TREATMENT AND MANAGEMENT OF ANAEMIA ASSOCIATED WITH CHRONIC KIDNEY DISEASE

This guidance does not override the individual responsibility of health professionals to make appropriate decision according to the circumstances of the individual patient in consultation with the patient and /or carer. Health care professionals must be prepared to justify any deviation from this guidance.

INTRODUCTION

The nature and continuing care of patients with renal anaemia requires a collaborative approach between clinicians, specialist nurses, allied health care professionals and patients. A system of shared care; encompassing specialist and primary care optimises care delivery and the continuing management of renal anaemia.

This guideline offers best practice advice on the diagnostic evaluation and assessment of renal anaemia, along with the management and maintenance using erythropoietin stimulating drugs, roxadustat and oral/IV iron.

The patients covered by this guideline are renal patients under the care of renal consultants within the Worcestershire Acute Hospitals Trust.

THIS GUIDELINE IS FOR USE BY THE FOLLOWING STAFF GROUPS:

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This is the most current document and should be used until a revised version is in place

Key amendments to this guideline

Date	Amendment	By:
27.03.12	Extended for 6 months without amendment to allow for further review.	Dr M Ferring
29.05.12	Extended for two years without amendment.	Dr M Ferring
05.08.15	Document extended for 12 months as per TMC paper approved on 22nd July 2015	TMC
10/7/18	Patient pathway updated	Dr M Ferring
7th Jan 2021	Document review date extended by 12 months in line with amendment to Key Document Policy	Dr Ferring
15th December 2021	Document extended for 6 months to allow for thorough review	Specialist Medicine Divisional Governance
17th March 2022	Document extended until the end of the year to allow for thorough review	Dr Jasper Trevelyan
8th August 2022	Document extended for further 8 months, while awaiting inclusion of NICE approved drug into trust formulary	Specialist Medicine Divisional Governance
25th April 2023	Document updated and approved for 3 years	Specialty Medicine DMB/ MSC

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INTRODUCTION

The care of patients with renal anaemia requires a system of shared care between primary and secondary care. The delivery of care is detailed in the following guideline, which applies the principles set out in the NICE guidance NG203 (2021) and TA807 (2022) to the clinical care of Worcestershire patients. Specifically, the guideline addresses the three components of renal anaemia management:

1. Diagnostic evaluation of renal anaemia
2. Anaemia correction using erythropoetin stimulating agents (ESAs), Roxadustat and / or iron, and
3. Maintenance of target haemoglobin (Hb).

Disease Background

Anaemia in patients with Chronic Kidney Disease (CKD) may develop in response to a variety of causes.

Healthy kidneys produce a hormone called erythropoietin that stimulates the bone marrow to produce red blood cells. Moderate to severe CKD may affect the ability of the kidneys to stimulate red blood cell production, resulting in insufficient erythropoietin production leading to the development of anaemia. Erythropoietin deficiency is the primary cause of anaemia associated with CKD and becomes more common as Glomerular Filtration Rate (GFR) declines, it is almost universal in end stage kidney disease.

Other causes of renal anaemia include functional or absolute iron deficiency, blood loss (either occult or overt) and deficiency of folate and or vitamin B12.

Possible adverse effects of anaemia include risk of cardiovascular complications (eg left ventricular hypertrophy), exacerbation of symptoms such as tiredness, lethargy, shortness of breath, reduced cognition and concentration, sleep disturbances and reduced immune response. This can lead to an increase in hospital admissions and impaired quality of life.

If patients with CKD who are found to be anaemic (Hb 110 g/litre or less), NICE guidance NG8 (2015) recommends that these patients are fully evaluated to identify whether any other factors other than erythropoietin deficiency are the cause of anaemia. In particular, iron deficiency is common and should be corrected. prior to commencement of additional therapies. There are two options for treatment of anaemia in CKD3-5 in patients with satisfactory iron stores. These are Erythropetin stimulating agents (ESAs) or Roxadustat. These therapies are discussed in more detail in section ..below

Anaemia treatment should be offered to all patients with CKD “who are likely to benefit in terms of quality of life and physical function”. Therefore, NICE guidance NG8 suggests aspirational Hb range between 100 and 120 g/litre, do not wait until Hb levels are outside the aspirational range before adjusting treatment. (eg take action when Hb levels are within 5 g/litre of the range’s limits)
However full correction of anaemia to the adult Hb reference range is associated with higher mortality, which seems counterintuitive, but has level one evidence.

PROTOCOL

Initial assessment (Algorithm 1)
The likely cause of anaemia needs to be established and confirmed as being due to CKD. Anaemia in CKD is typically normochromic, normocytic, hypoproliferative in the context of a GFR of < 60 ml/min, with a normal white cell and platelet count. Thus, anaemia should be routinely investigated in patients with Hb 110g/l or less of if the patient develops symptoms attributable to anaemia.

Correction of anaemia in CKD (Algorithm 2, 3, 4, table 1 & 2)
The aim of treatment is to maintain the aspirational Hb range between 100 and 120g/ litre. Prior to starting ESA or Roxadustat, the need for iron therapy needs to be assessed. Iron should be given if iron deficiency is confirmed. Iron status should be monitored to achieve a target ferritin of greater than 100mcg/litre and transferrin saturations greater than 20%. A trial of oral iron should be offered in the first instance. If after 1-3 months, satisfactory iron levels are not achieved or oral iron is not tolerated, Intravenous Iron should then be offered. In people treated with iron, serum ferritin levels should not rise above 800mcg/litre. Review the dose of iron when serum ferritin levels reach 500mcg/litre to prevent this from happening.

ESA or Roxadustat treatments are commenced if anaemia without iron deficiency is confirmed. Patients are counselled on, and provided with information on both treatment options. A decision on which agent is initiated takes into account patient and/or carer's preferences and characteristics. These therapies are discussed in more detail below.

Erythropoietin stimulating treatments

They are various brands of ESAs available. Neo-Recormon (Epoetin-Beta) is the most commonly used formulation within WAHT. The required dose for Neo-Recormon is calculated at 60 units/per kg weekly in the first instance. The ESA dose should be adjusted according to the response, i.e. rise of Hb (target 10-20 g/l) achieved by 4 weeks. In order to keep Hb levels within the aspirational range, do not wait until Hb levels are outside the aspirational range before adjusting treatment. (ie take action when Hb levels are within 5g/litre of the range's limits). Further monitoring of Hb every 2- 4 weeks is needed until an Hb of 110g/l is reached.
Poor response to ESA, despite increasing doses, requires further medical assessment of the patient.

Maintenance of stable Hb target in CKD (algorithm 5)
Once target range Hb (100–120g/l) is achieved, the ESA dose is maintained unless there is a further rise in Hb, or reduced if Hb continues to rise. In order to keep Hb levels within the aspirational range, do not wait until Hb levels are outside the aspirational range before adjusting treatment. (ie take action when Hb levels are within 5g/litre of the range's limits). Four-weekly Hb measurements are recommended until Hb stable (i.e. when Hb remains within target range). Thereafter, Hb can be monitored every 3 months, unless there are clinical symptoms of anaemia, angina, heart failure, or there is blood loss. Ferritin, transferrin saturations and BP should be monitored every 3 months if stable.

Blood pressure guideline (BP):
ESA treatment can increase blood pressure and result in uncontrolled hypertension. This may result in accelerated hypertension and hence requires careful monitoring.

- ESA therapy should not be started if blood pressure (BP) is > 160/100mmHg
- In principle BP is best controlled at 140/80mmHg or better by the time ESA therapy is started
- If BP rises > 180/105mmHg during ESA treatment and is still raised after three consecutive readings (within a 1-month time frame) or if the patient is symptomatic with hypertension, further ESA injections should be withheld until BP is adequately controlled. Antihypertensive medications should be reviewed in order to achieve this.

In general, BP should be monitored for the first 2 months at weekly intervals. Thereafter, BP check should be at least once every 2 months. Depending on individual patients' needs, more frequent or less frequent monitoring may be appropriate.

Patient Pathway for patients on ESAs:

For patients opting for ESA therapy, they will be invited to attend the renal anaemia clinic for ESA therapy to be initiated. (Correction phase) During this time where possible patients/carers will be taught how to administer their own injections. At clinic visit 5 patients will have repeat blood tests taken to appraise their response to ESA therapy. Future dose of ESA therapy will then be established (Maintenance phase). At clinic visit 6 patients will be issued with a further 6 ESA injections that will be supplied by pharmacy at WRH and instructions for further administration in the community. Arrangements will be made with the patient to have repeat blood tests taken 4-6 weeks later. This will allow for further monitoring and dose changes as required. Patients will have on going monitoring of blood tests will be undertaken by the Renal Anaemia Team and direct liaison with the patient by telephone regarding their future doses and administration will be made. GP's will be informed by letter. All patients will continue to be seen by the nephrologists during their scheduled renal clinic appointments.

Modifications to this pathway may be considered in exceptional cases to accommodate individual patients' needs (for example patient is too frail to attend anaemia clinic frequently).

Delivery of care and responsibilities ESA's

GP Advice:

Advice on renal anaemia management is given to primary care at each clinic visit in the form of the clinic letter, and the specialist nurse or the nephrologists may be contacted if there are queries outside of clinic visits.

ESA treatment requires regular monitoring of blood pressure, Hb, ferritin and transferrin saturations. It is desirable to share this monitoring with primary care whenever possible for patient convenience.

For patients who are not able to self-administer their own injections, it may be necessary for these ESA injections to be administered by the practice nurse based within local GP surgery's or district nurses for housebound patients.

Supply of ESA:

ESA is currently prescribed via the renal anaemia clinic, and supplied from WRH pharmacy. Alternatively, where appropriate, this may be prescribed by FP10 prescription and posted to the patient who would then obtain it from a local pharmacy.

Roxadustat (Evrenzo)

Roxadustat is also indicated for treatment of adult patients with symptomatic anaemia associated with chronic kidney disease (CKD) stages 3 to 5. It inhibits hypoxia-inducible factor, prolyl hydroxylase (HIF-PH) enzymes, which regulate genes involved in erythropoiesis during the adaptive response to hypoxia. By inhibition of HIF-PH, roxadustat stimulates a coordinated erythropoietic response that includes an increase of plasma endogenous erythropoietin, regulation of iron transporter proteins and reduction of hepcidin (an iron regulator protein that is increased during inflammation in CKD). This results in improved iron bioavailability, increased Hb production and increased red cell mass.

Patient criteria;

- CKD 3-5*
- Hb less than 105 g/l
- Satisfactory iron stores

Patients on renal replacement therapy (RRT) are not included in this guideline

Administration

Evrenzo is taken three times per week on non-consecutive days.
The tablets should be swallowed whole; they cannot be chewed or crushed.
For patients on phosphate binders, or supplements that contain calcium, iron, magnesium or aluminium, roxadustat should be taken 1 hour before or after these agents.

Initial Dosing

Initial dosing of Roxadustat is based on the patient's weight;

Weight up to 100 kg – initiate at 70 mg, 3 times a week.
Weight >100kg – initiate at 100mg, 3 times a week.

Dose adjustment Follow up and Monitoring for patients on roxadustat (table 1)

Hb should be checked every 2 weeks until target Hb of 100-120g/L is achieved.
The dose is adjusted to according to the response in a step-wise approach 4 weeks after initiation, and every 4 weeks thereafter. If, however the Hb increases by more than 20g/L, the dose should be reduced by one step immediately.
The dose adjustment whether up or down, follows a stepwise approach according to the sequence of available dosing.

Stepwise dose adjustment for roxadustat – *see table 1*

20 mg: 40 mg: 50 mg: 70 mg: 100 mg: 150 mg: 200 mg: 250 mg: 300 mg: 400 mg

Once Hb target is achieved and stabilised, Hb should be monitored every 4 weeks or if clinically indicated. Once Hb has been is consistently within target, the frequency of monitoring can be reduced at the clinician's discretion.
Maintenance dose ranges from 20 mg to 400 mg three times per week.

Treatment unresponsiveness
Inadequate response to treatment with roxadustat should prompt a search for causative factors. Nutrient deficiencies should be corrected. Inter-current infections, occult blood loss, haemolysis, underlying haematologic diseases or bone marrow fibrosis may also compromise the erythropoietic response. **In the event of non-responsiveness after 24 weeks of treatment, Roxadustat should be discontinued.**

Table 1: Dose adjustment regimen

Change in Hb over the previous 4 weeks	**Current Hb level:**			
	<105g/L	**105 - 119g/L**	**120 - 129g/L**	**130g/L or higher**
Change in value of more than +10 g/L	No change	Reduce dose by one step	Reduce dose by one step	Pause treatment, monitor Hb level and restart when Hb is less than 120 g/L, at a dose that is reduced by two steps
Change in value between -10 and +10 g/L	Increase dose by one step	No change	Reduce dose by one step	
Change in value of less than -10 g/L	Increase dose by one step	Increase dose by one step	No change	

Switching from ESA therapies to roxadustat

Conversion of non-dialysis patients otherwise stable on ESA treatments has not been investigated. A decision to treat these patients with roxadustat should be based on a risk-benefit consideration for the individual patient.

Table 2: Starting dose of roxadustat to be taken three times per week in patients converting from an ESA

Darbepoetin alfa iv or sc dose (micrograms/week)	Epoetin Beta iv or sc dose (IU/week)	Roxadustat dose (milligrams three times per week)
< 25	<5 000	70
25 to < 40	5 000-8 000	100
40 – 80	8 000-16 000	150
> 80	>16 000	200

Duties of care in the renal anaemia clinic:

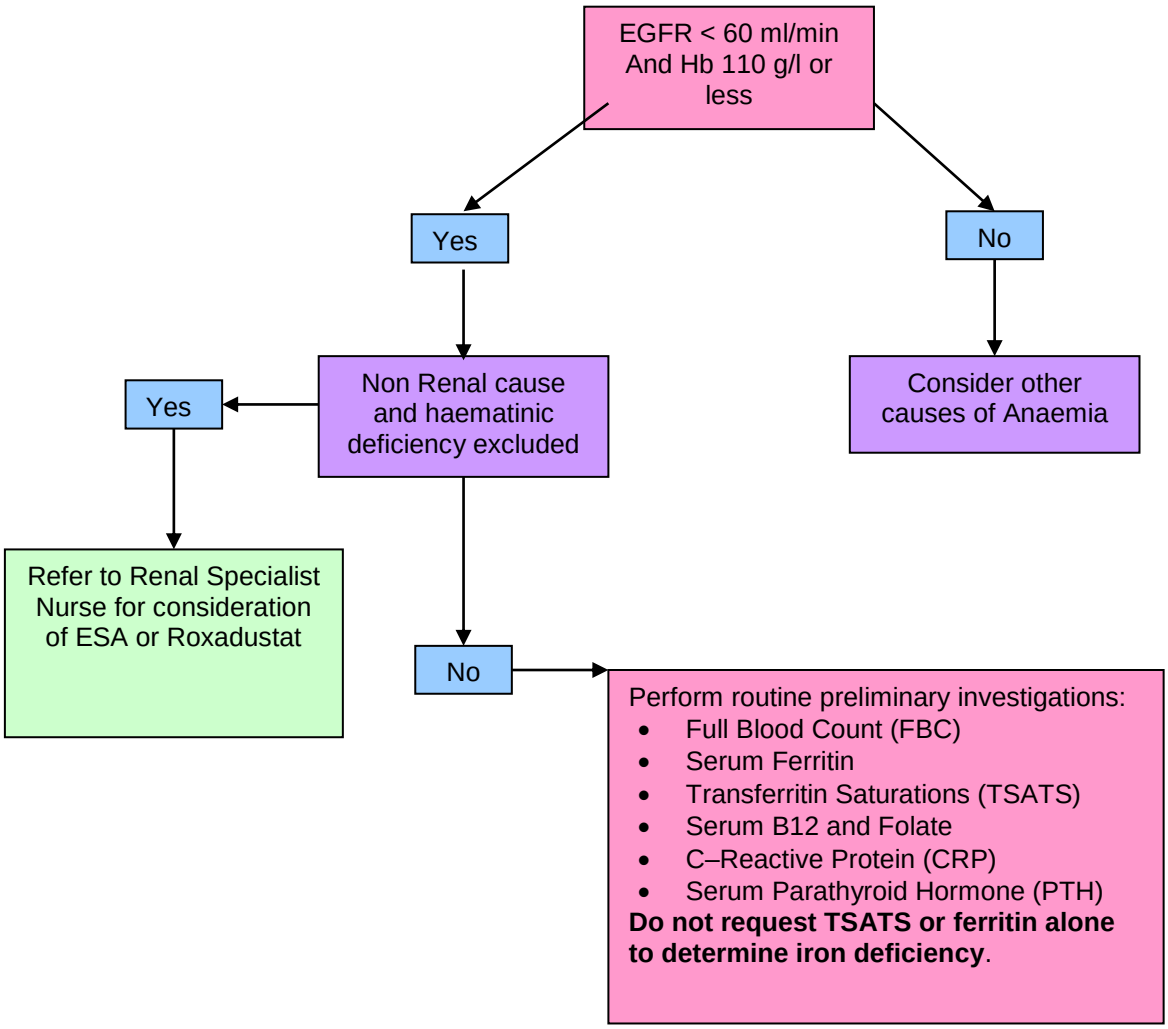
Aim of the renal anaemia clinic:

The renal anaemia clinic aims to provide clinically effective, consistent and safe management of patients with renal anaemia. Patients will be encouraged to participate within their care where possible. All patients will be under the care of a nephrologist within WAHT. Patients with a GFR <60 and Hb level of 110g/l or less will be referred to the renal anaemia service.

All patients will have preliminary investigations performed, and appropriate treatment pathway commenced (Iron therapy and/or ESA or Roxadustat therapy).
In the renal anaemia clinic, the assessment, commencement of appropriate treatment pathway and correction of renal anaemia is carried out by the Renal Anaemia Team, who are supported by nephrologists at WRH. Initial ESA therapy is administered by the Renal Anaemia Team in the clinic setting. Where possible patients/carers are taught how to administer their own injections. Since Roxadustat is an oral formulation, patients can commence treatment at home. Intravenous Iron therapy is administered in our medical day case department at WRH and arrangements for this are made by the Renal Anaemia Team. Practice is guided by trust protocols and algorithms within this protocol which are approved by WAHT Medicines Safety Committee. The nephrologists will be asked to assess patients, in particular if there is suspicion about a non-renal cause for anaemia, if there is poor ESA or Roxadustat response, or if there are problems with blood pressure and / or fluid retention.

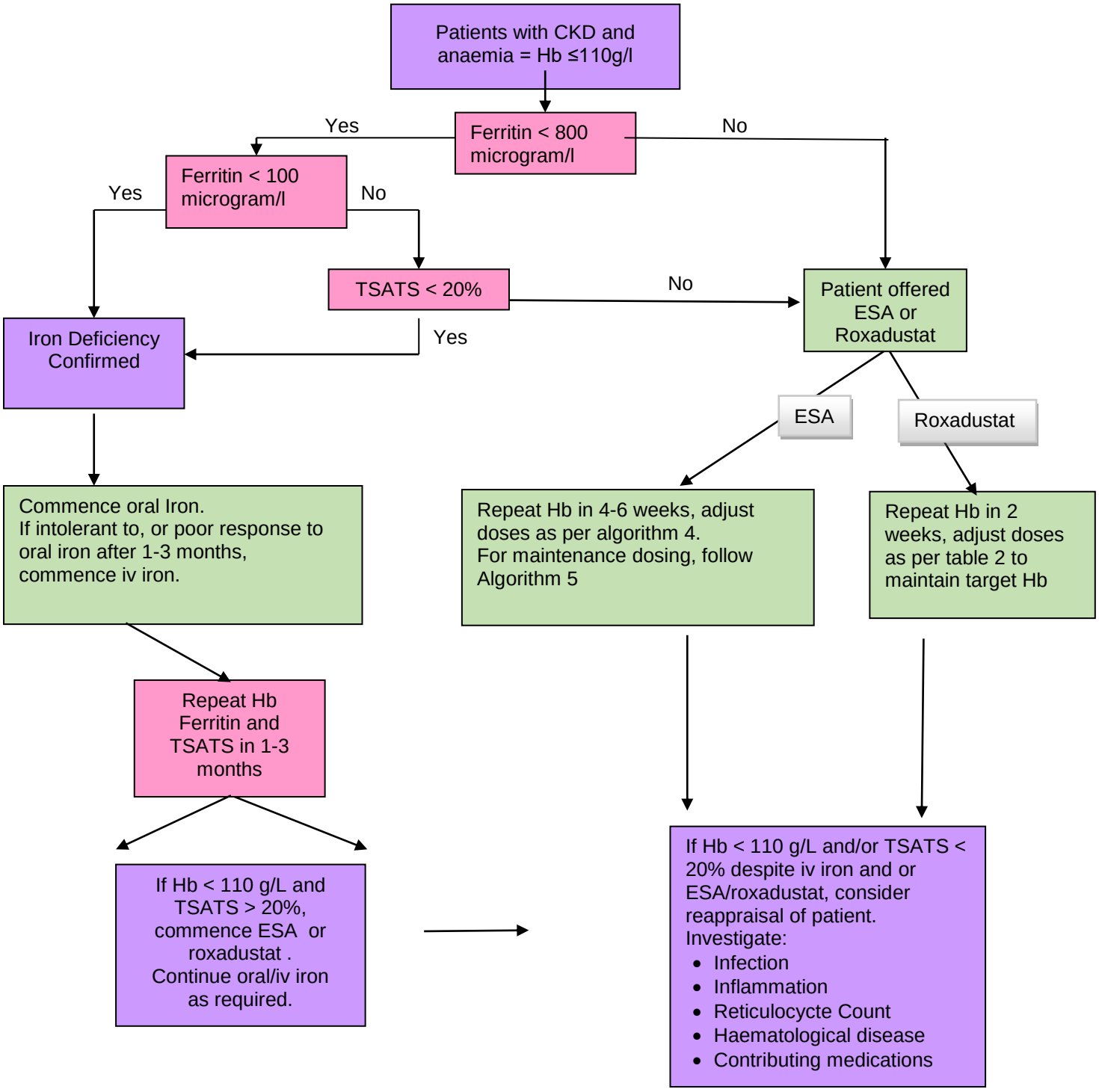
ALGORITHM 1

Algorithm for Diagnosis of Anaemia in CKD Adults



ALGORITHM 2

Algorithm for correction of anaemia in CKD (overview)



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ALGORITHM 3

Algorithm for the administration of IV Ferrinject (Ferric Carboxymaltose) in CKD patients with confirmed iron deficiency anaemia

Intravenous Iron is to be administered in patients with anaemia and iron deficiency defined as:
Hb<110g/l
Ferritin <100mcg/l or
TSATS <20%.

Who have not responded to a 1-3 month trial of oral iron or in patients who are intolerant of oral iron.

Hb [g/L]	**Patient weight**		
	<35 kg	**35-69kg**	**≥70kg**
<100	500mg	1500mg*	2000mg*
100-125	500mg	1000mg	1500mg*

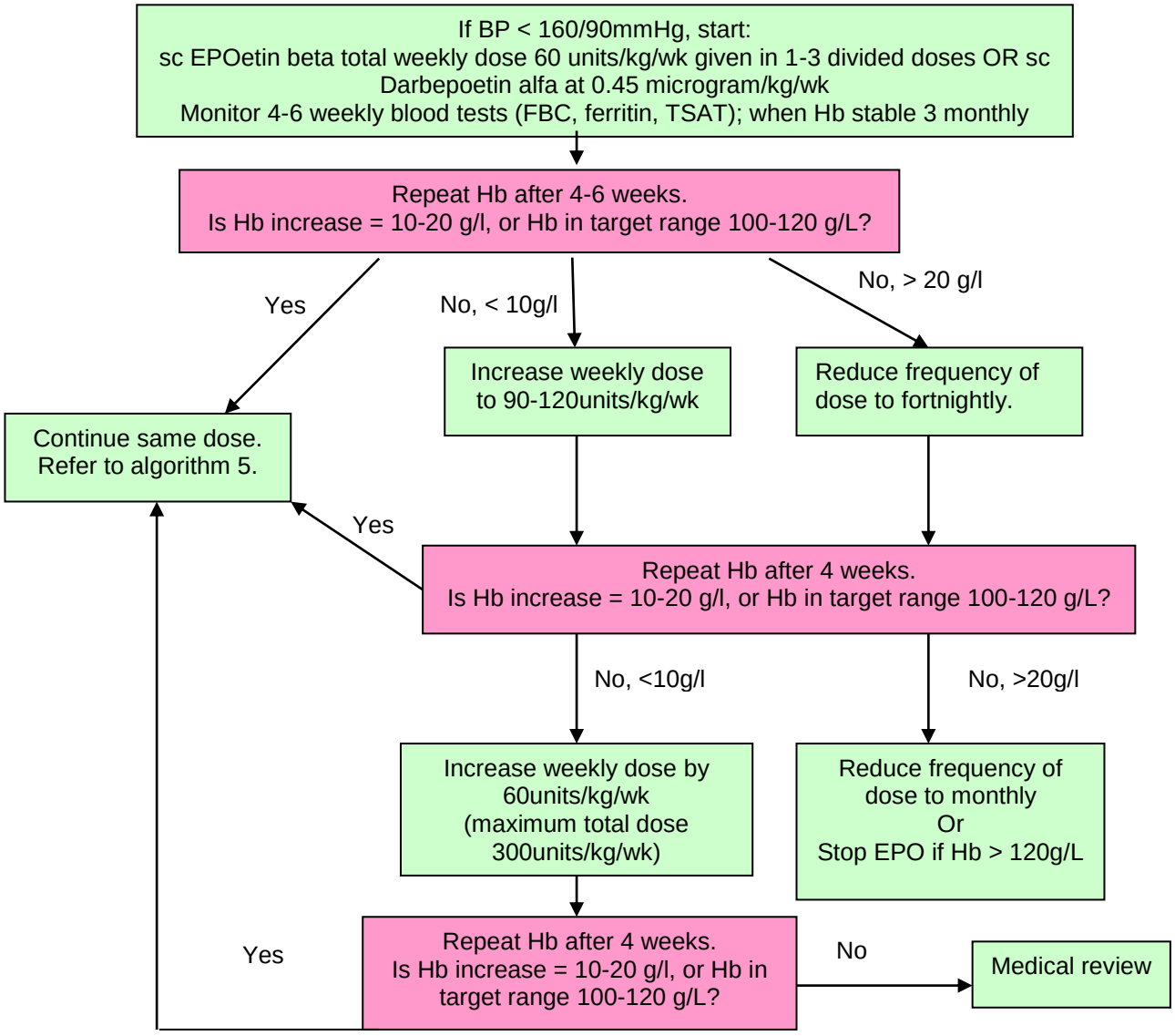
(*) Maximum weekly dose of iv ferric carboxymaltose is 1000 mg

1. A maximum injection of 1000 mg IV ferric Carboxymaltose can be given per week.
2. A further dose of IV iron is considered at the earliest a month later in the light of repeat blood tests (Hb, ferritin, TSAT) at 4-6 weeks if these still indicate anaemia and iron deficiency.
3. IV ferric Carboxymaltose is contra-indicated if known allergy to any IV iron preparation.
4. Caution: avoid if known severe asthma or allergic disorder; avoid in untreated acute infection.
5. Hb, Ferritin and TSATS to be checked 1month post treatment and 1-3 months thereafter.

Date	**Dose**	**Prescribed by**	**Time**	**Administered by**	**Checked by**
	Ferric Carboxymaltose **…….mg In 250 ml sodium chloride 0.9% over 30 minutes**				

ALGORITHM 4

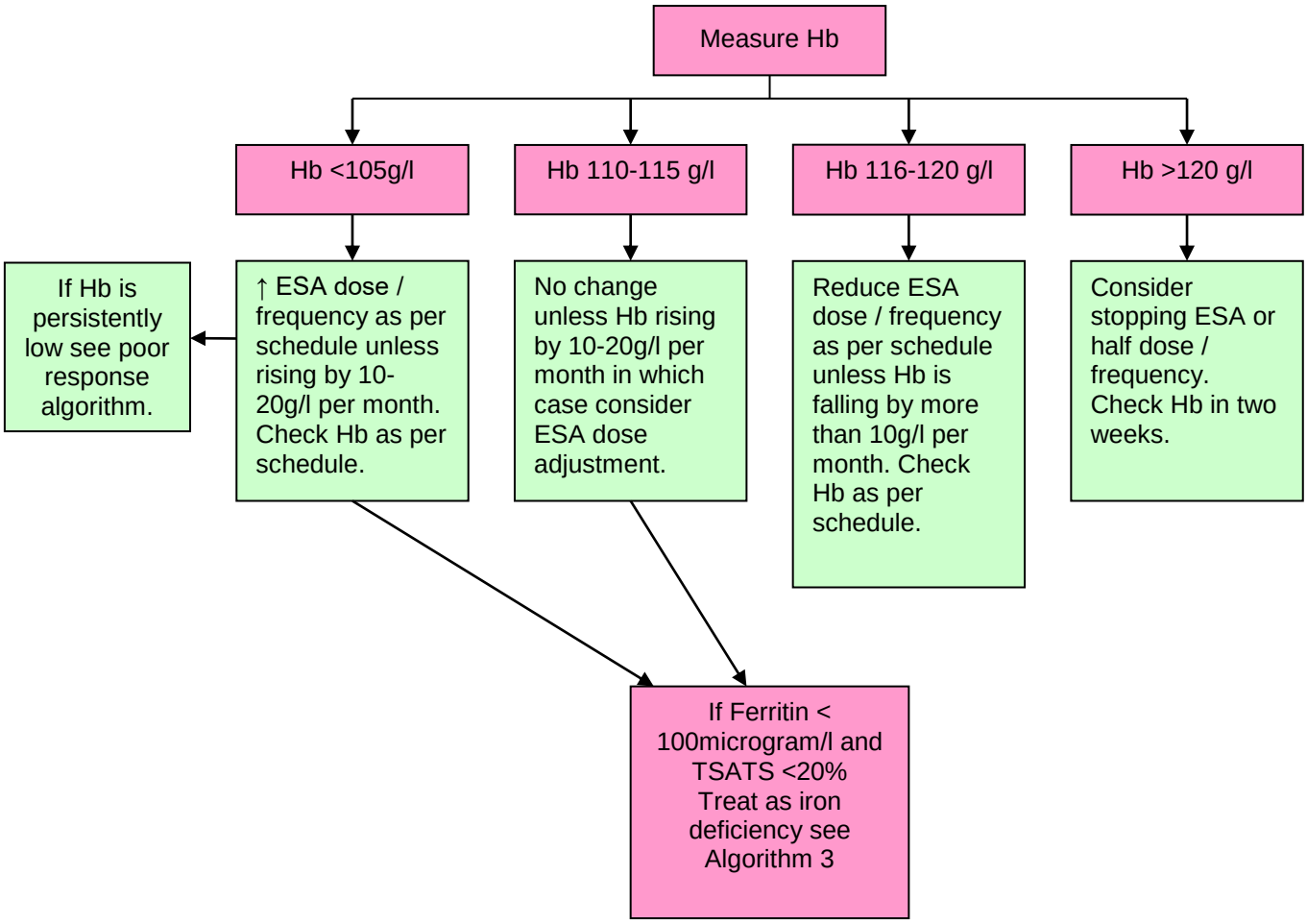
Algorithm for ESA prescribing for correction of anaemia



Whilst managing ESA, always continue to review and optimise iron status if there is iron deficiency (algorithm 2 and 3)

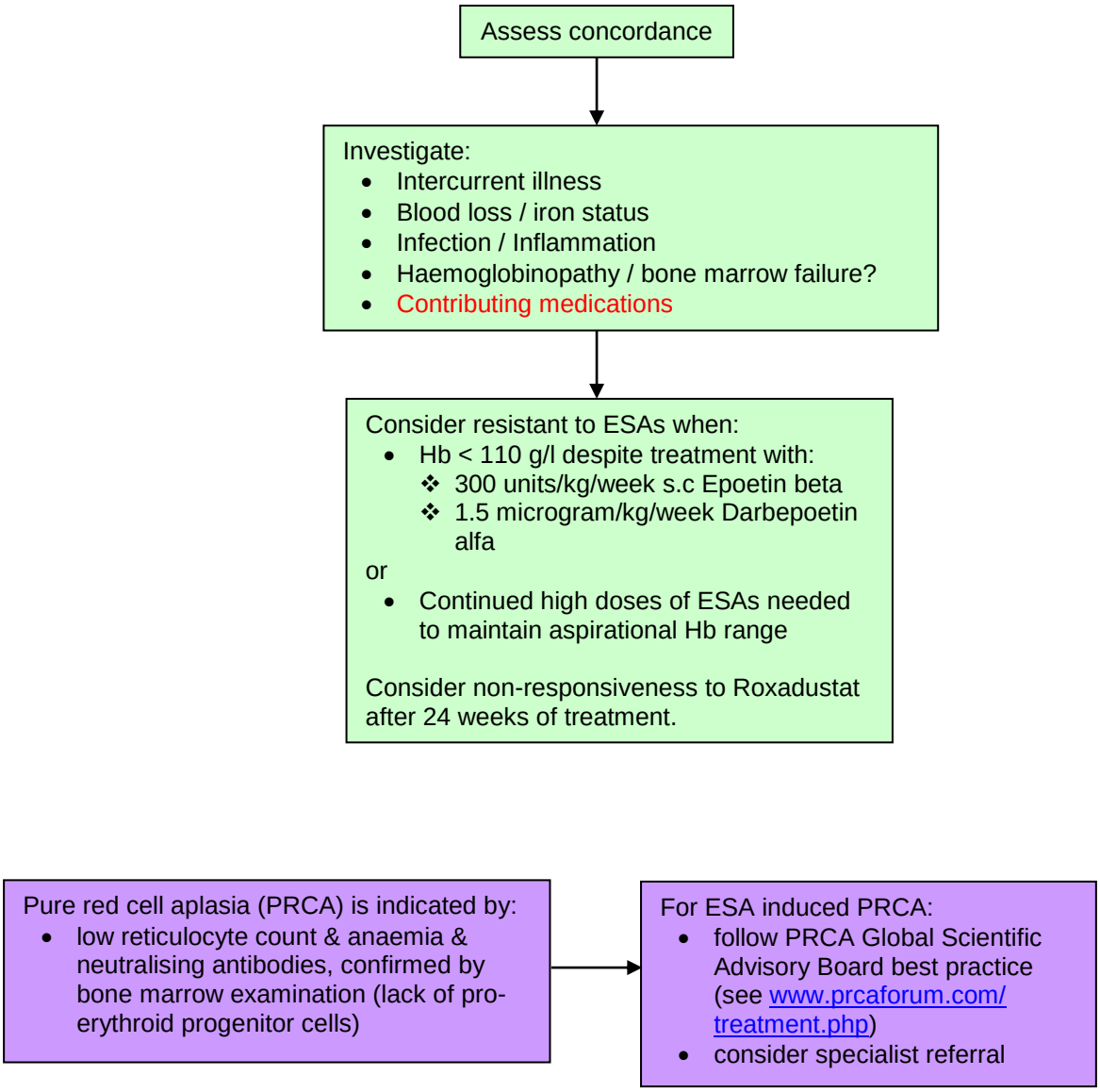
ALGORITHM 5

Algorithm for Hb Maintenance



ALGORITHM 6

Algorithm for poor response to ESA or Roxadustat



MONITORING TOOL

How will monitoring be carried out?
The Renal Anaemia Team monitors patients after initiation of anaemia treatment through appropriate blood tests and adjusts treatment by algorithms.
Also patients treated through the renal anaemia nurse continue to attend the renal clinic where they see the renal consultant who reviews all renal aspects including anaemia.

Who will monitor compliance with the guideline?
Renal nurse specialist / renal team to audit renal anaemia practice

STANDARDS	%	CLINICAL EXCEPTIONS
Full renal anaemia work-up blood tests on all new patients	100	Patient declines
Blood test monitoring after initiation of anaemia treatment	100	Patient declines
Administration of iv iron treatment if oral iron fails / not tolerated	100	Iv iron contra-indicated eg asthma or acute infection
EPO dose reviewed after 4 weeks and again within 3 months of initiation	100	Patient declines blood test
Roxadustat dose reviewed 4 weeks after initiation then 1-3 monthly thereafter	100	Patient declines blood test

REFERENCES

1. National Institute for Clinical Excellence (2021) Chronic kidney disease: assessment and management [NG203].; accessed via: https://www.nice.org.uk/guidance/ng203/chapter/Recommendations#monitoring-anaemia-treatment.

2. Roche (2006) Information for patients with anaemia and kidney disease. Welwyn Garden City.

3. Summary of product characteristics for IV ferric carboxymaltose; accessed via: https://www.medicines.org.uk/emc/product/5910/smpc

4.Roxadustat for treating symptomatic anaemia in chronic kidney disease: Technology appraisal guidance [TA807]: https://www.nice.org.uk/guidance/ta807

5. Medicines (emc):https://www.medicines.org.uk/emc/product/12835/smpc#gref

6.Scottish Medicine Consortium: https://www.scottishmedicines.org.uk/medicines-advice/roxadustat-evrenzo-full-smc2461/

7. European Medicines Agency: https ://www. ema.europa. eu/en/medicines/ human/ EPAR/ evrenzo

8. Summary of product characteristics for Evrenzo https://www.ema.europa.eu/en/documents/product-information/evrenzo-epar-product-information_en.pdf

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