FOUNDATIONS IN IRON DEFICIENCY

Prescribing information and adverse event reporting can be found at the end of this presentation

Adverse events should be reported. Reporting forms and information can be found at http://www.hpra.ie/homepage/about-us/report-an-issue.
Adverse events should also be reported to
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Email: medicalinfo_UK@viforpharma.com

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IE-FCM-2300078 I Date of preparation: September 2023

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- Please do not distribute, forward or share this material further including with patients
- The information presented in this slide deck is accurate and up to date as of August 2023

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Ferinject® (ferric carboxymaltose) indication[1]

Ferinject is indicated for the treatment of iron deficiency when:

– oral iron preparations are ineffective
– oral iron preparations cannot be used
– there is a clinical need to deliver iron rapidly

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

1. Ferinject® Summary of Product Characteristics.

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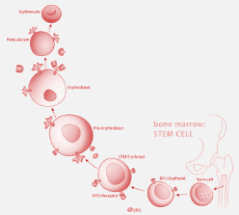
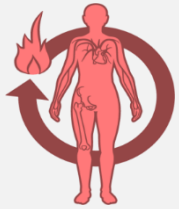
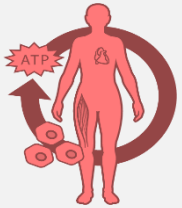
IRON IS NEEDED FOR MANY CELLULAR PROCESSES IN SPECIFIC ORGANS



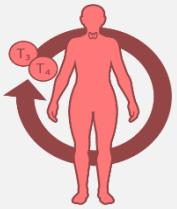
Erythropoiesis



Immune System

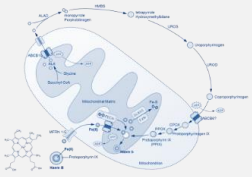


Energy Metabolism & Muscle Function



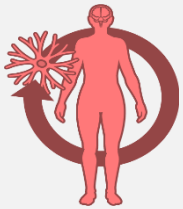
Hormone Production

Cell Cycle Regulation

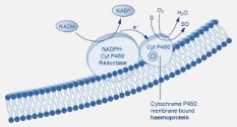


Haem & Iron-Sulfur Cluster Synthesis

DNA Replication and Repair



Brain Development & Function



Cytochrome P450

And for many more…

Adapted from Nemeth E (KDIGO conference), 2019[1] and Musallam KM, et al. 2018.[2]

1. Nemeth E (KDIGO conference, 2019). Available at: https://kdigo.org/wp-content/uploads/2019/06/KDIGO-2019-Nemeth-for-posting.pdf. Accessed September 2022.
2. 2. Musallam KM, Taher AT. *Curr Med Res Opin*. 2018;34:81-93.

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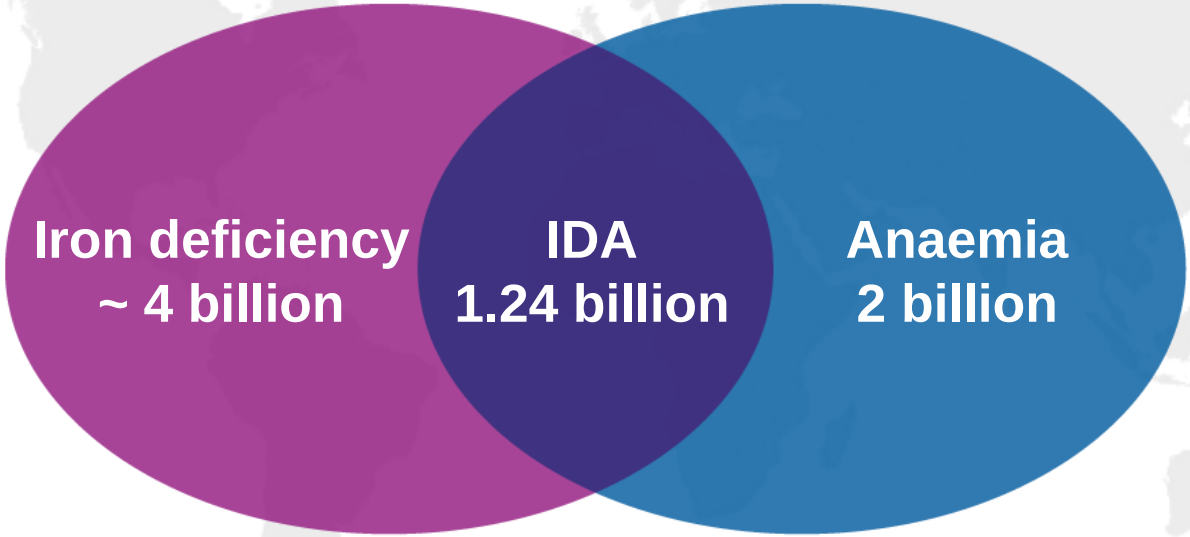
WORLDWIDE PREVALENCE

- Iron deficiency is the most prevalent nutritional deficiency worldwide[1,2]



1. Stelle I, et al. *Proc Nutr Soc.* 2019;78:19-26. 2. GBD 2016. *Lancet.* 2017;390:1211-1259.

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DEFINITION OF ID AND ANAEMIA – WORLD HEALTH ORGANIZATION

Iron Deficiency

The WHO defines iron deficiency as a ferritin level of:[1]

- <15 μg/L in adults and children > 5 years in the absence of inflammation
- < 70 μg/L in adults and children > 5 years in the presence of inflammation

Anaemia

The WHO defines anaemia as a haemoglobin level of:[2]

- <120 g/L in non-pregnant adult women
- <110 g/L in pregnant adult women
- <130 g/L in adult men

Hb, Hemoglobin ; WHO, world health organisation

1. WHO (2020). Available at: https://www.who.int/publications/i/item/9789240000124. Accessed September 2022. 2. WHO (2011). Available at: http://www.who.int/vmnis/indicators/haemoglobin.pdf. Accessed September 2022.

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IRON HAS TO BE TAKEN IN THROUGH DIET[1,2]

- **Iron is naturally present in food. It occurs in two forms:**

Source: Haemoglobin and myoglobin from meat, poultry, and fish

Absorption:
- Highly bioavailable (25%-35%)
- Absorption is not affected by other dietary components

Source: Cereals, pulses, legumes, fruits and vegetables

Absorption:
- Low bioavailability (3%-20%)
- Absorption affected by phytic acid, polyphenols, calcium and peptides

1. Clifford et al. 2015. Available at: http://www.ext.colostate.edu/pubs/foodnut/09356.html Accessed September 2022. 2. Abbaspour N, et al. *J Res Med Sci.* 2014;19(2):164-74.

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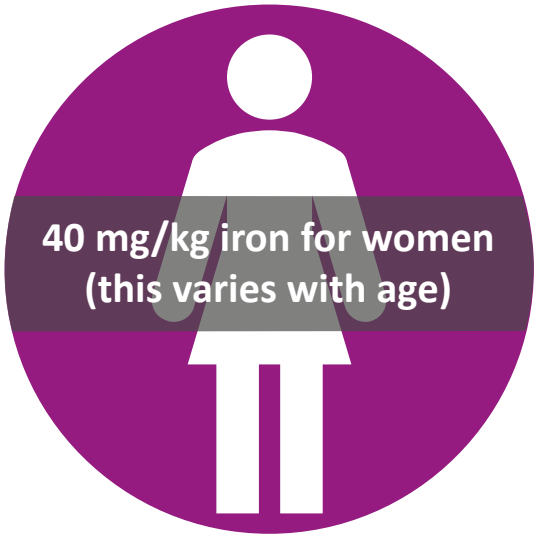
IRON IN THE HUMAN BODY

- It is estimated that for the healthy individual total body iron content is approximately **3–5g**[1,2]



1. Barragán-Ibañez G, et al. *Rev Med Hosp Gen Mex.* 2016;79:88-97. 2. Crichton RR, et al. 4th ed Bremen: Uni-Med Verlag; 2008.

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DIETARY IRON DAILY REQUIREMENTS IN IRELAND

- The **average person must absorb ~1–2 mg of iron per day** from dietary sources[1]

		Reference nutrient intake (RNI) for iron[2]	**Median iron intake in Ireland[3,4]**
Sex	Age	mg/day	mg/day
Men	≥19 years	8.7	Approx 14.7 mg/day
Women	19–50 years	14.8	Approx 11.9 mg/day
	>50 years	8.7	

1. Schmidt PJ. J Biol Chem. 2015;290:18975-18983.
2. BNF 2021. Available at: https://www.nutrition.org.uk/media/nmmewdug/nutrition-requirements.pdf . Accessed October 2022.
3. MILMAN, N. Dietary Iron Intakes in Men in Europe Are Distinctly Above the Recommendations: A Review of 39 National Studies From 20 Countries in the Period 1995 - 2016. Gastroenterology Research, North America, 13, dec. 2020. 1. Available at: <https://www.gastrores.org/index.php/Gastrores/article/view/1344/1342>. Date accessed: 28 Oct. 2022
4. Milman NT. J Nutr Metab. 2019;2019:7631306.

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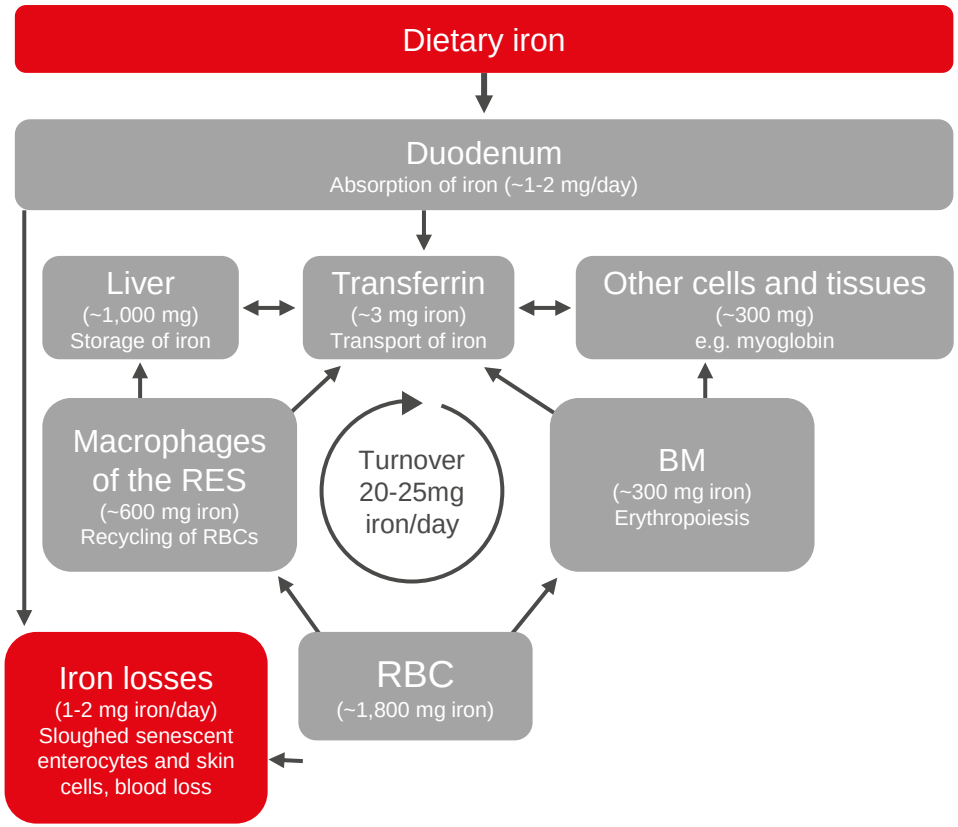
REFRESHER:
IRON TURNOVER IN THE BODY

- The average iron content in the body is about 3-4g and is distributed between RBCs, macrophages of the reticulo-endothelial system, liver, bone marrow, muscles and other tissues. A dynamic equilibrium is maintained by iron circulating between the different compartments. Excess iron is mainly stored in the liver as ferritin but can also be stored in other tissues. Almost all of the iron released by the breakdown of haemoglobin from RBCs is re-used. Only 1-2mg of iron is lost per day, which must be replaced by dietary absorption.[1-3]



RES, reticuloendothelial system; BM, bone marrow; RBC, red blood cell. Adapted from Stein et al, 2010; Crichton RR, et al. 2008.

1. Stein J, et al. *Nat Rev Gastroenterol Hepatol.*2010;7:599-610. 2. Crichton RR, et al. 4th ed Bremen: Uni-Med Verlag; 2008. 3. Wallace DF. *Clin Biochem Rev.* 2016;37(2):51-62.

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NORMAL BODY IRON STORES

66% of iron within the body is **found within haemoglobin** in red blood cells[1]

Type of iron		Amount of iron	
		mg	Body total (%)
Functional iron	Haemolgobin	2,500	66
	Myoglobin, haem and non-haem iron containing proteins	300	8
Transport iron	Plasma	4	<1
Storage iron	Ferritin and haemosiderin	1,000	26
		3,804	**100**

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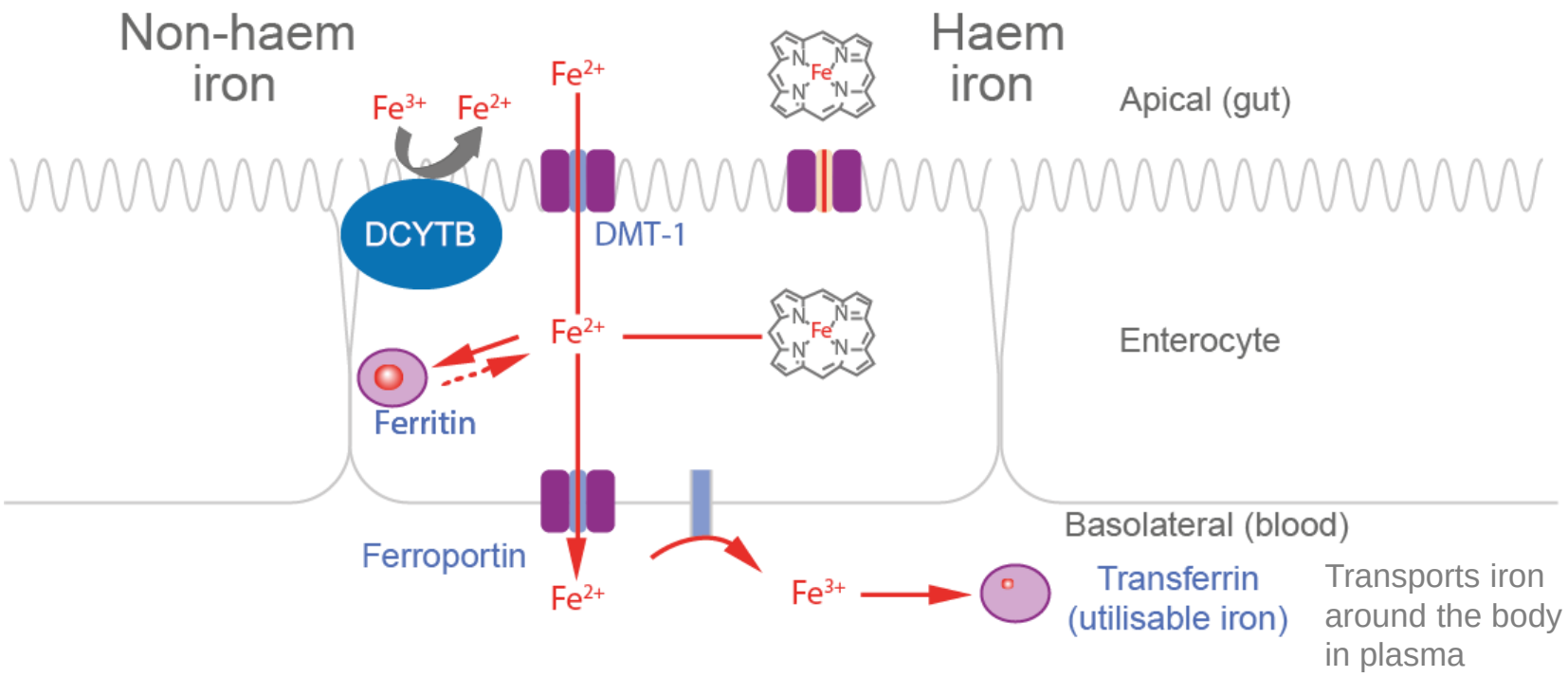
1. Beard JL. *J Nutr.* 2001;131:568S-580S.

INTESTINAL IRON ABSORPTION

- Haem iron enters the cells of the gut directly. Non haem-iron must be converted from the ferric state to the ferrous state[1]



DCYTB, duodenal cytochrome B; DMT-1, divalent metal transporter-1

1. Wallace DF. *Clin Biochem Rev*. 2016;37:51-62.

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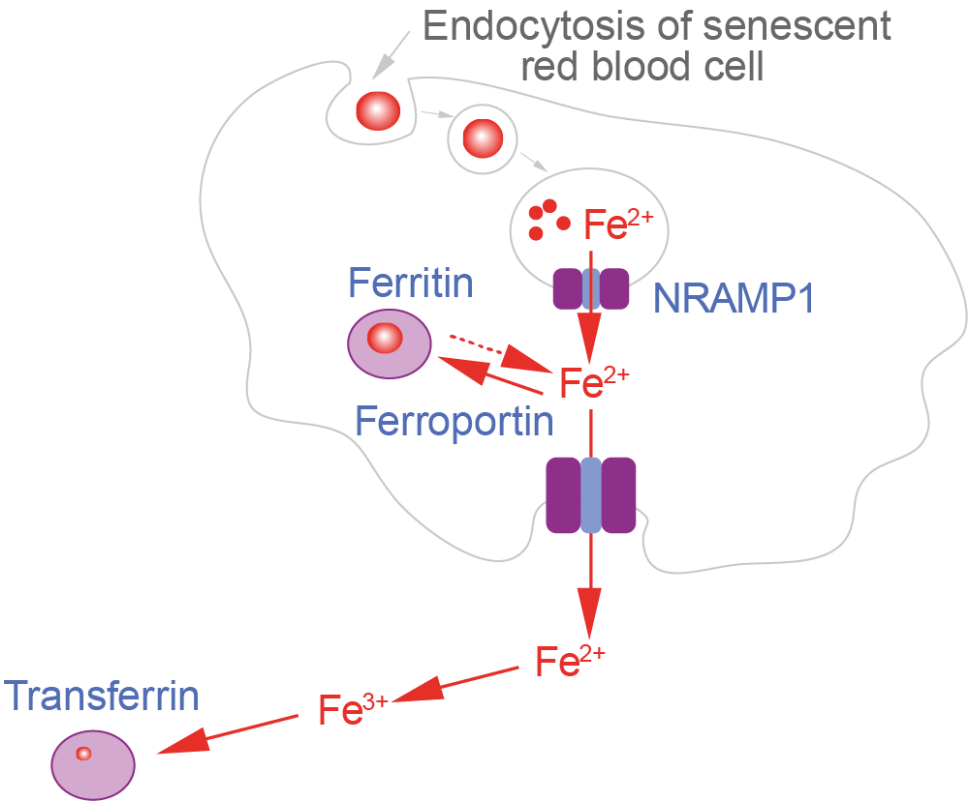
IRON RECYCLING

90% of the body's iron requirement is achieved through recycling old RBCs[1,2]



NRAMP1, natural resistance associated macrophage protein 1. Adapted from Conrad ME, Umbreit JN, 2000.

1. Conrad ME, Umbreit JN. *Am J Hematol.* 2000;64:287-298. 2. Slusarczyk P, Mleczko-Sanecka K. *Genes (Basel).* 2021;12(9):1364.

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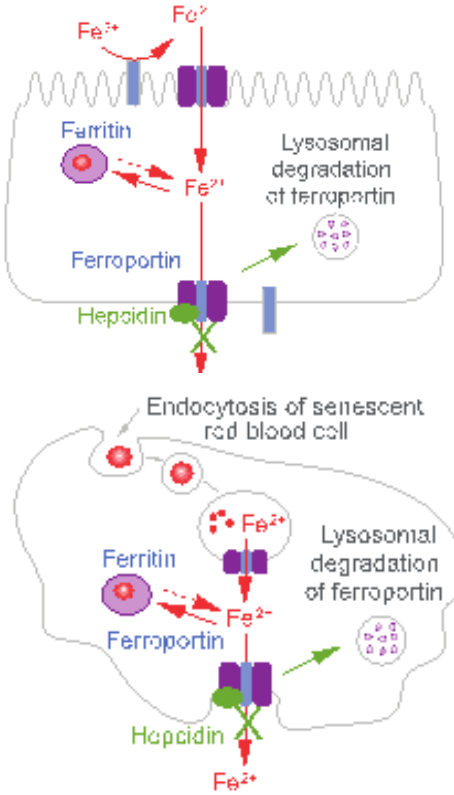
THE ROLE OF HEPCIDIN IN CELLULAR IRON REGULATION

During inflammation, hepcidin production increases, which reduces the availability of iron[1]

Inflammation (e.g.IL-6 ↑)
increases ***hepcidin***
production in the liver

Hepcidin ↑



Enterocyte

↑ hepcidin blocks enterocyte iron absorption[2-5]

Macrophage

↑ hepcidin blocks macrophage iron release[2-5]

1. Wallace DF. *Clin Biochem Rev.* 2016;37:51-62. 2.Collins JF, et al. *J Nutr.* 2008;38:2284-2288. 3.Weiss G, Schett G. *Nat Rev Rheumatol.* 2013;9:205-215.
4. Gasche C, et al. *Inflamm Bowel Dis.* 2007;13:1545-1553. 5. McDonagh T, Macdougall IC. *Eur J Heart Fail.* 2015;17:248-262.

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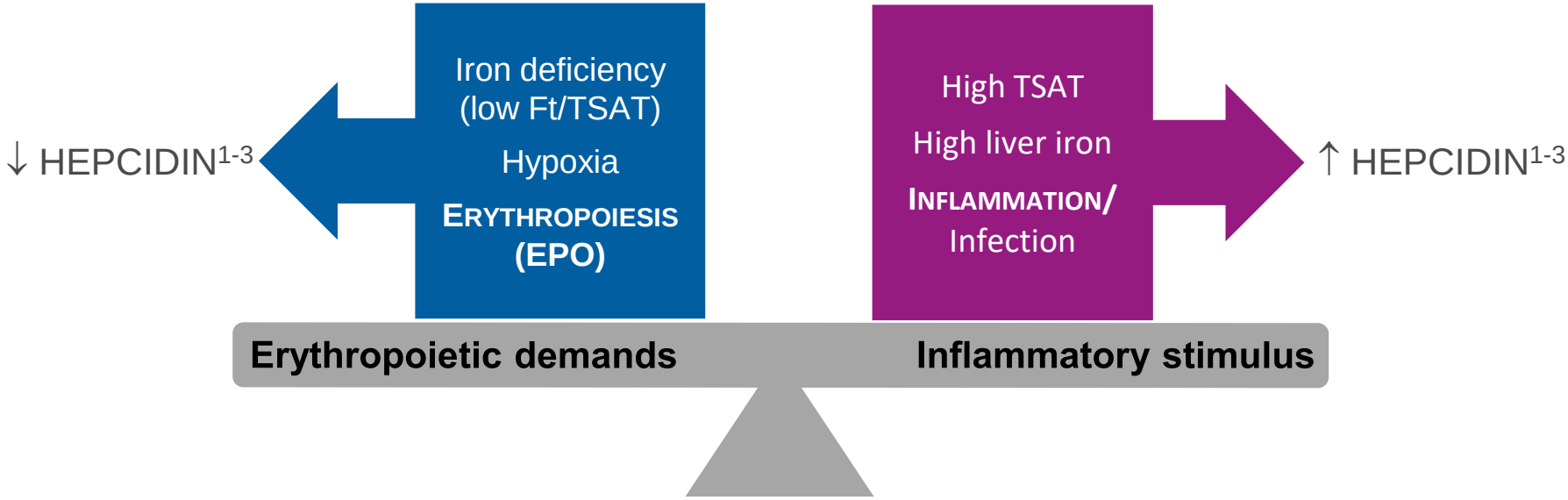
INFLAMMATION AND ERYTHROPOIESIS BOTH REGULATE IRON HOMEOSTASIS



1. Galaris D, et al. *Biochim Biophys Acta Mol Cell Res.* 2019;1866:118535. 2. Nemeth E, Ganz T. *Acta Haematol.* 2009;122(2-3):78-86.
3. Hawula ZJ, et *al. Pharmaceuticals (Basel).* 2019;12:170.

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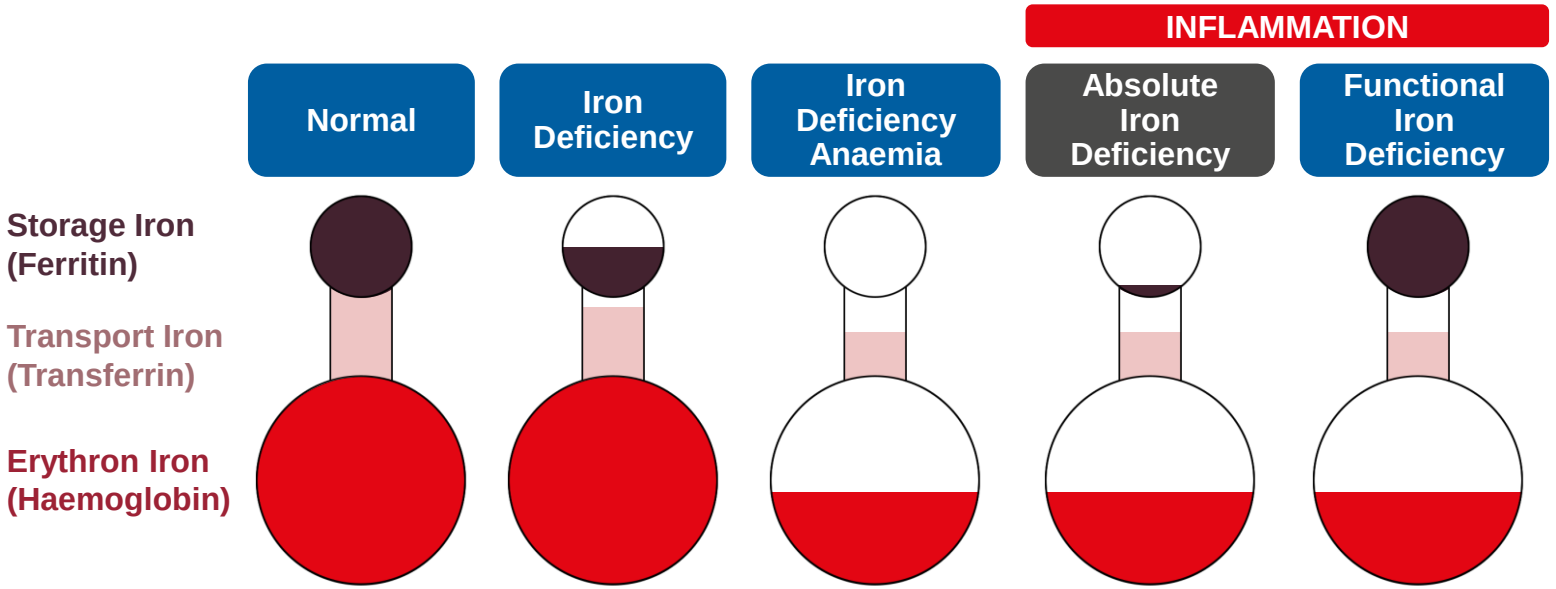
WHAT IS IRON DEFICIENCY?

Absolute Iron Deficiency = low body iron stores

Iron–restricted Erythropoiesis or 'Functional' Iron Deficiency = inability to access stores to support erythropoietic demands

Anaemia = low Hb or low RBC concentration



Adapted from Crichton RR et al. 2008.[1]

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1. Crichton RR, et al. 4th ed Bremen: Uni-Med Verlag; 2008.

ABSOLUTE OR FUNCTIONAL?

- **Iron deficiency develops when loss of iron is not sufficiently compensated by adequate dietary intake[1-3]**

	TYPE OF IRON DEFICIENCY	
	Absolute	Functional
	Iron Stores Depleted	Demand for Iron Outweighs its Release from Stores
Poor Iron Intake	✓	
Blood Loss	✓	
Impaired Iron Absorption	✓	
Elevated Circulating Hepcidin		✓
Rapid Increase in Erythropoiesis		✓

1. Goodnough LT. *Transfusion.* 2012;52:1584-1592. 2. Clifford et al. 2015. Available at: http://www.ext.colostate.edu/pubs/foodnut/09356.html Accessed September 2022.
3. Locatelli F, et al. *Nephrol Dial Transplant.* 2013;28:1346-1359.

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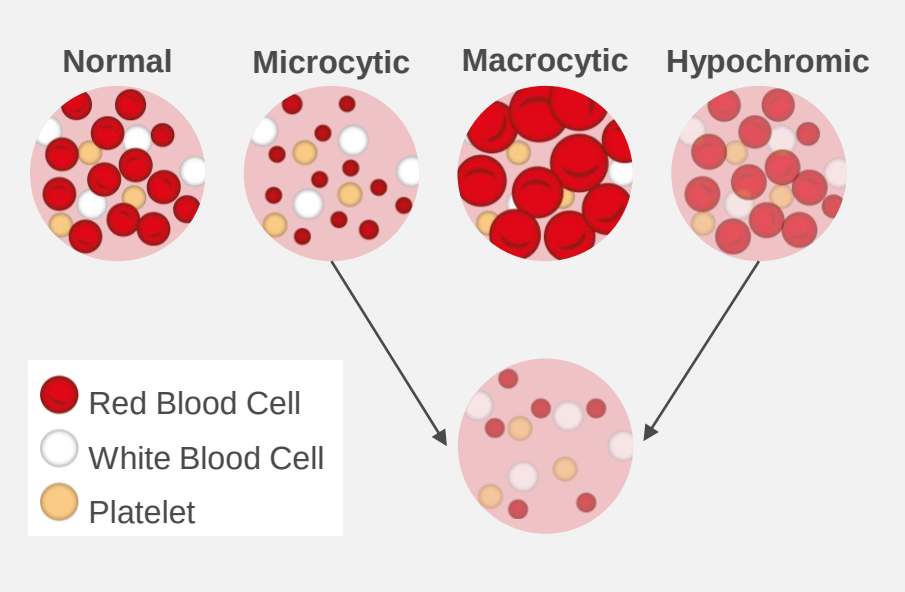
DIAGNOSIS OF ID AND IDA



- Low Hb
- Low haematocrit

Anaemia

- Low MCV (microcytic)
- Low MCH (hypochromic)

Probable IDA

Tests of iron status (including TSAT and ferritin)

Adapted from Lynch S. The rationale for selecting and standardizing iron status indicators. In: World Health Organization. Report: Priorities in the assessment of vitamin A and iron status in populations, Panama City, Panama, 15–17 September 2010. Geneva, World Health Organization, 2012.

MCH, mean cell haemoglobin; MCV, mean cell volume; TSAT, transferrin saturation.

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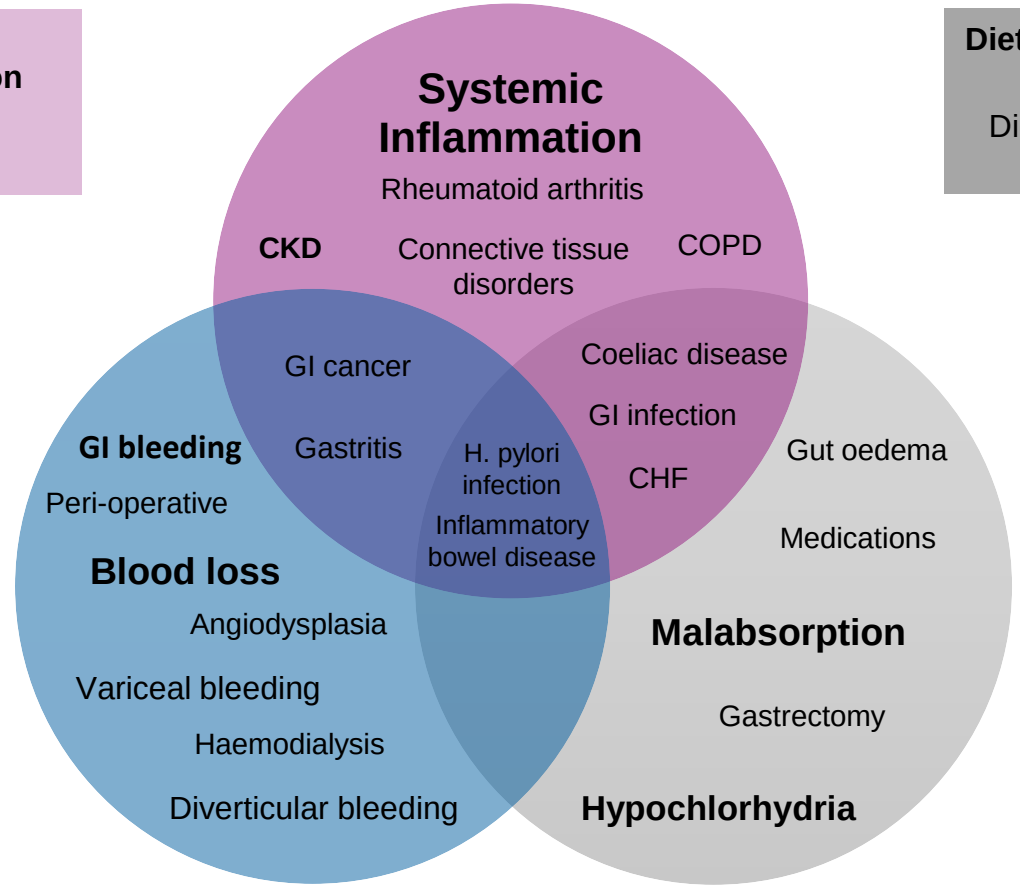
CAUSES OVERLAP

Increased demand for iron
Childhood
Pregnancy

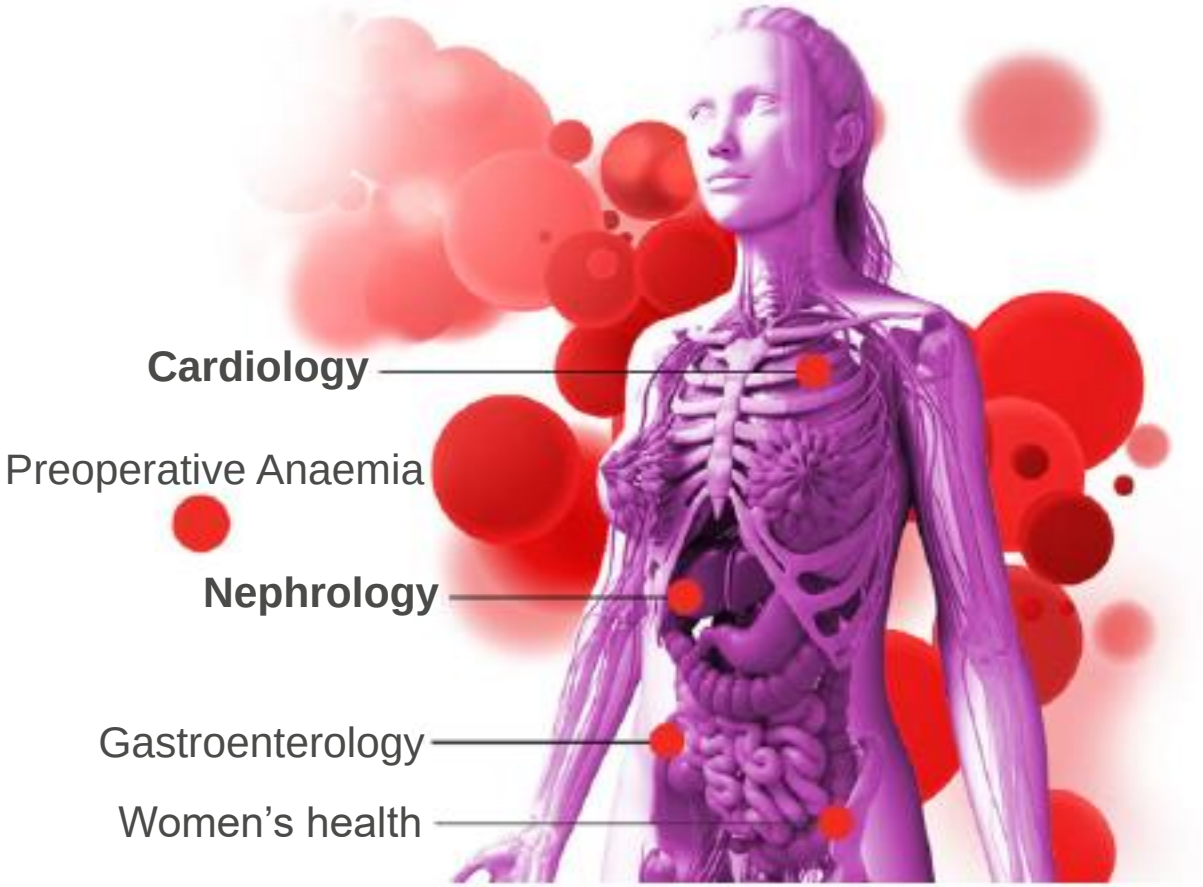


Dietary insufficiency
Poor appetite
Dietary restrictions

Adapted from Goodnough LT. 2012.[1]

1. Goodnough LT. *Transfusion.* 2012;52:1584-1592.

IMPORTANCE OF IRON IN THE BODY



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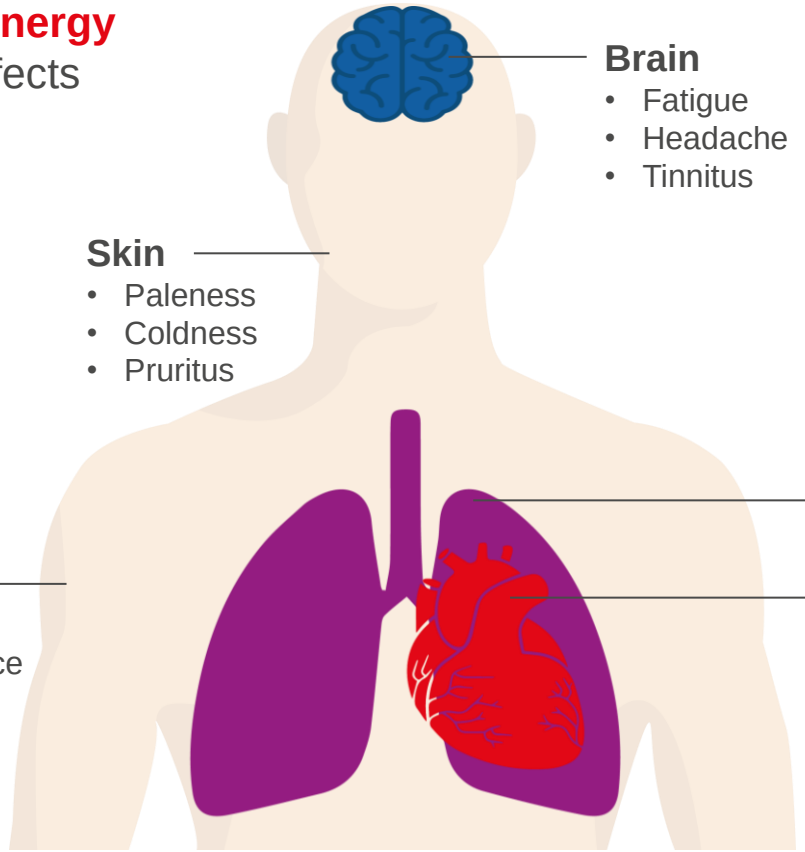
SIGNS AND SYMPTOMS OF IDA

Iron deficiency affects the energy output of all cells and the effects of IDA are widespread



Brain
- Fatigue
- Headache
- Tinnitus

Skin
- Paleness
- Coldness
- Pruritus

Lungs
- Breathlessness

Heart
- Palpitations
- Tachycardia
- Chest pain*
- Angina*
- Heart failure*

Muscle
- Exercise intolerance

Nails
- Nail changes

* In severe anaemia
Adapted from NICE, 2021.[1]

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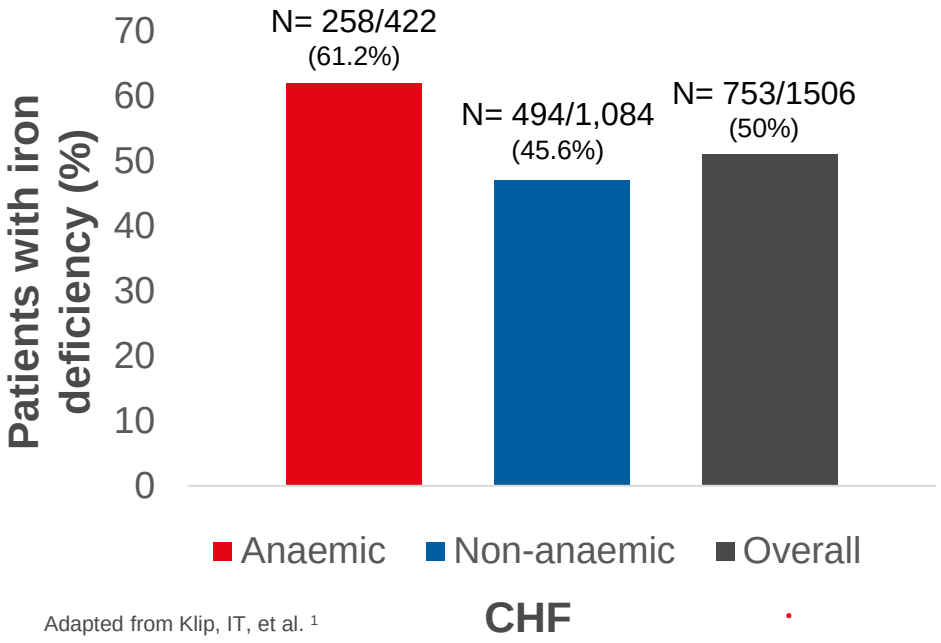
1. NICE (2021). Available at: https://cks.nice.org.uk/topics/anaemia-iron-deficiency/. Accessed September 2022.

IRON DEFICIENCY IN CHRONIC HEART FAILURE (CHF)

- **Iron deficiency in patients with CHF** may occur in 50% of patients and can be caused by a number of factors[1-3]

Prevalence[1]



Adapted from Klip, IT, et al. [1]

Anaemia in CHF

- Iron deficiency:
  - Iron malabsorption e.g. gut oedema
  - Poor iron intake
  - Blood loss e.g. anti-platelet use
  - Chronic inflammation
  - Co-existent CKD
- Haemodilution
- Low bone marrow activity e.g. cytokines (TNF- α) or insensitivity to epo
- B_{12} or folate deficiency

Purple text: causes related to iron deficiency

International pooled cohort comprising 1,506 patients with chronic HF

- ID defined as a ferritin level <100 Mg/L or ferritin 100 -299 ug/L with a transferrin saturation <20%
- Anaemia was defined as a hemoglobin level <12 g/dL in women and <13 g/dL in men.

1. Klip, IT, et al. *Am Heart J.* 2013;165:575-582. 2. Cohen-Solal A, et al. *Heart.* 2014;100(18):1414-20. 3. Jankowska EA, et al. *J Cardiac Fail.* 2011;17:899-906.

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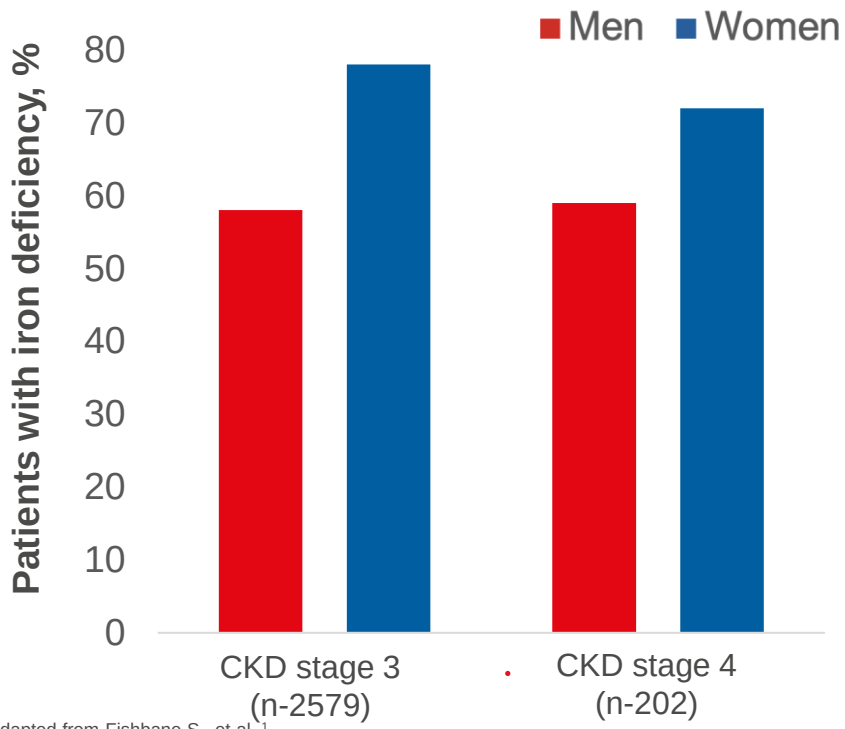
IRON DEFICIENCY IN CHRONIC KIDNEY DISEASE (CKD)

Iron deficiency can occur in 60-70% of patients with CKD and is multifactorial[1]

Prevalence[1]



Adapted from Fishbane S., et al. [1]

Causes: Anaemia in CKD

(eGFR <60ml/min/1.73m^2)

- Iron deficiency
  - Poor iron intake
  - Blood loss
  - Chronic inflammation
  - Elevated hepcidin
- Decreased erythropoietin
- Infection
- Short red blood cell life span
- Bone marrow suppression due to uremia
- B_{12} or folate deficiency
- Osteitis fibrosis cystica (secondary hyperparathyroidism)
- Aluminum toxicity

Purple text causes related to iron deficiency*

Patients with CKD requiring haemodialysis may lose up to 3 g of iron each year due to blood loss[2]

1. Fishbane S, et al. *Clin J Am Soc Nephrol.* 2009;4:57-61. 2. Kalantar-Zadeh K, et al. *Adv Chronic Kidney Dis*. 2009;16:143-151.

* Iron deficiency in this study was defined as serum ferritin < 100 ng/ml or TSAT < 20%.[1]

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GUIDELINES: IRON DEFICIENCY ANAEMIA TREATMENT IN CKD

PROFESSIONAL ASSOCIATION	DEFINITION OF ANAEMIA (Hb, g/dL)	RECOMMENDED IRON DEFICIENCY THRESHOLD VALUES		MAXIMUM FERRITIN LIMIT FOR PEOPLE TREATED WITH IRON ND-CKD		INITIATION OF ESA & IRON STATUS
		Serum ferritin (ug/L)	TSAT (%)	Serum ferritin (µg/L)	TSAT (%)	
KDIGO[1]	<13 (men); <12 (women)	No recommendation	No recommendation	<500 µg/L	<30%	Address all correctable causes of anaemia (including iron deficiency and inflammatory status) prior to initiation of ESA therapy
NICE (NG203)[2]	<11 and symptomatic	<100	<20	<800 µg/L**	–	ESA therapy should not be initiated in the presence of absolute iron deficiency without also managing the iron deficiency
UK Renal Association[3]	<11 and symptomatic	<100*	<20	<800 µg/L**	>20%	Patients should be iron replete to achieve and maintain target Hb whether receiving ESAs or not

***Do not request transferrin saturation or serum ferritin measurement alone to assess iron deficiency status in people with anaemia of CKD.**
****In order to prevent this, review the dose of iron when serum ferritin levels reach 500 ug/l (related to 800ug/L ferritin upper limits .**

Retic.Hb, reticulocyte haemoglobin content; Hb, haemoglobin; CKD, Chronic kidney disease; HRC, hypochromic red blood cells; KDIGO, Kidney Disease: Improving Global Outcomes; NICE, National Institute for Health and Care Excellence; TSAT, transferrin saturation.

1. KDIGO (2012). Available at: https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-Anemia-Guideline-English.pdf. Accessed September 2022. 2. NICE (2021). Available at: https://www.nice.org.uk/guidance/ng203. Accessed September 2022. 3. The Renal Association (2020). Available at: https://ukkidney.org/sites/renal.org/files/Updated-130220-Anaemia-of-Chronic-Kidney-Disease-1-1.pdf. Accessed September 2022.

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TREATMENT OF IRON DEFICENCY ANAEMIA: WHAT THE GUIDELINES SAY

Iron supplementation is recommended in all patients with CKD and IDA to replete iron stores to help achieve and maintain target Hb levels

- before considering or when starting ESAs[1]
- during maintenance ESA therapy[1]

Treatment of Anaemia with Iron Therapy[1]

NICE recommends in patients with ND-CKD and not on ESA, a trial of oral iron before offering IV iron therapy. If they are intolerant of oral iron or target Hb levels are not reached within 3 months, offer IV iron therapy and for patients receiving ESA offer only oral iron if IV iron therapy is contraindicated, or the person chooses not to have IV iron therapy

Carry out testing to diagnose iron deficiency and determine potential responsiveness to iron therapy and long-term iron requirements every 3 months

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1. NICE guideline [NG203] Published: 25 August 2021. Available at https://www.nice.org.uk/guidance/ng203. Assessed August 2022

ESC GUIDELINE RECOMMENDATIONS: IRON DEFICIENCY IN CHRONIC HEART FAILURE

2021 European Society of Cardiology guidelines:

Recommendation – Class I; Level of evidence: C[1]
It is recommended that all patients with HF be periodically screened for anaemia and iron deficiency with a full blood count, serum ferritin concentration and TSAT.

2023 focused update to the 2021 ESC guidelines:

Recommendation – Class I; Level of evidence: A[2]
Intravenous iron supplementation is recommended in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to alleviate HF symptoms and improve quality of life.

Recommendation – Class IIa; Level of evidence A[2]
Intravenous iron supplementation with ferric carboxymaltose or ferric derisomaltose should be considered in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to reduce the risk of HF hospitalization.

1. McDonagh TA, et al. Eur J Heart Fail. 2021;00:1-128.
2. McDonagh TA, et al. Eur Heart Journal 2023 00, 1-13

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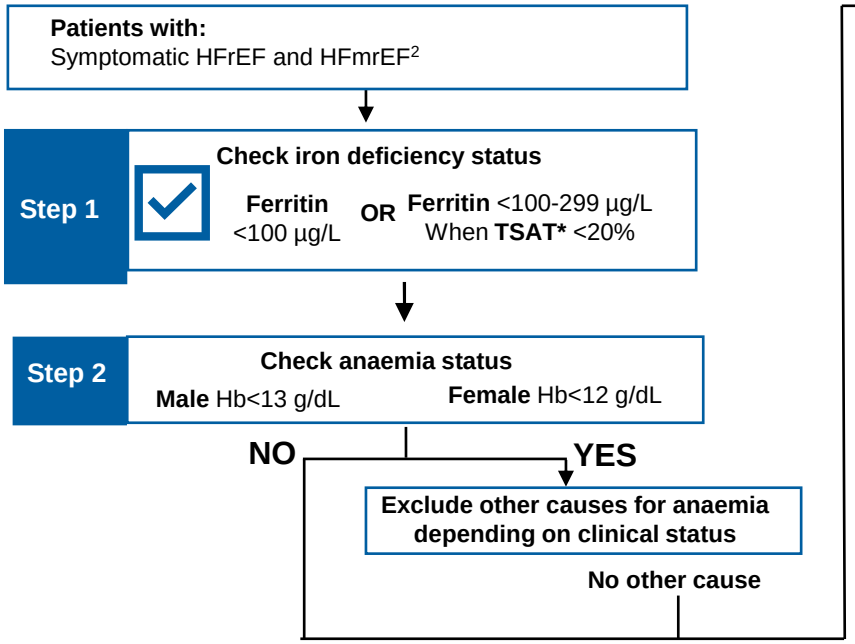
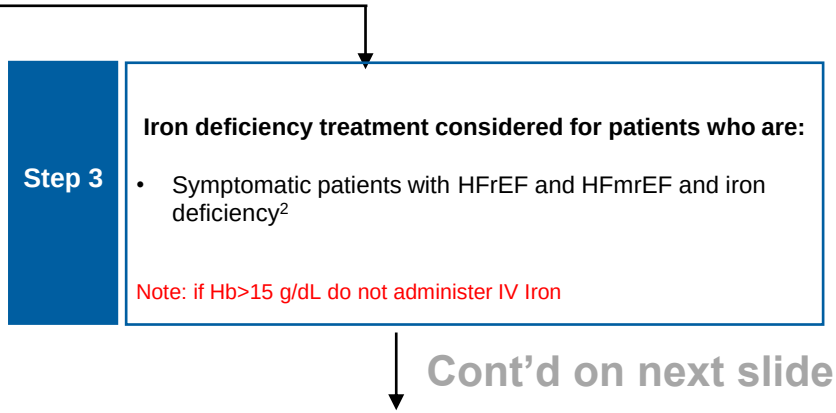
ALGORITHM – DIAGNOSIS AND TREATMENT OF IRON DEFICIENCY IN PATIENTS WITH HEART FAILURE[1,2]

HOW

Screening, diagnosing, treating and monitoring for ID in patients with HF





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The focused update to 2021 ESC guidelines recommend Intravenous iron supplementation with ferric carboxymaltose or ferric derisomaltose should be considered in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to reduce the risk of HF hospitalization.

Algorithm adapted from Sindone A et al, *J Clin Med 2022*;11:2976

The correction of ID using ferric carboxymaltose has been shown to improve HF symptoms, exercise capacity and QoL in symptomatic patients with ID and HFrEF[3] and has the potential to reduce rehospitalisations for HF in symptomatic patients with ID and LVEF<50% stabilised after acute heart failure, although the trial primary endpoint was not met [4]

*TSAT = (concentration of serum iron/total capacity to bind iron) x 100.
Hb, haemoglobin: HF, heart failure: HFREF, heart failure with reduced ejection fraction: ID, Iron deficiency: IV, intravenous: LVEF, lft ventricular ejection fraction: TSAT, transferrin saturation.

1. Sindone A, et al. *J Clin Med.* 2022;11:2976. 2. McDonagh TA, et al, Eur Heart Journal 2023 00, 1-13. 3. Ponikowski P et al, Eur Heart J. 2015 Mar 14; 36(11):657-68 4. Ponikowski P. et al, Lancet 2020; 396:1895 - 904

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ALGORITHM – DIAGNOSIS AND TREATMENT OF IRON DEFICIENCY IN PATIENTS WITH HEART FAILURE[1]

Cont'd from previous slide

For dosing with ferric derisomaltose refer to the relevant SmPC

Step 3 Cont'd

Consider **IV ferric carboxymaltose** to correct iron deficiency+

Calculate iron need using the table:

Haemoglobin		Patient body weight		
g/dL	Mmol/L	<35 kg	<35kg to <70kg	**≥70 kg**
<10	<6.2	30mg/kg body weight[2]	1500mg	2000mg
10 to <14	6.2 to <8.7	15 mg/kg body weight[2]	1000mg	1500mg
≥14	≥8.7	15 mg/kg body weight[2]	500mg	500mg

Step 4

Check ferritin + TSAT
At next scheduled visit (preferably after 3 months)

Step 5

Check ferritin + TSAT
1-2 times per year
Or if change in clinical picture or Hb decreases

Algorithm adapted from Sindone A et al, *J Clin Med* 2022;11:2976

Summary of dosing and administration of Ferinject for adults and adolescents aged 14 years and older:[2]

A single Ferinject administration should not exceed: 15 mg iron/kg body weight (for administration by intravenous injection) or 20 mg iron/kg body weight (for administration by intravenous infusion) OR 1,000 mg of iron (20 mL Ferinject).
The maximum recommended cumulative dose of Ferinject is 1,000 mg of iron (20 mL Ferinject) per week. If the total iron need is higher, then the administration of an additional dose should be a minimum of 7 days apart from the first dose.
A single maximum daily dose of 200 mg iron should not be exceeded in haemodialysis-dependant chronic kidney disease patients aged 14 years and above.

Please refer to SmPC for the maximum weekly dose for patients with body weight < 35kg.
Please refer to SmPC for dosing considerations in patients aged 1-13. Ferinject® is not recommended for use in children under 1 year of age.

*TSAT = (concentration of serum iron/total capacity to bind iron) x 100. †Note: The use of ferric carboxymaltose has not been assessed in paediatric patients, and therefore treatment with ferric carboxymaltose is not advised in children less than 14 years of age. Full prescribing information can be found in the latest Summary of Product Characteristics.
Hb, haemoglobin: HF, heart failure: HFREF, heart failure with reduced ejection fraction: ID, Iron deficiency: IV, intravenous: LVEF, lft ventricular ejection fraction: TSAT, transferrin saturation.

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1. Sindone A, et al. *J Clin Med.* 2022;11:2976. 2. Ferinject® Summary of Product Characteristic

TREATMENT OPTIONS FOR ANAEMIA AND IRON DEFICIENCY

Replacement of iron

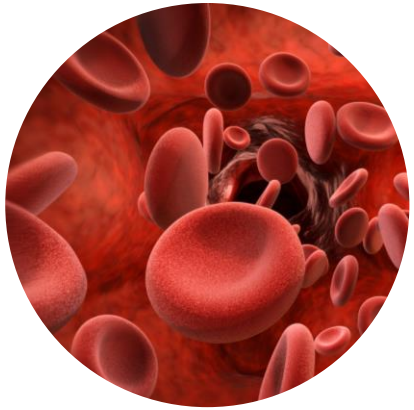
Oral iron

Intravenous iron

Replacement of RBC and EPO

Blood transfusion

ESA therapy



RBC, red blood cells; EPO, erythropoietin; ESA, erythropoietin stimulating agents

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ORAL IRON – BENEFITS AND LIMITATIONS

Benefits[1,2]

- Widely used and easily administered
- Relatively inexpensive
- Avoid need for outpatient visits
- New formulations and administration schedules in development may counteract some limitations of oral iron

Limitations[1,2]

- Frequent GI adverse effects
- Adherence can be poor
- Absorption may be impaired due to inflammation (hepcidin)
- Other medications and food may reduce absorption
- May be inadequate during ESA therapy, chronic blood loss or when there is a need for rapid Hb improvement

ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; GI, gastrointestinal.

1. Camaschella C. *Blood.* 2019;133(1): 30-39. 2. Jimenez K, et al. *Gastroenterol Hepatol (N Y).* 2015;11(4):241-50.

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INTRAVENOUS IRON – BENEFITS AND LIMITATIONS

- **Intravenous iron is indicated for treatment of iron deficiency** when oral iron preparations are ineffective or cannot be used or when there is the clinical need to deliver iron rapidly

Benefits

- Bypasses need for GI absorption and is incorporated more rapidly into RBCs than oral iron[1]
- Encourages treatment adherence[2]
- More rapid effect (vs oral iron)[2,3,4]
- Delays/avoids need for ESA therapy[3]

Limitations

- Risk of hypersensitivity reactions (including anaphylaxis)[3]
- Requires IV access and medical expertise for administration[1,5]
- Higher cost compared to oral iron[1]
- Injection site reactions are common[6]

GI, gastrointestinal; IV, intravenous; RBC, red blood cell.

1. Macdougall IC. *Curr Med Res Opin*. 2010;26:473-482.
2. Qunibi WY. *Arzneimittelforschung* 2010;60:399-412.
3. Macdougall IC, et al. *Nephrol Dial Transplant.* 2014;29:2075-2084.
4. Camaschella C. *Blood.* 2019;133:30-39.
5. EMA (2013). Available at: https://www.ema.europa.eu/en/documents/referral/intravenous-iron-containing-medicinal-products-article-31-referral-assessment-report_en.pdf. Accessed September 2022.
6. CHMP. Assessment report for Iron containing IV medicinal products, 13 Sep 2013;EMA/549569/2013

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BLOOD TRANSFUSIONS DO NOT CORRECT IRON STORES

Benefits

- Improves anaemia symptoms[1]
- Benefits patients who:[1]
  - Are non-responsive to ESA therapy
  - Require rapid correction of anaemia e.g. in a perioperative environment

Limitations

- Immune reactions, blood-borne infections and transfusion mismatch[1]
- Associated with poor patient outcomes and increased costs[2]
- ERBP recommends restrictive blood transfusion strategy[3]
- Risk of allo-sensitisation to HLA antibodies and may delay/preclude renal transplant[4]

ERBP, European Renal Best Practice; HLA, human leukocyte antigen.

1. KDIGO (2012). Available at: https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-Anemia-Guideline-English.pdf. Accessed September 2022. 2. Leahy MF, et al. *Transfusion.* 2017;57:1347-1358. 3. Locatelli F, et al. *Nephrol Dial Transplant.* 2013;28:1346-1359. 4. Obrador GT, Macdougall IC. *Clin J Am Soc Nephrol.* 2013;8:852-860.

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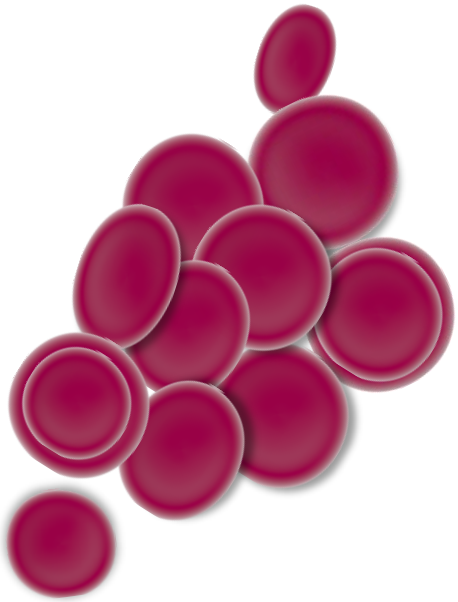
ESA THERAPY CORRECTS EPO DEFICIENCY BUT DOES NOT CORRECT IRON STORES



Benefits

- Effectively corrects anaemia in ND-CKD[1]
- Shows clinical benefits and improves QoL[1]
- Reduces the need for blood transfusions[2]

However

- Iron deficiency is the most common cause of **resistance to ESA** (ESA 'hyporesponsiveness')[3,4]
- ESA therapy **increases the need for iron** by stimulating the synthesis of new RBCs[5,6]
- Iron stores often cannot be mobilised fast enough to meet the demand of increased erythropoiesis[6]
- Expensive
- Concerns raised over safety[7-10]

ESA, erythropoietin stimulating agents; ND-CKD, non-dialysis dependent chronic kidney disease; QoL, quality of life; RBC, red blood cell.

1. Kalra PA. Br J Cardiol. 2011;18(Suppl 2):S1–S15; **(2)** KDIGO Clinical Practice Guideline for Anaemia in Chronic Kidney Disease. Kidney Int Suppl. 2012;2: 283–287; **(3)** Hörl WH. Nephrol Dial Transplant 2002;17(Suppl 11):35–38; **(4)** Locatelli F et al. ERBP Guidelines. Nephrol Dial Transplant. 2004;19(Suppl. 2):ii1–ii47; **(5)** Besarab A, Coyne DW. Nat Rev Nephrol. 2010;6:699–710; **(6)** Goodnough L. Transfusion. 2012;52:1584–1592; **(7)** Besarab A et al. N Engl J Med. 1998;339:584–590; **(8)** Drueke T et al. N Engl J Med. 2006;355:2071–2084; **(9)** Singh AK et al. N Engl J Med. 2006;355:2085–2098; **(10)** Pfeffer MA et al. N Engl J Med. 2009;361:2019–2032.

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WHAT IS THE EXPECTED RESPONSE TO ORAL IRON IN A PATIENT WITHOUT CHRONIC INFLAMMATION?

How much iron is needed for an Hb increase of 1 g/dL (just accounting for Hb deficit)?

Iron deficit (mg) = (ΔHb g/dL) x BW (kg) x 2.4[1]

Factor 2.4 = [70[2] mL_{blood}/kg_{bw} x 3.4[3] mg_{Fe}/g_{Hb}] /100 mL/dL

For someone with 65 kg_{bw}

an increase in Hb of 1 g/dL → 156 mg Fe required

How long will it take per 1g/dL increase in Hb[4]?

~16 days

16.3% absorption for consecutive-day
60 mg dose
9.78 mg every day

~24 days

21.8% absorption for alternate-days
60 mg dose
13.1 mg every other day

British national formulary (BNF) response to oral iron (Ferrous sulphate)

Dosage recommended for treatment of IDA in adults[5]

- 200 mg (equivalent to 65 mg iron) once daily, reduced if not tolerated to 200mg once daily on alternate days for adults

Therapeutic response[5]

- For once daily dosing, the haemoglobin concentration should rise by at least 10 g/L after 2 weeks of treatment, or 20 g/L after 4 weeks of treatment.
- For alternate day dosing, the haemoglobin concentration should rise by at least 10g/L after 4 weeks of treatment.
- When Hb is in the normal range, treatment should be continued for a further 3 months to replenish iron stores. After treatment monitor blood count periodically (e.g. every 6 months) to detect recurrence.

(1) Ganzoni A. M. Schweizerische Medizinische Wochenschrift. 1970;100(7):301-303. **(2)** Muraki et al. Interact Cardiovasc Thorac Surg. 2018, 27(6):802-807; **(3)** Bernhart and Skeggs. J Biol Chem. 1943;147:19-22; **(4)** calculations based on data from Stoffel et al. Lancet Haematol. 2017;4(11):e524-e533. **(5)** British National Formulary. Ferrous sulphate. Available at https://bnf.nice.org.uk/drug/ferrous-sulfate.html, Accessed August 2023.

IE-FCM-2300078 l Date of preparation: September 2023 Prescribing information can be found on the final slides

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Ferinject® (ferric carboxymaltose)

Prescribing Information - Ireland

For full prescribing information refer to the Summary of Product Characteristics (SmPC)

Active Ingredient: Ferric carboxymaltose (50mg/mL)
Presentation: Dispersion for injection/infusion. Available as a 2mL vial (as 100mg of iron), 10mL vial (as 500mg of iron) and 20mL vial (as 1000mg of iron).
Indication: Treatment of iron deficiency when oral iron preparations are ineffective or cannot be used or if there is a clinical need to deliver iron rapidly. The diagnosis must be based on laboratory tests.
Dosage and Administration: The posology of Ferinject follows a stepwise approach:
Step 1: Determination of the iron need:
The individual iron need for repletion using Ferinject is determined based on the patient's body weight and haemoglobin (Hb) level, using the simplified table in the SmPC. Two doses may be required to replenish the total iron need.
Step 2: Calculation and administration of the maximum individual iron dose(s):
Based on the total iron need determined, the appropriate dose(s) of Ferinject should be administered:
In adults and adolescents aged 14 years and older, the maximum single dose is 15 mg iron/kg body weight (for administration by intravenous injection) or 20 mg iron/kg body weight (for administration by intravenous infusion) and the maximum recommended cumulative dose of Ferinject is 1,000 mg of iron (20 mL Ferinject) per week.
In children and adolescents aged 1 to 13 years, the maximum single dose is 15 mg iron/kg body weight, and the maximum recommended cumulative dose of Ferinject is 750 mg of iron (15 mL Ferinject) per week.
In all cases, if the total iron need is higher, then the administration of an additional dose should be a minimum of 7 days apart from the first dose.
Administration rates for intravenous injection using undiluted dispersion:
For iron doses of 100mg to 200mg, there is no prescribed administration time. For doses >200mg to 500mg, Ferinject should be administered at a rate of 100mg iron/min. For doses >500mg to 1,000mg, the minimum administration time is 15 min.
Administration of intravenous drip infusion:
For iron doses of 100mg to 200mg, there is no prescribed administration time. For doses >200mg to 500mg, Ferinject should be administered in a minimum of 6 mins. For doses >500mg to 1,000mg, the minimum administration time is 15 mins.
Ferinject must only be diluted in 0.9% m/V NaCl but should not be diluted to concentrations less than 2 mg iron/mL.
Step 3: Post-iron repletion assessments
Contraindications: Hypersensitivity to Ferinject or any of its excipients. Known serious hypersensitivity to other parenteral iron products. Anaemia not attributed to iron deficiency. Iron overload or disturbances in utilisation of iron.
Special warnings and precautions: Parenterally administered iron preparations can cause potentially fatal anaphylactic reactions. The risk is enhanced for patients with known allergies, a history of severe asthma, eczema or other atopic allergy, and in patients with immune or inflammatory conditions. There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction). Ferinject should only be administered in the presence of staff trained to manage anaphylactic reactions where full resuscitation facilities are available (including 1:1000 adrenaline solution). Each patient should be observed for 30 minutes following administration. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Symptomatic hypophosphataemia leading to osteomalacia and fractures requiring clinical intervention has been reported. Patients should be asked to seek medical advice if they experience symptoms. Serum phosphate should be monitored in patients who receive multiple administrations at higher doses or long-term treatment, and those with existing risk factors. In case of persisting hypophosphataemia, treatment with ferric carboxymaltose should be re-evaluated. In patients with liver dysfunction, parenteral iron should only be administered after careful risk/benefit assessment. Careful monitoring of iron status is recommended to avoid iron overload. There is no safety data on the use of single doses of more than 200mg iron in haemodialysis-dependent chronic kidney disease patients. Parenteral iron must be used with caution in case of acute or chronic infection, asthma, eczema or atopic allergies. It is recommended that treatment with Ferinject is stopped in patients with ongoing bacteraemia. In patients with chronic infection a benefit/risk evaluation has to be performed. Caution should be exercised to avoid paravenous leakage when administering Ferinject. The efficacy and safety of Ferinject has not been investigated in children below 1 year of age. Ferinject is therefore not recommended for use in children in this age group.
Special Populations: In adults and adolescents aged 14 years and older, a single maximum daily dose of 200 mg iron should not be exceeded in haemodialysis-dependent chronic kidney disease patients.
In children aged 1 to 13 years with chronic kidney disease requiring haemodialysis, the efficacy and safety of Ferinject has not been investigated. Ferinject is therefore not recommended for use in children aged 1 to 13 years with chronic kidney disease requiring haemodialysis.
A careful risk/benefit evaluation is required before use during pregnancy. Ferinject should not be used during pregnancy unless clearly necessary and should be confined to the second and third trimester. Foetal bradycardia may occur during administration of parenteral irons, as a consequence of hypersensitivity. The unborn baby should be carefully monitored during administration to pregnant women.
Undesirable effects: Common (≥1/100 to <1/10): Hypophosphataemia, headache, dizziness, flushing, hypertension, nausea, injection/infusion site reactions. Rare (≥1/10,000 to <1/1,000): Anaphylactic reactions. Frequency not known: Kounis syndrome, hypophosphataemic osteomalacia. Please consult the SmPC in relation to other undesirable effects

Legal category: POM
MA Number: PA0949/004/001
Date of Authorisation: 19.07.2007
MA Holder: Vifor France, 100-101 Terrasse Boieldieu, Tour Franklin La Défense 8, 92042 Paris La Défense Cedex, France

Ferinject® is a registered trademark

Document number: IE-FCM-230001
Date of preparation: 06/2023

Additional information is available on request

Adverse events should be reported. Reporting forms and information can be found at: https://www.hpra.ie
Adverse events should also be reported to
Vifor Pharma UK Ltd. Tel: +44 1276 853633.
Email: MedicalInfo_UK@viforpharma.com

Venofer® (iron sucrose)
Prescribing Information - Ireland

For full prescribing information refer to the Summary of Product Characteristics (SmPC)

Active ingredient: Iron sucrose (20mg/mL)
Presentation: Solution for injection/infusion. Available as a 5mL vial (as 100mg of iron).
Indication: Treatment of iron deficiency 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, and in chronic kidney disease when oral iron preparations are less effective. The diagnosis of iron deficiency must be based on appropriate laboratory tests.
Dosage and Administration: The total cumulative dose of Venofer, equivalent to the total iron deficit (mg), must be individually determined for each patient, based on haemoglobin level and body weight and calculated with the Ganzoni formula. The total single dose must not exceed 200 mg of iron given not more than three times per week.
Administration for intravenous drip infusion:
Venofer must be diluted only in sterile 0.9% m/V sodium chloride solution up to a maximum dilution of 1 mg/ml. For iron doses of 50mg, minimum infusion time is 8 minutes. For doses of 100mg, minimum infusion time is 15 minutes. For doses of 200mg, the minimum administration time is 30 min.
Intravenous injection: Venofer may be administered by slow intravenous injection at a rate of 1 ml undiluted solution per minute and not exceeding 10 ml Venofer (200 mg iron) per injection.
Administration into dialysis machine: Venofer may be administered during a haemodialysis session directly into the venous line of the dialysis machine under the same conditions as for intravenous injection.
Contraindications: Hypersensitivity to Venofer or any of its excipients. Known serious hypersensitivity to other parenteral iron products. Anaemia not attributed to iron deficiency. Iron overload or disturbances in utilisation of iron.
Special warnings and precautions: Parenterally administered iron preparations can cause potentially fatal anaphylactic/anaphylactoid reactions. The risk is enhanced for patients with known allergies, a history of severe asthma, eczema or other atopic allergy, and in patients with immune or inflammatory conditions. There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction).
Venofer should only be administered in the presence of staff trained to manage anaphylactic reactions where full resuscitation facilities are available (including 1:1000 adrenaline solution). Each patient should be observed for 30 minutes following administration. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. In patients with liver dysfunction, parenteral iron should only be administered after careful risk/benefit assessment. Careful monitoring of iron status is recommended to avoid iron overload. Parenteral iron must be used with caution in case of acute or chronic infection, asthma, eczema or atopic allergies. It is recommended that treatment with Venofer is stopped in patients with ongoing bacteraemia. In patients with chronic infection a benefit/risk evaluation has to be performed. Caution should be exercised to avoid paravenous leakage when administering Venofer.
Special populations: The use of Venofer has not been studied in children. A careful risk/benefit evaluation is required before use during pregnancy. Venofer should not be used during pregnancy unless clearly necessary and should be confined to the second and third trimester. Foetal bradycardia may occur during administration of parenteral irons, as a consequence of hypersensitivity. The unborn baby should be carefully monitored during administration to pregnant women.
Undesirable effects Common (≥1/100 to <1/10): Dysgeusia, hypotension, hypertension, nausea and injection/infusion site reactions. Frequency not known: Anaphylactoid/anaphylactic reactions and Kounis syndrome. Please consult the SmPC in relation to other undesirable effects.
Legal category: POM
MA Number: PA 949/001/002
Date of Authorisation: 11.09.2009
MA Holder: Vifor France, 100-101 Terrasse Boieldieu, Tour Franklin La Défense 8, 92042 Paris La Défense Cedex, France

Venofer® is a registered trademark

Document number: IE-VEN-220000
Date of preparation: May 2022

Additional information is available on request

Adverse events should be reported.
Reporting forms and information can be found at
http://www.hpra.ie/homepage/about-us/report-an-issue
Adverse events should also be reported to Vifor Pharma UK Ltd. Tel: +44 1276 853633
Email: medicalinfo_UK@viforpharma.com