



## GUIDELINES FOR IRON INFUSION USE IN ADULTS

### SIGNS AND SYMPTOMS OF IRON DEFICIENCY AND IDA IN ADULTS:

Even in the absence of anemia, isolated iron deficiency causes symptoms and warrants investigation and treatment. Early stage iron deficiency can exist without overt anemia, but with other non-hematological symptoms<sup>7</sup> due to deficiency of iron containing cellular enzymes and unsaturated myoglobin. Some patients may be asymptomatic.<sup>13</sup>

<ul style="list-style-type: none"><li>• Fatigue</li><li>• Cold intolerance</li><li>• Headaches</li><li>• Restless leg syndrome*</li></ul>	<ul style="list-style-type: none"><li>• Nail changes, e.g. koilonychia (spoon nails)</li><li>• Angular cheilitis</li><li>• Pica/pagophagia (ice craving)</li><li>• Decreased aerobic work performance</li></ul>	<ul style="list-style-type: none"><li>• Hair loss</li><li>• Adverse pregnancy outcome</li><li>• Impaired immune function</li><li>• Irritability/depression</li></ul>
---	---	--

### INDICATIONS FOR INTRAVENOUS IRON INCLUDE <sup>3</sup>:

- Contraindications to oral iron, or compliance or tolerance (side effect) issues
- Pregnancy (beyond the first trimester) and postpartum if oral iron not suitable or effective, or to prevent physiological decompensation
- Comorbidities which may impact on absorption (e.g. Intestinal mucosal disorders), or bone marrow response
- Chronic kidney disease receiving erythropoiesis-stimulating agent therapy
- Ongoing iron losses that exceed absorptive capacity
- Requirement for rapid iron repletion (e.g. prevention of physiological decompensation or preoperatively for non-deferrable surgery)

### MAKING THE CHOICE

- Oral iron therapy is suitable and effective as first line therapy in most patients, including most obstetric patients with iron deficiency or iron deficiency anaemia. Although the initial rise in haemoglobin (Hb) is more rapid with parenteral iron, the rise in Hb at 12 weeks is similar to that observed during oral iron therapy.<sup>3</sup>
- Iron isomaltoside achieve an increase in Hgb, ferritin, and transferrin saturation (TSAT) at week 1 and 2 better than iron sucrose but by week 8 both preparations are the same.<sup>5,6</sup>

### INTRAMUSCULAR THERAPY

**It is not recommended** due to risks of unpredictable absorption, anaphylaxis, and local complications (e.g. pain, permanent staining of the skin, sarcoma formation).<sup>1,2</sup>

### INTRAVENOUS THERAPY

Two preparations of intravenous iron (IV) are approved for IV use at Brockville Hospital ambulatory Care Program:

- 1- Iron sucrose (Venofer<sup>®</sup>)
- 2- Iron isomaltoside (Monoferric<sup>®</sup>) [Refer to Table 1 for comparison information](#)



## GUIDELINES FOR IRON INFUSION USE IN ADULTS

**Table 1: Comparative Chart between Iron Sucrose and Iron Isomaltoside**

Comparison Parameter	Iron Sucrose (VENOFER®)	Iron Isomaltoside (MONOFERRIC®)
Available strength	20 mg/mL (5 mL vial)	100 mg/mL (1 mL, 5 mL, 10 mL vials)
Recommended total dose for an average weight 70 Kg with target increase of Hbg 3 g /dL	Dose 1000 mg	Dose 2000 mg
Drug cost	\$ 395	\$ 900
Number of visits	3 to 4 visits	2 visits
Infusion time per visit	90 minute	20 minute
Cumulative Infusion time	5 hrs	40 minutes
Additional Cost of labour/ tubing/ minibag	\$ 236	\$58
Total Cost Per Course	\$ 631 (+++)	\$ 958 (+)
Patient Convenience	+	+++
Safety <sup>(1)</sup> : Risk of infusion Reaction	+	+
Increase in Hbg, and ferritin from baseline at week 1, 2 <sup>(6)</sup>	++	+++
Increase in Hbg from baseline at week 4, 8 <sup>(6)</sup>	++	++
Increase in ferritin from baseline at week 4,8 <sup>(5,6)</sup>	++	++
Increase in TSAT from baseline at week 1,2,4 <sup>(6)</sup>	++	+++
Increase in TSAT from baseline at week 8 <sup>(6)</sup>	++	++
Efficacy <sup>(5,6)</sup>	++	++
Contraindications <sup>(8-10)</sup>	<ul style="list-style-type: none"> <li>• Hypersensitivity to product or any component of the formulation</li> <li>• Serious hypersensitivity to other parenteral iron products,</li> <li>• Decompensated liver cirrhosis or active hepatitis;</li> <li>• Non-iron-deficiency anemia (e.g. hemolytic anemia);</li> <li>• Iron overload (e.g. hemochromatosis; hemosiderosis);</li> <li>• History of multiple allergies</li> <li>• 1<sup>st</sup> trimester of pregnancy</li> </ul>	
Common Adverse Reactions <sup>(8-10)</sup>	<ul style="list-style-type: none"> <li>• Hypotension</li> <li>• Headache,</li> <li>• Nausea,</li> <li>• Muscle Cramps,</li> </ul>	<ul style="list-style-type: none"> <li>• Skin rash</li> <li>• Hypophosphatemia</li> <li>• Nausea<sup>(10)</sup></li> </ul>



## GUIDELINES FOR IRON INFUSION USE IN ADULTS

Comparison Parameter	Iron Sucrose (VENOFER®)	Iron Isomaltoside (MONOFERRIC®)
	<ul style="list-style-type: none"> <li>Nasopharyngitis, Sinusitis, Respiratory Tract Infection<sup>(9)</sup></li> </ul>	
<b>Monitoring</b> <sup>(8-10)</sup>	<b>Parameter</b>	<b>Time frame</b>
	<ul style="list-style-type: none"> <li>Hct, Hgb,</li> <li>serum ferritin,</li> <li>iron, transferrin,</li> <li>percent transferrin saturation (TSAT),</li> <li>Total iron binding capacity (TIBC)</li> </ul>	<ul style="list-style-type: none"> <li>When deciding to start or continue IV iron infusion</li> <li>At least 4 weeks after starting IV iron infusion therapy, and continue to monitor monthly (Labwork should be done at least 48 hrs after the last iron dose was given)</li> </ul>
	<ul style="list-style-type: none"> <li>In patients with CKD also receiving erythropoietin ,</li> </ul>	<ul style="list-style-type: none"> <li>Repeat TSAT and ferritin at least every 3 months</li> </ul>
	<ul style="list-style-type: none"> <li>Signs and Symptoms of Hypersensitivity reaction: (wheezing, difficulty breathing, periorbital edema, loss of consciousness, cardiac/ respiratory arrest)</li> <li>Signs and Symptoms of Infusion reaction: (itchiness, warm sensation, urticaria, chest tightness, hypertension, hypotension, back / muscle pain)</li> </ul>	<ul style="list-style-type: none"> <li>During and <math>\geq 30</math> minutes following infusion</li> </ul>
<b>Dosing Considerations</b> <sup>(8-10)</sup>	<ul style="list-style-type: none"> <li>Maximum single dose of iron sucrose in all other patients is 300 mg every week.</li> <li>Maximum single dose of iron sucrose to be given at a time in Non-dialysis CKD patients is 500 mg but <b>with limited experience</b>.</li> <li>Maximum total cumulative iron sucrose dose administered in 14 days is 1000 mg elemental iron.</li> </ul>	<ul style="list-style-type: none"> <li>The maximum single dose 20 mg/Kg or 1500 mg whichever is lower. If the total cumulative dose exceeds these limits, divide in 2 doses by administering the maximum allowable dose in the 1<sup>st</sup> administration, if feasible, and administer the 2 doses at least one week apart.</li> </ul>



## GUIDELINES FOR IRON INFUSION USE IN ADULTS

### DIAGNOSIS AND TESTING OF IRON DEFICIENCY

**Table 2: Laboratory Findings in Iron Deficiency:**

Lab Test	Normal	Iron deficiency without anemia	Iron deficiency with mild anemia	Severe iron deficiency with severe anemia
Hgb	Normal range*	Normal range*	90 to 120 g/L	60 to 70 g/L
RBCs size and appearance	Normal	Normal	Normal or slight Hypochromia (↓ MCHC)	Microcytosis £ (↓ MCV) & Hypochromia (↓ MCHC)
Serum ferritin ¥	Normal 40 to 200 mcg/L	↓ ¶ Less than 40 mcg/L	↓↓ Less than 20 mcg/L	↓↓↓ Less than 10 mcg/L
Serum iron ≠€	Normal	Normal	↓ Less than 10.7 umol/L	↓↓ Less than 7.1 umol/L
Total Iron-binding capacity (TIBC); transferrin	Normal (53.7 to 64.4 umol/L)	Normal (53.7 to 69.8 umol/L)	↑ (62.6 to 71.6 umol/L)	↑↑ (greater than 73.4 umol/L)
Transferrin saturation (TSAT) €	20 to 50%	20%	↓ Less than 20 %	↓↓ Less than 10%
Reticulocyte Hgb	Normal	Normal	↓	Data not available
Bone marrow iron stain	Adequate iron present	Iron absent		
Erythrocyte zinc protophyrin	Normal	Normal	↑	↑↑

Adopted from UpToDate: Causes and diagnosis of iron deficiency. Available at [Link](#). Accessed on Jan 4<sup>th</sup> 2021.

MCHC= Mean corpuscular hemoglobin concentration; MCV mean corpuscular volume; total iron binding capacity; RBC: red blood cell; TSAT: transferrin saturation. TSAT is the ratio of serum iron to TIBC = (serum iron / TIBC X 100)



## GUIDELINES FOR IRON INFUSION USE IN ADULTS

\* The normal range for hemoglobin varies by age and sex (adult men, 14 to 17.5 g/dL; adult women, 12.3 to 15.3 g/dL)

£ *Microcytosis is a late finding of iron deficiency. It may also be caused by thalassemia. Thus the absence of microcytosis doesn't exclude iron deficiency anemia and its presence doesn't confirm it.*

¶ The exact value of serum ferritin is not well established; some clinicians may use a lower value for diagnosing iron deficiency.

¥ Ferritin is diagnostic test of choice but because it is an acute phase reactant it may be unreliable in patients with anemia of chronic disease, and malignancy. Some pregnancies have an acute phase response. Thus, a borderline ferritin should prompts full set of iron studies including serum iron, TIBC, and calculation of TSAT. Higher levels of serum ferritin do not exclude iron deficiency. Serum ferritin may be in the range of (30 to 40 mcg/L) with chronic illnesses such as diabetes or up to 100 mcg/L in CKD, SLE, acute inflammation, liver disease, and idiopathic pulmonary hemosiderosis or rheumatoid arthritis.

≠ Serum iron is low in iron deficiency, anemia of chronic diseases (ACD) and iron deficiency anemia (IDA). However, by itself, it is not diagnostic of any condition and it must be evaluated among other parameters.

€ Serum iron can fluctuate with dietary intake, iron supplementation and diurnally. This can falsely elevate the TSAT by raising serum iron level. To avoid interference draw iron studies test after an overnight fast and at least 48 hrs after the intravenous iron dose.

\*\*Low Serum iron, high TIBC, and low TSAT may help in the diagnosis of iron deficiency especially when serum ferritin is reported normal or high.

**Table 3: Laboratory Findings in IDA Versus ACD:**

LAB TEST	LAB TEST RESULTS IN			
	IDA	ACD	ACD + IDA	IDA during pregnancy
Hgb	↓ Less than 120 g/L			1 <sup>st</sup> trimester : < 110 g/L 2 <sup>nd</sup> and 3 <sup>rd</sup> trimester : < 105 g/L
Serum ferritin	↓	↑	↓ or normal	↓ or borderline
Serum iron	↓	↓	↓	↓
TIBC	↑	↓	↓ or normal	↑ in 2 <sup>nd</sup> and 3 <sup>rd</sup> trimester
TSAT	↓ < 20%	↓ or normal < 24% in CKD	↓ < 20%	↓ < 20%

Adopted and modified from Iron Deficiency – Investigation and management. Ministry of Health Services British Columbia June 15<sup>th</sup> 2010. Available at: [Link](#)



## GUIDELINES FOR IRON INFUSION USE IN ADULTS

### INTRAVENOUS IRON DOSE CALCULATION

Table 4: Recommended Total Iron Dose Based on Weight and Desired Hgb Increase in Adults

Body weight	Recommended Total Iron Sucrose Dose (mg)						
	Desired Hgb Change (g/dL) = Target Hgb – current Hgb						
	1	2	3	4	5	6	7
40	600 mg	700 mg	800 mg	900 mg	1000 mg	1100 mg	1300 mg
45	600 mg	700 mg	800 mg	900 mg	1000 mg	1100 mg	1400 mg
50	600 mg	700 mg	900 mg	1000 mg	1100 mg	1200 mg	1500 mg
55	600 mg	800 mg	900 mg	1000 mg	1200 mg	1300 mg	1600 mg
60	600 mg	800 mg	900 mg	1100 mg	1200 mg	1400 mg	1700 mg
65	700 mg	800 mg	1000 mg	1100 mg	1300 mg	1400 mg	1700 mg
70	700 mg	800 mg	1000 mg	1200 mg	1300 mg	1500 mg	1800 mg
75	700 mg	900 mg	1000 mg	1200 mg	1400 mg	1600 mg	1900 mg
80	700 mg	900 mg	1100 mg	1300 mg	1500 mg	1700 mg	2000 mg
85	700 mg	900 mg	1100 mg	1300 mg	1500 mg	1700 mg	2100 mg
90	700 mg	900 mg	1100 mg	1400 mg	1600 mg	1800 mg	2200 mg
95	700 mg	1000 mg	1200 mg	1400 mg	1600 mg	1900 mg	2300 mg
100	700 mg	1000 mg	1200 mg	1500 mg	1700 mg	1900 mg	2400 mg

Nomogram is based on GANZONI formula for calculating iron deficit

#### HOW TO CALCULATE TOTAL DOSE OF IRON SUCROSE?

<sup>3</sup>Use GANZONI Formula or the nomogram to determine the total recommended dose of iron in mg to reach target Hgb.

Refer to Intravenous Iron infusion order set and Ottawa Hospital parenteral therapy manual for dilution and administration information.

$$\text{Total iron need (mg)} = \text{body weight}^a \text{ (Kg)} \times [\text{target Hgb}^b - \text{actual Hgb (g/dL)} \times 2.4] + \text{iron stores (mg)}^c$$

a. Use ideal body weight for obese patients (i.e. BMI above 30 Kg/m<sup>2</sup>); In Pregnancy, use pre-pregnancy weight or ideal body weight if obese prior to pregnancy.

b: Target Hgb is 15 g/dL but a lower value may be used based on clinical judgement. For pregnant and patients with CKD target Hgb (11 g/dL) <sup>3</sup>

c: The iron stores vary from 500 mg to 1000 or use 10 to 15 mg iron/kg body weight, if weight is 35 Kg or less



## GUIDELINES FOR IRON INFUSION USE IN ADULTS

**Table 3: Factors Predisposing To increased Risk Of Hypersensitivity Reaction To Iron Infusion**

- Previous reaction to intravenous iron.
- Fast iron infusion rate.
- History of other drug allergy or allergies.
- Severe asthma or eczema.
- Mastocytosis.
- Severe respiratory or cardiac disease.
- Old age.
- Treatment with beta-blockers, ACE inhibitors.
- Pregnancy (first trimester).\*
- Systemic inflammatory disease (e.g. rheumatoid arthritis, lupus erythematosus).\*\*
- Anxiety (patient or staff).

<sup>4</sup>Adopted from Rampton D et al. Hypersensitivity reactions to intravenous iron: guidance for risk minimization and management. *Haematologica* 2014; 99 (11) PP. 1671

### REFERENCES:

- 1- Gastroenterological Society of Australia. *Clinical update: Iron deficiency, First Edition*. Sydney, Australia, Digestive Health Foundation, 2008. Available at:
- 2- Silverstein SB, Gilreath JA, Rodgers GM. Intravenous Iron Therapy: A Summary of Treatment Options and Review of Guidelines. *J Pharm Pract.* 2008 Dec;21(6):431–43.
- 3- Iron Product Choice and dose calculation for adults. Guidance for Australian Health Providers. March 2016. Available at: [Link](#). Accessed on Dec 23, 2020.
- 4- Rampton D et al. Hypersensitivity reactions to intravenous iron: guidance for risk minimization and management. *Haematologica* 2014; 99 (11) PP. 1671
- 5- Bhandari S. et al. A randomized, open-label trial of iron isomaltoside 1000 (Monofer®) compared with iron sucrose (Venofer®) as maintenance therapy in haemodialysis patients. *Nephrol Dial Transplant* 2015 ; 30: PP 1577
- 6- Auerbach M. et al. A prospective, multi-center, randomized comparison of iron isomaltoside 1000 versus iron sucrose in patients with iron deficiency anemia; the FERWON-IDA trial. *Am. J. Hematol.* 2019; 94:1007-1014
- 7- Blaustein D A. et al. The safety and efficacy of an accelerated iron sucrose
- 8- Iron sucrose product monograph
- 9- Iron Sucrose Drug Information. UpToDate. Available at: [Link](#) Accessed on Dec 23, 2020
- 10- Iron isomaltoside Drug information. UpToDate. Available at: [Link](#) Accessed on Dec 23, 2020
- 11- UpToDate: Causes and diagnosis of iron deficiency. Available at [Link](#). Accessed on Jan 4<sup>th</sup> 2021.
- 12- KDIGO. Anemia in CKD [Internet]. *Kidney Disease Improving Global Outcomes (KDIGO); 2012 [cited 2019 May 20]*. Available from: [Link](#)
- 13- Iron Deficiency – Diagnosis and management. . Ministry of Health Services British Columbia. April 17<sup>th</sup> 2019. Available at: [Link](#) Accessed on Jan 4<sup>th</sup> 2021