Erythropoiesis Stimulating Agent (ESA) and Intravenous Iron prescribing, supply and monitoring at Cardiff and Vale UHB
Nephrology and Transplant Unit

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Introduction

Anaemia of Chronic Kidney Disease is a frequent complication for Pre-Dialysis, Peritoneal Dialysis, Haemodialysis Unit, Home Haemodialysis and Kidney Transplant patients with a negative impact on quality of life. Fortunately, for most patients, it is treatable with Erythropoietis Stimulating Agents (ESAs) and Iron as the mainstays of pharmacological therapy.

The focus for this document is to support the Nephrology and Transplant (N&T) Multidisciplinary Team at Cardiff and Vale UHB effectively prescribe, supply and monitor ESA and iron therapy. ESAs are hospital only drugs for adult patients with anaemia of CKD and over the past 10 years national procurement strategies, including therapeutic tenders, have secured significant financial savings on ESAs prescribed by hospital teams. Clinical practice, in terms of which ESA brand to prescribe, can change to fit the most cost effective option(s) on the All Wales ESA Contract. For example, the 2015 contract directs that Epoetin Alfa (Eprex®) and Methoxy Polyethylene Glycol Epoetin Beta (Mircera®) are the preferred options locally and nationally.

Guidance is provided here on the choice of ESA brand and starting doses for patients in the various N&T treatment modalities and the selection of an appropriate prescribing and supply scheme to ensure the chosen ESA gets to the patient efficiently.

The prescribing and supply schemes are overseen by the C&V Anaemia of CKD Service so it is essential that this team is kept informed about all ESA patients. Alongside this it is crucial that Vitaldata is updated to accurately reflect the current ESA brand and dose for patients across all N&T treatment modalities. This supports regular audit of the service and is particularly important for patients on home delivery because their prescriptions are generated using Vitaldata.

ESA monitoring requirements and dose adjustment strategies are also described here. Monitoring is outlined in detail at the end of this document in the “ESA Monitoring Pathway for Haemoglobin and Blood Pressure” – this pathway (updated in February 2018) is sent to the patient’s GP when they are commenced on an ESA and also serves as a reference for anyone involved with ESAs, eg to confirm when and where to check Hb and BP. ESA related monitoring is predominantly undertaken in secondary care and first review of results and subsequent action is always the responsibility of the N&T team even when the Hb/BP has been obtained in primary care.

Detailed clinical advice on the investigation and diagnosis of Anaemia of CKD and the management of poor response to ESA therapy is beyond the scope of this document – refer to published guidance such as the 2015 update to the NICE CG “Anaemia Management in CKD”.

To provide an insight into local ESA prescribing activity, the results of a snapshot audit in April 2017 are presented below (includes N&T patients in Cardiff & Vale, Aneurin Bevan and Cwm Taf Health Boards):

- Total cohort of ESA patients – approx 900
  - ~35% are pre-dialysis patients
  - ~5% are peritoneal dialysis patients
  - ~50% are haemodialysis patients
  - ~10% are renal transplant patients
• Eprex prescribed for ~60% of patients
  o Mean dose approx 8000 units/week
• Mircera prescribed for ~40% of patients
  o Mean dose approx 60 mcg/month

Alongside ESAs, iron is an integral component of anaemia therapy for most patients. The 2015 update of the NICE CG on “Anaemia Management in CKD” provided more focus than previous versions on diagnosis and management of iron deficiency in patients with CKD. It states that diagnosis of iron deficiency anaemia should not be based on haemoglobin and ferritin alone, as had previously been the practice within C&V UHB. Of the various NICE recommended diagnostic options, Transferrin Saturation (TSAT) is now freely available at UHW and other hospitals in C&V, Cwm Taf and Aneurin Bevan HBs and must be monitored alongside ferritin for all patients with anaemia of CKD.

Low serum ferritin is a marker of “suboptimal iron stores”, however it can be raised in the presence of inflammation or infection and it also doesn’t indicate how much circulating iron is available to support the accelerated erythropoiesis induced by ESAs. If there is not enough available iron or it can’t be mobilised quickly from the ferritin stores a “functional iron deficiency” will result and the patient’s Hb is unlikely to improve with an ESA. Such patients often have a normal serum ferritin but a low TSAT level identifying functional iron deficiency and the need for iron therapy.

Ferritin and TSAT must be checked and corrected before initiating ESA therapy and during ESA therapy. Correction of suboptimal iron stores and/or functional iron deficiency is essential for a number of reasons eg:
• Can delay or even avoid the need for ESA therapy
• Facilitates quicker correction of anaemia when ESA therapy is initiated
• Helps to maintain Hb in target range
• Avoids unnecessary ESA dose escalation
• Early intervention with iron therapy can prevent a drop in Hb

Patients with little residual renal function and severe, symptomatic anaemia can start ESA therapy alongside iron treatment.

Within N&T, iron is commonly prescribed intravenously and there are various formulations available. In recent years, clinical practice has shifted to Total Dose Infusions (TDI) of iron for all modalities except Haemodialysis Units. Intravenous iron must be prescribed and administered cautiously in view of the risk of “free iron” related infusion reactions (rare, self limiting, resolve quickly on cessation of infusion) and even anaphylaxis (extremely rare). Patients with autoimmune diseases, asthma or other atopic conditions and other drug allergies are more likely to experience iron infusion reactions.

This document aims to support the N&T MDT in the investigation, treatment and monitoring of iron deficiency in patients with anaemia of CKD. For further details refer to published guidance such as the 2015 update to the NICE CG “Anaemia Management in CKD”. For specific advice on local practice for prescribing and administration of intravenous iron contact the N&T Pharmacy Team.
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Cardiff Renal Unit Iron Prescribing Policy for Patients with Anaemia of CKD

Cardiff Renal Unit ESA and Iron Prescribing Policy for Patients with Anaemia of CKD: Summary of monitoring requirements for Haemoglobin, Ferritin and Transferrin Saturation

ESAs for adult patients with Anaemia of Chronic Kidney Disease: ESA Monitoring Pathways for Haemoglobin and Blood Pressure
Cardiff Renal Unit ESA Prescribing Policy:
Initiation of ESA therapy

Potential new ESA patient
- Haemoglobin (Hb) consistently below 110g/l
- Rule out +/- treat other causes of anaemia
- ESAs are not a temporary treatment for anaemia (e.g., AKI patients, early stages post renal transplant) – initiation must be on the basis that treatment will take at least a month to produce any benefits and will potentially be lifelong
- Confirm diagnosis of Anaemia of CKD and that patient is likely to benefit from long term ESA therapy (improved Quality Of Life)
- Check for sub-optimal iron stores (Ferritin) and functional iron deficiency (TSAT) – correct deficiencies with oral or intravenous iron before prescribing an ESA
- Assess clinical risk vs benefit of ESA therapy based on patient’s PMH
- Discuss benefits and risks of long term ESA therapy with patient

Further information
Refer to NICE Clinical Guideline “Anaemia Management in CKD” (2015 update) to support treatment plan and prescribing decision to initiate ESA therapy

ESA Prescribing options
- Mircera® or Eprex® (in line with 2015 All Wales ESA Contract)
- Equally effective clinically, same monitoring requirements, different frequency of injections

Methoxy Polyethylene Glycol Epoetin Beta (Mircera®)
Long acting ESA
Monthly subcutaneous dose regimen during correction and maintenance phases of treatment

Epoetin Alfa (Eprex®)
Short acting ESA
Weekly (or twice weekly) subcutaneous dose regimen during correction and maintenance phases of treatment

Administration of ESA injections
First option is train patient to administer their own injections (prescribe Mircera® or Eprex®)
Other options if this is not possible (prescribe Mircera®)
- Carer
- District Nurse
- GP Practice Nurse

Starting dose for ESA therapy – considerations
- Patient’s weight
- Pre-treatment Hb level
- Severity of anaemia symptoms
- Residual renal function
- Importance of prescribing the lowest effective ESA dose to treat anaemia of CKD
- Dose needs rounding up or down to fit with range of pre-filled syringes

Starting dose for ESA
Majority of patients can be initiated on one of the following regimens

<table>
<thead>
<tr>
<th>Patient weight</th>
<th>Mircera® (once a month)</th>
<th>Eprex® (once a week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70kg or less</td>
<td>30 or 50mcg</td>
<td>2000 to 4000 units</td>
</tr>
<tr>
<td>71 to 100kg</td>
<td>50 or 75mcg</td>
<td>3000 to 5000 units</td>
</tr>
<tr>
<td>101kg and over</td>
<td>75 or 100mcg</td>
<td>4000 to 6000 units</td>
</tr>
</tbody>
</table>

UHW Anaemia of CKD service
This multidisciplinary team oversees all the ESA prescribing and supply schemes
Contact the service via ext 48453 or e-mail anaemia.office@wales.nhs.uk with details of all new ESA patients
Vitaldata must be updated with all new ESA patients to support regular audit of the anaemia of CKD service
Contact Nephrology and Transplant Pharmacy Team (ext 41233 or ext 46324 or bleep 5707) for further advice about initiating ESA therapy
Potential new ESA patient
- Haemoglobin (Hb) consistently below 110g/l
- Rule out +/- treat other causes of anaemia
- Confirm diagnosis of Anaemia of CKD and that patient is likely to benefit from long term ESA therapy (improved Quality Of Life)
- Check for sub-optimal iron stores (Ferritin) and functional iron deficiency (TSAT) – correct deficiencies with intravenous iron before prescribing an ESA
- Assess clinical risk vs benefit of ESA therapy based on patient’s PMH
- Discuss benefits and risks of long term ESA therapy with patient

Further information
Refer to NICE Clinical Guideline “Anaemia Management in CKD” (2015 update) to support treatment plan and prescribing decision to initiate ESA therapy

ESA Prescribing options (in line with 2015 All Wales ESA Contract)
**Epoetin Alfa (Eprex®)**
Aim to prescribe for all HD unit and Home HD patients
Short acting ESA
Twice or Three times a week dose regimen during correction and maintenance phases of treatment
Methoxy Polyethylene Glycol Epoetin Beta (Mircera®)
Alternative option only if there is a clear clinical contraindication to Eprex®
Monthly dose regimen during correction and maintenance phases of treatment

Administration of Eprex® injections
HD unit
- Subcutaneous injection by HD unit nursing staff
- Intravenous injection as second line option (eg patient refuses subcut or concerns about drug absorption subcutaneously in patients with very high BMI)
- Subcut and iv doses are not equivalent (iv dose 10 to 30% higher to achieve same clinical effect)
Home HD
- Subcutaneous injection by patient or carer

Starting dose for ESA therapy – considerations
- Patient’s weight
- Pre-treatment Hb level
- Severity of anaemia symptoms
- Importance of prescribing the lowest effective ESA dose to treat anaemia of CKD
- Dose needs rounding up or down to fit with range of pre-filled syringes

Starting dose for Eprex®
Majority of patients can be initiated on one of the following regimens

<table>
<thead>
<tr>
<th>Patient weight</th>
<th>Eprex® dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>70kg or less</td>
<td>2000 or 3000units twice a week</td>
</tr>
<tr>
<td>71 to 100kg</td>
<td>3000 or 4000units twice a week</td>
</tr>
<tr>
<td>101kg and over</td>
<td>4000 or 5000units twice a week</td>
</tr>
</tbody>
</table>

Range of Eprex® pre-filled syringes
1000, 2000, 3000, 4000, 5000, 6000, 8000, 10000 units

UHW Anaemia of CKD service
This multidisciplinary team oversees all the ESA prescribing and supply schemes
Contact the service via ext 48453 or e-mail anaemia.office@wales.nhs.uk with details of all new HD unit and Home HD ESA patients
Vitaldata must be updated (by HD unit team, Home HD team or anaemia office) with all new ESA patients to support regular audit of the anaemia of CKD service
Contact Nephrology and Transplant Pharmacy Team (ext 41233 or ext 46324 or bleep 5707) for further advice about initiating ESA therapy
Cardiff Renal Unit ESA Prescribing Policy: ESA patients transferring to Haemodialysis from other renal modalities

Haemodialysis Unit and Home Haemodialysis Patients

Majority of patients starting HD will already be on ESA therapy
- Mircera® or Eprex®
- Changes to ESA brand and/or prescribing and supply scheme may be required when the patient starts regular haemodialysis.

HD Unit patients
- Switch to Eprex® prescribed and administered using supply held at the HD unit
- For patients on Mircera® brand switch plan required (see below)
- To reduce wastage, patient can use up existing ESA supplies at home before switching to HD Unit Eprex®

Home HD patients
- Can continue with current ESA brand and prescribing and supply scheme or
- Consider switching Mircera® patients to Eprex® as the standard ESA for HD patients (see below)

ESA brand switching - Mircera® to Eprex® for haemodialysis patients
There is no defined conversion factor to switch a Mircera® dose in mcg to an Eprex® dose in units
The following guidance supports a safe and sensible conversion from Mircera® to Eprex®
- It assumes that the current Mircera® dose and overall management of anaemia of CKD is stable with Hb in target range
- Consider higher or lower switching dose of Eprex® if Hb trend is below or above target range
- ESA dose requirements generally increase when patients transfer to HD (eg due blood loss on machine or loss of residual renal function)
- Dose switch advice less reliable with particularly high or low Mircera® doses
- Start Eprex® two weeks after last dose of Mircera® given
- Treat with initial switch dose of Eprex® for at least 4 weeks before reviewing need for dose adjustment alongside Hb levels
- Contact Nephrology and Transplant Pharmacy Team (ext 41233 or ext 46324 or bleep 5707) for further advice about ESA brand switching

<table>
<thead>
<tr>
<th>Current monthly Mircera® dose</th>
<th>Switch to Eprex® dose of....</th>
</tr>
</thead>
<tbody>
<tr>
<td>30mcg</td>
<td>2000units once or twice a week</td>
</tr>
<tr>
<td>50mcg</td>
<td>2000units or 3000units twice a week</td>
</tr>
<tr>
<td>75mcg</td>
<td>3000units or 4000units twice a week</td>
</tr>
<tr>
<td>100mcg</td>
<td>4000units or 5000units twice a week</td>
</tr>
<tr>
<td>120mcg</td>
<td>5000units or 6000units twice a week</td>
</tr>
<tr>
<td>150mcg</td>
<td>6000units or 7000units twice a week</td>
</tr>
<tr>
<td>200mcg</td>
<td>8000units or 9000units twice a week</td>
</tr>
<tr>
<td>250mcg</td>
<td>10000units or 11000units twice a week</td>
</tr>
<tr>
<td>360mcg</td>
<td>12000units or 14000units twice a week</td>
</tr>
</tbody>
</table>

UHW Anaemia of CKD service
This multidisciplinary team oversees all the ESA prescribing and supply schemes
Contact the service via ext 48453 or e-mail anaemia.office@wales.nhs.uk with details of all ESA changes when patients transfer to HD Unit or Home HD
Vitaldata must be updated (by HD unit team, Home HD team or anaemia office) with all ESA changes when patients transfer to HD unit or Home HD to support regular audit of the anaemia of CKD service
Contact Nephrology and Transplant Pharmacy Team (ext 41233 or ext 46324 or bleep 5707) for further advice about ESA brand switching
Cardiff Renal Unit ESA Prescribing Policy: Correction and Maintenance Phases of Anaemia of CKD treatment with ESAs

All Modalities (Pre-Dialysis, Peritoneal Dialysis, Home Haemodialysis, Renal Transplant and Haemodialysis Unit Patients)

ESA therapeutic targets
- Correction phase to achieve Hb of 100 to 120g/l followed by
- Maintenance phase to keep stable Hb 100 to 120g/l
- Aim to increase Hb by 10 to 20g/l per month during correction phase
- Improved quality of life and physical function for patient

ESA monitoring (Haemoglobin, Blood Pressure and Iron)
- Check Hb every 4 weeks during correction phase
- Check Hb every 8 to 12 weeks during maintenance phase
- Check Hb 4 weeks after an ESA dose change
- Check BP every 4 weeks during correction phase only
- Check Iron status via serum ferritin and transferrin saturation (TSAT) every 4 to 12 weeks during correction and maintenance phase

 ESA dose adjustment
- During correction phase, if Hb rise < 10g/l/month, increase ESA dose by 25 to 50%
- During correction phase, if Hb rise > 20g/l/month, decrease ESA dose by 25 to 50%
- Following ESA initiation or dose change, wait at least 4 weeks before considering ESA dose adjustment
- During maintenance phase change dose according to Hb trend, rather than isolated results
- During maintenance phase, adjust by 25 to 50% to keep stable Hb 100 to 120g/l

To reduce wastage, aim to utilise patient's existing ESA supply by temporarily adjusting the current pre-filled syringe dose before starting new prescription (this can also allow a dose change to be implemented quickly)
- Micrera dose interval can temporarily be shortened to fortnightly or extended to every 6 or 8 weeks
- Eprex dose interval can temporarily be adjusted to once, twice or three times a week
- For Micrera and Eprex it may be possible to temporarily double the dose (ie two syringes) while keeping to the same dose frequency

If there is a poor response to therapy, investigate and treat other causes of anaemia before increasing ESA dose, eg
- Iron deficiency
- Blood loss (eg gastrointestinal)
- Active infection
- Active inflammatory conditions
- Severe secondary hyperparathyroidism

Further information
Refer to NICE Clinical Guideline “Anaemia Management in CKD” (2015 update) and “C&V UHB ESA Monitoring Pathways” (2018 update) to support prescribing decisions during correction and maintenance phases of ESA therapy for anaemia of CKD

UHW Anaemia of CKD service
This multidisciplinary team oversees all the ESA prescribing and supply schemes
Contact the service via ext 48453 or e-mail anaemia.office@wales.nhs.uk with details of all ESA dose adjustments
Vitaldata must be updated with all new ESA dose changes to support regular audit of the anaemia of CKD service
Contact Nephrology and Transplant Pharmacy Team (ext 41233 or ext 46324 or bleep 5707) for further advice about dose adjustment and monitoring for ESA therapy
Cardiff Renal Unit ESA Prescribing Policy

ESA prescribing
- For treatment of adult patients with anaemia of CKD, ESAs classed as hospital only drugs
- Cost effective prescribing utilising All Wales Contract prices
- ESAs can be prescribed by a specialist N&T medical, pharmacist or nurse prescriber

Pre-Dialysis, Peritoneal Dialysis, Home Haemodialysis and Renal Transplant patients

ESA prescribing and supply scheme options
- Home Delivery (Mircera® or Eprex®)
- UHW Pharmacy (Mircera® or Eprex®)

Prescribing and supply of ESAs via Home Delivery or UHW pharmacy – what’s the best option for my patient?

Pre-Dialysis patients
prescribed Mircera® or Eprex®

Home Haemodialysis patients
prescribed Eprex® or Mircera®

First ESA prescription for any N&T patient (1 to 3 months supply) likely to be written and dispensed via hospital during outpatient clinic appointment or inpatient admission

Home Delivery (all patients)
- Anaemia of CKD service must be contacted to set up home delivery for individual patients
- Patient will be registered with home delivery company
- Prescription generated electronically using Vitaldata and given to prescriber for clinical review and signature
- Prescription sent to home delivery provider
- Prescription valid for up to 12 months
- ESA delivered to patient’s home in instalments every 3 months
- Prescriptions are VAT exempt but there is a charge for each home delivery

UHW Pharmacy (first line option)
- Patients to collect ESA as part of routine clinic appointment (every 1 to 3 months)
- Prescribed on standard hospital outpatient prescriptions
- Dispensed from main pharmacy or satellite pharmacy in N&T outpatients
- Include VAT but no other charges (for Mircera® this makes it a more cost effective option than home delivery)

Transplant Patients
- Prescribed by pharmacist alongside their anti-rejection drugs
- Dispensed at satellite pharmacy in N&T outpatients
- Can also be prescribed by medical or nurse prescriber

Peritoneal Dialysis Patients
- Can be prescribed and dispensed in satellite pharmacy in N&T outpatients but this must be done in advance of afternoon PD clinic (pharmacy open 9am to 12.30pm)
- Patient or PD team to contact N&T Pharmacy Team to order prescriptions (ext 41222 or ext 46324 or e-mail cardiff.transplantpharmacy@wales.nhs.uk)
- Can also be prescribed by medical or nurse prescriber

UHW Anaemia of CKD service
This multidisciplinary team oversees all the ESA prescribing and supply schemes
Contact the service via ext 48453 or e-mail anaemia.office@wales.nhs.uk with details of selected prescribing and supply scheme for all new ESA patients or if a patient’s scheme changes
Vitaldata must be updated with all new ESA patients to support regular audit of the anaemia of CKD service and generation of prescriptions for home delivery patients
Contact Nephrology and Transplant Pharmacy Team (ext 41233 or ext 46324 or bleep 5707) for further advice about ESA prescribing and supply schemes
**Cardiff Renal Unit ESA Prescribing Policy: Prescribing and Supply schemes for ESAs**

**ESA prescribing**
- For treatment of adult patients with anaemia of CKD, ESAs classed as hospital only drugs
- Cost effective prescribing utilising All Wales Contract prices
- ESAs can be prescribed by a specialist N&T medical, pharmacist or nurse prescriber

**ESA prescribing and supply scheme options**

**Eprex®**
- Prescribed on HD unit drug chart
- Administered as subcutaneous injection by HD unit nursing staff
- Eprex® held as a stock on all HD units – direct delivery of drug from manufacturer to HD units

**Mircera®**
- Prescribed on HD unit drug chart but only if there is a clear clinical contraindication to Eprex®
- Administered as subcutaneous injection by HD unit nursing staff or patient at home
- Not a stock drug on HD units so set up home delivery as per patients in other renal modalities (contact anaemia office)

**ESA prescribing and supply for patients transferring to Haemodialysis Unit from other renal modalities**
Change Mircera®/Eprex® via home delivery or UHW pharmacy to prescribing and supply of Eprex via HD unit as described above
- Use up patient’s existing supply of ESA before making the change
- Update anaemia office (eg to cancel home delivery)

**UHW Anaemia of CKD service**
This multidisciplinary team oversees all the ESA prescribing and supply schemes
Contact the service via ext 48453 or e-mail anaemia.office@wales.nhs.uk with details of patients initiating ESA therapy at their HD unit or ESA patients transferring to HD unit from other renal modalities
Vitaldata must be updated with all ESA changes when patients transfer to HD unit and when ESA doses are adjusted at the unit – this is crucial to support regular audit of the anaemia of CKD service and can be done by HD unit team or anaemia office
Contact Nephrology and Transplant Pharmacy Team (ext 41233 or ext 46324 or bleep 5707) for further advice about ESA prescribing and supply for HD unit patients
# Cardiff Renal Unit ESA Prescribing Policy: Prescribing and Supply schemes for ESAs

## Summary

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>1st line ESA prescribing and supply scheme</th>
<th>2nd line ESA prescribing and supply scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Dialysis</td>
<td>Home Delivery</td>
<td>Eprex® or Mircera®</td>
</tr>
<tr>
<td>Peritoneal Dialysis</td>
<td>UHW Pharmacy</td>
<td>Eprex® or Mircera®</td>
</tr>
<tr>
<td>Home Haemodialysis</td>
<td>Home Delivery</td>
<td>Mircera® (if Eprex® contraindicated)</td>
</tr>
<tr>
<td>Haemodialysis Unit</td>
<td>HD Unit Stock</td>
<td>Eprex® or Mircera®</td>
</tr>
<tr>
<td>Renal Transplant</td>
<td>UHW Pharmacy</td>
<td></td>
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</tbody>
</table>

## Treatment modality

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>1st line ESA</th>
<th>2nd line ESA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Dialysis</td>
<td>Mircera® or Eprex®</td>
<td>Eprex® or Mircera®</td>
</tr>
<tr>
<td>Peritoneal Dialysis</td>
<td>Mircera® or Eprex®</td>
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<td>Home Haemodialysis</td>
<td>Eprex®</td>
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</tr>
<tr>
<td>Haemodialysis Unit</td>
<td>Mircera® or Eprex®</td>
<td>Eprex® or Mircera®</td>
</tr>
<tr>
<td>Renal Transplant</td>
<td>Mircera® or Eprex®</td>
<td>Eprex® or Mircera®</td>
</tr>
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## Notes

- **1st line ESA**: Mircera® or Eprex®
- **2nd line ESA**: Eprex® or Mircera®
- **Prescribing and supply scheme**: Home Delivery, UHW Pharmacy, HD Unit Stock, UHW Pharmacy.
Potential new iron therapy patient
- Confirmed diagnosis of Anaemia of CKD (Hb consistently below 110g/l)
- Sub-optimal iron stores (Ferritin < 100mcg/l) and/or
- Functional iron deficiency (TSAT <20%)

Patients not on ESA therapy
- Correction of iron deficiency can improve Hb independently of ESAs
- Need for ESA can be avoided or delayed

Patients already on ESA therapy
- Iron deficiency most common cause of poor response to ESA therapy
- Investigate and treat iron deficiency before increasing ESA dose

Balancing Hb, Ferritin, TSAT, ESA therapy and Iron therapy
- If Hb <100g/l and Ferritin/TSAT indicate iron deficiency, prescribe iron therapy and hold off ESA dose increase
- If Hb in target range 100 to 120g/l but Ferritin/TSAT indicate iron deficiency, prescription of iron should be considered to prevent a drop in Hb (dependent on patient’s modality, Hb trend, severity of iron deficiency)
- If Hb >120g/l but Ferritin/TSAT indicate iron deficiency, prescription of iron is not required (review ESA dose)
- If Hb and TSAT indicate need for iron therapy but Ferritin 500 to 800mcg/l iron can be prescribed cautiously but consider lower dose (do not prescribe iron if Ferritin >800mcg/l)
- Prescribe iron therapy according to the trend in Hb/Ferritin/TSAT rather than isolated results

Iron therapy prescribing options for N&T patients (ESA naive or on ESA therapy)
- Intravenous iron widely used (first line for haemodialysis unit, home haemodialysis and peritoneal dialysis patients)
- Oral iron (eg Ferrous Fumarate 210mg TDS) is an option for pre-dialysis and transplant patients but if not tolerated or ineffective after 3 months treatment switch to intravenous

Pre-Dialysis and Transplant
High dose, low frequency IV Iron
600mg to 1000mg as a Total Dose Infusion (TDI)
Iron Isomaltoside 1000 (Monfer®) or Ferric Carboxymaltose (Ferinject®)
Administered at UHW Renal Day Unit (see iv iron referral pathway) or occasionally the local DGH

Peritoneal Dialysis and Home Haemodialysis
High dose, low frequency IV Iron
600mg to 1000mg as a Total Dose Infusion (TDI)
Iron Isomaltoside 1000 (Monfer®) or Ferric Carboxymaltose (Ferinject®)
IV iron prescribed at monthly MDT meetings and administered at UHW Home Therapies clinic or training beds

Haemodialysis Unit
Low dose, high frequency IV Iron
200mg single dose repeated 3 to 5 times as a “loading dose” regimen (max 600mg per week) or 100 or 200mg regularly every 2 to 4 weeks as a “maintenance dose”
Iron Sucrose (Venofer®)
IV iron prescribed at MDT meetings and administered at unit

Monitoring and review following IV iron therapy
Aim to maintain Ferritin 100 to 500mcg/l and TSAT >20%
- Check Hb/Ferritin/TSAT 4 to 8 weeks post iron treatment
- If Hb not in target range and Ferritin/TSAT still indicate iron deficiency then prescribe more IV iron (review dose regimen) and investigate other causes of iron deficiency

Ongoing iron monitoring for all patients with anaemia of CKD
Haemodialysis Unit and Home Haemodialysis Patients (Check Hb, Ferritin and TSAT every 8 to 12 weeks)
Pre-dialysis, Transplant and Peritoneal Dialysis Patients (Check Hb, Ferritin and TSAT every 12 weeks)

UHW Anaemia of CKD service
Vitaldata must be updated (by the MDTs in various modalities or the Renal Day Unit) with details of iron therapy (oral and intravenous) to support regular audit of the anaemia of CKD service
Contact Nephrology and Transplant Pharmacy Team (ext 41233 or ext 46324 or bleep 5707) for further advice about prescribing, administration and monitoring of iron therapy
Summary of monitoring requirements for Haemoglobin, Ferritin and Transferrin Saturation (all modalities)

**Correction phase of treatment**
- Hb every 4 weeks
- Aim to increase Hb by 10 to 20g/l per month
- Aim to achieve Hb of 100 to 120g/l

**Following ESA dose change**
- Wait at least 4 weeks before reviewing ESA dose following initiation or dose adjustment
- Check Hb every 4 weeks until Hb and ESA dose stable

**Maintenance phase of treatment**
- Review Hb every 8 to 12 weeks
- Aim to maintain stable Hb 100 to 120g/l
- Dose adjust in response to Hb trends not isolated results
- Review iron status before increasing ESA dose

**Correction phase of treatment**
- Check baseline Ferritin and TSAT
- Correct suboptimal iron stores (Ferritin <100mcg/l) and/or functional iron deficiency (TSAT <20%) before commencing ESA therapy

**Initiating iron therapy**
- Pre-Dialysis, Transplant, Peritoneal Dialysis and Home Haemodialysis
  - High dose, low frequency IV Iron as Total Dose Infusion (TDI); eg Monofer®
  - Oral iron an option for non dialysis patients
- Haemodialysis Unit
  - Low dose, high frequency IV Iron; eg Venofer®

**Maintenance phase of treatment (monitoring)**
- Review Ferritin and TSAT every 8 to 12 weeks
- Aim to maintain stable Ferritin 100 to 500mcg/l and TSAT >20%
- Review Hb alongside Ferritin and TSAT before prescribing further IV iron

**Maintenance phase of treatment (prescribing)**
- Pre-Dialysis, Transplant, Peritoneal Dialysis and Home Haemodialysis
  - Prescribe further Iron TDIs to treat iron deficiencies
- Haemodialysis Unit
  - Prescribe short courses of low dose, high frequency IV Iron to treat iron deficiencies or
  - Prescribe continuously in a smaller dose to prevent iron deficiencies
Erythropoiesis Stimulating Agents (ESAs) for adult patients with Anaemia of Chronic Kidney Disease

ESA Monitoring Pathways for Haemoglobin and Blood Pressure

February 2018 update
Background
The endogenous hormone Erythropoietin predominantly originates from the kidneys - its main action is to stimulate the bone marrow to produce red blood cells. Chronic Kidney Disease (CKD) patients become anaemic because of Erythropoietin deficiency. Without treatment the anaemia will invariably be persistent and symptomatic for the patient. Anaemia contributes to the development of left ventricular hypertrophy and is an independent risk factor for cardiovascular morbidity and mortality in CKD patients.

Recombinant Human Erythropoietins such as epoetin alfa (Eprex®), epoetin beta (Neorecormon®), darbepoetin alfa (Aranesp®) and methoxy polyethylene glycol epoetin beta (Mircera®) are the mainstay of treatment for anaemia of CKD and as a group of drugs are now described as Erythropoiesis Stimulating Agents (ESAs). The use of ESAs to correct anaemia in CKD patients has been shown in numerous studies to improve quality of life measurements such as patient wellbeing, appetite, sexual health and mental health. They have also been shown to improve physical parameters such as exercise capacity, stamina and symptoms of angina and peripheral vascular disease.

ESAs are widely prescribed for CKD patients of various treatment modalities - End Stage Renal Disease patients on Haemodialysis or Peritoneal Dialysis, Pre-Dialysis patients (including those opting not to receive long term dialysis therapy) and Renal Transplant patients. They are an effective and well tolerated treatment for these patients.

More information about ESAs and associated therapies such as intravenous iron can be found in the NICE clinical guideline “Anaemia management in people with Chronic Kidney Disease” (2015 update - nice.org.uk/guidance/ng8).

ESA prescribing and supply
ESA prescribing and supply schemes for adult patients with anaemia of CKD under the care of the Cardiff Renal Unit are centralised at the University Hospital of Wales (UHW).

GP are not expected to prescribe ESAs for these patients and the Shared Care Protocols are no longer in place for adult patients with anaemia of CKD.

Pre-Dialysis, Transplant, Peritoneal Dialysis and Home Haemodialysis patients:
- Receive their ESA via a home delivery service or directly from UHW pharmacy during routine nephrology clinic appointments.
- ESA administered as a subcutaneous injection, usually weekly, fortnightly or monthly depending on the agent prescribed.

Haemodialysis Unit patients:
- Given their ESA from a stock held on each unit.

All ESA prescribing and supply schemes will be managed by the Anaemia of CKD Service (including nephrologists, specialist nurses and renal pharmacists) at UHW.
**ESA therapeutic targets**

Prescribing of ESAs should be considered in patients with CKD when their Haemoglobin (Hb) is <110g/l. Treatment will be offered to patients who are likely to benefit in terms of quality of life and physical function and ESAs may be prescribed on a trial basis so that benefits can be evaluated regularly.

The aim for most adult patients on ESA therapy is to achieve and then maintain stable Hb levels between 100 and 120g/l, in accordance with recommendations from NICE.

- During correction phase of treatment, the aim is to increase Hb by 10-20g/l per month.
- Correction phase usually lasts for around 3 months.
- Dose of ESA will usually be increased (by 25-50%) if Hb rise <10g/l/month or reduced (by 25-50%) if >20g/l/month.
- ESA dose adjustments are less frequent during the maintenance phase, the main triggers being a trend for the Hb to remain below 100g/l or above 120g/l.

Typical maintenance doses per week for ESAs generally lower for non-dialysis patients (eg epoetin alfa 4000units weekly) and the highest doses are required by haemodialysis patients (eg epoetin alfa 4000units three times a week).

MHRA guidance from 2007 highlights an association between using ESAs to achieve Hb >120g/l and an increased risk of death and cardiovascular events in patients with CKD. It is important that the lowest effective ESA dose is used to treat anaemia of CKD and that Hb levels consistently >120g/l are avoided for the majority of patients.

**ESA monitoring – Haemoglobin (Hb)**

Patients on ESAs require regular monitoring of Hb on a long term basis:

- Every 4 weeks during correction phase of treatment with ESAs.
- Every 4 weeks following ESA dose change, usually for 2 to 3 months after dose change.
- Every 4 to 12 weeks during maintenance phase of treatment with ESA. For the majority of stable patients a Hb check every 3 months is clinically appropriate.
- Selected patients may require monitoring every 2 weeks on a temporary basis if Hb is particularly unstable.

**ESA monitoring – Blood Pressure (BP)**

Hypertension is a potential side effect of ESAs (generally linked to the rise in Hb, particularly if the increase is too rapid or if Hb above target range for anaemia of CKD) so patients require regular monitoring of BP but only on a short term basis:

- Every 4 weeks during correction phase of treatment with ESAs, usually for a period of 3 months only.
- Every 4 weeks following ESA dose change or following significant rise in Hb (eg >20g/l in 4 weeks) or if Hb above target range for anaemia of CKD, usually for 2 to 3 months only and/or until Hb and ESA dose are stable.
- Selected patients may require monitoring every 2 weeks on a temporary basis if BP is particularly unstable.
- In the maintenance phase of treatment (Hb stable in target range and ESA dose stable), additional ESA specific BP monitoring is not required above and beyond the standard checks of BP for any CKD patient done at CKD clinics or the GP practice.

The consultant looking after the patient will always have overall responsibility for review of Hb results during ESA therapy. They will also be responsible for review of BP results specific to ESA therapy as described above. Subsequent action in response to these results (eg adjustment of ESA dose) will also be the consultant’s responsibility. However, for a small number of patients, changes to Hb and BP which are picked up as part of monitoring will be unrelated to ESA therapy (eg a sudden and significant drop in Hb due to an occult GI bleed) and as such may be referred to the GP for further investigation and management.
For haemodialysis unit patients on ESAs, all Hb and BP checks are undertaken at their haemodialysis unit (patients attend three times a week).

For peritoneal dialysis, home haemodialysis and renal transplant patients on ESAs, all Hb and BP checks are undertaken at routine outpatient clinic appointments at UHW (patients attend every 1 to 3 months).

For pre-dialysis CKD patients on ESAs, the majority of Hb and BP checks are undertaken at routine renal outpatient clinic appointments at UHW or local DGH. Some pre-dialysis CKD patients (in particular the frail elderly) may only be attending the renal clinic every 4-6 months so need a Hb and BP check in the community in the interim period, particularly in the anaemia correction phase of treatment after commencing ESA therapy. To avoid additional hospital appointments purely for ESA related monitoring, the nephrology team may ask the District Nurse, Community Phlebotomy Service or GP Practice Nurse to take a blood sample for a FBC and a blood pressure reading. To minimise additional work for primary care, whenever possible:

- FBC request forms will be given to the patient by the nephrology team.
- Home BP monitoring will be promoted. Patients will be encouraged to obtain their own BP monitor or if this is not possible the CKD service can purchase BP monitors for selected patients. The CKD team can also train the patient/carer on how to operate the device.

Responsibility for first review of the Hb and BP results obtained in primary care will always remain with the consultant or specialist nurse looking after the patient:

- Hb results from bloods taken by a Practice Nurse or District Nurse or Community Phlebotomy Service will automatically reach the UHW Renal Unit database via local haematology labs.
- BP readings obtained by Practice Nurse or District Nurse will be followed up by the patient’s specialist nurse. If there are any concerns about a BP reading obtained in primary care this can be telephoned through to the UHW anaemia of CKD service (02920 748453) by the patient or practice/district nurse.

The Monitoring Pathways for Hb and BP described here provide further details, particularly for GP practices and District Nurses supporting the UHW anaemia of CKD service by taking blood samples and blood pressure readings. They also intended to clarify situations where further investigation and management of a patient’s Hb or BP may be referred back to the GP because they are unrelated to ESA therapy or anaemia of CKD.

If Hb or BP results are not available because patient hasn’t attended their CKD clinic or GP practice, this will be followed up by the CKD team. ESA therapy will be discontinued if there are repeated problems with patient not adhering to the monitoring regimen.

**Other monitoring related to ESAs**

Iron status will be monitored regularly in ESA patients (for example serum ferritin, serum percentage hypochromic red blood cells or serum transferrin saturation) to ensure they have optimal iron stores and do not develop functional iron deficiency. These investigations will be undertaken at CKD clinics. If iron therapy is required this can be given intravenously (given at UHW or a DGH more local to the patient) or orally (prescribed by hospital initially and then GP).

Aims of iron therapy in patients with anaemia of CKD:

- Ferritin >100mcg/l required before commencing an ESA for most patients.
- Ferritin 100 to 500mcg/l to be maintained during treatment with an ESA for most patients.
- Transferrin Saturation >20% or Percentage Hypochromic Red Cells <6% to be maintained during treatment with an ESA.

To maximise the effectiveness of ESA therapy, other factors affecting response to treatment must first be investigated and treated if appropriate. These include iron status (see above), serum folate and vitamin B12 levels, sources of excess blood loss (eg gastrointestinal), active inflammatory or infective conditions and uncontrolled secondary hyperparathyroidism.
ESA monitoring pathway for Haemoglobin:
Correction and maintenance phase of treatment with ESAs

Bloods taken at routine CKD clinic appointment at UHW or patient’s local DGH

Or

Bloods taken by District Nurse, Community Phlebotomy Service or GP Practice Nurse (FBC forms given to patient by CKD team)

Haemoglobin (Hb)
(every 1 to 3 months long term according to phase of treatment)

All Hb results reported on UHW systems and checked by a CKD nurse or doctor from the consultant team looking after the patient

Significant drop in Hb (eg >20g/l in 4 weeks) but unrelated to anaemia of CKD and management with ESAs

Clinical decision of UHW consultant team to refer to GP for further investigation of anaemia

Or

Clinical decision of UHW consultant team to further investigate anaemia via UHW

Significant rise in Hb (eg >20g/l in 4 weeks) or Hb consistently above target range - ESA dose reduced, withheld or ESA stopped by UHW

Patient and GP updated of changes to ESA therapy

Hb stable in target range or small increase/decrease or unchanged (all related to anaemia of CKD and management with ESAs) – ESA dose adjusted as required by UHW

Patient and GP updated of changes to ESA therapy

Or

Patient and GP updated of changes to ESA therapy
Haematology laboratories will have contact numbers at UHW to urgently report significant abnormalities in Hb results (even if blood sample taken at a GP practice or by District Nurse).

Patients are on ESA therapy to manage anaemia of CKD but they may also develop anaemia of other aetiology, the management of which is beyond the scope of this and other documents related to ESAs. This is particularly important in situations where there is an acute and unexplained clinically significant fall in Hb (eg >20g/l in 4 weeks) unrelated to ESA therapy, emphasising the need for both the GP and nephrologist to have active roles in investigating and managing anaemia in CKD patients. The abnormal results will first be reviewed by the UHW consultant nephrologist team who may opt to investigate the Hb drop through referral to other specialists at UHW, but further investigation and management can also be referred to the GP, particularly if future advice and investigation will be required via the patient’s local DGH rather than UHW.

Cases of chronic poor response to ESA therapy despite appropriate dosing (where other obvious causes of anaemia are ruled out) will be managed by UHW nephrologists initially but may require input from patient’s GP or local DGH as part of ongoing investigations into the patient’s low Hb.
ESA monitoring pathway for Blood Pressure:
Correction phase of treatment with ESAs or following ESA dose increase or following significant rise in Hb (eg >20g/l in 4 weeks)
(generally for 3 months only after ESA commenced/ESA dose increase/Hb rise)

Blood Pressure check at routine CKD clinic appointment at UHW or patient’s local DGH
Or
Blood Pressure check by District Nurse or patient/carer at home
Or
Blood Pressure check by GP Practice Nurse

CKD team contacts patient to obtain Blood Pressure result or Patient (or carer) or District/Practice Nurse contacts UHW with Blood Pressure result

Blood Pressure (BP) (monthly - only for 3 months and/or until Hb and ESA dose stable)

All BP results recorded on UHW systems and checked by a CKD nurse or doctor from the consultant team looking after the patient

Clinically significant rise in BP above baseline level for patient

Hypertension potentially ESA related (eg rapid rise in Hb; >20g/l in 4 weeks)

ESA dose reduced, withheld or ESA stopped by UHW

Patient and GP updated of changes to ESA therapy

Hypertension unlikely related to ESA therapy

Plus/Minus

Treatment of hypertension via UHW consultant team

Or

Hypertension referred to GP for pharmacological management (with advice from consultant team if required on choice and dose of antihypertensive) or non-pharmacological management
Hypertension is a recognised side effect of ESAs usually related to the increasing Hb. As such, it generally only occurs in the first 4 to 12 weeks after the patient commences an ESA (correction phase of treatment), after an ESA dose increase, if the Hb increases too rapidly or if the Hb increases above the target range. In these cases hypertension should respond to ESA dose reduction or withholding ESA temporarily.

Also in these instances, pharmacological (or non-pharmacological) management of the raised blood pressure may be indicated. Although this will generally be undertaken by the CKD clinics, decisions about antihypertensive treatment plans will often require the involvement of the GP.

In the maintenance phase of treatment (ie Hb stable in target range and ESA dose stable) hypertension as a side effect of ESAs is extremely unlikely so there is no requirement for BP monitoring additional to that which would normally be required for a CKD patient not on ESA therapy.

So BP still needs to be monitored (at CKD clinics and/or GP practice) in the maintenance phase but the need is directed by the fact that they are CKD patients rather than because they are on ESAs.

Hypertension in a patient with stable Hb in target range and stable ESA dose would not result in any changes to the ESA therapy. Other causes of raised blood pressure need to be investigated and treated.

In general, hypertension during any phase of treatment with ESAs can be treated according to UK guidance produced by British Hypertension Society or NICE for example. This can be undertaken via the GP practice with advice from UHW renal unit on choice and dose of antihypertensive if required.

CKD patients occasionally present with malignant hypertension. ESAs may be temporarily withheld in such patients until BP is under control (irrespective of Hb or stability of ESA dose).

Contact details
- UHW Anaemia of CKD Service 02920 748453 or 02920 748452 or e-mail anaemia.office@wales.nhs.uk
- UHW Renal Pharmacy Team 02920 746324 or 02921 841222
- All patients have a named Consultant who can be contacted for advice about anaemia of CKD and ESA therapy. Within each consultant team there are Specialist Nurses who are also points of contact about anaemia of CKD and ESA therapy. Consultants and Specialist Nurses can be contacted via UHW.

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