Guidelines for utilisation and administration of erythropoiesis stimulating agents (ESAs) ,intravenous iron and Roxadustat (HIF-PH inhibitor) in adults with chronic kidney disease

Reference no.: CG-CLIN/4654/25

1. Introduction

This document outlines our quality standards for management of Anaemia management of Chronic Kidney Disease (ACKD) using the guidance in the Renal Association Standards Document (Fourth Edition, updated Nov 2010) and NICE guidelines (June 2015, revised 2021).

2. Aim and Purpose

This guideline is to be used across all the renal services at UHDB and acts as a guide to the management of renal anaemia. It is intended primarily to assist the anaemia team and nursing staff in the management of renal anaemia and should be used in conjunction with the clinical opinion of the responsible renal consultant.

All patients receive appropriate anaemia management taking into consideration the patients individual needs. With on-going communication between patient, carer, and primary care provider to ensure safe monitoring of patient's individual treatment plan. This will be overseen by the anaemia nurse specialist and renal consultant.

Through implementation of this guideline, we aim to:

- Optimise the effective use of iron, Erythropoiesis stimulating Agents (ESA's) and Roxadustat (HIF -PH)
- Reduce the need for blood transfusion
- Reduce hospitalisation
- Minimise / improve symptoms of anaemia and Improve quality of life

3. Definitions, Keywords

ACKD	Anaemia management of chronic kidney disease
CKD	Chronic Kidney Disease
eGFR	estimated Glomerular Filtration Rate
ESA's	Erythropoiesis Stimulating Agent
Haematinics	Ferritin level, transferrin saturation, Vit B12 level & Folate level
Hb	Haemoglobin
HIF-PHI	hypoxia-inducible factor prolyl hydroxylase inhibitor
NICE	National Institute of Health and care Excellence

Roxa	Roxadustat (Everenzo)
SJS	Stevens-Johnson Syndrome
TEN	Toxic Epidermal Necrolysis
TDI	Total Dose of Iron

BACKGROUND

ACKD, a common complication of CKD is primarily due to reduction in erythropoietin production and lack of iron (including functional iron deficiency) due to kidney damage. Anaemia usually develops as the eGFR falls below 35ml/min and worsens with declining eGFR. Possible adverse effects of anaemia include reduced oxygen use, increased cardiac output, left ventricular hypertrophy, reduced cognition and concentration, reduced libido, and immune responsiveness.

Effective management is possible using oral and intravenous iron preparations and genetically engineered ESA's or HiFi. Increasing haemoglobin levels results in major improvements in quality of life, exercise capacity, cognitive function, sexual function, nutrition, sleep patterns, immune responsiveness, and cardiac status.

To ensure safe and effective management of renal anaemia, treatment should follow established guidelines.

INITIAL ASSESSMENT

Anaemia associated with CKD should be investigated for the causes and possible treatment irrespective of the grade of kidney disease if their Hb level falls to 110g/l or less

OR

If they develop symptoms of anaemia such as tiredness, lethargy, shortness of breath and palpitations.

CKD should be considered as a possible cause of anaemia in a patient with an eGFR of <30ml/min (< 45ml/min in diabetes) who has had:

- Evaluation and correction of haematinic status
- Consideration of possible blood loss,
- Recognition and treatment of infection/ inflammatory disease
- Optimal treatment of hyperparathyroidism

MANAGEMENT OF ACKD

For all patients check.

Hb, Ferritin, T Sats, B12, Folate, eGFR and PTH.

Reticulocyte count can be helpful.

The aim of treatment is to Maintain the aspirational Hb range between 100 and 120 g/l. Correction to physiologically normal Hb levels with ESAs or HIF-PHI is not usually recommended in people with

ACKD. All patients should achieve an individual target haemoglobin concentration after assessment of their co morbidities and quality of life.

MANAGEMENT OF IRON DEFICIENCY

Iron supplementation is indicated to correct symptomatic iron deficiency therapy to patients with anaemia of CKD who are iron deficient and not receiving ESA/HIF-PHI therapy. Iron is essential to optimise efficacy of ESA and HIF-PHI. Discuss the risks and benefits of treatment options. Take in to account the person's choice.

Absolute iron deficiency in CKD is defined as a serum Ferritin < 100 µg /L however normal or high serum ferritin values (≥100 µg /L) do not exclude iron deficiency, as it could be due to other causes as infection or inflammation.

Iron repletion is usually defined as, ferritin >100 µg /L and TSAT >20%. Serum ferritin should not generally exceed 800 µg /L in patients treated with iron.

Non - Dialysis CKD patients or those with a renal Transplant

Oral iron may be adequate to correct iron deficiency in patients with CKD not receiving dialysis. To minimise side effects and to optimise absorption alternative day dosing rather than multiple daily doses can be considered.

Intravenous iron

Should be offered to patients with absolute or functional iron deficiency anaemia if they are intolerant of oral iron or target Hb level are not reached within 3 months (NICE, 2021).

The standard is Ferric carboxymaltose 1g (Ferrinject) to be given as a TDI.

See appendix 1 for administration details and dosing considerations / special circumstances

Haemodialysis

Measure haematinics three monthly to be reviewed on HD unit rounds. The dosing is based on ferritin unless clinician feels not representative of iron stores.

Iron Sucrose (venofer): is the IV iron of choice. Each Dose is given as a slow undiluted bolus into the venous additive port of the dialysis lines during haemodialysis treatment. Iron is essential to ensure maximum efficacy of ESA. Marrow iron is poorly mobilised in CKD, so repletion of marrow stores is vital.

The following regimes in Table 1 are indictive and can be tailored to the Hb trend.

Table 1 Indicative IV Iron dosing on HD

Ferritin (ug/l)	Iron Supplementation
<200	TDI (Iron sucrose 200mgx1/wk. for 5 weeks) then as per clinician
201-300	Iron sucrose 100mg weekly
301-500	Iron sucrose 100mg fortnightly
501-800	Iron sucrose 100mg monthly

>801	Consider monthly iron at Clinicians discretion consider infection/ inflammation

Consideration for cessation of iron supplementation in HD

Remember that acute inflammation/infection increases the ferritin levels. During or after acute illness the significance of elevated levels should be interpreted individually. In these cases, it would be appropriate to do a TSAT level to aid decision making.

When serum ferritin > 800micrograms/L and or TSAT > 50% iron administration should be reviewed and consideration given to suspending. Iron can be recommenced at a lower frequency when ferritin level is falling.

CRITERIA FOR STARTING ESA or Roxadustat (HIF-PH INHIBITORS)

ESA or Roxadustat (HIF-PH inhibitor) therapy should not be initiated in the presence of absolute iron deficiency without managing the iron deficiency.

Treatment with ESA or Roxadustat (HIF -PH inhibitors) should be considered in patients with symptomatic anaemia when other causes of anaemia unlikely and when Hb is <105g/l. Caution is required in initiating ESA or Roxadustat (HIF -PH inhibitors) in patients with uncontrolled hypertension, history of seizures, active malignancy or history of thrombotic events.

The choice between Subcutaneous ESA (Mircera or Aranesp) and Roxadustat for non- dialysis patients with CKD should be made with the patient.

Roxadustat (Everenzo)

HIF-PH inhibitors are licenced for use in CKD-associated anaemia. Roxadustat (Everenzo) is the only HIF-PH inhibitor currently licenced for use in UK and is approved for use by NICE for adult patients if:

- They have stage 3 to 5 CKD.
- They are iron replete.
- They are not receiving dialysis at the start of treatment.
- Roxadustat may be continued in patients receiving dialysis if treatment was commenced prior to starting dialysis

Roxadustat should not be initiated in.

- Women planning on becoming pregnant or during pregnancy or Breast Feeding
- Patients with severe hepatic impairment
- Patients with Peanut or Soya Allergy or any of the excipients

Starting Roxadustat in ESA naive patients:

- 70mg x3/week if body weight < 100 kg
- 100mg x3/week if body weight > 100 kg

Sometimes the clinician may switch from injected ESA to Roxa for clinical or patient choice reason, see Table 2 for dose conversions from ESA

Table 2 Starting dose of Roxadustat in patients converting from an ESA

Aranesp IV or SC dose (mcg /fortnight)	**Epoetin IV or SC dose (IU/ week)**	**Mircera SC dose (mcg /month)**	**Roxadustat (mg x 3 times /week)**
≤50	≤5,000	≤75	70
50 to 80	5,000 to 8,000	75 to 120	100
80 to 160	8,000 to 16,000	120 to 200	150
≥160	≥16,000	≥200	200

Mircera/Aranesp SC

Subcutaneous Mircera monthly is the preferred choice of ESA **Non - Dialysis CKD patients, Patients on PD or with a renal Transplant** but Aranesp can also be used SC.

Independent administration by patients is desirable whenever possible. Patients should be assessed for self-administration. If this is not a safe and reliable option, explore family support, also Practice nurse or district nurse services can be utilised.

See Table 3 for suggested starting doses by weight.

Aranesp IV

Aranesp IV is the ESA of choice for patients receiving haemodialysis. Each Dose is given into the venous additive port of the dialysis lines during haemodialysis treatment.

See Table 3 for suggested for starting doses by weight. See Table 4 for guidance on dose conversion

Table 3 Starting doses in ESA naïve patients

Body weight (kg)	Aranesp IV or SC dose (mcg/14D)	On dialysis Mircera SC dose (mcg/28D)	Pre-dialysis Mircera SC dose (mcg/28D)
45-60	40	50	30
61-80	60	75	50
81-125	80	100	75
>125	100	120	100

Table 4 Starting dose of Aranesp in patients converting from Mircera

Pre-dialysis Mircera SC dose (mcg/28D)	Aranesp IV or SC dose (mcg/14D)
30	20
50	30
75	50
100	60
150	100
200	120

ADVICE FOR HEALTHCARE PPROFESSIONALS:

Remember that the Red blood cell half-life 6 weeks therefore review of Hb more often should be done with caution and avoidance of repeat changes inside 6 weeks is good practice. Normal changes should only be one stage on the ladder up or down and remember to ensure they are iron replete. Consider reduction of 2 dose stages if rapid rise in Hb possibly coupled with holding dose.

Patients' blood pressure should be controlled before initiating ESA's, NICE (2021) advocate an aspirational BP of < 150/90 mmHg. CKD patients receiving ESA's may be at more risk of hypertension due to the possibility of increased plasma viscosity. Regular blood pressure checks are required to ensure blood pressure is not increasing with Hb.

Treatment may need to be suspended if blood pressure is uncontrolled. Serious loss of blood pressure control related to ESA is more likely when the rate of correction is excessive.

Be aware of very rare cases of severe cutaneous adverse reactions including Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN), in patients receiving ESA.

Advise patients of the signs and symptoms of severe skin reactions at initiation and instruct them to stop treatment and seek immediate medical attention if they develop widespread rash and blistering; these rashes often occur following fever or flu like symptoms.

Discontinue all ESA permanently in patients who develop severe cutaneous adverse reaction such as SJS or TEN.

Report all suspected adverse reactions. For more information please see https://www.gov.uk/drug-safety-update/recombinant-human-erythropoientins-very-rare-risk-of-severe-cutaneous-adverse-reactions-scars

MONITORING and dose optimisation

During correction phase Hb level should be monitored every 2 to 4 weeks until target Hb is reached and reviewed with the clinician

During maintenance phase Hb should be monitored every 4 weeks. In some circumstances in non-dialysis CKD patients longer periods up to 8-12 weeks can be considered in those established on a stable dose of treatment.

Dose adjustments should aim to maintain Hb in aspirational target range of 100-120g/l.

- Avoid frequent dose adjustments.
- Aim to make adjustments based on trends (do not wait to be out of range)

Tables 5 - 9 give guidance on dose adjustments and dosing ladders.

Table 5 Suggested dose adjustment for Roxadustat

Change in Hb over the previous 4 weeks	Current Hb level(g/l)			
	<105	105-119	120-129	>130
>+10g/dl	No change	Reduce dose by one step	Reduce dose by one step	Withhold dose & monitor Hb Resume dosing when Hb is <120 ,at a dose that is reduced by two steps
Between -1.0and + 1.0g/dl	Increase dose by one step	No change	Reduce dose by one step	
<-1.0g/dl	Increase dose by one step	Increase dose by one step	No change	

Table 6 Suggested ESA Dose adjustment guide during maintenance

Change in Hb over the previous 4 weeks	Current Hb level(g/l)		
	<105	105-125	>125
>+1.0g/dl	No change	No change	May need to hold or reduce dose
Between -1.0 and + 1.0g/dl	Consider increase in dose by one step	No change	May need to hold or reduce dose
<-1.0g/dl	Increase dose by one step	No change	No change

Table 7 Dose ladder for Roxadustat

Roxadustat dose ladder										
mg every Monday, Wednesday and Friday	20	30	50	70	100	150	200	250	300	400
Not on Dialysis: Do not exceed dose of 3mg/kg Body Weight or 300mg 3 times per week whichever is lower Dialysis Patients do not exceed 3mg/kg Body Weight or 400mg 3 times per week whichever is lower										

Table 8 Dose ladder for Mircera

Mircera dose ladder						
mcg per 28D	30	50	75	100	150	
mcg per 14D				50	75	100

Table 9 Dose ladder for Aranesp

Aranesp dose ladder						
mcg per 14 D	40	60	80	100	120	150
mcg per 7 D	40	60	80	100	120	150

ESA RESISTANCE

Around 5% to 10% of patients with end-stage renal disease show resistance to ESAs. The commonest causes are under-dialysis, concordance and chronic infections.

After bleeding and haemolysis have been excluded, people with ACKD should be considered resistant to ESA when there is a continued need for the administration of high doses of ESAs to maintain the aspirational Hb range (NICE 2006) This is an indication to Investigate for pure red cell aplasia (PRCA) – Is indicated by a low reticulocyte count, together with anaemia and the presence of anti-erythropoietin antibodies.

Consider referring people with ESA resistance to a haematology service, particularly if an underlying haematological disorder is suspected.

4. References (including any links to NICE Guidance etc.)

National Institute for Health and Care Excellence (2015) Chronic kidney disease: managing anaemia. National Institute for Health and Clinical Excellence (NICE):9-29. - Updated to be replaced by NICE NG203 (2021: section 1.8 Managing Anaemia)

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The Renal Association Clinical Practice Guideline Anaemia of Chronic Kidney Disease. Updated-130220-Anaemia-of-Chronic-Kidney-Disease-1-1.pdf (ukkidney.org)

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Moore, R.A., Gaskell, H., Rose, P. and Allan, J. (2011) Meta-analysis of efficacy and safety of intravenous ferric carboxymaltose (Ferinject) from clinical trial reports and published trial data. BMC Blood Disorders; 11:4.

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5. **Documentation Controls** (these go at the end of the document but before any appendices)

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<tr><td>1</td><td>Jan 2025</td><td>Dr Joanna McKinnell</td><td colspan="2">New guideline</td></tr>
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<tr><td colspan="6">Intended Recipients: All patients under the care of University Hospitals of Derby and Burton renal services . Renal unit of RDH , Lichfield dialysis unit</td></tr>
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Appendix .1

Intravenous iron preparations

Iron sucrose 20mg/ml (Venofer) 100 mg /5 ml vial.

Administered by intravenous injection using undiluted solution of up to 200 mg. Each dose can be administered into the venous additive port of the dialysis lines during haemodialysis treatment .

IV Iron preparation of choice for all haemodialysis patients

Maximum single dose 200 mg (100 mg if patient weighs < 45 kg)

Ferric carboxymaltose 50 mcg /ml (Ferrinject) 1000 mg /20 ml vial

Ferrinject 500 mg - 1000 mg can be diluted in 100mls 0.9% saline infused over 15 minutes (500 mg if patients body weight < 45 kg)

Contraindications

Hypersensitivity to iron sucrose / ferric carboxymaltose or its excipients

Iron overload / acute infection

Intravenous iron use is unlicenced for use in the first trimester (0-12 weeks) of pregnancy.

Risk of hypersensitivity is increased in patients with:

Known allergies.

Those with history of severe asthma ,eczema or other atopic allergy.

Immune / inflammatory conditions (eg, Systemic lupus erythematosus, rheumatoid arthritis)

In these patients, IV iron products should only be used if the benefits are clearly judged to outweigh the potential risks.

Intravenous iron administration

All registered nurses who have been assessed as being competent in University hospitals of Derby and Burton (UHDB) can administer intravenous iron .

Caution is needed with every dose of intravenous iron even if it has been well tolerated previously . Test dose not required.

Patients should be closely monitored for signs of hypersensitivity during and after administration of an iron product .

Administration of intravenous iron should be documented on renal vital data system in addition to the patient's drug card/ prescription.

All female patients under the age of 50 years should be asked if they might be pregnant . Intravenous iron is not licensed for use in the first trimester of pregnancy.

Side effects to both iron preparations are mainly anaphylactoid reactions such as headache, hypotension, nausea , vomiting and dizziness. Patients should be informed of the possibility of

reactions and advised to notify the nurse immediately if they occur. If a patient suffers side effects consider reducing the dose and or rate of administration and discuss with renal anaemia nurse specialists, renal doctors or renal pharmacists.

In the event of anaphylactic reaction discontinue the infusion immediately and seek medical attention .