INTRAVENOUS IRON INFUSION: IRON POLYMALTOSE (FERROSIG®) AND FERRIC CARBOXYMALTOSE (FERINJECT®)

PRACTICE GUIDELINE

DOCUMENT SUMMARY/KEY POINTS

- This practise guideline provides guidance for the administration of intravenous iron to paediatric patients. It is intended for children with proven iron deficiency anaemia and for teams regularly administering intravenous iron (Haematology, Gastroenterology, Nephrology and General Paediatrics - after discussion with the respective consultant). For nephrology patients with chronic kidney disease stage 3-5 including those on peritoneal dialysis, there are alternative target and monitoring regimes – please see Appendix 1. **All other teams should consult with the Haematologist on call in regards to indication and dosing of intravenous iron.**
- Intravenous iron is not without risk and should primarily be used for children with proven severe iron deficiency anaemia unable to take or absorb oral iron. Whenever possible, oral iron should be used to treat iron depletion, iron deficiency or iron deficiency anaemia in children. Additional parental/guardian consent for treatment with intravenous iron is required prior to infusion.
- Iron deficiency anaemia is defined by microcytic hypochromic anaemia with a low ferritin (or low iron stores in the bone marrow). Intravenous iron is not indicated if anaemia is not due to iron deficiency, and is generally not appropriate for patients with iron depletion or iron deficiency without significant anaemia. If there is any uncertainty regarding diagnosis, consult with the Haematologist on-call.
- There are two intravenous iron formulations available at SCHN: iron polymaltose (Ferrosig®) and ferric carboxymaltose (Ferinject®). They differ in formulation, administration, side effects, price and age limits. **Please read carefully to choose the correct product for your patient**.
- Iron polymaltose (Ferrosig®) is the only parenteral iron formulation suitable for total iron replacement in one single infusion. Ferric carboxymaltose (Ferinject®) is not suitable for

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total iron replacement in one single infusion if the patient requires a high dose. If total iron replacement in one single dose is required, please use iron polymaltose (Ferrosig®).

- Due to the risk of anaphylaxis it is recommended to consider premedication. Facilities for resuscitation must be available. It is recommended that adrenaline, promethazine and hydrocortisone are prescribed on the PRN chart and are available on the ward prior to starting infusion.
- The intravenous iron dose is prescribed as elemental iron. The dose for each patient needs to be calculated individually and depends on the actual haemoglobin, target haemoglobin for age and body weight. For iron polymaltose (Ferrosig®) there is no maximum dose per infusion. For ferric carboxymaltose (Ferinject®) do not exceed maximum allowable dose per infusion; this is up to 20mg/kg (maximum 1000mg) per infusion per week.
- Ferric carboxymaltose (Ferinject®) is formally approved for treatment of severe iron deficiency anaemia in children 14 years and older. The SCHN drug committee has approved the use of ferric carboxymaltose (Ferinject®) from the age of 9 months.
- Ferric carboxymaltose (Ferinject®) is not approved for use in patients less than 9 months of age.

CHANGE SUMMARY

- N/A – new Network document.
- SCH Iron Infusions: Pre-Dialysis, Peritoneal Dialysis and Haemodialysis Patients guideline has been incorporated into this guideline and therefore it has been rescinded.

READ ACKNOWLEDGEMENT

- All nursing, medical and pharmacy staff involved in administration, prescribing and dispensing of iron polymaltose (Ferrosig®) or ferric carboxymaltose (Ferinject®) must read and acknowledge (sign-off) that they understand the contents of this document.

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Introduction

Iron deficiency anaemia is common. The vast majority of patients can and should be treated with oral iron replacement, which is equally effective, safer and cheaper than the intravenous preparation. Intravenous iron can be considered in patients with severe iron deficiency anaemia where there is non-adherence, intolerance, non-absorption or inadequate response to oral iron preparations. Whenever possible, oral iron should be given preference in treating iron depletion, iron deficiency or iron deficiency anaemia in children. Intravenous iron infusions are not appropriate for patients without significant anaemia (i.e. not indicated for low ferritin alone – see definition below).

Several parenteral iron products are available in Australia. Iron polymaltose (Ferrosig®) is suitable for total iron replacement in one single infusion. However, due to the risk of infusion related adverse reactions, iron polymaltose must be given as a slow infusion over several hours.[1,3,4]

Ferric carboxymaltose (Ferinject®)[2,3], a non-dextran intravenous iron preparation may be used to deliver doses up to 20 mg/kg (max 1000 mg) per infusion per week over a shorter time, reducing infusion time and monitoring requirements. Iron carboxymaltose (Ferinject) is not suitable for total iron replacement in a single infusion if the required dose exceeds the maximum allowed dose or if patient unable/unwilling to return for subsequent doses. In those cases, use iron polymaltose (Ferrosig®) instead.

Definitions

- Iron depletion/low iron stores: low ferritin with normal MCV and haemoglobin
- Iron deficiency: low ferritin and MCV/MCH, but normal haemoglobin
- **Iron deficiency anaemia: low ferritin, low MCV/MCH and low haemoglobin**

  Note: Ferritin is the most useful marker for assessment of iron status. Serum iron is not suitable to assess iron deficiency.
- Normal ranges for ferritin:
  - Prepubertal children: greater than10 microg/L
  - Menstruating females: greater than 15 microg/L
  - Pubertal males: greater than 20 microg/L.

  Note: ferritin is an acute phase reactant and may be falsely elevated in the context of acute infectious and inflammatory conditions. If possible, assess iron status 2-3 weeks after acute illness has resolved.

Contraindications[1-4]

Ferrosig®	Ferinject®
Iron polymaltose (Ferrosig®) should not be given to patients with any of the following conditions: • Hypersensitivity to iron polymaltose complex or known hypersensitivity to other intravenous iron products • Patients with a history of severe allergy or previous anaphylaxis • Anaemia not attributed to iron deficiency • Evidence of iron overload or disturbances in utilisation of iron • Acute infections or illnesses, including fever • Chronic polyarthritis • Bronchial asthma • Infectious or inflammatory renal complaints in the acute phase • Uncontrolled hyperparathyroidism • Hypophosphataemia • Decompensated hepatic cirrhosis, inflammation of the liver and infectious hepatitis • First trimester of pregnancy	Ferric carboxymaltose (Ferinject®) should not be given to patients with any of the following conditions: • Hypersensitivity to ferric carboxymaltose or known hypersensitivity to other intravenous iron products • Patients with a history of severe allergy or previous anaphylaxis • Anaemia not attributed to iron deficiency • Evidence of iron overload or disturbances in utilisation of iron • Acute infections or illnesses including fever • Uncontrolled hyperparathyroidism • Hypophosphataemia • First trimester pregnancy • **Patients < 9 months of age**

Note: Parenteral use of iron has resulted in fatal anaphylactoid reactions. Although this is rare, intravenous iron should only be used in patients in whom a clearly established indication for parental iron therapy exists, confirmed by appropriate laboratory tests and where oral iron is not appropriate.

Anaphylactic reactions occur most frequently within the first several minutes. Test doses are not generally recommended.

Precautions[1-4]

Ferrosig®	Ferinject®
• Concomitant administration of angiotension converting enzyme (ACE) inhibitors may increase the incidence of adverse effects associated with parenteral iron, e.g. erythema, abdominal cramps, nausea, vomiting and hypotension • Patients with rheumatoid arthritis and other inflammatory/autoimmune conditions (SLE) may experience delayed reactions including fever and exacerbation/reactivation of joint pain • Use with caution in patients with significant cardiovascular diseases	• Sodium restricted patients: 1 mL of undiluted Ferinject® contains up to 5.5 mg (0.24 mmol) of sodium.
• Hypersensitivity and anaphylactoid reactions. • History of significant allergy or eczema.	
• Use with caution in hepatic impairment.	
• Extravasation may cause permanent skin discoloration. Do not administer intravenous iron if intravenous access is not secure, questionable or cannot be monitored regularly during infusion.	
• Use with caution in second and third trimester of pregnancy. Use only if benefits outweigh possible risks.	
• Concomitant use of oral and IV iron is discouraged. Supplementation with oral iron should be held until 1 week after the patient has received the last intravenous dose.	
• For further information consult product information.	
• Depending on the dilution of the products, fluids volumes and administration rates need to be carefully reviewed for small children and children at risk of fluid overload.	

Monitoring of response IV iron

- FBC, ferritin and reticulocyte count 1-2 weeks prior to intended infusion. A recent haemoglobin is essential for accurate dose calculation.
- FBC, ferritin and reticulocyte count 4 weeks post IV iron infusion to document response. **Note:** blood tests may be required earlier depending on the clinical situation.

- Monitoring of electrolytes, renal parameters and liver function tests may be needed for selected patient groups or if side effects are suspected, please discuss details with respective consultant.

Prescribing Guide

- Intravenous iron must be prescribed by a Medical Officer.
- Prescribers should prescribe (EMR or IV fluid chart) as: ….. mg iron (as iron polymaltose or ferric carboxymaltose) in ….. mL 0.9% sodium chloride over …. minutes. For dilution guide see Preparation.
- The infusion rate should also be specified, ensuring that the rate is appropriate for the individual patient. For infusion rate see Administration.

All doses in this protocol are expressed as milligrams of elemental iron.

Dosage[1-4]

Ferrosig®	Ferinject®
No maximum dose per infusion	**Do not exceed weekly dose of 20 mg/kg (max. 1000 mg)**

Elemental iron dose required (mg) = Body weight (kg) x (target Hb – actual Hb in g/L) x 0.24 + iron depot

For significantly overweight patients use ideal body weight for iron dose calculation.

Target haemoglobin (may be individualised for specific patients):

6 months to 2 years	3-5 years	6-12 years	>12 years
100-110 g/L	110-120 g/L	120-130 g/L	130- 150 g/L

Iron depot:

- 15 mg/kg for body weight < 35 kg
- 500 mg for body weight ≥ 35 kg

Round down to nearest 100 mg if weight is < 50 kg

Round up to nearest 100 mg if weight >50 kg

Pre-medication

Ferrosig®	Ferinject®
Premedication should be considered for all patients	Premedication to be considered for individual patients (history of atopia or allergies)
To be given prior to commencing intravenous iron: • **Hydrocortisone:** 2 mg/kg IV (maximum 100 mg) 5-10 minutes prior • **Antihistamine:** oral Loratadine 30-60 minutes prior (or intravenous Promethazine 5-10 minutes prior) • **Antipyretic:** oral Paracetamol 30-60 minutes prior	

Emergency medications

Due to the rare possibility of anaphylaxis it is recommended that iron infusions are only administered in locations where cardiopulmonary resuscitation facilities are available. Adrenaline, promethazine and hydrocortisone must be available on the ward should they be required.

Note: Patient specific doses should be calculated and prescribed (as prn) in the EMR/medical records by the medical team prior to the commencement of the infusion. Doses are only administered if required.

- **Adrenaline 1:1000 injection (1 mg/mL) (Dose: 0.01 mg/kg to a maximum dose of 0.5 mg IM) if required**
- **Promethazine injection (Dose: 0.5 mg/kg to a maximum of 25 mg IV) if required**
- **Hydrocortisone injection (Dose: 4 mg/kg to a maximum of 100 mg IV for children less than 12 years or 300 mg for children older than 12 years IV) if required**

Preparation

- Pharmacy stocks the following preparations for dilution: Ferrosig® 100 mg elemental iron in 2 mL and Ferinject® 500 mg elemental iron in 10 mL.
- All iron infusions are made up by nursing staff on the ward according to the prescribed dose of elemental iron. The diluent is always sterile 0.9% sodium chloride ONLY. Do not use any other fluid. Do not add any other medication.
- The prescribed dose of iron is added to 50 mL, 100 mL, 250 mL or 500 mL (standard bags) of 0.9% sodium chloride.
- **Ensure that the volume of** 0.9% sodium chloride **and maximum rate of infusion are appropriate for the age and size of patient, clinical situation and do not exceed maintenance fluid rates** (see *Administration*). Please note that both infusions can be run *slower* if required in small children or children at risk of fluid overload.

Ferrosig®

- Maximum concentration 5 mg/mL

Ferrosig® Dose	Suggested volume of 0.9% sodium chloride (standard bags) Less volume can be used provided the final concentration does not exceed 5 mg/mL
100-500 mg	100 mL
501-1000 mg	250 mL
1000-2500 mg	500 mL

- Draw up iron polymaltose using a filter needle to remove any glass particles from cracked ampoules.
- Change needle prior to loading bag; load bag using aseptic technique.
- Diluted solution is stable for 12 hours at 2 to 8ºC but should be used as soon as practicable.

Ferinject®

- For stability considerations, Ferinject® dilutions must have a concentration of 2 mg iron/mL or greater

Ferinject® Dose	Suggested volume of 0.9% sodium chloride (standard bags)
100 - 200 mg	50 mL
201 - 500 mg	100 mL
501 -1000 mg	250 mL

- Inspect vials visually for sediment and damage before use. Use only if sediment free and homogeneous. Use aseptic technique to draw up.
- Diluted solution is stable for 12 hours at 2 to 8ºC but should be used as soon as practicable. Concentrations less than 2 mg/mL are not stable.

Administration

Intravenous iron should be administered as a continuous infusion via a secure intravenous access and using a volumetric infusion pump. Note that extravasation of intravenous iron may cause permanent skin discoloration (brown stain).

Infusion rates

Infusion rates and administration are **different** for each product. Please ensure the correct table is chosen depending on product choice.

Iron Polymaltose - Ferrosig®

For Ferrosig® the infusion rate starts low and is gradually increased as tolerated according to the infusion rate table below. The rates below may need to be reduced so that they do not exceed allowed maximum tolerated for the individual (max. rate not exceeding maintenance). The rate may need to be further reduced if the child is at risk of fluid overload. Note: An iron polymaltose infusion can always be run slower if required.

	Total final volume 100mL	Total final volume 250mL	Total final volume 500mL
First 30 mins	**3 mL/hr**	**7.5 mL/hr**	**15 mL/hr**
Next 30 mins	**6 mL/hr**	**15 mL/hr**	**30 mL/hr** *Do not exceed this rate if patient <15 kg*
Next 30 mins	**12 mL/hr**	**30 mL/hr** *Do not exceed this rate if patient <15 kg*	**60 mL/hr** *Do not exceed this rate if patient 15 – 40 kg*
Next 30 mins	**18 mL/hr** *Do not exceed this rate if patient <5 kg*	**45 mL/hr**	**90 mL/hr** *Do not exceed this rate if patient 40 – 75 kg*
Final rate until finished	**24 mL/hr**	**60 mL/hr**	**120 mL/hr**

Ferric Carboxymaltose - Ferinject®

In adults, Ferinject® is often used neat and infused over a few minutes only. For children, Ferinject® is usually diluted and infused over a longer period as a short infusion. The suggested infusion times below are guidelines. They may need to be longer for some patients so that the rate does not exceed the allowed maximum tolerated for the individual (max. rate not exceeding maintenance). Please note that the infusion time can always be longer if patient is small or at risk of volume overload. In older, stable patients with a weight of >30 kg, the infusion time of a 250 mL bag may be shortened to 15-20 minutes if tolerated.

Ferinject® **Dose**	**Volume of NS solution**	**Suggested infusion time**
100 - 200 mg	50 mL	15-20 minutes
201 - 500 mg	100 mL	20-30 minutes
501 - 1000 mg	250 mL	30-45 minutes

Adverse Effects[1-4]

Ferrosig®	Ferinject®
Severe reactions (uncommon) o Anaphylaxis (can occur within the first minutes) o Tachycardia, hypotension, circulatory collapse o Syncopal reactions o Bronchospasm, chest pain **Less severe reactions** o Extravasation (injury including permanent brown staining of the skin) o Nausea and vomiting (may be caused by excessive infusion rate) o Headache, dizziness o Joint and muscle pain, back pain, arthralgia, sensation of stiffness of the arms, legs or face. o Flushing, sweating, chills and fever o Rash, hypersensitivity reactions, pruritus, urticaria, angioneurotic oedema o Generalised lymphadenopathy o Hypophosphataemia	**Severe reactions (rare)** o Anaphylaxis o Tachycardia, hypotension o Chest pain **Less severe reactions** o Extravasation (injury including permanent brown staining of the skin) o Nausea, vomiting and gastrointestinal symptoms o Headache, dizziness o Hypertension, flushing, injection-site reactions o Fatigue, paraesthesia, malaise, fever, rigors o Back pain, myalgia, arthralgia o Rash, hypersensitivity reactions, pruritus, urticaria, peripheral oedema o Increase of liver function tests o Hypophosphataemia
Less severe adverse reactions may occur up to by 1-2 days after treatment.	
For a full list of adverse reactions consult product information.	

Monitoring[1-4]

Ferrosig®	Ferinject®
Blood Pressure, Pulse and Respiration rate must be attended and documented on the standard paediatric observation chart (SPOC) as follows:	
• Prior to infusion • Every 15 minutes for 75 minutes • Every 30 minutes until the end of the infusion • 30 minutes after the end of infusion	• Prior to infusion • 5 minutes and 30 minutes after administration
Injection site should be monitored within the first 5 minutes and every 15-30 minutes during the infusion for possible extravasation	
Note: Anaphylaxis most likely occurs within the first several minutes of administration.	
Patients should be closely monitored for signs of hypersensitivity. Stop injection or infusion immediately and initiate appropriate management, including contacting the medical team. Observe patient for early onset of the following symptoms (cease infusion and initiate a **Clinical Review or Rapid response/ARREST** call): • **Bronchospasm with dyspnoea (Rapid Response)** • **Fainting, syncope, significant tachycardia, significant hypotension, circulatory collapse, anaphylaxis (Rapid Response or ARREST Call)** • Flushing, sweating, chills and fever, chest and back pain • If blood pressure or pulse rate change by 20% the infusion should be stopped and a **Clinical Review** call made. Specific limits for notification should be set and documented in the medical record by the medical team prior to the commencement of the infusion. Refer to the SPOC for appropriate response depending on the individuals observations. Depending on patient's diagnosis the intervals of observations may be varied by the medical team.	
The Clinical Emergency Response System MUST be activated and a Rapid Response or ARREST CALL is to be via the hospital Switchboard at 2222 in the event of ANY anaphylactic reaction and commencement of anaphylaxis management.	

References

1. Ferrosig® Product Information MIMS [Online], https://www.mimsonline.com.au.acs.hcn.com.au/Search/FullPI.aspx?ModuleName=Product%20Info&searchKeyword=ferrosig&PreviousPage=~/Search/QuickSearch.aspx&SearchType=&ID=65580001_2 [Accessed on 16/01/2020; Last updated 1/7/2017]
2. Ferinject® Product Information MIMS [Online] https://www.mimsonline.com.au.acs.hcn.com.au/Search/FullPI.aspx?ModuleName=Product%20Info&searchKeyword=ferinject&PreviousPage=~/Search/QuickSearch.aspx&SearchType=&ID=91220001_2 [Accessed on 16/01/2020; Last updated 1/7/2019]
3. Ferric carboxymaltose: Ferinject® and Iron polymaltose: Ferrosig®. Product information for intravenous iron preparations available in Australia. Available at: http://www.ebs.tga.gov.au
4. Australian Injectable Drugs Handbook (AIDH) 7th edition. Ferric carboxymaltose. Iron polymaltose. Available at: https://aidh.hcn.com.au/browse/about_aidh
5. BNF for Children, June 2017 [Online] https://www.medicinescomplete.com.acs.hcn.com.au/#/search/bnfc/ferinject?offset=0 [Accessed on 16/01/2020; Last update April 2019].
6. MHRA Drug Safety Update: Intravenous Iron and hypersensitivity reactions: new strengthened recommendations to manage and minimise risk [Online] https://www.gov.uk/drug-safety-update/intravenous-iron-and-serious-hypersensitivity-reactions-strengthened-recommendations. Article citation: Drug Safety Update vol 7, issue 1 August 2013: A1. [Accessed on 16/01/2020; Last updated August 2013].
7. Clinical use of intravenous iron: administration, efficacy, and safety. Auerbach et al. Hematology ASH Educ Program. 2010;2010:338-47.
8. Intravenous Ferric Carboxymaltose in Children with Iron Deficiency Anemia Who Respond Poorly to Oral Iron. Powers et al. J Pediatr 2017;180:212-6.
9. Effectiveness and safety of ferric carboxymaltose treatment in children and adolescents with inflammatory bowel disease and other gastrointestinal diseases. Laass et al. BMC Gastroenterology 2014, 14:184
10. Experience with intravenous ferric carboxymaltose in patients with iron deficiency anemia. Bregman et al. Ther Adv Hematol 2014, Vol. 5(2) 48– 60 DOI: 10.1177/ 2040620714521127

Appendix 1

Chronic kidney disease (CKD) stage 3-5 and peritoneal dialysis patients

International consensus for both iron and haemoglobin targets and monitoring regimes differ for children with chronic kidney disease compared to the general population and reflect their specific clinical needs.

Monitoring of iron status:

- Patients with chronic renal impairment not yet receiving an erythropoiesis stimulating agent should have their iron status checked 3 monthly.[1]
- Following commencement of erythropoiesis stimulating agent monitor every 4 weeks or whenever the dose is increased.[2]
- Once target haemoglobin has been reached monitor every 3 months.[1,2]

Absolute iron deficiency in children with CKD can be defined as:

- Ferritin <100mg/L for non-dialysis patients and < 200 mg/L for dialysis patients[1,2], or
- Transferrin saturation (TSAT) <20%.[1,2]

Target levels for patients with CKD stage 3-5:

- *Iron studies on erythropoiesis stimulating agent*:
  - Ferritin 200 - 500 microgram/L[1]
  - Transferrin saturation 20 – 30 %[1]

  Note: If ferritin levels are >500 microg/L discuss infusion with consultant.
- *Haemoglobin target for children with CKD maintained on erythropoiesis stimulating agents*:
  - 6 months to 2 years = 110 g/L
  - Over 2 years = 120 g/L

References for Appendix 1:

1. CARI guidelines – Haematological Targets; April 2012. (www.kidney.org.au/cari/index.htm)
2. NKF- KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease, Kidney International vol 2, (4) 2012 http://www.kidney-international.org