LINCOLNSHIRE CLINICAL COMMISSIONING GROUPS in association with UNITED LINCOLNSHIRE HOSPITALS TRUST SHARED CARE GUIDELINE:

Erythropoiesis Stimulating Agents (ESA's) in the treatment of Anaemia of Chronic Kidney Disease (CKD) stages 4 & 5.

Epoetin Beta (NeoRecormon®), Darbepoetin alfa (Aranesp®), and Epoetin Alfa (Eprex®)

This guideline only applies to the use of these drugs via subcutaneous injection. All intravenous use is the responsibility of the renal service.

General Principles

Shared Care Responsibilities:

In its guidelines on responsibility for prescribing (circular EL (91) 127) between hospitals and general practitioners, the Department of Health has advised that legal responsibility for prescribing lies with the doctor who signs the prescription. (*BNF* 70, September 2015 – March 2016 ,pg 4).

Aims:

(1) The aim of shared care guidelines is to provide information and/or guidance to GPs and hospital staff relating to the potentially complex implications of sharing patient care for a specific drug between primary and secondary/tertiary care.

(2) Specific shared care guidance should be available for any high cost drug, high-risk drug therapy or device that may be prescribed for a patient following specialist referral. Such guidance will only be produced where shared care is considered an appropriate option.

(3) Each guideline will include a clear statement of the responsibilities of both the GP and the specialist unit within the overall provision of the treatment to the patient.

(4) Shared care guidelines will ensure that the GP has sufficient information available to undertake to prescribe a specialist treatment if s/he so wishes. It is not the intention of these guidelines to insist that GPs prescribe such treatment and any doctor who does not wish to accept clinical or legal responsibility to prescribe such a drug is under no obligation to do so. Nonetheless the development of a shared care guideline will only be undertaken within the context of a broad acceptance between Lincolnshire Prescribing and Clinical Effectiveness Forum (PACEF) and secondary/tertiary care that GP prescribing of such a treatment is appropriate within the constraints of formal shared care. Any drug approved for the development of a shared care guideline will automatically be classified as amber on the Lincolnshire Traffic Lights List and, if high-cost, will be supported financially through the High Cost Drugs Reserve. Thus there should be no financial reason why a GP should be deterred from prescribing a high cost drug under a shared care guideline.

Further copies

Further copies of any guidelines in this series are available from Prescribing and Medicines Optimisation Team Prescribing Advisers.

Date of Issue: February 2016
Review date: February 2018

Principles of shared care

The General Medical Council published their Good Practice in Prescribing and Managing Medicines and which came into effect 25th February 2013. A section of the guidance provides recommendations for the sharing of care which applies to any instance when care is shared between different services.

Good practice recommendation 35.

- Decisions about who should take responsibility for continuing care or treatment after initial diagnosis or assessment should be based on patients best interest rather than on convenience or the cost of the medicine and associated monitoring or follow-up

Good practice recommendation 36.

- Shared care requires the agreement of all parties including the patient. Effective communication and continuing liaison between all parties to a shared care agreement is essential.

Good practice recommendation 37.

- If you prescribe at the recommendation of another doctor, nurse or other healthcare professional, you must satisfy yourself that the prescription is needed, appropriate for the patient and within the limits of your competence.

Good practice recommendation 38.

- If you delegate assessment of a patients' suitability for a medicine, you must be satisfied that the person to whom you delegate has the qualifications, experience, knowledge and skills to make the assessment. You must give them enough information about the patient to carry out the assessment required

Good practice recommendation 39.

- In both cases, you will be responsible for any prescription you sign.

Good practice recommendation 40.

- If you recommend that a colleague, for example a junior doctor or general practitioner, prescribes a particular medicine for a patient, you must consider their competence to do so. You must satisfy yourself that they have sufficient knowledge of the patient and the medicine, experience (especially in the case of junior doctors) and information to prescribe. You should be willing to answer their questions and otherwise assist them in caring for the patient, as required

Good practice recommendation 41

- If you share responsibility for a patient's care with a colleague, you must be competent to exercise your share of clinical responsibility.

You should:

a) Keep yourself informed about the medicines that are to be prescribed for the patient
b) Be able to recognise serious and frequently occurring adverse side effects
c) Make sure appropriate clinical monitoring arrangements are in place and that the patient and the healthcare professionals involved understand them
d) Keep up to date with relevance guidance on the use of the medicines and on the management of the patient's condition

Good practice recommendation 42

- In proposing a shared care arrangement, specialists may advise the patient's general practitioner which medicine to prescribe. If you are recommending a new or rarely prescribed medicine you should specify the dosage and means of administration and agree a protocol for treatment. You should explain the use of unlicensed medicines and departures from authoritative guidance or recommended treatments and provide both the general practitioner and the patient with sufficient information to permit the safe management of the patient's condition.

Good practice recommendation 43

- If you are uncertain about your competence to take responsibility for the patients continuing care you should seek further information or advice from the clinician with whom the patient's care is shared or from another experienced colleague. If you are still not satisfied you should explain this to the other clinician and to the patient and make appropriate arrangements for their continuing care.

Introduction

This shared care protocol should be read in conjunction with the Summary of Products Characteristics (SPC) for the particular brand of Erythropoiesis Stimulating Agent (ESA) which is being prescribed.
Initiation of treatment should be the responsibility of a renal consultant.

Drug Details

Approved Name: Epoetin alfa, Epoetin beta, Darbepoetin alfa
Brand Name: Eprex, NeoRecormon, Aranesp
Form: Prefilled syringes
In line with the MHRA recommendations for Erythropoiesis Stimulating Agents (ESAs) (December 2007), this SCA complies with the recommendations on target haemoglobins, and should only be used for the anaemia of renal disease. ESAs should only be used for patients with renal disease if symptoms of anaemia are present.

Specialist Responsibilities

The specialist secondary/tertiary care service will:

1. Confirm diagnosis of anaemia associated with Chronic Kidney disease (CKD).
2. Send a letter to the GP suggesting that shared care is agreed for this patient. Either enclose a copy of the shared care protocol or the GP should be signposted to where they can find a copy of the shared care protocol e.g. the PACEF website http://lincolnshire-pacef.nhs.uk/lincolnshire-prescribing-and-clinical-effectiveness-forum-pacef.
3. Carry out baseline measurements of haemoglobin, serum ferritin, transferrin saturation rate, Full Blood Count, vitamin B12, folate and CRP, and before commencing therapy will communicate these to the GP.
4. Ensure that blood pressure is stable and well controlled, and any antihypertensive therapy is maximised before initiating the ESA.
5. Initiate treatment with the ESA and ensure patient is stabilised on treatment before transferring the prescribing responsibility to the GP.
6. Provide patient with information leaflet and patient held record card for blood pressure and date of next haemoglobin check.

7. Provide the patient with training in administration of the ESA, in conjunction with company training, or arrange administration in Primary Care.
8. Ensure that arrangements are in place for regular monitoring of the patient's blood pressure (BP). Initially blood pressure needs to be monitored every 2 weeks , increasing to once weekly if concerns, and decreasing to monthly if stable and within target (<130/80 for all renal patients and lower for some). Each patient will be provided with an individualised care plan stating their BP target.
9. Anti-hypertensive therapy should be adjusted by the GP to achieve target BP.
10. Provide the GP with clear instructions as to the initial dose of ESA including details of any dose titration that might be required and when the patient will next be reviewed in clinic.
11. Periodically (at one-to six-monthly intervals in clinic) review the patient's clinical condition.
12. Prescribe and arrange for administration of Intravenous(I/V) iron when necessary.
13. Communicate promptly any changes in biochemistry monitoring and modification of ESA dose to the GP.
14. Have a mechanism in place to receive rapid referral of a patient from the GP in the event of deteriorating clinical condition.
15. Follow up any adverse drug reactions reported by the GP and report back to the GP.
16. Advise the GP on when to stop treatment (if appropriate).

GP Responsibilities

The GP will:

1. Notify the consultant in writing, within two weeks, if they agree to share care.
2. Prescribe the ESA in accordance to written instructions received from the specialist service.
3. Ensure regular monitoring of the patients blood pressure if arrangements have been made for this to be carried out at their local surgery.
3. Monitor the Hb monthly for the first 3 months then every 2-3 months depending on stability.
4. Haemoglobin levels should be monitored one month after each dose change.
5. Monitor ferritin every 2-3 months with transferrin saturations and alert the secondary care team of the Hb or ferritin fall outside the target limits (aspirational range for Hb 100– 120g/l; ferritin less than 200 micrograms/litre or transferrin saturation rate less than 20%).
6. Provide repeat prescriptions according to recommendations on dosage by the renal unit, Lincoln County Hospital.
7. Monitor the patients overall health and wellbeing.
8. Monitor the patient for adverse drug reactions and remain vigilant to the risk of potential drug interaction.
9. Carry out any investigations that are communicated and deemed appropriate.

Referral Criteria

1. Pre-existing uncontrolled hypertension must be treated.
2. The current iron status of patients is established by measuring serum ferritin and transferrin saturation rate. If serum ferritin is less than 200micrograms per litre and the transferrin saturation rate is less than 20% a course of intravenous iron will be prescribed.
3. Baseline measurements of haemoglobin , folate (range 4.8-18.7 micrgrams/L), vitamin B12 (range 197-771ng/L) and CRP(less than 8mg/l) are established

Licensed Indications

Epoetin alfa (Eprex®) Epoetin beta (NeoRecormon®), Darbepoetin alfa(Aranesp®) are all licensed for treatment of symptomatic anaemia associated with chronic renal failure in patients on dialysis and for symptomatic anaemia associated with chronic renal failure in patients not yet on dialysis.

Recommended Dosage and Administration

Starting Dose: The starting dose is determined according to body weight and is also dependent upon whether the patient is established on dialysis or pre-dialysis. Erythropoiesis stimulating drugs should be initiated when the haemoglobin has been lower than 11g/dl on at least two recordings more than two weeks apart or the patient develops symptoms attributable to anaemia. Other causes of anaemia should be excluded and iron stores should be adequate prior to initiation of therapy. The target haemoglobin is 100 to 120g/l. However, this is individualised for each patient according to the existence of other co-morbidities.

To keep the Hb level within the aspirational range, do not wait until Hb levels are outside the aspirational range before adjusting treatment (for example, take action when Hb levels are within 5g/l of the range's limits i.e at 105g/L and 115g/L

Erythropoeitin should not be administered if the blood pressure is ≥ 190/100mmHg – Blood pressure control should be reviewed and addressed and the erythropoietin given once the BP is below this level.

Pre-dialysis, peritoneal dialysis or home haemodialysis patients:

Epoetin beta (NeoRecormon®), Epoetin alfa(Eprex®): 25-50 units per kg twice per week by subcutaneous injection
Darbepoetin (Aranesp®): up to 0.45micrograms per kg once a week by subcutaneous injection
Dose is titrated at monthly intervals according to response
Although epoetin alfa and beta are clinically indistinguishable the prescriber must specify which is required.

Background Pharmacology

Human erythropoietin is an endogenous glycoprotein hormone that is the primary regulator of erythropoiesis through specific interaction with the erythropoietin receptor on the erythroid progenitor cells in the bone marrow. The production of erythropoietin primarily occurs in and is regulated by the kidney in response to changes in tissue oxygenation. Production of endogenous erythropoietin is impaired in patients with chronic renal failure and the primary cause of their anaemia is due to erythropoietin deficiency.

Darbepoetin alfa stimulates erythropoiesis by the same mechanism as the endogenous hormone. Darbepoetin alfa has five N-linked carbohydrate chains whereas the endogenous hormone and recombinant human erythropoietins (r-HuEPO) have three. The additional sugar residues are molecularly indistinct from those on the endogenous hormone. Due to its increased carbohydrate content darbepoetin alfa has a longer terminal half-life than r-HuEPO and consequently a greater in vivo activity. Despite these molecular changes, darbepoetin alfa retains a very narrow specificity for the erythropoietin receptor.

Preparations Available

All preparations should be stored in a refrigerator at 2 – 8^{o} C

Prefilled syringes containing 1000, 2000, 3000, 4000, 5000, 6000, 8000 and 10 000 units (Eprex and NeoRecormon)
Prefilled syringes containing 10, , 20, 30, 40, 50, 60, 80, 100, 130 150,300 and 500 micrograms darbepoetin (Aranesp)

Adverse Effects

The most important side effect is hypertension which occurs in about 35% of patients and is dose dependent. Hypertension should be treated with conventional therapies. Severe resistant and uncontrolled hypertension requires suspension of therapy until blood pressure is controlled. Erythropoeitin should not be given if the BP is ≥ 190/100. Hypertensive encephalopathy and seizures are rare but recognised complications of uncontrolled hypertension associated with the use of erythropoiesis stimulating drugs.
Dose dependent increase in platelet count during initiation of treatment.

Other side effects include influenza-like symptoms at the initiation of treatment, clotting of arteriovenous fistulae, hyperkalaemia and skin reactions.
The CSM advise: There have been very rare reports of pure red cell aplasia in patients treated with epoetin alfa. If a diagnosis of pure red cell aplasia is made, treatment with epoetin alfa must be discontinued and testing for erythropoetin antibodies considered. Patients who develop pure red cell aplasia should not be switched to another form of erythropoetin.

Drug Interactions

ACE inhibitors and Angiotensin II receptor antagonists: antagonism of hypotensive effect and increased risk of hyperkalaemia.
Ciclosporin & tacrolimus – there is a potential for interaction since the immunosupressants are bound to red blood cells. Monitor immunosuppressant level and adjust dose if Hb rises.

Precautions and Contraindications

Precautions

Inadequately treated or poorly controlled hypertension (monitor blood pressure, reticulocyte counts, haemoglobin and electrolytes)
Interrupt treatment if blood pressure uncontrolled – erythropoietin should not be given if the BP is ≥190/100mmHg.– sudden stabbing migraine like pain is warning of a hypertensive crisis.
Sickle-cell disease – lower target haemoglobin concentration may be appropriate
Exclude other causes of anaemia; give iron supplements if necessary.
Ischaemic vascular disease, thrombocytosis (monitor platelet count for first eight weeks), epilepsy, malignant disease, chronic liver failure,
Avoid in cardiovascular disease including recent myocardial infarction and cerebrovascular accident,
Pregnancy - no evidence of harm, benefits probably outweigh risk of anaemia and of transfusion.
Breastfeeding - unlikely to be present in milk; minimal effect on infant. **Darbepoetin is contraindicated in breastfeeding mothers.**
Malignant disease – increase in unfractionated or low molecular weight heparin dose may be needed in dialysis.
Risk of thrombosis may be increased in patients when used for anaemia before orthopaedic surgery or when used for anaemia in adults receiving cancer chemotherapy.

Contraindications

Severe uncontrolled hypertension.
Pure red cell aplasia following erythropoietin therapy
Patients unable to receive thromboprophylaxis.
Darbepoetin is contraindicated in breastfeeding mothers.

Monitoring

Prior to commencement of therapy.

Pre-existing uncontrolled hypertension must be treated.
Blood Pressure should be checked at the practice. BP should be monitored on an ongoing basis (every 2 weeks initially, increasing to once weekly if concerns, and decreasing to monthly if stable and within target (<130/80 for all renal patients and lower in some.) Each patient has an individualised care plan for BP on their BP

cards.
Maximising iron stores will optimise the response to erythropoiesis stimulating therapy. The current iron status of patients is established by measuring serum ferritin and transferring saturation rate.
Baseline measurements of haemoglobin, reticulocyte count, folate, vitamin B12 and CRP are established.

After initiation of therapy

The dose is titrated at intervals of 3-4 weeks to achieve a maximum rise in haemoglobin of 1g/dl per month (correction phase).
When the target haemoglobin is achieved (100-120g/l) the dose should be reduced by 50% and haemoglobin monitored every 4-6 weeks with titrated dose adjustments to maintain within target limits. (maintenance phase)
Haemoglobin levels should be monitored one month after each dose change.

Treatment should be reviewed and secondary care team alerted if haemoglobin falls outside target range of 100 -120g/l, urgent specialist advice should be sought if Hb > 130g/l or <85g/l. If Hb > 130g/L erythropoietin should be stopped whilst specialist advice is being sought.

Indication of Likely Cost of Therapy in Primary Care

Approximate NHS Cost of treatment (February 2013):
Epoetin Beta (NeoRecormon®): 2000units twice weekly for 4 weeks = £112.23, £1,459 per year.
Epoetin Alfa (Eprex®): 2000units twice weekly for 4 weeks = £88.50 , £1,151 per year.
Darbepoetin alfa (Aranesp®): 20microgram once weekly for 4 weeks= £234.90, £3,054 per year.

Information Given to the Patient

Patient information leaflet available with each container of ESA
Hand held blood pressure measurement card

Contact Details

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References

1. BNF Volume 70September 2015 .
2. Leicestershire Medicines Strategy Group Shared Care Agreement Version 1.1 September 2010
3. NICE Guidance (NG8 June 2015)
4. SPC Epoetin Beta (Neo-Recormon®), Darbepoetin alfa (Aranesp®) Epoetin Alfa (Eprex®)
5. The Dudley Group of Hospitals ESCA: Erythropoietic Stimulating Agent(ESA) Therapy (formerly known as EPO) For the correction of anaemia of Chronic Kidney Disease. Approved June 2011. For review June 3013.

6. Shared care information for Erythropoietin and Darbepoetin. NHS Plymouth, NHS Devon, NHS Cornwall & Isles of Scilly. Last updated 06.06.2012

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Updated February 2016

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