁷ recommend that patients not receiving hemodialysis receive a trial of oral iron before IV therapy is offered, and to offer IV therapy if there is an intolerance to oral iron or hemoglobin levels are not reached within three months. For people receiving hemodialysis, it recommends IV iron therapy unless it is contraindicated, or the person chooses not to receive treatment.⁵⁷ Patients receiving erythropoiesis-stimulating agents (ESA) are recommended receiving IV iron, with the

^b A full version of the guidance is only available to health region staff.

exception of children not receiving hemodialysis.⁵⁷ Guidance from the UK Renal Association includes similar recommendations, additionally stating that parenteral iron should be avoided in patients with active infection.³¹ The British Committee for Standards in Haematology published guidelines for IDA in pregnancy (2016).²⁶ It recommends that parenteral iron should be considered from the second trimester onward and during the postpartum period for women with confirmed iron deficiency who fail to respond or have an intolerance to oral iron. The Northern Ireland Transfusion Committee also recommends IV iron for patients with CKD if there is no improvement in hemoglobin, an intolerance to oral iron, or if the patient is receiving regular hemodialysis.²⁸

Gastrointestinal Conditions

The Norfolk and Norwich University Hospitals NHS Foundation Trust issued guidance in 2017 for using IV iron in patients with IDA with IBD or a “gastro-related” disorder.³⁰ They suggest that iron sucrose and FCM can be used in any patient diagnosed with IBD under the care of a gastroenterologist who is intolerant of iron preparations. This excludes patients with anemia not caused by iron deficiency, patients with an allergy to the preparation, patients in the first trimester of pregnancy, and those with active infections.³⁰

Safety

Lastly, the UK has endorsed the policy statement made in 2013 by the EMA regarding the safe administration of IV iron.^{16,58,59} This guidance was issued in response to concerns originating in France about serious hypersensitivity reactions to IV iron. It notes that IV iron should only be given in environments where patients can receive adequate monitoring (including close monitoring for 30 minutes after administration) and where resuscitation facilities are available. It recommends stopping treatment if a hypersensitivity reaction occurs (more information can be found in the Administration and Monitoring section of this scan). This statement recommends against using IV iron in the first trimester of pregnancy and to weigh risks carefully when considering use in the later stages. It also suggests against using test doses because of the risk of false reassurance. It states that prescribing, dosing, administration, and safety information differs between formulations, that the individual product information should be consulted before and during use, and that patients with known hypersensitivity should not receive treatment.

Australia

Three sources of guidance or policy on IV iron were identified from Australian sources.

The Australian Red Cross Blood Service endorses the National Blood Authority guidelines.⁴² They state that IV iron is indicated when oral iron cannot be used, when it is not effective or poorly tolerated, or where rapid restoration of iron stores is required. This guidance defers to local health services guidelines and protocols, and the product information for the specific preparations, suggesting not to interchange product-specific protocols.⁴² The National Blood Authority guidance states that preoperative IV iron should be used in surgical patients with suboptimal iron stores in whom substantial blood loss is anticipated. It also recommends IV iron if oral iron is contraindicated or not well-tolerated or effective, and if rapid iron repletion is clinically important (e.g., less than two months to non-deferrable surgery).⁴² It also provides specific practice points for patients with IBD, noting that IV iron may be required in patients intolerant of oral iron or to avoid aggravation of intestinal inflammation.⁴²

The National Blood Authority also issued an accompanying resource on iron product choice.³⁹ It notes that indications for IV iron include contraindications to oral iron, or adherence or tolerance issues; pregnancy (beyond the first trimesters and postpartum) if oral iron is not suitable or effective; comorbidities that may impact absorption (intestinal mucosal disorders) or bone marrow response; chronic renal impairment receiving ESA therapy; ongoing iron losses that exceed absorptive capacity; requirement for rapid iron repletion (e.g., because of physiological decompensation or preoperatively for non-deferrable surgery). It recommends referring to local guidelines and product-specific information about administration, and to avoid interchanging product-specific information.³⁹

The St George and Sutherland Hospitals and Health Services (South Eastern Sydney Local Health District) Clinical Drug Information Business Rule for IDA states that IV iron may be indicated if oral therapy is contradicted, if enteric absorption of iron is defective, if patient non-compliance or persistent gastrointestinal intolerance makes oral therapy impractical in patients with CKD or end-stage kidney disease, or if there is a worsening of IDA or a suboptimal response to ESAs despite oral iron.⁴³ It also recommends not using IV iron in the first trimester of pregnancy; for anemia not caused by iron deficiency; in the case of hypersensitivity, iron overload, decompensated hepatic cirrhosis; and if administration is via an arteriovenous fistula or graft.⁴³

New Zealand

The Best Practice Advocacy Centre New Zealand provides a fact sheet on IV iron (specifically FCM). More information from this resource is summarized in the following section on Clinical Criteria and Reimbursement Restrictions.

A New Zealand review⁴⁹ resource summarizing guidelines for health professionals refers to the ECCO–European Crohn’s and Colitis Organisation guidance for people with IBD. This recommends IV iron as a first-line treatment in patients with clinically active IBD, previous intolerance to oral iron, hemoglobin levels of less than 19 g/dL, and in patients requiring ESA.⁴⁶

France

Two guidance resources on the use of IV iron from sources in France were identified — one providing safety guidance⁵³ and one providing a regulatory framework for IV iron administration in patients undergoing hemodialysis.⁵⁵ Their recommendations pertain to administration, monitoring, and product preference, and are summarized elsewhere in this scan.

Clinical Criteria and Reimbursement Restrictions for Parenteral Iron in Selected Countries With a Universal Pharmacare Program

Limited information was found regarding clinical criteria and reimbursement restrictions for parenteral iron in Australia, New Zealand, and France (Appendix 4). Reimbursement criteria appear to have shifted with the introduction of FCM in Australia and New Zealand; some of the statements summarized are based on FCM. While reimbursement is available for IV iron products, patients must have unsuccessfully completed a trial of oral iron unless they meet other eligibility criteria, or a specialist prescribes treatment. In France, restrictions on outpatient use have been introduced in response to safety concerns.

Australia

SA Health in South Australia published an information sheet about the South Australian Medicines Formulary (state-wide) criteria for IV iron preparations.⁴⁰ It states that FCM has restricted formulary inclusion. Specifically, outpatients are eligible for a Pharmaceutical Benefits Scheme (PBS) supply of FCM, as are in-patients via an individual patient use request process wherein the second dose can be provided when the first dose is given as an outpatient if there is proven intolerance to iron polymaltose.⁴⁰ The PBS is a program that provides lists of subsidized medicines under two formularies designated for single and multi-brand medicines. In 2014, FCM had been available in Australia as a private prescription for more than three years and is the third parenteral iron formulation (and fourth product) to be listed on the PBS for IV correction of IDA.³⁵ In 2013, PBAC — the Pharmaceutical Benefits Advisory Committee — recommended listing FCM on the PBS as an unrestricted benefit.³⁵ It is listed for IDA where oral preparations are not tolerated, ineffective, or otherwise inappropriate with a laboratory test-based diagnosis. According to the SA [South Australia] Health information sheet,⁴⁰ both iron polymaltose standard and rapid formulations are on the formulary as a preferred medicine. Iron sucrose has a restricted formulary inclusion, whereby a proven systemic hypersensitivity to iron polymaltose or FCM is required before use.^{40,41}

New Zealand

In New Zealand, in 2014, it was announced that FCM would be listed in Part II of Section H (the *Hospital Medicines List* of pharmaceuticals that can be used in district health board hospitals) of the national Pharmaceutical *Schedule*, subject to the restriction that treatment with oral iron has been proven ineffective or is clinically inappropriate.⁴⁵

A report from the Best Practice Advocacy Centre New Zealand notes that FCM has been added to the Community Pharmaceutical Schedule and can be prescribed for a range of patients with IDA, subsidized subject to Special Authority approval. Previously, iron polymaltose was the only subsidized parenteral option available to patients in primary care.⁴⁷ FCM is fully subsidized. Special Authority approval criteria for prescribing FCM in the community includes patients with IDA who have trialed and been adherent with oral iron but for whom it was ineffective or where intolerable adverse effects were observed, who require rapid correction of iron deficiency, and for patients with a condition where evidence favours the use of IV iron (including symptomatic heart failure, CKD Stage 3 or higher, and active IBD). It can be prescribed either when initiated by a general practitioner if the patient's serum ferritin is less than or equal to 20 mcg/L or with the recommendation of a relevant specialist (an internal medicine physician, obstetrician, gynecologist, or anesthetist).

The Canterbury District Health Board *Obstetric Intravenous Iron Infusion Prescription (Antenatal & Postnatal)* for pregnancy includes criteria for using FCM.⁵¹ Antenatally, the patient needs have confirmed IDA and one or more criteria — including fetal compromise, failure of a trial of oral iron therapy because of side effects, high iron requirements, or persistent anemia after six to eight weeks — and greater than or equal to 36 weeks' gestation.⁵¹ Postnatally, IV iron is indicated following postpartum hemorrhage if the patient is hemodynamically stable.⁵¹

Pinnacle Midlands Health Network provides an [Advanced Primary Options Information Manual](#), with guidance for general practice to access a range of funded community treatments for patients enrolled in the region.⁴⁴ There are different criteria depending on the region (i.e., Tairāwhiti and Lakes, Taranaki, Waikato). In Tairāwhiti and Lakes, IV iron is funded for those who meet the PHARMAC–Pharmaceutical Management Agency Special Authority approval

criteria for prescribing subsidized FCM in the community described earlier.⁴⁸ In Taranaki and Waikato, program funding is provided for patients when treatment has been prescribed by a specialist.⁴⁸ Only FCM prescribed by a health board specialist is funded under the service.⁴⁸ In 2017, the PHARMAC guidance was revised to state that eligible people could receive FCM in some general practitioners' clinics or other community-based settings. Patients still need to meet Special Authority criteria. FCM is listed in Section B (Community Pharmaceuticals) of the Pharmaceutical Schedule (pharmaceuticals subsidized when prescribed in the community setting).

The *POAC Criteria for Funded Ferric Carboxymaltose Infusion*⁵² states that a recommendation from a specialist is required for POAC (or Primary Options for Acute Care) funding. It must be on the grounds that the patient has been adherent with oral iron treatment but that it is ineffective; or that treatment with oral iron has resulted in dose-limited intolerance; or the patient has symptomatic heart failure, CKD Stage 3 or more, or active IBD and oral iron is unlikely to be effective; or if rapid correction of anemia is required. POAC will fund IV FCM if recommended by a specialist, even where the criteria are not yet met. Patients may also pay out of pocket or the specialist may provide a hospital prescription.⁵²

France

The Committee for Medicinal Products for Human Use states that, in France since 2014, iron products have been considered in hospital reserve and are no longer available on an outpatient basis; they can only be prescribed, dispensed, and administered within health care facilities.⁵⁶

Preferred Parenteral Iron Preparation(s) in Selected Countries With a Universal Pharmacare Program

Limited information was identified on preferred IV iron preparations in the countries of interest (Appendix 3). The introduction of FCM in these jurisdictions have shifted preference toward this product. However, for certain conditions and in certain regions or facilities, preferences for other preparations or alternative strategies are stated. Many of the identified resources indicate that convenience of administration, as well as the ability to administer a larger dose in less time, and the product safety profile may impact preferences.

UK

According to several sources,^{4,27,33,34} four IV iron preparations are available in the UK: iron sucrose, low-molecular-weight iron dextran, FCM, and iron isomaltoside. There is some guidance and environmental data on preferred formulations in the UK context.

A study on the experience of running rapid access anemia clinics in the UK⁴ reports that the careful selection of the preparation is required because of its impact on the design of the IV iron protocol. The authors note that cost is a differentiating factor and that the products are not clinically equivalent because of differences in their administration regimen, contraindications, and the related effect on patient experience and viability, and risk management of the service.⁴ Their practice was to conduct regular reviews of the recommendations with the availability of new data and products, and as patients' needs changed. Initially the clinic used iron sucrose due to experience with the product and availability, but because of the upper limit on the dose that can be administered in a single sitting and the test dose required, the clinics switched to low-molecular-weight iron dextran, which allows for a higher dose infusion. However, as this still required a test dose and close

patient monitoring, and a long duration of dose infusion, it restricted the number of patients who could be seen. Around this time, FCM and iron isomaltoside were introduced in the UK and the clinics switched to FCM.⁴ The product enables a rapid high-dose infusion of iron, enabling more patients to be treated, and improves the convenience of the procedure. Iron isomaltoside was considered less attractive by these authors, as there are a greater number of patient groups with contraindications.⁴ FCM was thus used as first-line therapy, but the clinics emphasized the importance of maintaining a selection of products on the hospital formulary in case of circumstances where a different preparation is more appropriate.⁴

Chronic Kidney Disease

NICE guidance for patients with CKD⁵⁷ recommends that high-dose, low-frequency IV iron should be considered as the treatment of choice; however, it does not specify an IV iron preparation. A high-dose, low-frequency treatment is administered in less than two infusions (i.e., a minimum of 500 mg per infusion) whereas a low dose, high frequency, is administered in more than two infusions (i.e., typically 100 mg to 200 mg per infusion). It also recommends that a low-dose, high-frequency treatment may be more appropriate in patients receiving in-centre hemodialysis.³¹ NICE encourages providers to consider the preferences of the person with anemia of CKD, as well as the nursing and administration costs, the cost of the local drug supply, and the provision of resuscitation facilities. The Royal College of Nursing UK guideline states that iron isomaltoside is indicated in adults for the treatment of iron deficiency in patients on dialysis with CKD.²⁷

Inflammatory Bowel Disease

Antrim Area Hospital in the UK reports it adopted the 2015 ECCO–European Crohn’s and Colitis Organisation guidelines for IBD⁴⁶ and that it has used iron isomaltoside since October 2016, as it allows for the delivery of high doses in a single administration.³²

New Zealand

In New Zealand, three preparations (as of 2016) of IV iron were available: FCM, iron polymaltose, and iron sucrose. In New Zealand, FCM has been on the *Hospital Medicines List* for use in district health board hospitals since 2014.⁴⁹

A review article summarizing guidelines and recommendations notes that the choice of formulation should consider the convenience of administration.⁴⁹ It reports that iron sucrose requires multiple patient visits because of the maximum dose and repeated IV access, and that, similarly, iron polymaltose has a dose limit. On the other hand, FCM is suggested to offer advantages, as it can be rapidly infused using doses of up to 1,000 mg of iron in a single 15-minute infusion without a test dose — which may be an attractive option for use in the outpatient or community setting. It notes “FCM is thus the preferred IV agent for iron replacement in the outpatient setting.” Similarly, a guidance note by the Best Practice Advocacy Centre New Zealand⁴⁷ states that “ferric carboxymaltose is likely to be the preferred option for most patients requiring parenteral iron supplementation, as it can provide a higher dose of iron administered in a shorter timeframe.”

Australia

There are three preparations of IV iron available in Australia: FCM, iron polymaltose, and iron sucrose.^{36,42,43}

In Australia, FCM is may be preferred over the other available preparations. Specifically, the PBAC – the Pharmaceutical Benefits Advisory Committee – noted that FCM would have an advantage over iron polymaltose in terms of administration time and would address a clinical need in Australia.³⁵

The National Blood Authority issued a resource outlining iron product choice.³⁹ It states that iron polymaltose may have a higher incidence of severe systemic reactions than iron sucrose and FCM, and that hypophosphatemia has been reported with all three preparations.³⁹ The resource suggests that the risk of hypophosphatemia may be higher with FCM but doesn't outright recommend one product over the other. A Health Victoria resource on iron infusion notes that practice varies across the region, with some hospitals using FCM exclusively,³⁶ and also observing that a total dose infusion can only be administered with iron polymaltose. According to an infusion procedure from the Sunshine Coast Hospital and Health Service,³⁸ the preferred option for administering IV iron is iron polymaltose using a standard slow dose and, when rapid infusion is required, using a total rapid dose. For day admission patients excluding renal patients, FCM is preferred; and for renal day admission, iron polymaltose, or FCM.³⁸ St George/Sutherland Hospitals and Health Services Clinical Drug Information Business Rule⁴³ states that the duration of administration, and the previous administration of IV iron products, must be considered when prescribing, and that formulations of IV iron with rapid infusion capabilities are favourable. Iron is available as FCM and iron polymaltose in these facilities. The business rule recommends that respective safety profiles of the two drugs should be considered.

France

In France, several iron-based preparations are available for IV injection, including FCM, iron dextran, iron sucrose, and iron sucrose similars.⁵⁶ A manufacturer-funded survey of French and Spanish pharmacists showed that the majority of decisions about the choice of IV iron preparation were driven by the hospital formulary or guidelines and protocols that direct drug dispensing.⁵⁴ In the remaining cases, the physician or pharmacists made the decision.⁵⁴

One observational study in France reported that the typical IV iron products available include iron sucrose and FCM.²¹ It noted that indications for FCM included intestinal bleeding, malabsorption, pernicious anemia, pancreatitis, occlusive syndrome, and intolerance and refractory to oral iron.²¹ The choice of FCM versus iron sucrose depended on the length of stay (less than three days for FCM and three days or more for iron sucrose). The study observed that FCM reduces waiting times and waiting list pressure, and hospital costs. It concluded that the choice of IV iron must consider the patient's length of hospital stay, and their clinical and biological condition.²¹ The regulatory framework on iron administration for patients undergoing hemodialysis from the Association des Insuffisants Rénaux de Beauce et Perche (AIRBP) notes that the preferred preparation for these patients is iron sucrose.⁵⁵

Administration and Monitoring of Parenteral Iron in Selected Countries With a Universal Pharmacare Program

Administration

Dosing

Most of the resources identified recommended referring to the individual product information for dosing and administration guidance, and to not interchange guidance between different preparations.

Safety Measures

Groups in the UK,^{24,27,57} Australia,^{37,42} New Zealand,^{47,50} and France^{53,55} all recommend that IV iron should be administered where resuscitation facilities are available and where appropriately trained staff are present and able to provide emergency care and monitoring for hypersensitivity reactions and extravasation. A clinical procedure document from the Northern NSW (New South Wales)³⁷ Local Health District in Australia recommends that patients receiving IV iron and their carers be provided with education including indication for use, intended effect, risks and benefits, and potential side effects prior to commencement of the infusion. Most sources note that a test dose is no longer required, as it may not accurately reflect the risk of adverse effects.

Monitoring

Monitoring During the Procedure

Most resources recommend monitoring the patient for approximately the first 30 minutes after infusion with IV iron.^{27,53,55} A clinical procedure document from Northern NSW Local Health District in Australia³⁷ states that the frequency of monitoring requirements during and immediately after the procedure differs by IV iron product. In its guidance for using IV iron (i.e., FCM) in pregnant women, the Canterbury District Health Board recommends recording in the Modified Early Obstetric Warning Score chart during the infusion.⁵¹

Post-Treatment Monitoring

The amount of post-treatment monitoring required may vary by condition.

The Greater Glasgow and Clyde Area Drug and Therapeutics Committee²⁴ recommends follow-up blood testing in patients with IDA receiving IV iron one month after treatment. A guidance note by the Best Practice Advocacy Centre⁴⁷ New Zealand recommends checking hemoglobin levels monthly until they have normalized, with blood samples taken at least one a week after receiving IV iron. Once stabilized, testing can be reduced to once every three months but may vary depending on individual patient requirements.

NICE guidelines for treating iron deficiency in patients with CKD⁵⁷ recommend that people with anemia of CKD should not have iron levels checked earlier than one week after receiving IV iron. This guidance⁵⁷ states that the length of time to the monitoring of iron status is dependent on the product used and the amount of iron given. The guideline recommends monitoring the iron status every one to three months in people receiving hemodialysis, and every three months in people who are pre-dialysis or receiving peritoneal dialysis, but not if they have a normal full blood count. The Renal Association in the UK³¹ also recommends regular monitoring of iron status (every one to three months) in patients with CKD receiving IV iron to monitor for iron overload.

Limitations

This Environmental Scan was based on a review of the publicly available literature on the topic. The search may have failed to identify some relevant resources and information, and as a result it may not capture some of the existing guidance or policies on IV iron. As English is not the official language of several of the countries of interest (France and Germany), it is possible that the search and review of information from these countries was less comprehensive. The literature identified was not subject to critical appraisal, so insights on the quality of the any policies listed is out of the scope of this report.

Where available, we summarized information about clinical criteria, reimbursement restrictions, preferred preparations, and administration and monitoring. However, as this report did not include direct stakeholder perspectives, it is unclear whether these sources reflect current clinical policy or practice.

The availability of different parenteral iron formulations varies across jurisdictions. As such, policies and practices in these regions may not be generalizable to the Canadian setting. This applies to the case of FCM, which is available in all the countries addressed in this report, but not in Canada.

Conclusions and Implications for Decision- or Policy-Making

IV iron is an important treatment option for anemia but is not the only treatment option. Other treatment options include oral formulations, which are substantially less costly than IV iron preparations. The utilization of IV iron has increased with the emergence of safer and more effective preparations, and evidence, supporting its superior effectiveness at correcting anemia in various conditions.

This Environmental Scan identified a variety of guidance, policy, and practice resources related to the use of IV iron in the countries of interest with a universal pharmacare program. Generally, IV iron is recommended for use when a trial of oral iron has failed, unless there is an indication for immediate use. Reimbursement for IV iron typically requires that patients meet specific clinical criteria, or that they obtain a prescription from a specialist, but the jurisdictions captured in this report provide public coverage in most cases if patients meet these criteria. Some criteria included restrictions or preferences for certain preparations of IV iron, largely based on the preparations approved for use. Preferences have shifted with the introduction of FCM. FCM is noted to be the preferred preparation in many cases, but not exclusively, and many sources emphasize that individual patient needs and convenience should influence the choice of preparation. Finally, there was consistent guidance that IV iron be administered with appropriate monitoring and with access to emergency services.

Canadian clinical practice guidelines share some similarities with the guidance and policies summarized from countries with a universal pharmacare program. For instance, the 2018 Alberta Toward Optimized Practice clinical practice guideline for IDA⁶⁰ and the guidelines from the Guidelines and Protocol Advisory Committee (British Columbia Ministry of Health, Doctors of BC)¹⁹ recommend that IV iron should only be used when oral iron fails or is not tolerated, or if the patient meets specific clinical criteria. Likewise, the Ontario Drug Benefit Formulary documentation on frequently requested drugs that are part of the Exceptional Access Program includes reimbursement criteria for two iron products.⁶¹ Iron dextran and

iron sucrose can be accessed for the treatment of IDA (confirmed by bloodwork) where the patient has demonstrated intolerance to oral iron therapy or has not responded to adequate therapy with oral iron.⁶¹ A search of online formularies for Canadian provinces and territories indicates that reimbursement for individual IV iron preparations may vary by jurisdiction (i.e., it is likely that not all products approved in Canada are available in all Canadian jurisdictions). For example, in British Columbia,⁶² iron sucrose is listed on the BC Pharmacare Formulary; in Alberta,⁶³ iron dextran is listed by Alberta Health; and in Ontario, the IV iron products listed on the Ontario Drug Benefit Formulary are only available as part of the Exceptional Access Program.⁶⁴ This may not reflect the availability in the hospital setting. Similar to the safety recommendations in other jurisdictions, Canadian expert consensus supports the presence of health care professionals who can manage hypersensitivity reactions and ensure patient safety.⁶⁵ One policy document from the BC Women's Hospital & Health Centre from 2017 indicates that all physicians should order IV iron sucrose for patients requiring IV iron replacement therapy.⁶⁶ This differs from other jurisdictions in this report, where FCM was the most commonly preferred preparation for IDA when IV iron is indicated. The main difference between Canada and the other jurisdictions is that the available IV iron formulations differ. In Canada, iron sucrose, iron isomaltoside, ferric gluconate, and iron dextran are available, but other preparations such as FCM are not yet approved and marketed. Of the guidance and policies that this Environmental Scan identified, two of these formulations — iron sucrose and iron isomaltoside — were mentioned. Some guidance recommends their use if preferred formulations (e.g., FCM and iron polymaltose) are contraindicated or unavailable, or if patients have longer in-patient stays and are less likely to be inconvenienced by multiple infusions. The present variation in practices for IV iron are consistent with older data reporting that the choice of IV iron preparation and product dosing schedule varied substantially across 12 countries between 1999 and 2011.⁶⁷

Overall, the resources identified suggest that other jurisdictions are providing access to, and funding for, IV iron, while encouraging that oral iron be used first-line, when appropriate. Established clinical criteria and individual patient context should inform the decision to reimburse and administer IV iron, and to select the appropriate product.

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Appendix 1: Status of Parenteral Iron Preparations in Canada^{21,65,68}

Generic Name	Trade Name	Manufacturer	Regulatory Status in Canada	Indication ^a	Product Information ^a	Availability in Countries With Universal Pharmacare Programs
Iron isomaltoside	MONOFERRIC	Pfizer Canada Inc.	Marketed/ 2018	Treatment of iron deficiency anemia in adult patients who have intolerance or are unresponsiveness to oral iron therapy	100 mg elemental iron/mL for IV use	UK
Iron sucrose	Venofer	American Regent, Inc.	Marketed/ 2001	Treatment of IDA in: <ul style="list-style-type: none"> • non-dialysis-dependent CKD patients receiving an erythropoietin • non-dialysis-dependent CKD patients not receiving an erythropoietin • hemodialysis-dependent CKD patients receiving an erythropoietin • peritoneal dialysis-dependent CKD patients receiving an erythropoietin 	20 mg elemental iron/mL, 5 mL single-dose vials, for IV use	UK, New Zealand, Australia, France
Sodium ferric gluconate	FERRLECIT	Sanofi Canada	Marketed/ 2005	Treatment of IDA in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy	12.5 mg elemental iron/mL for IV use	—
Ferumoxytol	Feraheme	Amag Pharmaceuticals, Inc.	Cancelled post-market	Treatment of IDA in adults with CKD	30 mg elemental iron/mL (510 mg/ 17mL) for IV use	—

Generic Name	Trade Name	Manufacturer	Regulatory Status in Canada	Indication ^a	Product Information ^a	Availability in Countries With Universal Pharmacare Programs
Iron dextran	Dexiron	American Regent, Inc.	Marketed/ 1996 ^b	Treatment of patients with documented iron deficiency in whom oral iron administration is unsatisfactory or impossible	50 mg elemental iron/mL, 2 mL single-dose vials, for IV use	UK, France
	INFUFER	Sandoz Canada	Cancelled post-market	Treatment of patients with documented iron deficiency in whom oral administration is unsatisfactory or impossible	50 mg elemental iron/mL for IV or IM use	
Ferric carboxymaltose	Ferinject, Injectafer	American Regent, Inc.	No status (unavailable) ^c	Treatment of IDA in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron, and in adult patients with non-dialysis-dependent CKD	750 mg elemental iron/ 15 mL single-dose vial for IV use	UK, New Zealand, Australia, France
Iron polymaltose complex	Ferrosig/ FERRUM H ^d	Sigma Pharmaceuticals, LLC	No status (unavailable)	NR	50 mg elemental iron/mL 2mL injection for IV use	New Zealand, Australia

CKD = chronic kidney disease; IDA = iron deficiency anemia; IM = intramuscular; IV = intravenous; NR = not reported.

^a May vary by jurisdiction.

^b To be discontinued.

^c Available in Australia, Europe, New Zealand, and the US.

^d In Australia.

Appendix 2: Countries of Interest With a Universal Pharmacare Program

Australia ⁶⁹	The Pharmaceutical Benefits Advisory Committee (PBAC)
France ⁷⁰	Ministry of Health: National Health Insurance–Union Nationale des Caisses d’Assurance Maladie (UNCAM)
Germany ⁷¹	Federal Joint Committee (G-BA)
New Zealand ⁷²	Pharmaceutical Management Agency (PHARMAC)
UK ⁷³	National Health Service (NHS)

Appendix 3: Guidance and Preferences for Parenteral Iron Use and Formulations in Selected Countries With a Universal Pharmacare Program

Organization	Guidance for Use of IV Iron	Preparations of Iron Available ^a	Preferred Iron Preparation	Considerations Informing Choice
Iron Deficiency Anemia				
UK				
Greater Glasgow & Clyde Area Drug and Therapeutics Committee (NHS) ²⁴	IV iron should be used as last resort treatment and only in cases stated in the guidance	Iron isomaltoside, FCM	NR	NR
Royal College of Nursing ²⁷	<p>IV iron suggested as first-line treatment:</p> <ul style="list-style-type: none"> • if surgery planned less than 6 weeks after IDA diagnosed • for pregnancy, with severe IDA or where diagnosis occurs after 34 weeks' gestation • for women with severe postpartum anemia <p>Also recommended for:</p> <ul style="list-style-type: none"> • patients unable to tolerate or who have poor adherence to oral iron, excluding patients with known hypersensitivity to IV iron • anemia not caused by iron deficiency • iron overload • people in the first trimester of pregnancy 	NR	NR	NR
Northern Ireland Transfusion Committee (Guidelines & Audit Implementation Network) ²⁸	<p>Recommends switching from oral to IV iron if:</p> <ul style="list-style-type: none"> • there is no improvement in Hb status after 3 months of treatment • there is a history of malabsorption or chronic IBD • major surgery must proceed in < 3 weeks' time • the patient has functional iron deficiency (e.g., CKD on hemodialysis) 	NR	NR	NR
Rapid Access Anemia Clinic ⁴	NR	FCM, iron isomaltoside, iron dextran, iron sucrose	FCM	NR

Organization	Guidance for Use of IV Iron	Preparations of Iron Available ^a	Preferred Iron Preparation	Considerations Informing Choice
Australia				
Australian Red Cross Blood Service / National Blood Authority Guidelines ⁴²	<p>IV iron is indicated:</p> <ul style="list-style-type: none"> when oral iron cannot be used, when it is not effective or poorly tolerated, or where rapid restoration of iron stores is required when rapid repletion is clinically important (e.g., < 2 months to non-deferrable surgery) preoperatively, in surgical patients with suboptimal iron stores in whom substantial blood loss is anticipated in pregnancy beyond the first trimesters and postpartum if oral iron is not suitable or effective in patients with ongoing iron losses that exceed absorptive capacity <p>Administration should be based on local health services guidelines and protocols, and the product information for specific preparations, which should not be interchanged</p>	NR	NR	NR
St George/Sutherland Hospitals and Health Services (New South Wales Government South Eastern Sydney Local Health District) Clinical Drug Information Business Rule ⁴³	<p>IV iron may be indicated, if:</p> <ul style="list-style-type: none"> oral therapy is contraindicated enteric absorption of iron is defective there is patient non-compliance, or persistent gastrointestinal intolerance makes oral therapy impractical there is a worsening of IDA or suboptimal response to ESAs, despite oral iron <p>IV iron should not be used:</p> <ul style="list-style-type: none"> in the first trimester of pregnancy for anemia not caused by iron deficiency in the case of hypersensitivity in patients with iron overload, in patients with decompensated hepatic cirrhosis if administration is via an arteriovenous fistula or graft 	FCM, iron polymaltose	Preparations with rapid infusion capabilities are preferred	Duration of administration, safety profiles, previous preparations administered

Organization	Guidance for Use of IV Iron	Preparations of Iron Available ^a	Preferred Iron Preparation	Considerations Informing Choice
Pharmaceutical Benefits Advisory Committee (PBAC) ⁶⁹	NR	NR	FCM	Administration time, ability to address clinical need
Health Victoria ³⁶	NR	NR	NR	Some hospitals exclusively offer FCM; a total dose infusion is only possible with iron polymaltose
Sunshine Coast Hospital and Health Service ³⁸	NR	NR	In-patients: Iron polymaltose (standard slow dose or total rapid dose) Day patients: FCM	NR
New Zealand				
Best Practice Advocacy Centre New Zealand ⁴⁷	NR	NR	FCM	Convenience of administration
France				
Delpeuch et al. ²¹	NR	Iron sucrose, FCM	FCM if < 3 days' hospital stay, and iron sucrose if ≥ 3 days' hospital stay	Length of hospital stay, patient's clinical and biological condition
Blood Transfusions				
UK				
National Institute for Health and Care Excellence ²⁹	Consider IV iron before or after surgery in patients with IDA who cannot tolerate or absorb iron, are unable to comply with oral therapy, are diagnosed with functional iron deficiency, or in cases where the time between the diagnosis of anemia and surgery is predicted to be insufficient for oral iron to be effective	NR	NR	NR

Organization	Guidance for Use of IV Iron	Preparations of Iron Available ^a	Preferred Iron Preparation	Considerations Informing Choice
Chronic Kidney Disease				
UK				
National Institute for Health and Care Excellence ⁵⁷	<p>Patients not receiving hemodialysis:</p> <ul style="list-style-type: none"> • should receive a trial of oral iron before IV therapy is offered; IV therapy should be offered if patient is intolerant to oral iron, or Hb levels are not reached within 3 months <p>Patients receiving hemodialysis:</p> <ul style="list-style-type: none"> • should receive IV iron therapy unless it is contraindicated, or the person chooses not to receive treatment 	NR	“High-dose, low-frequency” IV iron administered in less than 2 infusions (no preparation specified), except in patients receiving in-centre hemodialysis in whom low-dose, high-frequency IV iron is considered appropriate	Patient preferences, nursing and administration costs, cost of local drug supply, provision of resuscitation facilities
Renal Association ³¹	<p>Same recommendations as NICE, 2015</p> <p>In addition, avoid parenteral iron in patients with active infection</p>	NR	NR	NR
Northern Ireland Transfusion Committee ²⁸	IV iron recommended for patients with CKD if no improvement in Hb, if intolerant to oral iron, or if patient is receiving regular hemodialysis	NR	NR	NR
Royal College of Nursing ²⁷	N/A (see statements for IDA)	NR	Iron isomaltoside	NR
Australia				
Australian Red Cross Blood Service / National Blood Authority Guidelines ⁴²	IV iron is indicated in patients with chronic renal impairment receiving ESA therapy	NR	None stated	Iron polymaltose may have a higher incidence of severe systemic reactions than iron sucrose and FCM; hypophosphatemia was reported with all three preparations but may be higher with FCM

Organization	Guidance for Use of IV Iron	Preparations of Iron Available ^a	Preferred Iron Preparation	Considerations Informing Choice
St George/Sutherland Hospitals and Health Services (New South Wales Government South Eastern Sydney Local Health District) Clinical Drug Information Business Rule ⁴³	IV iron is indicated in patients with CKD or end-stage kidney disease	NR	NR	Duration of administration
Sunshine Coast Hospital and Health Service ³⁸	NR	NR	Renal day admission patients: FCM or iron polymaltose	NR
France				
Association des Insuffisants Rénaux de La Région Beauce et Perche (AIRBP) ⁵⁵	NR	NR	Iron sucrose preferred for patients undergoing hemodialysis	NR
Gastrointestinal Conditions				
UK				
Norfolk and Norwich University Hospitals NHS Foundation Trust ³⁰	In patients with IDA or “gastro-related” disorders	NR	NR	NR
Antrim Area Hospital ³²	NR	NR	Iron isomaltoside for patients with IBD	NR
Australia				
Australian Red Cross Blood Service / National Blood Authority Guidelines ⁴²	<ul style="list-style-type: none"> IV iron may be required in patients who are intolerant of oral iron or to avoid aggravation of intestinal inflammation IV iron is indicated in patients with comorbidities that may impact absorption (e.g., intestinal mucosal disorders) 	NR	NR	NR

Organization	Guidance for Use of IV Iron	Preparations of Iron Available ^a	Preferred Iron Preparation	Considerations Informing Choice
St George/Sutherland Hospitals and Health Services (New South Wales Government South Eastern Sydney Local Health District) Clinical Drug Information Business Rule ⁴³	IV iron is indicated in patients with persistent gastrointestinal intolerance if it makes oral therapy impractical	NR	NR	NR
New Zealand				
New Zealand review summarizing the European Crohn's and Colitis Organisation (ECCO) guidance ⁴⁹	Use IV iron in patients with IBD, when: <ul style="list-style-type: none"> • IBD is clinically active • the patient has previous intolerance to oral iron • Hb levels < 19 g/dL • in patients requiring ESA, IV iron is recommended as first-line treatment 	NR	FCM	Convenience of administration
Safety Guidance				
UK				
European Medicines Agency ^{16,58} Endorsed by the UK ⁵⁹	<ul style="list-style-type: none"> • IV iron should only be administered in environments where patients can receive adequate monitoring (including close monitoring for 30 minutes after administration) and where resuscitation facilities are available • Treatment should be stopped if a hypersensitivity reaction occurs • IV iron should not be used in the first trimester of pregnancy and risks should be weighed carefully when considering use in later stages • Test doses should not be used due to the risk of false reassurance • Prescribing, dosing, administration, and safety information differs between formulations, and individual product information should be consulted before and during use • Patients with known hypersensitivity should not receive treatment 	NR	NR	NR

CKD = chronic kidney disease; ESA = erythropoiesis-stimulating agent; FCM = ferric carboxymaltose; Hb = hemoglobin; IBD = inflammatory bowel disease; IDA = iron deficiency anemia; IV = intravenous; NHS = National Health Service; NR = not reported.

^aSee Appendix 2 for country-specific information.

Appendix 4: Clinical Criteria and Reimbursement Restrictions for Parenteral Iron in Selected Countries With a Universal Pharmacare Program

Organization	Clinical Criteria or Reimbursement Restrictions
Australia^a	
SA [South Australia] Health ⁴⁰	<ul style="list-style-type: none"> Iron polymaltose (rapid and standard formulations) are listed as preferred medicine on state formulary. Outpatients with IDA are eligible for PBS supply of FCM as are in-patients via an Individual Patient Use request process; the second dose can be provided when the first dose is given as an outpatient and if there is proven intolerance to iron polymaltose. Iron sucrose has restricted formulary inclusion; proven hypersensitivity to iron polymaltose or FCM is required before use.
Pharmaceutical Benefits Advisory Committee (PBAC) ⁶⁹	In 2013, PBAC recommended listing FCM on the national PBS as an unrestricted benefit, where oral preparations are not tolerated, ineffective, or otherwise inappropriate with a laboratory-based diagnosis.
New Zealand	
Pharmaceutical Management Agency (PHARMAC) ⁷²	FCM is listed in Part II of Section H (Hospital Medicines List) of the national Pharmaceutical Schedule, subject to the restriction that treatment with oral iron has been proven ineffective or is clinically inappropriate. It is also listed in Section B (Community Pharmaceuticals).
Best Practice Advocacy Centre New Zealand ⁴⁷	<ul style="list-style-type: none"> FCM has been added to the Community Pharmaceutical Schedule (PHARMAC). It can be prescribed for a range of patients with IDA and fully subsidized subject to Special Authority approval. Special Authority approval applies to patients with IDA who have trialed and been adherent with oral iron but for whom it was ineffective or where intolerable adverse effects were observed, who require rapid correction of iron deficiency, and for patients with a condition where evidence favours the use of IV iron (including symptomatic heart failure, CKD stage 3 or higher, and active IBD). Prior to this, iron polymaltose was the only subsidized parenteral option available in primary care.
Canterbury District Health Board Obstetric Intravenous Iron Infusion Prescription (for pregnancy) ⁵¹	<p>For access to FCM:</p> <ul style="list-style-type: none"> Antenatally, patients need to have confirmed IDA and one or more criteria including fetal compromise, failure of a trial of oral iron therapy due to side effects, high iron requirements, or persistent anemia after 6 to 8 weeks, greater than or equal to 36 weeks' gestation. Postnatally, IV iron is indicated following postpartum hemorrhage if the patient is hemodynamically stable.
Pinnacle Midlands Health Network ⁴⁴	<ul style="list-style-type: none"> IV iron is funded for patients who meet the PHARMAC Special Authority approval criteria for prescribing subsidized FCM in the community in Tairāwhiti and Lakes. Program funding is provided for patients when treatment has been prescribed by a specialist in Taranaki and Waikato.
Primary Options for Acute Care ⁵²	To receive POAC funding for an FCM infusion, a recommendation from a specialist is required. It must be based on certain criteria reflective of Special Authority approval criteria, although POAC will fund FCM if recommended by a specialist regardless if criteria are met. If funding is not available by this route, patients may pay out of pocket or a specialist might provide a hospital prescription.
France	
Committee for Medicinal Products for Human Use ⁵⁶	Since 2014, iron products have been considered in hospital reserve and are no longer available on an outpatient basis. They can only be prescribed, dispensed, and administered within health care facilities.

FCM = ferric carboxymaltose; IBD = inflammatory bowel disease; IDA = iron deficiency anemia; IV = intravenous; PBS = Pharmaceutical Benefits Scheme; PHARMAC = Pharmaceutical Management Agency; POAC = Primary Options for Acute Care.

^aFCM has been available in Australia as a private prescription for more than three years and is the third parenteral iron formulation (and fourth product) to be listed on the Pharmaceutical Benefits Scheme.