Medicines Optimisation Programme Board (MOPB)

Drug	**Erythropoietic stimulating agents (ESAs)**
Indication	Symptomatic anaemia associated with chronic renal failure[1,2].
Decision	Aranesp® (Darbepoetin) and Eprex® (Epoetin) within their licenced indications for treatment of symptomatic anaemia associated with chronic renal failure are RECOMMENDED for patients in secondary care prescribing. Note: Dialysis-induced anaemia is commissioned by NHS England.
Date	20th December 2018
Evidence	**NICE guideline 8 Chronic Kidney Disease (June 2015)** Offer treatment with erythropoietic stimulating agents (ESAs) to people with anaemia of CKD who are likely to benefit in terms of quality of life and physical function.

Recommendation to MOPB

Position Statement: The prescribing of Erythropoietic Stimulating Agents (ESAs) is supported by West Essex CCG for people with anaemia of CKD who are likely to benefit in terms of quality of life and physical function.

NHS West Essex Clinical Commissioning Group does commission Erythropoietic stimulating agents (ESAs) for people with anaemia of CKD and who are likely to benefit in terms of quality of life and physical function.

The following products are included within the classification of ESA's; however this list may not be exhaustive: Eprex®, Aranesp®.

Note: Dialysis-induced anaemia is commissioned by NHS England.

Rationale for recommendation

Effectiveness

NICE NG8 Chronic kidney disease: managing anaemia (June 2015)
Offer treatment with erythropoietic stimulating agents (ESAs) to people with anaemia of CKD who are likely to benefit in terms of quality of life and physical function.

Cochrane Database Syst Rev. 2005 Jul 20;(3):CD003266.
Recombinant human erythropoietin for chronic renal failure anaemia in pre-dialysis patients.

BACKGROUND:
Treatment with recombinant human erythropoietin (rHu EPO) in dialysis patients has been shown to be highly effective in terms of correcting anaemia and improving quality of life. There is debate concerning the benefits of rHu EPO use in pre-dialysis patients which may accelerate the deterioration of renal function. However the opposing view is that if rHu EPO is as effective in pre-dialysis patients, improving the patients sense of well-being may result in the onset of dialysis being delayed.

Objectives:
To assess the effects of rHu EPO use in pre-dialysis patients with renal anaemia.

Search strategy:
The initial search included 13 electronic databases (1980 to May 2001) an internet search (August 1997), handsearching of Kidney International (1983 to May 1997), contact with known investigators and biomedical companies, and reference list of relevant articles. For this update we searched the Cochrane Renal Group's specialised register (June 2004) and The Cochrane Library (Issue 3, 2004).

Selection criteria:
Randomised controlled trials (RCTs) or quasi-RCTs comparing the use of rHu EPO with no treatment or placebo in pre-dialysis patients.

Data collection and analysis:
Only published data were used. Quality assessment was performed by two assessors independently. Data were abstracted by a single author onto a standard form, a sample of which was checked by another author. Results were expressed as relative risk (RR) or weighted mean difference (WMD) with 95% confidence intervals (CI).

Main results:
Fifteen trials (461 participants) were included. There was a marked improvement in haemoglobin (WMD 1.82 g/dL, 95% CI 1.35 to 2.28) and haematocrit (WMD 9.85%, 95% CI 8.35 to 11.34) with treatment and a decrease in the number of patients requiring blood transfusions (RR 0.32, 95% CI 0.12 to 0.83). The data from studies reporting quality of life or exercise capacity demonstrated an improvement in the treatment group. Most of the measures of progression of renal disease showed no statistically significant difference. No significant increase in adverse events was identified.

Authors' conclusions:
Treatment with rHu EPO in pre-dialysis patients corrects anaemia, avoids the requirement for blood transfusions and also improves quality of life and exercise capacity. We were unable to assess the effects of rHu EPO on progression of renal disease, delay in the onset of dialysis or adverse events. Based on the current evidence, decisions on the putative benefits in terms of quality of life are worth the extra costs of pre-dialysis rHu EPO need careful evaluation.

Short-acting erythropoiesis-stimulating agents for anaemia in predialysis patients (Review)
Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD011690.

Background
The benefits of erythropoiesis-stimulating agents (ESA) for chronic kidney disease (CKD) patients have been previously demonstrated. However, the efficacy and safety of short-acting epoetins administered at larger doses and reduced frequency as well as of new epoetins and biosimilars remains uncertain.

Objectives
This review aimed to evaluate the benefits and harms of different routes, frequencies and doses of epoetins

Authors' conclusions
Epoetin alpha given at higher doses for extended intervals (two or four weekly) is non-inferior to more frequent dosing intervals in maintaining final Hb levels with no significant differences in adverse effects in non-dialysed CKD patients. However the data are of low methodological quality so

that differences in efficacy and safety cannot be excluded. Further large, well designed, RCTs with patient centred outcomes are required to assess the safety and efficacy of large doses of the shorter acting ESAs, including biosimilars of epoetin alpha, administered less frequently compared with more frequent administration of smaller doses in children and adults with CKD not on dialysis.

Safety

Medicines and Healthcare products Regulatory Agency (MHRA)

9 January 2018 Advice for healthcare professionals:

- we are aware of very rare cases of severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), in patients receiving recombinant human erythropoietins (r-HuEPOs); some cases were fatal
- more severe cases were recorded with long-acting r-HuEPOs (darbepoetin alfa and methoxy polyethylene glycol-epoetin beta)
- advise patients of the signs and symptoms of severe skin reactions at initiation and instruct them to stop treatment and seek immediate medical attention if they develop widespread rash and blistering; these rashes often occur following fever or flu-like symptoms
- discontinue all r-HuEPOs permanently in patients who develop severe cutaneous adverse reactions such as SJS or TEN
- report all suspected adverse reactions to HuEPOs on a Yellow Card

11 December 2014 Recombinant human erythropoietins: new advice for prescribing
Over-correction of haemoglobin concentration may increase the risk of death and serious cardiovascular events in patients with chronic kidney disease; it may increase the risk of thrombosis and related complications in patients with cancer.
Results of studies suggest that treatment of anaemia with r-HuEPOs in patients with chronic kidney disease to achieve relatively high target haemoglobin concentrations may be associated with increased risk of mortality and cardiovascular morbidity.

Possible side effects for all EPOETINS include[3]:

Common or very common

- Arthralgia; embolism and thrombosis; headache; hypertension (dose-dependent); influenza like illness; skin reactions; stroke

Uncommon

- Hypertensive crisis (in isolated patients with normal or low blood pressure); respiratory tract congestion; seizure

Rare or very rare

- Thrombocytosis

Frequency not known

- Pure red cell aplasia (more common following subcutaneous administration in patients with chronic renal failure)

Patient factors

SmPC Aranesp® (Darbepoetin)

Correction phase
In patients not on dialysis, the following initial doses can be administered subcutaneously as a single injection: 0.75 µg/kg once every two weeks or 1.5 µg/kg once monthly. If the increase in haemoglobin is inadequate (less than 1 g/dl (0.6 mmol/l) in four weeks) increase the dose by approximately 25%. Dose increases must not be made more frequently than once every four weeks.
Maintenance phase
In patients not on dialysis, Aranesp may continue to be administered as a single injection once

weekly or once every two weeks or once monthly. For patients treated with Aranesp once every two weeks, after the target haemoglobin has been achieved, Aranesp may then 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.
If a dose adjustment is required to maintain haemoglobin at the desired level, it is recommended that the dose is adjusted by approximately 25%.

SmPC Eprex® (Epoetin)
Adult patients with renal insufficiency not yet undergoing dialysis
Where intravenous access is not readily available EPREX may be administered subcutaneously.
Correction phase
Starting dose of 50 IU/kg, 3 times per week, followed if necessary by a dosage increase with 25 IU/kg increments (3 times per week) until the desired goal is achieved (this should be done in steps of at least four weeks).
Maintenance phase
During the maintenance phase, EPREX can be administered either 3 times per week, or in the case of subcutaneous administration, once weekly or once every 2 weeks.
Appropriate adjustment of dose and dose intervals should be made in order to maintain haemoglobin values at the desired level: haemoglobin between 10 g/dL and 12 g/dL (6.2 to 7.5 mmol/L). Extending dose intervals may require an increase in dose.
The maximum dosage should not exceed 150 IU/kg 3 times per week, 240 IU/kg (up to a maximum of 20,000 IU) once weekly, or 480 IU/kg (up to a maximum of 40,000 IU) once every 2 weeks

References

1. SmPC Aranesp https://www.medicines.org.uk/emc/product/7993/smpc [Accessed 18.10.18]
2. SmPC Eprex https://www.medicines.org.uk/emc/product/3441/smpc [Accessed 18.10.18]
3. British National Formulary https://bnf.nice.org.uk [Accessed 18.10.18]