University Hospitals Coventry & Warwickshire NHS Trust Clinical Guideline (full)
Anaemia management for chronic kidney disease, peritoneal dialysis, renal transplant and haemodialysis patients

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Superseded UHCW Clinical Guideline(s): (if applicable)	V7
UHCW Associated Records:	
Keywords:	Anaemia Haemoglobin Iron management

Clinical Operating Procedures relating to this guidance (please list)	
Summary version available	☐

Guideline clinical content

Clinical Guidelines assist in decision-making; they do not replace clinical judgement. Regardless of the strength of evidence, it remains the responsibility of the clinician to interpret the application of the clinical guidance to local circumstances and the needs and wishes of the individual patient. Where variations of any kind do occur, it is important to document the variations and the reason for them in the patient's health record. If in doubt, seek senior advice.

Introduction
(Why this Trust-wide Clinical Guideline is necessary. Include reference to any relevant national guidelines, statutory requirements or other recommendations Identify the risk(s) the guideline will address.)

The management of anaemia should be considered in people with Chronic Kidney Disease when their haemoglobin (Hb) level is less than 110g/L. (NICE clinical guideline 114. 2011).

Uraemic patients derive considerable benefit from the correction of anaemia with ESA therapy, to avoid long-term complications. Anaemia itself is associated with the development of cardiac damage because of extra work to maintain adequate tissue oxygenation.

Prospective randomised controlled trials of patients on dialysis have shown that treatment with ESAs results in improvement in quality of life, exercise capacity, cardiac function, and cognitive function. (Renal Association Clinical Practice Guidelines - 2010).

There are several possible explanations for anaemia in CKD patients, but relative deficiency of iron and erythropoietin are usually dominant as the glomerular filtration rate falls. Erythropoietin is a hormone produced by the kidneys in response to reductions in oxygen delivery in anaemia.

Evaluation should include other factors which can cause anaemia, including blood loss, inflammation, infection, hyperparathyroidism etc. As far as possible, other causes of anaemia must be diagnosed and corrected before commencing Erythropoeitin Stimulating Agents (ESAs).

For ease of understanding this guideline please be aware of the following classifications:

- A stable or 'maintenance' patient has Hb level in the target range of 105 – 115 g/L.
- A stable or 'maintenance' patient has a Reticulocyte haemoglobin equivalent (Ret-He) level > 29 pg.

Detecting ESA Resistance – After other causes of anaemia, such as intercurrent illness or chronic blood loss have been excluded, people with anaemia of CKD should be considered resistant to ESA's when an aspirational Hb range is not achieved despite treatment with 1.5mcg/kg/week Aranesp. e.g. approximately 100 mcg/week for a 70 kg patient

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Standardised, clearly documented and evidence based prescribing, using a clearly defined guideline, will enable audit of results achieved against the Renal Association Standards (2010) and Nice Guidelines in Anaemia Management 114 (2011) and Chronic kidney disease: managing anaemia NG8 (2014).

To standardise the management of renal anaemia, including criteria for the administration of a blood transfusion, iron supplementation, dose of Erythropoeitin Stimulating Agents (ESAs), optimal rate of correction of anaemia and target haemoglobin.

This clinical guideline will apply to all clinical staff in Renal Services caring for patients with Chronic Kidney Disease (CKD), including pre-dialysis, conservative management patients and who receive renal replacement therapy (peritoneal dialysis, haemodialysis or transplant).

This guideline is classified as an 80:20 guideline: this refers to care that will be given to the majority of renal patients. There will be a smaller group of patients who will require alternative medical interventions as deemed appropriate by the clinical team. The 80:20 approach provides basic guidance for junior doctors and renal nurses to make clinical decisions in the majority of cases.

In all cases when advice from a senior colleague is recommended, communication should follow the SBAR principle.

Definitions
(List and define terms / abbreviations / acronyms used in the document. If there are none, write NONE)

Anaemia is defined as a state in which the quality or quantity of circulating red blood cells is below normal (NICE 2015).

Blood haemoglobin (Hb) concentration serves as the key indicator for anaemia because it can be measured directly and has an international standard (NICE 2015)

Guideline details
(This is the main body of the guideline containing the detailed requirements, which will support implementation and decision-making. Use subheadings as required.)

Consent

Healthcare professionals should follow the Department of Health's advice on consent. If someone does not have capacity to make decisions, healthcare professionals should follow the Code of Practice the accompanies the Mental Capacity Act and the supplementary Code of Practice on Deprivation of Liberty Safeguards (NICE 2015)

Patient Education

All renal patients will have information provided for them on lifestyle and health promotion and adaptation to chronic disease in the form of structured planned education on anaemia management. The content will be relevant to a renal patient's clinical and psychological requirements which are adaptable to their educational and cultural background.

Blood Pressure Management for Haemodialysis patients (on ESA Therapy)

It is difficult to define an absolute BP level at which ESA should be withheld. The decision to withhold an ESA dose depends on previous stable BP levels and whether there is a progressive rise. Note that particular caution is needed following ESA dose change during either induction or maintenance phase of treatment.

Any patient who shows a trend of increasing BP should have an early medical assessment at a HD QA review.

Any asymptomatic patient with an unexplained high BP reading should be assessed by a Registered Nurse on the following dialysis day and, if BP still high, have a medical review.

If a patient is symptomatic, for example, headache, shortness of breath with unexpected high BP then immediate medical assessment may be required.

Monitoring Blood Pressure for all other CKD patients

Blood pressure will be monitored in clinics and at home and if blood pressure increases, Renal Nurse Specialists will discuss with medical staff.

The Administration of a Blood Transfusion

In CKD patients in whom kidney transplantation is a treatment option, blood transfusions should be avoided where possible. (NICE Guideline 114 and Renal Association Guideline 5.1).

CKD patients with multiple co-morbidities, particularly Ischaemic Heart Disease, may require transfusion at a higher Hb than 75g/L, but a blood transfusion should only be prescribed by a member of the Renal Medical team at UHCW when clinically indicated and the patient is symptomatic, for example, with angina. The cause of the anaemia should be investigated and treated accordingly to avoid the need for further blood transfusion.

In asymptomatic patients with anaemia, there may be situations where a blood transfusion is clinically indicated (NICE 2015) and prescribed by a member of the Renal Medical team at UHCW. In Stable CKD patients with Hb below 75g/L a blood transfusion may be prescribed – see Appendix 1. An alternative approach is to start Iron (IV or oral) and ESA together, particularly if the patient is well and on the transplant list. When ESA and iron are started together, particular attention should be paid to the rate of rise in haemoglobin.

Role of blood transfusion in managing ESA resistance

- Consider referring people with ESA resistance to a haematology service, particularly if an underlying haematological disorder is suspected. (NICE 2015)

- Evaluate and discuss the risks and benefits of red cell transfusion with the person or, where appropriate, with their family or carers. (NICE 2015)

- Take into account the person's symptoms, quality of life, underlying conditions and the chance of a future successful kidney transplant, in addition to Hb levels, when thinking about the need for red cell transfusion**.** (NICE 2015)

- Consider a trial period of stopping ESA in people who have ESA resistance. Review the rate of red cell transfusion between 1 and 3 months after stopping ESA therapy. If the rate of transfusion has increased, consider restarting ESA therapy.**(NICE 2015)**

Diagnostic tests to determine iron status and predict response to iron therapy

To diagnose iron deficiency use reticulocyte Hb content (CHr; less than 29 pg) or reticulocyte Hb equivalent.

- If the person has thalassaemia or thalassaemia trait, use a combination of transferrin saturation (less than 20%) and serum ferritin measurement (less than 100 micrograms/litre). **NICE 2015]**

<u>Iron Deficiency in CKD patients</u>

Iron deficiency is the most common cause of poor response to ESA's ((Li et al 2003)

Iron deficiency anaemia should be considered/diagnosed in people with Stage 3 - 5 CKD if the Ret-He level < 29pg

ESA therapy should not be initiated in the presence of iron deficiency without also managing the iron deficiency (NICE 2011)

Patients in the maintenance phase of ESA therapy should have Ret-He >29p

<u>Monitoring Iron Levels</u>

Oral iron is often poorly absorbed in patients with renal failure and intravenous treatment may be required. However, a 3 month trial of oral iron should normally be given in CKD and PD patients before the commencement of intravenous (IV) iron. The BNF has the following warning:

A European review was initiated due to safety concerns regarding the risk of serious hypersensitivity reactions, including when used during pregnancy. All IV iron products can cause serious hypersensitivity reactions, these may occur even when a previous administration has been tolerated (including a negative test dose). Fatal outcomes have been observed.

The other practical reason why oral iron should be started first in CKD and PD is that it can be initiated and continued in primary care – sometimes the only treatment that is required in CKD is oral iron – ie it is simple, cheap, safe and effective.

HD patients are different - in the majority of patients, absorption of oral iron is insufficient to avoid a negative iron balance, and consequent iron deficiency

Target ret-He level > 29pg in all CKD patients (NICE 2014)

Serum ferritin levels should not rise above 800mcg/l. In order to prevent this iron dosage is reviewed when serum levels reach 500mcg/l (NICE 2011), in the absence of acute or chronic sepsis.

A high Hb is <u>not</u> a reason for reducing iron replacement in haemodialysis patients, apart from those few patients with a confirmed diagnosis of polycythaemia, who may benefit from being iron deficient

1: Haemodialysis Patients: Patients will routinely be treated with Intravenous Iron Sucrose (Venofer). Iron carboxymaltose (Ferinject) may be used in cases of intolerance to Venofer

a) Maintenance IV Iron is given as a regular supplement to **haemodialysis patients** to prevent iron deficiency.

Home Haemodialysis Patients:

It is acknowledged that there is an MHRA Drug Safety Update in place which advises the risk of hypersensitivity reactions in patients receiving intravenous iron preparations. This recommends only administering iv Iron where there are staff trained to evaluate and manage anaphylactic or anaphylactoid reactions as well as resuscitation facilities available.

After reviewing the literature and consulting with other national Home HD Leads it was felt that this risk is small. In the context of patients receiving Home HD, itself a treatment which carries a risk of complications, it is felt acceptable to offer iv Iron therapy at home if the patient wishes and consents following discussion of these risks. This practice is followed at other Home HD centres throughout the UK.

Therefore if a patient on Home HD requires iv Iron therapy these risks should be discussed with them and two options offered;

1. Intravenous Ferinject to be given on the Renal Day Unit as required (expected to be 2-6 monthly)

2. Intravenous Venofer supplied to be given at home as per the

Venofer Procedure for in-centre HD. Patients should be given:

- A copy of the MHRA guidance (Appendix 5)
- A copy of the iv Iron consent form. One copy should be signed and placed in the case notes (Appendix 6)
- A copy of a letter from MHRA to Dr Lipkin on behalf of the UK Home HD Group (Appendix 7)

2: Continuous Ambulatory Peritoneal Dialysis (CAPD), Automated Peritoneal Dialysis (APD) and those not on dialysis.

Early detection of iron deficiency from Stage 3 CKD is a key component of anaemia management. CKD Stage 3 and Peritoneal Dialysis patients should receive oral iron for a trial period of 3 months and the response reviewed.

The BNF states: Parenteral iron is generally reserved for use when oral therapy is unsuccessful because the patient cannot tolerate oral iron, or does not take it reliably, or if there is continuing blood loss, or in malabsorption. With the exception of patients receiving haemodialysis, parenteral iron does not produce a faster haemoglobin response than oral iron provided that the oral iron preparation is taken reliably and is absorbed adequately.

Indications:

All patients with Ret-He < 29pg should receive an iron supplement prior to commencing ESA therapy.

Consider causes for anaemia other than iron deficiency.

There are two IV Iron preparations available to this group of patients:

Iron sucrose (eg, Venofer) can be given intravenously once a week

Iron carboxymaltose (Ferinject) can be given as a single total dose

Dosing regimen for CKD and PD should be based on a calculation of iron deficiency

Monitoring Haemoglobin Levels

Ideal target 105 – 115 g/L - Audit range: 100-120g/L (NICE, 2015).

Patients being treated with ESA should have their Hb level monitored:

every 2–5 weeks in the induction phase of ESA therapy

every 1–3 months in the maintenance phase of ESA therapy (NICE 2015)

Take action when HB levels are within 5g/litre of the audit range limits (NICE 2015)

Patients on hospital haemodialysis will have bloods taken every 5 weeks to fit in

with HDQA, or as clinically indicated

Patients who are pre-dialysis or receiving CAPD/APD patients on ESA will have 3 monthly bloods taken or as clinically indicated.

Planning the commencement of ESA Therapy

Medical staff should consider any patient who fits the criteria above for treatment, check the basic lab screen as detailed below to initiate treatment for commencement of ESA.

Patients must be iron replete to achieve and maintain target haemoglobin whether receiving ESA therapy or not. (Renal Association Guideline 3.1)

Basic lab screen - required for any patient being considered for treatment with ESAs (Renal Association Guideline 1.6) :

-Full blood count
-Ret-He and Ferritin
-CRP – to assess inflammation
-B12, folate

-

Extended lab screen (only if clinically indicated)
Additional investigation of anaemia which should be carried out prior to commencement of ESAs where there are clear clinical indications.

- Investigation for occult gastrointestinal blood loss
- Myeloma screen
- Serum aluminium (if the patient is taking aluminium phosphate binders)
- PTH
- Investigations for haemolysis – eg DCT, blood film, LDH and Haptoglobin
- Haemoglobinopathy screen
- Reticulocyte count- to assess bone marrow production of Hb (optional).
- Bone marrow examination

Measurement of Erythropoietin levels and antibody levels for the diagnosis or management of anaemia should not be routinely considered for people with anaemia of CKD.

It is important to control BP before initiating ESA therapy,

Consult the shared cared guidelines, which define roles and responsibilities of secondary care, when managing and monitoring the treatment of patients with anaemia of CKD.

A patient centred care plan should include:

- continuity of drug supply
- flexibility of where the drug is delivered and administered
- the lifestyle and preferences of the patient
- desire for self-care where appropriate
- regular review
- appropriate route and frequency of administration of ESA
- effective documentation is evident which is accurate and transparent

Treatment with Erythropoeitin Stimulating Agents

Dose and regimen will depend upon body weight and eGFR and the product to be prescribed. Occasionally, iron therapy and ESA may be started at the same time. Once a stable target Hb has been achieved the Hb should be monitored every 1 – 3 months in Chronic Kidney Disease (CKD and CAPD patients who are clinically stable

ESA's need not be administered where the presence of co-morbidities, or the prognosis, is likely to negate the benefits of correcting the anaemia (NICE 2011).

ESA Therapy and Cancer Patients

NICE guidelines advise that patients who are already on ESA and then develop cancer can continue to use ESA.

Decisions about ESA use in renal patients with cancer should only be made after discussion with the patients Consultant.

ESA Therapy and Transplant Patients

Newly transplanted patients occasionally need temporary ESA therapy. Therefore consider:

If Hb $\leq$ 70g/L consider blood transfusion with or without ESA

If Hb $\geq$ 70 – 100 g/L – consider commencing ESA therapy

Stop ESA therapy when Hb is 110g/L (usually 1 – 2 months later).

Correction Phase

If a patient's Hb is above the target range on repeated measurement consider the following:

- 50% ESA dose reduction or alternate dose (whichever is more convenient to the patient)
- Rarely ESA is withheld for a period of time. If this is the case a specific plan for re-starting must be in place, usually when Hb falls to <120g/L
- Consider losing a circuit if Hb $\geq$ 135g/L

If a patient's Hb is below the target range consider:

- If Hb $\leq$ 100g/L – Increase ESA by 25%, wait approximately 4 weeks increase ESA dose again. If ESA resistant carry out a non- response screen

Dose changes must be discussed at the patients QA review.

During a correction phase a patient must have a management plan in place, an assessment of the following must be included in the plan

Hb checked more frequently
- Assessment of the patient's blood pressure

Please note: the frequency of assessment as above will be different whilst the patient is in the correction phase compared to the maintenance phase

Monitoring Haemoglobin after initiation of ESA

The ideal rate of rise of Hb following initiation of ESA is 7g/L/month. A rate of 20g/L/month should not be exceeded.

To keep the Hb level within range, do not wait until Hb is outside the range - take action if there is a trend when Hb levels are within 5 g/L of the range limits (NICE 2011) ie 100-105 and 115-120 g/L

ESA dose should be increased / decreased using the dosage table(Appendix 4) when repeated Hb measurements fall out of range 105-115g/L – it is rarely appropriate to change ESA dose because of a single reading, unless this is part of a clear trend..

If Hb rises too high, for example, > 125 g/L the following actions may be appropriate:

1. Reduce ESA by one or two stages.

2. Consider discontinuing ESA, but arrange appropriate frequency of Hb monitoring and restart ESA soon after Hb fall into target range. (Do NOT let Hb fall too low). It will usually be appropriate to restart ESA at a lower dose.

3. If Hb very high, consider losing a circuit or venesection (Hb ≥ 135 g/L)

Be particularly careful to control BP and to treat any rapid rise in BP, irrespective of absolute BP reading, in patients with a high or rapidly rising Hb. ESA-associated hypertensive encephalopathy is a real risk in these patients.

Monitoring anaemia status during the maintenance phase – for all patients on ESA therapy

Blood Test	Patient Population	When
Haemoglobin	Haemodialysis CKD/PD/Txp	5 weekly 3 monthly
Ret-He	All patients	1-3 monthly
Ferritin	All Patients	3-6 monthly
B12 Folate	All Patients	annually

Non Response to ESA therapy – consider the following:
- Assess marrow response with a Reticulocyte count

- Haematinic deficiency (Iron, B12, Folate)
- Functional Iron deficiency (TSAT <20%)

- Infection: CRP – commonest cause for a drop in Hb.
- Occult gastrointestinal (GI) bleed –, especially if history of indigestion or changes in bowel habit. GI studies may need to be organised.
- Overt gastrointestinal (GI) bleed – i.e rectal bleeding, malaena. Upper and lower GI studies as appropriate
- PTH
- Non-concordance
- Under - dialysis
- Haemolysis – LDH or Haptoglobin screen especially patients with Lupus or Mechanical Valves

Rare Causes:
- Development of Erythropoeitin antibodies
- Haemoglobinopathies
- Aplastic Anaemia
- Aluminium Toxicity
- Marrow Fibrosis

End of clinical content

Guideline Governance

Implementation (If the guideline relates to a service, pathway or external agency, provide details and reference any associated clinical operating procedure (COP) or corporate business record (CBR))

N/A

Training (Provide details of how any associated training is delivered, target audience, and if online training is available provide link. If training provided in Trust or Departmental induction, please specify to which staff groups.)

N/A

Patient Information (Reference any associated Patient information leaflets)

N/A

Audit & Monitoring (Detail how the implementation and effectiveness of the clinical guideline will be monitored)				
Aspect being monitored	Monitoring method	Responsible department(s)	Frequency	Group / committee receiving report & responsible for actions
Hb, Ret-He, Ferritin, Dose of ESA	Audit	Renal Services	annually	QIP's

End of Governance content				

Guideline References

CEBIS Evidence Summary (, NICE Guidelines, and other National Guidance. Other national guidance may include those issued by speciality college, patient safety agency, monitoring agencies, or other external governing bodies)	
References cited in guideline	Grade*
NICE Clinical Guideline 141. Anaemia Management in People with chronic kidney disease. February 2011	5
Clinical Practice Guidelines (2010) Anaemia of CKD UK Renal Association 5th Edition	5
NICE Clinical Guideline. Anaemia Management in People with chronic kidney disease. June 2015	5

***Grade:- The references are graded through the CEBIS process according to the criteria outlined below.**

Grade of evidence	Based on
1	Systematic review or meta-analysis
2	Randomised controlled trial/s
3	Controlled study without randomisation (e.g. case controlled) or quasi-experimental study, such as a cohort study
4	Descriptive studies such as case series and reports.
5	Expert opinion, narrative review

Add any Appendices below
(Please use a "Page Break" before each appendix, and list each clearly in the section on the title page. Appendices may include a summary, a flowchart, a proforma, or other materials, but its purpose must be clearly identified)

Appendix 1- Management of a patient receiving Intravenous Iron with Sever Anaemia

Appendix 2 - Haemodialysis Iron Management Based on Monthly Ferritin Result

Appendix 3 - Referral for Erythropoietin Stimulating Agent Therapy

Appendix 4 - Recommended starting doses for ESAs – Step Dose Cahrt

Appendix 5 - - Intravenous iron and serious hypersensitivity reactions: new strengthened recommendations to manage and minimise risk

Appendix 6 – Patient Letter/Consent Form

Appendix 7 – Reply letter from MHRA

Appendix 8 - Monitoring Tool

1.0 APPENDICES

15.1 Appendices 1 – 8 as follows

Appendix 1- Management of a patient receiving Intravenous Iron with Sever Anaemia

Appendix 2 - Haemodialysis Iron Management Based on Monthly Ferritin Result

Appendix 3 - Referral for Erythropoietin Stimulating Agent Therapy

Appendix 4 - Recommended starting doses for ESAs – Step Dose Cahrt

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Appendix 6 – Patient Letter/Consent Form

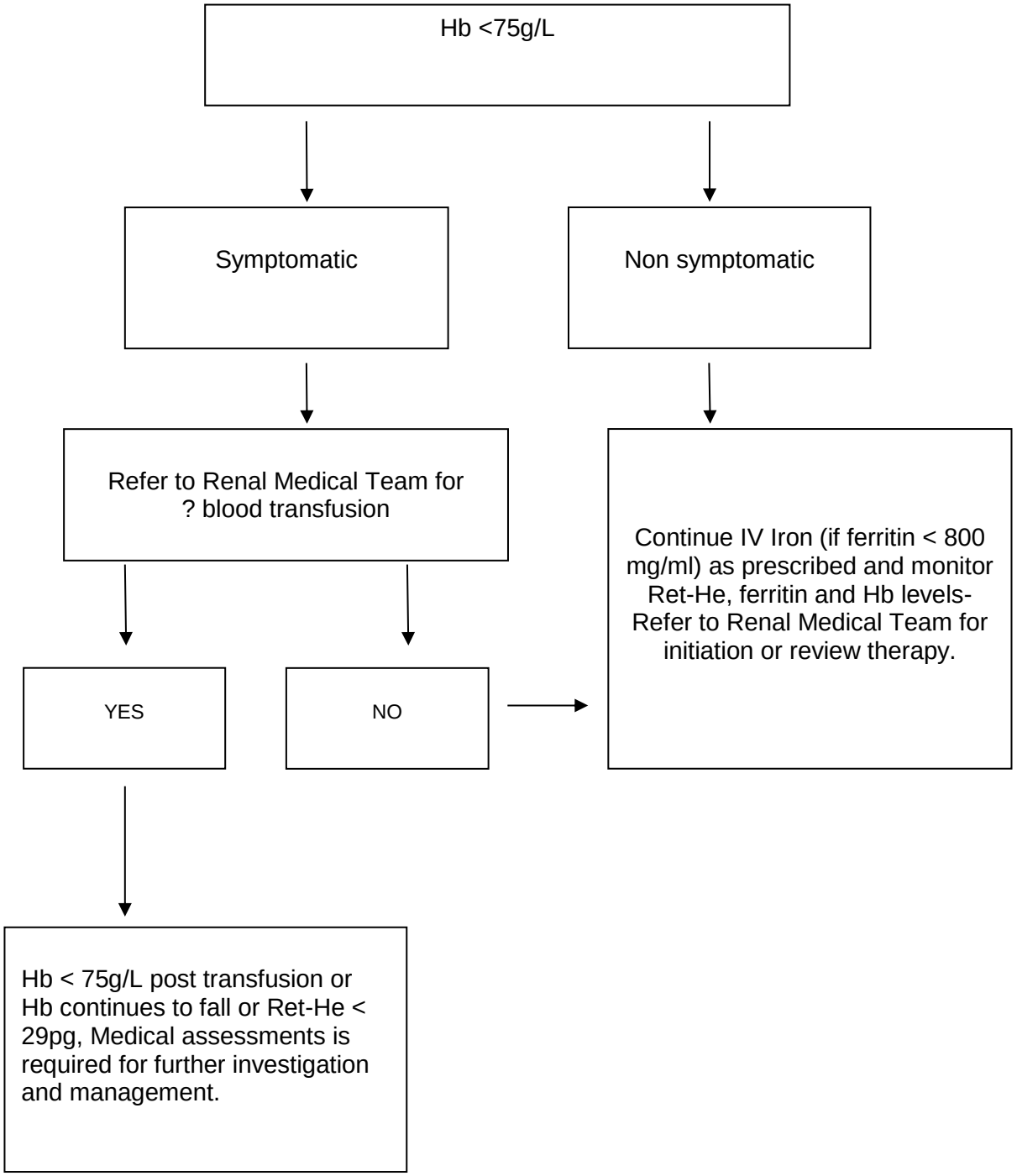
Appendix 7 – Reply letter from MHRA

Appendix 8 - Monitoring Tool

Appendix 1

Management of Patients Receiving IV Iron Who Have Severe Anaemia (Hb <75g/l)

1. Withhold IV Iron on the day of administration of blood transfusion-give next treatment
2. Document on IV Prescription Chart-request Hb and ferritin levels-check in 7 days
3. Document in patient care pathway



Appendix 2

Haemodialysis Iron Management
Based on Monthly Ferritin Result

Venofer

If Ret He <29pg give 100mg Venofer **once per week** and then review at HD QA.

If Ret-He 29-35pg give 100mg Venofer **alternate weeks** and then review at HD QA.

If Ret-He > 35pg give 100mg Venofer **once per month** and review in HD QA

If Ferritin result > 500mg/ml – Reduce frequency of IV iron; If Ferritin result > 800mg/ml **STOP** Venofer (if raised CRP inform member of renal medical team - Dialysis SpR) A higher ferritin level may be deemed appropriate by the patient's renal consultant

Ferinject

For occasional patients needing Ferinject, it should be given as follows:

If Ret He <29pg administer Ferinject 500mg in 10ml over 10 minutes via the venous port of the extracorporeal circuit (post dialyser) **MONTHLY**

If Ret-He >29 give 500mg in 10ml over 10 minutes via the venous port of the extracorporeal circuit (post dialyser) **ALTERNATE MONTHS**

If Ferritin result > 500mg/ml – Reduce frequency of IV iron; If Ferritin result > 800mg/ml **STOP** (if raised CRP inform member of renal medical team - Dialysis SpR) A higher ferritin level may be deemed appropriate by the patients renal consultant

If a patient's Hb is above the target range, consider the following:

- 50% ESA dose reduction or alternate dose (whichever is convenient to the patient)
- Consider losing a circuit if Hb $\geq$ 135 g/L
- Rarely ESA is withheld for a period of time. If this is the case a specific plan for re-starting must be in place, usually when Hb falls to <120g/L

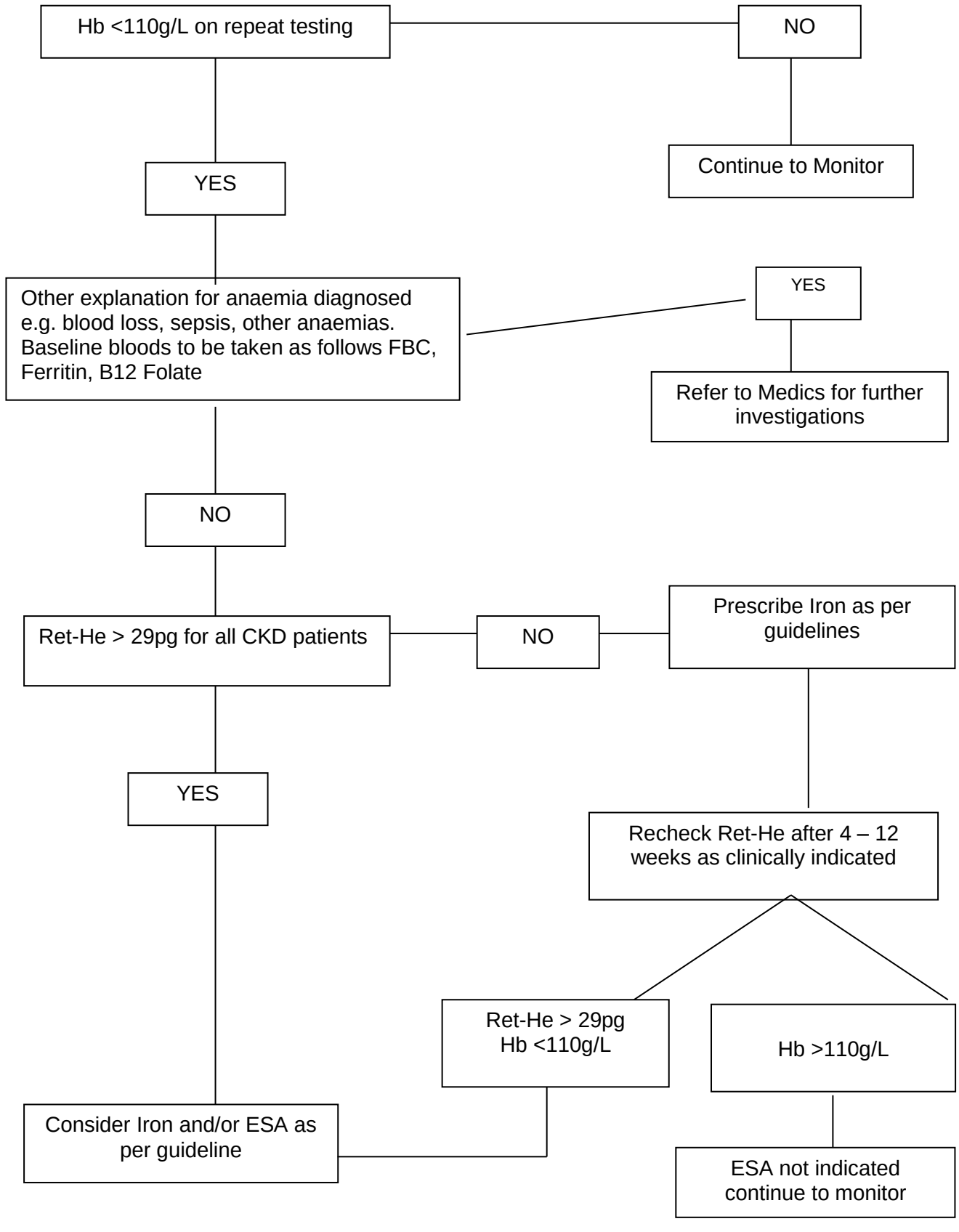
If a patients Hb is below the target range consider:

- If Hb $\leq$ 100g/L – Increase ESA by 25% wait approximately 4 weeks and if no response, carry out a non- response screen and/or increase ESA dose again.

Dose changes must be discussed and confirmed at the patient's QA review.

Appendix 3

Referral for Erythropoietin Stimulating Agent Therapy



Appendix 4

Aranesp Dose Step Chart

Usually go to next step. May skip a step upwards if no response at all, or downwards if too great.
Patients may start on higher or lower dose if very large or small (ie <50 Kg or > 90Kg)
Note: Do not increase the starting dose on the basis of a low pre-treatment Hb.

Step	Dose	Frequency	Comment
1	20 micrograms	Monthly	
2	20 micrograms	Every 3 weeks	
3	20 micrograms or 40 micrograms	Fortnightly Monthly	
4	40 micrograms	Every 3 weeks	
5	**40 micrograms**	**Fortnightly**	**Usual start dose for CKD/PD unless the patient is small and/or starting iron at the same time**
6	**30 micrograms** or 40 micrograms	**Weekly** Every 10 days (eg Mon/Thur alt week)	**Usual start dose for HD** useful for CKD/PD
7	40 micrograms	weekly	
8	50 micrograms	weekly	
9	60 micrograms	weekly	
10	80 micrograms	weekly	
11	100 micrograms	weekly	ESA Resistant
12	150 micrograms	weekly	Maximum Dose

Appendix 5

Drug Safety Update

Volume 7, Issue 1 **August 2013**

Latest advice for medicines users

Intravenous iron and serious hypersensitivity reactions: new strengthened recommendations to manage and minimise risk

Article date: 07 August 2013

Summary
A Europe-wide review of intravenous iron products for iron deficiency and anaemia has recommended strengthened measures are taken to manage and minimise the risk of hypersensitivity reactions, which may be life-threatening or fatal as outlined in this article

Intravenous (IV) iron products are indicated in the treatment of iron deficiency and anaemia when iron supplements cannot be given or have not worked. Hypersensitivity reactions are well known to occur rarely with IV iron products, and may be life-threatening or fatal. Warnings about this risk are given in the product information.

European review

A European review of IV iron products has taken place after concerns in France about the risk of serious hypersensitivity reactions, especially in pregnant women. The review has recommended strengthened advice to ensure correct prescribing and administration, and early detection and effective management of hypersensitivity reactions.

Further information on hypersensitivity reactions

Serious hypersensitivity reactions, including life-threatening and fatal anaphylactic and anaphylactoid reactions, have been reported in patients receiving IV iron. These reactions can occur even when a previous administration has been tolerated (including a negative test dose). Caution is therefore needed with every dose of IV iron, even if previous administrations have been well tolerated.

The product should be given in accordance with the specific posology and method of administration stated in the product information. IV iron should only be given in an environment where the patient can be adequately monitored, and where resuscitation facilities are available. In case of a hypersensitivity reaction, treatment should be stopped immediately and appropriate management initiated.

Use in pregnancy

Iron-deficiency anaemia in the first trimester of pregnancy can usually be treated with oral iron (ie, IV iron should not be used). Later in pregnancy, any benefits of using IV iron should be carefully weighed against the risks: anaphylactic or anaphylactoid reactions could have serious consequences for both mother and foetus.

Test dose

Previously, an initial test dose has been recommended for some IV iron products before administration of the first dose to a new patient. However, there are no clear data that an initial test dose minimises risk: conversely, it may give false reassurance because hypersensitivity reactions have been reported in patients that had a negative initial test dose. Therefore, an initial test dose on first use of an IV iron product for a patient is no longer recommended. All references to this recommendation will be removed from relevant product information.

Please note that the advice for administration of a product remains otherwise unchanged. For example, for iron dextrans (CosmoFer), a slower rate of administration for the first 25 mg of iron is required for every dose.

Advice for healthcare professionals:

The prescribing, dosing, administration, and safety information differs between IV iron product formulations, and the individual product information should be consulted before and during use.

Prescribing

- An IV iron product should not be used in patients with known hypersensitivity to the active substance, the product itself, or any of its excipients; it should also not be used in patients with known serious hypersensitivity to any other parenteral iron product
- The risk of hypersensitivity is increased in patients with: known allergies (including drug allergies); immune or inflammatory conditions (eg, systemic lupus erythematosus, rheumatoid arthritis); or those with a history of severe asthma, eczema, or other atopic allergy. In these patients, IV iron products should only be used if the benefits are clearly judged to outweigh the potential risks
- IV iron should not be used during pregnancy unless clearly necessary. Treatment should be confined to the 2nd or 3rd trimesters, if the benefit is clearly judged to outweigh the potential risks for both mother and foetus

Administration and monitoring

- IV iron should be administered in strict accordance with the posology and method of administration described in the product information for each individual product (note that advice varies between products)
- Caution is needed with every dose of intravenous iron that is given, even if previous administrations have been well tolerated
- IV iron products should only be administered when staff trained to evaluate and manage anaphylactic or anaphylactoid reactions—as well as resuscitation facilities—are immediately available
- Patients should be closely monitored for signs of hypersensitivity during and for at least 30 minutes after every administration of an IV iron product
- In the event of a hypersensitivity reaction, treatment should be stopped immediately and appropriate management initiated

Information for patients

- Healthcare professionals should inform patients of the risk and potential seriousness of a hypersensitivity reaction before every administration. Patients should be informed of the relevant symptoms and advised to tell their doctor or nurse straight away if any of these occur

Reporting of suspected adverse drug reactions

- The safety of IV iron products will continue to be monitored closely in the UK and Europe. You can help by reporting via the Yellow Card Scheme any suspected adverse reactions to IV iron products. We are particularly interested in reports of suspected anaphylactic or anaphylactoid hypersensitivity reactions. Please ensure to include the name of the specific product administered (www.mhra.gov.uk/yellowcard)

Further information:

European Medicines Agency Statement

Article citation: Drug Safety Update vol 7, issue 1 August 2013: A1.

References

Page last modified: 09 September 2013

Appendix 6

Dear Home Haemodialysis patient,

You will probably have been aware that there has recently been a concern regarding the safety of intravenous (iv) Iron. The Medicines and Healthcare products Regulatory Agency (MHRA) sent out a Strengthened Recommendation on the use of iv Iron in August 2013. This recommendation is attached and can be found on their website at http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON300398
This recommendation followed concern from France about hypersensitivity (allergic) reactions to iv Iron. The recommendation states that caution is needed with *every* dose of iv Iron, even when previous administrations (i.e. "test doses") have been well tolerated. It also recommends that iv Iron products should only be administered when staff trained to evaluate and manage anaphylactic or anaphylactoid reactions—as well as resuscitation facilities—are immediately available.
It is because of this recommendation we withdrew the prescription of iv Iron (Venofer) to home haemodialysis (HD) patients.

Dr Graham Lipkin, Clinical Vice-President of the Renal Association has been in correspondence with the MHRA and received the attached reply. In summary, the MHRA remains clear in its guidance above but also states, "…a doctor may prescribe off-label if they consider that it is necessary, for medical reasons, in order to meet to the specific needs of a patient and with the patient's informed consent."
We have since been in discussion with a number of other renal centres with Home HD programmes. Many are planning to continue to offer patients iv Iron at home with patients' consent, on the basis that:

- The perceived risk is felt to be small
- The risk of allergic reactions to iv Iron is likely to be smaller than other risks associated with invasive treatments such as Home HD
- Many patients felt that the convenience of administering iv Iron at home justified this small increased risk

We are therefore willing to offer two options to patients on the Home HD programme at UHCW:

1. When necessary, attend the renal day unit at UHCW for an injection of Ferinject.
    - This is a larger dose of iron than Venofer and would typically be required every 2-6 months.
2. Continue to self-administer Venofer at home.
    - This would be on the acceptance that:
        - The prescription is "off-label" and the risks stated above, whilst thought to be small, are recognised and real
        - You must have someone present during, and for 30 minutes after, the administration of the iv Iron

Consent
I have read and understood the above statement and would like to opt for Option ……..

Patient	**Doctor**
Name	Name
Signature	Signature
Date	Date

Appendix 7

MHRA 151
Buckingham Palace Road
London SW1W 9SZ United
Kingdom **mhra.gov.uk**

Dr Graham Lipkin
Clinical VP
Renal Association
Consultant Nephrologist
Queen Elizabeth Hospital
Birmingham
UHBFT
10 October 2013

Dear Dr Graham Lipkin

Thank you for your further communication regarding Intravenous Iron products and the new strengthened recommendations to manage and minimise the risk of serious hypersensitivity reactions.
With your further communication you have forwarded a letter from the UK Home Haemodialysis Group.
I appreciate the concerns raised by the healthcare professional signatories to the letter and I note the experience they have had to date with IV iron sucrose in the expanding home haemodialysis population, in addition to that with in-centre patients.
As mentioned previously, warnings about the known risk of rare serious hypersensitivity reactions have been present in the product information for all IV Iron products for some time. In the product information that was approved prior to the recent European review for the innovator IV Iron Sucrose product 'Venofer', at the beginning of section 4.4 'Special warnings and precautions for use' it states '*Parenterally administered iron preparations can cause allergic or anaphylactoid reactions, which may be potentially fatal. Therefore, treatment for serious allergic reactions and facilities with the established cardio-pulmonary resuscitation procedures should be available.'*
The current recommendations have been strengthened to manage and minimise the risk of serious hypersensitivity reactions with all IV iron products. This includes highlighting that these reactions have been reported even when a previous administration has been tolerated (including a negative test dose) and that caution is therefore needed with every dose of IV iron.
The recent European review focused on serious hypersensitivity reactions. The data on the risk of hypersensitivity reactions with IV iron products comes mainly from post-marketing spontaneous reports and serious hypersensitivity reactions have been reported for all IV iron products in the review. The total number of life-threatening and fatal events reported is low. Whilst this data shows a clear association of IV iron products with hypersensitivity reactions, due to the recognised limitations of spontaneous reporting data it could not be used to robustly undertake comparative analyses or calculate accurate reporting rates.
In view of the limitations of the data available at the time of the review, further activities are being undertaken including yearly reviews of hypersensitivity reports with the different IV iron products and a study to further explore their safety. The safety of IV iron products will continue to be monitored closely in the UK and Europe.

Further to my previous letter the European Commission has now adopted the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) decision on IV Iron products. Further information on this procedure and it's outcomes are available on the EMAs website www.ema.europa.eu (page link http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Intravenous_ironcontaining_medicinal_products/human_referral_000343.jsp&mid=WC0b01ac05805c516f).
I hope that this further information is helpful. As mentioned previously, ultimately, as with all medicines, a doctor may prescribe off-label if they consider that it is necessary, for medical reasons, in order to meet to the specific needs of a patient and with the patient's informed consent.

With kind regards,

Yours sincerely,
Dr Andrea Wallington
Medical Assessor
Benefit Risk Management Group
MHRA
Email: Andrea.Wallington@mhra.gsi.gov.uk