DRUGS USED IN RENAL ANAEMIAS
DARBEPOETIN (ARANESP®, ARANESP SURECLICK®)

This shared care guideline sets out details for the sharing of care of patients with **RENAL ANAEMIA** prescribed **DARBEPOETIN**. These guidelines provide additional limited information necessary to aid in the treatment of patients with **RENAL ANAEMIA**. As with all shared care guidelines they highlight significant prescribing issues but should be used in conjunction with the ABPI summary of product characteristics (SPC/Data sheet) and ***do not*** replace them.

INTRODUCTION/BACKGROUND INFORMATION

Anaemia is an almost invariable consequence of chronic renal failure (CRF). It causes many debilitating symptoms, e.g. tiredness, lethargy, muscle fatigue, poor exercise capacity. Anaemia is also a major factor contributing to the high prevalence of cardiovascular disease in renal patients, and the consequent increased morbidity and mortality.

The main cause of renal anaemia is loss of peritubular cells in the kidney responsible for synthesis and secretion of erythropoietin (EPO).

Darbepoetin is a hyperglycosylated analogue of EPO, allowing the molecule to be more stable *in vivo.* Its mechanism of action, by stimulating the EPO receptor, is the same as that of endogenous and recombinant EPO.

INDICATIONS FOR THE PURPOSES OF THIS GUIDELINE

'Treatment of anaemia associated with chronic renal failure in adults and paediatric patients ≥ 11 years of age'.

EFFECTIVE PRACTICE COMMITTEE RECOMMENDATION

'Darbepoetin is a hyperglycosylated analogue of erythropoietin (EPO) with similar efficacy in achieving and maintaining control of haemoglobin levels in EPO-naïve patients and those previously stabilised on EPO. Darbepoetin should be initiated in secondary care. Once the patient's condition is clinically stable, prescribing for administration by the subcutaneous route may continue in primary care under a shared care arrangement.'

DOSAGE AND ADMINISTRATION

Darbepoetin dosage schedules are split into a correction and a maintenance phase.

CORRECTION PHASE: The initial dose of darbepoetin is 0.45micrograms per kg administered by subcutaneous (SC) or intravenous (IV) injection once a week. Alternatively for patients not on dialysis an initial dose 0.75microgrammes per kg could be administered every two weeks.

If the increase in haemoglobin is inadequate (less than 1 g/dl in four weeks) increase the dose by approximately 25%. Dose increases must not be made more frequently than once every four weeks.
If the rise in haemoglobin is greater than 2.5 g/dl in four weeks reduce the dose by between 25 and 50%, depending on the rate of increase. If the haemoglobin exceeds 13 g/dl, discontinue therapy until it falls below 12 g/dl and then restart the treatment at approximately 25% below the previous dose. The haemoglobin should be measured every one or two weeks until it is stable. Thereafter the haemoglobin can be measured periodically.

MAINTENANCE PHASE: In the maintenance phase, darbepoetin may continue to be administered as a single injection once weekly or once every two weeks. Dialysis patients converting from once weekly to once every other week dosing with darbepoetin should initially receive a dose equivalent to twice the previous once weekly dose. In patients not on dialysis, once the target haemoglobin has been achieved with once every two week dosing, Darbepoetin may be administered subcutaneously once monthly using an initial dose equal to twice the previous once every two week dose.

Dosing should be titrated as necessary to maintain the haemoglobin target.

The target haemoglobin concentration of 11 to 12 g/dl needs to be established for individual patients. If a dose adjustment is required to maintain haemoglobin at the desired level, it is recommended that the dose is adjusted by approximately 25%.
If the rise in haemoglobin is greater than 2.0g/dl in four weeks reduce the dose by approximately 25%, depending on the rate of increase. If the haemoglobin exceeds 13 g/dl, discontinue therapy until it falls below 12 g/dl and then restart the treatment at approximately 25% below the previous dose.

After any dose or schedule adjustment the haemoglobin should be monitored every one or two weeks. Dose changes in the maintenance phase of treatment should not be made more frequently than every two weeks.

When changing the route of administration the same dose must be used and the haemoglobin monitored every one or two weeks so that the appropriate dose adjustments can be made to keep the haemoglobin at the desired level.

CONTRAINDICATIONS:

- Patients who develop anti-erythropoietin antibodies and Pure Red Cell Aplasia (PRCA) following treatment with any erythropoietin should not receive any further epoetin or darbepoetin
- Darbepoetin is contraindicated in patients with hypersensitivity to darbepoetin, epoetin, or any of the excipients
- Poorly controlled hypertension
- Breast feeding
- Cardiovascular disease including recent myocardial infarction, cerebrovascular accident, unstable angina or history of thromboembolic disease.

PRECAUTIONS:

- Epilepsy.
- Active liver disease.
- Sickle cell anaemia.
- Patients with thrombocytosis.
- Malignancy.
- Pregnancy.

SIDE EFFECTS

Very common > [1 in 10] > Common > [1 in 100] > Uncommon > [1 in 1000] > Rare > [1 in 10000] > Very rare

Very common / common:

- Hypertension, increased risk of thrombosis, injection-site pain, and headache (stabbing migraine-like pain can be warning of hypertensive crisis).

Rare / Very rare:

- Hyperkalaemia, seizures, thrombocytosis, influenza-like symptoms, dyspnoea, PRCA and anaphylaxis.

MONITORING

The following parameters should be monitored in patients receiving darbepoetin therapy

Initial monitoring - undertaken in hospital

Monitoring	Guidance
Haemoglobin	Every one or two weeks (until levels are stabilised) ▪ During the correction phase ▪ During the maintenance phase after any dose adjustment ▪ If route of administration is changed ▪ If darbepoetin is substituted for epoetin
Ferritin	Baseline level to be taken prior to treatment

Subsequent monitoring

Haemoglobin level and blood pressure should be monitored both in general practice and the hospital settings.

Monitoring	Guidance
Blood pressure monitor every 2 weeks. Aim to keep BP <140/80 with anti-hypertensive medication	If blood pressure is >180/100 omit darbepoetin and control BP. **Inform renal department.** Blood pressure medication should generally be: 1. ACE inhibitor or Angiotensin receptor blockers (ARB) - use in glomerular disease but not with renovascular disease 2. Calcium Channel Blocker 3. Beta blocker 4. Diuretic 5. Others
Haemoglobin monitor monthly.	*Mark them "Copy results to Sue Hussain – Specialist Anaemia nurse RD&E"*
If Haemoglobin (Hb) > 12 g/dL and platelets > 500,000.	Advice obtained from anaemia nurse on dose alterations. Normally: 'Suspend the darbepoetin dose until Hb drops below 12g/dL and then restart the darbepoetin with a dose 25% below the dose prior to stopping.'
If Hb <10 g/dL and falling or patient is symptomatic.	Advice obtained from anaemia nurse on dose alterations. Normally: 'Double the darbepoetin If failure to respond to an increased dose of darbepoetin then contact the renal departmen
Potassium. Monitor monthly	Maintain within normal levels. Patients with hyperkalaemia should be referred

Other monitoring will take place during patient visits to the renal clinic:

- Test ferritin level every 2 or 3 months during treatment. Where possible, the blood test for ferritin should be taken by the GP practice **a week before** the patient's next visit to the hospital. This allows action on the results at the next appointment. Bloods sent should be marked for copying to the renal department.
- Monitoring of folic acid and vitamin B12 levels every 6 months in the renal clinic.

REFER TO THE SPECIALIST TEAM IF

- Hypertension (>180/100). Omit darbepoetin and inform renal department. **URGENT REFERRAL.**
- Haemoglobin outside of ranges recommended in monitoring or an increase of >2.5g/dL in a month.

COMMON/SIGNIFICANT DRUG INTERACTIONS

- Data available so far do not indicate any significant interaction of darbepoetin with other substances. There is some evidence to suggest that hyperkalaemia and antagonism of hypotensive effect of **ACE inhibitors and Angiotensin receptor blockers (ARB)** may occur.
- As **ciclosporin** and tacrolimus are bound to red blood cells there is a potential for a drug interaction. If darbepoetin and ciclosporin/tacrolimus are administered concurrently, monitoring of immunosupressant level is advised, with dose adjustment as Hb rises.

NOTES

- Supplementary iron therapy is recommended for all patients with serum ferritin values <150micrograms/l or whose transferrin saturation is below 20%, to ensure effective erythropoiesis.
- Non-response to treatment with darbepoetin should be investigated. Factors that may compromise an erythropoietic response include: deficiencies in folic acid, iron, or vitamin B12; intercurrent infections; occult blood loss; severe aluminium toxicity; haemolysis; underlying haematological disease; bone marrow fibrosis; and inflammatory or traumatic episodes.
- At the equivalent doses used in clinical trials (1microgram darbepoetin ≡ 200 units epoetin), the cost of these drugs is currently identical.
- **NICE Clinical Guideline 39: Anaemia management in people with chronic kidney disease issued September 2006.**

  http://www.nice.org.uk/Guidance/CG39

PRODUCT INFORMATION – correct at publication

Store at +2°C to +8°C in a refrigerator.

Darbepoetin (Aranesp®) - Available in pre-filled syringes at the following doses 10,15,20,30,40,50,60,80,100, 130, 150, 300 and 500 micrograms. Cost is £1.676 per microgram.

REFERENCES:

- Summary of Product Characteristics: Aranesp®, Aranesp SureClick® accessed January 2008.
- BNF 55 March 2008.
- NICE guidance CG039 accessed 15/11/2006.
- http://www.nice.org.uk/guidance/cg39
- European Best Practice Guidelines: **http://ndt.oupjournals.org/content/vol14/suppl_5/** accessed 09/01/04
- Renal Association guidelines: **http://www.renal.org/Standards/RenalStandards_2002b.pdf**
- NSF for renal diseases. **http://www.dh.gov.uk http://www.dh.gov.uk/en/Policyandguidance/Healthandsocialcaretopics/Renal/DH_4102636**

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AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

These are suggested ways in which the responsibilities for the management of patients with **renal anaemia** who are prescribed **darbepoetin** can be shared between the specialist and the general practitioner. GPs are **invited** to participate. If the GP is not confident to undertake these roles, then they are under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist**. If a specialist asks the GP to prescribe this drug the GP should reply to this request as soon as practical.**

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient and be accepted by them.

The doctor who prescribes the medication has the clinical and legal responsibility for the drug and the consequences of its use.

Specialist responsibilities:

- ❑ Initiation of **darbepoetin** and stabilisation of patient's condition for a minimum of 3 months.
- ❑ Provide the patient or patient's parents/guardians/carers with suitable written and verbal information about the drug prior to starting medication and discuss the benefits and side effects of treatment.
- ❑ Ensure that training in the administration of the drug is provided to the patient or patient's carer.
- ❑ Monitoring of haemoglobin, blood pressure, ferritin, potassium, folic acid, and vitamin B12 as described in the Shared Care Guideline.
- ❑ Prompt verbal communication followed up in writing to the GP of any changes in treatment, results of monitoring undertaken and assessment of adverse events.
- ❑ As appropriate, liaison with other members of the multidisciplinary team e.g. anaemia nurse, renal specialist nurse, renal pharmacist.
- ❑ Ask the GP whether they are willing to participate in shared care.
- ❑ Prescribing the drug until the patient's condition/dose is stabilised and the GP agrees to take over responsibility for prescribing.
- ❑ Specify review dates at clinically relevant time intervals for both the GP and the consultant.
- ❑ Advice to GPs on change in dose, monitoring requirements or when to stop treatment.
- ❑ Provide the GP with relevant contact information with clear arrangements for back-up advice and support should further assistance be required relating to this drug.
- ❑ Reporting adverse events to the CSM.

General Practitioner responsibilities:

- ❑ Reply to the request for shared care as soon as practical.
- ❑ Prescribing of **darbepoetin** after communication with specialists regarding the need for treatment and stabilisation of the condition.
- ❑ Arrange for monitoring of blood pressure and haemoglobin and (where possible) ferritin blood levels as outlined in the shared care guideline. **Ensure that blood monitoring forms include the note "Copy to Sue Hussain – Specialist Anaemia Nurse RD&E"**
- ❑ Responding to advice from secondary care on dose changes and frequency of monitoring.
- ❑ Prompt referral to a specialist if there is a change in the patient's health status.
- ❑ Reporting to and seeking advice from a specialist on any aspect of patient care which is of concern to the GP and may affect treatment.
- ❑ Reporting adverse events to the specialist and CSM.
- ❑ Stopping treatment in the case of a severe adverse event or as per shared care guideline.

Patient responsibilities:

- ❑ Report any adverse effects to their GP and/or specialist regarding their treatment.
- ❑ Ensure that they have a clear understanding of their treatment.
- ❑ Ensure they attend for monitoring requirements as per shared care guideline, including making appointment for monitoring of ferritin levels in general practice one week prior to attendance at renal clinic.
- ❑ Liaise with secondary care over dosage changes.
- ❑ Aware that treatment will be affected if patient does not attend for monitoring.

BACK-UP ADVICE AND SUPPORT

Contact details	Telephone No:	E-mail address
Dr R D'Souza	(01392) 402587	Richard.DSouza@rdeft.nhs.uk
Dr C Bingham	(01392) 406366	Coralie.Bingham@rdeft.nhs.uk
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Sue Hussain	(01392) 402532	Suzan.Hussain@rdeft.nhs.uk

Shared Care Agreement Letter - Consultant Request

To: Dr.....

Practice Address: .....

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Patient Name:	
Hospital number:	
Date of birth:	
Address:	

DIAGNOSED CONDITION: **.....**

I recommend treatment with the following drug: **.....**

I am requesting your agreement to sharing the care of this patient according to the Devon Primary Care Trust North and East Devon Health Community Shared Care Prescribing Guidelines for this drug.

Signed:	
Consultant name:	
Department:	
Contact telephone number:	
Date:	

GP RESPONSE

I agree/ do not agree* to share the care of this patient in accordance with the Shared Care Guideline.

Signed: ..... Date: .....

GP name: ..... *Delete as appropriate