South African National Essential Medicines List
Adult Hospital Level Medication Review Process
Component: Nephrology

MEDICINE CLASS REVIEW OF ERYTHROPOIESIS-STIMULATING AGENTS
Date: 21 April 2022

Key findings

- This review was to determine therapeutic equivalency amongst erythropoiesis-stimulating agents (ESA), and not to expand the indication from the current guidance of ESA for anaemia of chronic kidney disease in patients on dialysis to all patients.
- We searched PubMed and the Cochrane Library for published systematic reviews and meta-analyses of comparisons of erythropoietins against placebo as well as compared against each other, in patients with chronic kidney disease.
- Epoetin alfa and epoetin beta; methoxy polyethylene glycol epoetin beta and darbepoetin alfa have all demonstrated efficacy versus placebo in increasing haemoglobin and reducing need for transfusion.
- Haemoglobin increase was greater with erythropoietins than with placebo or no treatment, mean difference 1.90 g/dL, 95% CI 1.47 to 2.34: I2 =30%). Erythropoietins decreased need for transfusion compared with placebo: Recombinant erythropoietins (epoetin alfa and Beta and darbepoetin) (3 studies, 111 participants) relative risk (RR) of transfusion was 0.32, 95% CI 0.12 to 0.83; I2 = 0%) versus placebo, NNT = 5. Darbepoetin alfa (1 study with 4038 participants) reduced need for one or more blood transfusions, RR 0.60, 95% CI 0.53 to 0.69) versus placebo, NNT = 10.
- The evidence for improvements in Quality-of-Life measures was less certain, both for the ESA versus placebo and for ESAs versus each other.
- There was little difference in magnitude of improvement in quality-of-life measures between ESA options.
- There was little difference in safety profiles with respect to adverse events, all-cause mortality, and cardiovascular mortality, although comparative data was quite low quality.
- Dosing comparisons were difficult given that this review has summarised several different systematic reviews which included initiation at different clinical points and included different clinical dosing regimens. However, comparative recommended starting and switching doses are available.
- All options appear to be equally effective and international guidelines make no preferential recommendations for which ESA to prescribe.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE PROPOSAL:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
					X

Recommendation: The PHC/Adult Hospital Level Committee proposes that erythropoiesis-stimulating agents be recommended as a therapeutic group for patients with anaemia of chronic kidney disease (*strong recommendation).*
Rationale: Epoetin alfa and epoetin beta; methoxy polyethylene glycol epoetin beta and darbepoetin alfa are equally effective in increasing haemoglobin and preventing blood transfusions in chronic kidney disease. Harms and cardiovascular risks are similar and dose proportional. This has been demonstrated in several systematic reviews comparing various agents in various situations.
Level of Evidence: Moderate certainty evidence (Meta-analysis and systematic review; III Guidelines)

NEMLC RECCOMENDATION (MEETING OF 23 JUNE 2022):
The NEMLC accepted the proposal that erythropoiesis-stimulating agents be recommended as a therapeutic class. Furthermore, with the final ratification of the respective nephrology/urology chapter, NEMLC recommended that a circular be disseminated guiding on comparative dosing, dose switching and relevant pragmatic issues.

Monitoring and evaluation considerations:
- Dosing is patient specific and dependent on response
- There are recommended Hb limits in place which should not be exceeded because of the risk of adverse effects

Research priorities

EXECUTIVE SUMMARY

Date: 14 February 2022
Medicine (INN):Other antinaemic agents (Erythropoetin alfa and erythropoetin beta; darbepoetin alfa ; methoxy polyethylene glycol epoetin beta)
Medicine (ATC): B03XA (B03XA01, B03XA02 and B03XA02)
Indication (ICD10 code): Treatment of anaemia in chronic renal failure (N18.1-5†/N18.9† + (D63.8*/Z49.1-2)
Patient population:
Adults aged 18 years or older with anaemia due to chronic kidney disease (CKD).
- with or without dialysis
- all stages of CKD

Prevalence of the condition:
Level of Care: Secondary
Prescriber level: Medical Officer
Current Standard of Care: Currently erythropoetins are recommended in the Hospital level Standard Treatment Guidelines for anaemia associated with CKD in patients on dialysis programmes. Patients on chronic haemodialysis or peritoneal dialysis are often anaemic due to iron deficiency and deficiency of erythropoietin (EPO). Simultaneous administration of iron and EPO is recommended, as EPO should be administered in a patient with normal iron stores. Adequate iron stores are required to assist with red blood cell production immediately after EPO administration.
Findings:
There is not a significant difference in the several different ESA erythropoietin agents in terms of efficacy, as indicated by quality-of-life measures, haemoglobin responses or prevention of the need for transfusion. There was also no indication of any difference in safety profiles, as indicated by adverse events, all-cause mortality and cardiovascular mortality, although comparative data is often quite low quality.
Guideline recommendations on choice of ESA recommend this is dependent on factors such as availability and cost. None of the reviewed guidelines made specific recommendations or preferences for any of the agents over the other, although there are some specific recommendations for pharmacovigilance for biosimilars.
Reviewers: Ms Shelley McGee, Dr Simba Takuva
PTC affiliation: n/a
Funding support: None

2. NAME OF REVIEWERS

Ms Shelley McGee; Dr Simba Takuva

3. AUTHOR AFFILIATION AND CONFLICT OF INTEREST DETAILS

- Ms Shelley McGee: National Operations Manager at the Ophthalmological Society of South Africa, Combined PHC/Adult Hospital Level Committee member (2020-2023)
- Dr Simba Takuva: Perinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand and School of Health Systems and Public Health, Faculty of Health Sciences, University of Pretoria, Combined PHC/Adult Hospital Level Committee member (2020-2021)

SM and ST have no interests to declare relating to epoetins.

4. INTRODUCTION/BACKGROUND

Recombinant erythropoietin and its synthetic derivatives (epoetin alfa, epoetin beta, darbepoetin alfa, methoxy polyethylene glycolepoetin beta; collectively known as erythropoiesis-stimulating agents (ESAs)), are widely used to treat anaemia.

Erythropoietin is a glycoprotein made by peritubular cells in the kidney (with an additional smaller contribution from liver cells (15% total)) and is released in response to low tissue oxygen levels (hypoxia) through the actions of hypoxia-inducible factor to stimulate the formation and viability of red blood cells in the bone marrow (erythropoiesis)(1).

In the case of chronic renal failure, there is a reduced production of erythropoietin in the kidneys in response to hypoxia. This is associated with left ventricular dysfunction and heart failure, in addition to a reduction in exercise capacity and quality of life.

Symptoms caused by insufficient oxygen delivery to tissues in anaemia include weakness and fatigue, breathlessness, light-headedness, and palpitations. Observational cohort data show that anaemia in people who have chronic disease is also consistently associated with negative effects on quality-of-life role function and survival.

The use of iron therapies and erythropoiesis stimulating agents (ESAs) has allowed improvement in patients with anaemia of CKD.

Currently epoetins are recommended in the Hospital level Standard Treatment Guidelines for anaemia associated with CKD in patients on dialysis programmes (N18.1-5†/N18.9† + (D63.8*/Z49.1-2).

Patients on chronic haemodialysis or peritoneal dialysis are often anaemic due to iron deficiency and deficiency of erythropoietin (EPO). Simultaneous administration of iron and EPO is recommended, as EPO should be administered in a patient with normal iron stores. Adequate iron stores are required to assist with red blood cell production immediately after EPO administration.

The purpose of this therapeutic review was to identify whether there are any notable differences in the various available agents in terms of efficacy and safety, with a view to determining whether the agents may be considered a class, for the purpose of tendering.

5. PURPOSE / OBJECTIVE

PICO question: Therapeutic review. The objective of this analysis was to compare the existing ESA's in patients with anaemia of chronic renal failure. Although patients not yet on dialysis were included in the population group, it was not the intention of this comparison to expand on the current standard of care in the Standard Treatment Guidelines Hospital level (which addresses only patients on dialysis).

Population: Adults aged 18 years or older with anaemia due to chronic kidney disease (CKD).

- with or without dialysis
- all stages of CKD

Intervention: Erythropoiesis-Stimulating Agents (ESA) -

- epoetin alfa, epoetin beta, darbepoetin beta, methoxy polyethylene glycol-epoetin beta, OR biosimilar)
- any dose and administered via any route

Comparison: No treatment, Placebo, different dose of ESA

Outcomes:

Efficacy	**Safety**
Primary outcomes: - Health-Related Quality of Life measures - Achievement of haemoglobin target level - Preventing blood transfusion Secondary outcomes: - Clinical anaemia i.e., fatigue, dyspnoea etc	- All-cause mortality - All SAEs - End-stage kidney disease - Cardiovascular mortality - Worsening cardiovascular condition (i.e., worsening hypertension) - alloimmunisation

6. METHODS AND FINDINGS

Electronic searches for systematic reviews and meta-analyses were conducted on 04 October 2021 in PubMed and the Cochrane Library. The search strategies are shown in Appendix 1. Records were screened for relevance, and duplicates removed. Titles and abstracts were evaluated for relevance and only finally selected articles were sought in full text for evaluation (Prisma Flow Diagram Figure 1).

Figure 1. Prisma flow diagram of search results

13 Systematic Reviews and Meta-analyses met the inclusion criteria. These are summarized in full in Appendix 2.

IN addition, in response to requirements of the EML Expert Review Committee in October 2021, we sought out several international guidelines which make recommendations about ESAs in the treatment of anaemia in chronic renal disease, to understand whether these guidelines recommend one agent above others or distinguish between the different erythropoietin in any way in the treatment of chronic kidney disease.

Six international guidelines were included for evaluation, including an AGREE II assessment, with three demonstrating relatively high scores on evaluation. These are summarized with key recommendations in Appendix 3.

i. EFFICACY OF ESAs IN ANAEMIA IN CKD

A) Health Related Quality of Life Measures

Overall, the information available on the improvement of all agents on quality-of-life measures remains weak. Although most of the systematic reviews included in this analysis, examined quality of life as an outcome measure, few were able to report any convincing results. Little improvement was demonstrated against placebo, and no differences could be shown between one agent and another, nor in terms of different dosing regimens.

A.1) ESAs versus placebo

The systematic review and meta-analysis by Cody et al(2) was not able to demonstrate improvements in quality of life measures in a systematic way. Only a single study included in the review reported on quality of life improvement, and although it showed a statistically significant difference favouring treatment recombinant human erythropoeitin (rHuEPO), the study was far too small (N=14) to make a comparison.

Collister et al(3) were similarly unable to show that higher hemoglobin(Hb) targets resulted in statistically or clinically significant differences in SF-36 or KDQ (Kidney Dialysis Questionnaire) domains, in patients receiving or not receiving dialysis. Differences in HRQOL were further attenuated in studies at low risk of bias and in subgroups of dialysis recipients.

Johansen et al(4) found only one trial which examined the impact of EPO versus placebo in a randomized controlled trial, which also looked at high Hb and lower Hb patient subgroups. This study found a 22% increase in KDQ fatigue scale in the lower Hb treatment arm and a 26.2% increase in the higher Hb treatment arm compared to only a little change (2.3%) over 6 months in the placebo arm.

Palmer et al (5) examined darbepoetin versus placebo and against other ESAs. One large study (n=3531) included in the meta-analysis examined impact of darbopoetin on the SF-36 scale (as well as the physical functioning score of the SF-36) but found no significant differences versus placebo - Mean Difference, 95% CI: 0.5[-0.15,1.15] for SF-36 and Mean Difference, 95% CI for physical functioning: 0.2[-0.39,0.79]. Measurement of fatigue demonstrated a significant difference. Mean difference in the FACT-Fatigue score was: 1.4[0.71,2.09] (95% CI).

A.2) ESAs versus each other

Hahn et al(6) examined various dosing regimens of ESAs in predialysis patients. Only one study (PROMPT Study 2005) performed quality of life (QOL) assessments and reported no statistical differences in the final QOL scores between groups receiving epoetin once weekly or two weekly.

In a broader comparison of ESAs, Palmer at al (1) found that directly comparative data for the effectiveness of different ESA formulations based on patient-centred outcomes (such as quality of life, fatigue, and functional status) are sparse and poorly reported and current research studies were unable to inform care.

Saglimbene et al(7) found no trials which examined quality of life where MIRCERA was compared with other epoetins.

B) <u>Achievement of Haemoglobin Target Levels</u>

B.1) ESAs versus placebo

Cody et al(2) demonstrated that rHuEPO significantly increased Hb compared to placebo or no treatment (4 studies, 237 participants): Mean difference 1.90 g/dL, 95% CI 1.47 to 2.34; I2 =30%). This review did not differentiate between different rHuEPOs.

Palmer et al (5) examined darbepoetin versus placebo and against other ESAs, but did not report on achievement of Hb targets as an outcome.

B.2) ESAs versus each other

Alsalimy and Awaisu(8) analysed trials of Methoxy polyethylene glycol-epoetin beta versus darbepoetin alfa. They demonstrated that in CERA treatment changes in hemoglobin level from the baseline were clinically non-inferior to darbepoetin alfa.

Amato et al(9), comparing originator epoetin alfa with biosimilars found the mean Hb level at the end of the study in the intervention groups was 0.08 higher (from −0.05 lower to 0.2 higher). A comparison of epoetin alfa versus darbepoetin alfa found that the mean Hb level at the end of the study in the intervention groups was −0.54 lower (−1.54 lower to 0.46 higher). For epoetin beta versus methoxy polyethylene glycol-epoetinβ, the mean Hb level at the end of study in the intervention groups was 0.21 higher (−0.41 lower to 0.82 higher). No meaningful differences were found in any of the comparisons.

Hahn et al (10) in examining different dosing regimens of epoetin alpha and beta, found: there were no significant differences in final Hb levels when dosing every two weeks was compared with weekly dosing (4 studies, 785 participants: MD -0.20 g/dL, 95% CI -0.33 to -0.07), when four weekly dosing was compared with two weekly dosing (three studies, 671 participants: MD -0.16 g/dL, 95% CI -0.43 to 0.10) or when different total doses were administered at the same frequency (four weekly administration: one study, 144 participants: MD 0.17 g/dL 95% CI -0.19 to 0.53). Five studies evaluated different interventions. One study compared epoetin theta with epoetin alpha and found no significant differences in Hb levels (288 participants: MD -0.02 g/dL, 95% CI -0.25 to 0.21).

Palmer et al (5) compared mean change in haemoglobin (mg/dL) in patients (with CKD but not necessarily on dialysis) on darbepoetin or other ESAs. The analysis included one study in which the Hb target in the darbepoetin alfa arm was higher than in the epoetin arm, darbepoetin alfa increased Hb levels at the end of treatment (1 study, 84 participants): MD 1.33 g/dL, 95% CI 0.84 to 1.82) whereas in the study reporting treatment effects on end of treatment Hb values in which target values were similar for both darbepoetin alfa and darbepoetin alfa arms, end of treatment values were similar (1 study, 363 participants): MD -0.07 g/dL, 95% CI -0.27 to 0.13). The mean change in Hb was similar for

darbepoetin alfa and epoetin treatment in adults (3 studies, 1060 participants): MD 0.06 g/dL, 95% CI -0.08 to 0.19; IQ = 0%).

C) Preventing blood transfusion

C.1) ESAs versus placebo

Cody et al (2) found that the number of patients requiring blood transfusions was significantly less in the rHuEPO group than those in the placebo or no treatment group (3 studies, 111 participants): RR 0.32, 95% CI 0.12 to 0.83; I2 = 0%), NNT = 6 (95% CI 5 to 7).

Palmer et al found that Darbepoetin alfa versus placebo (One large study at generally low risk of bias, 4038 participants), darbepoetin alfa reduced need for one or more blood transfusions (RR 0.60, 95% CI 0.53 to 0.69); NNT = 10. However in this single trial prevention of blood transfusion was not a primary outcome of the analysis

Kouloridis et al(11) found that the total-study-period mean ESA dose was associated with a lower rate of transfusion requirement (IRR, 0.73; 95% CI, 0.68–0.79) versus no treatment.

C.2) ESAs versus each other

Amato et al(9) demonstrated that the relative risk of blood transfusion was not significantly less with darbepoetin alfa than with epoetins. At 12 months follow-up the relatively risk of a transfusion was 0.73 (95% CI 0.44–1.21) or 15 less per 1000 (from 30 less to 11 more). (3 studies, 1823 patients). This evidence was considered low quality due to risk of bias.

Hahn et al (10)showed:

- Epoetin alpha every two weeks versus every four weeks using same total dose of epoetin - There were no significant differences in the number requiring transfusions (2 studies, 470 participants): RR 1.26, 95% CI 0.53 to 2.98).
- Epoetin alpha weekly versus every two weeks using same total dose of epoetin - There were no significant difference in the number requiring transfusion (3 studies, 580 participants): RR 1.56, 95% CI 0.71 to 3.45).
- Epoetin alpha different doses given every four weeks - There was no significant difference in patients requiring transfusions.

In Palmer et al, Darbepoetin alfa versus epoetin results were less certain (2 studies, 483 participants) - darbepoetin alfa had uncertain effects on need for blood transfusions compared to epoetin.

In studies comparing darbepoetin alfa with methoxy polyethylene glycol-epoetin beta, darbepoetin alfa had inconclusive effects on need for blood transfusion therapy (2 studies, 799 participants): RR 0.82, 95% CI 0.58 to 1.17; IQ = 0%).

Intravenous versus subcutaneous treatment IV darbepoetin alfa therapy had uncertain effects on need for blood transfusions (2 studies, 183 participants): RR 1.15, 95% CI 0.30 to 4.38),

Palmer et al(1) also demonstrated that all ESA agents significantly reduced blood transfusions versus placebo, but that no agent, when compared to any of the other agents, managed to significantly reduce requirements for blood transfusion. In network analyses, there was moderate to low confidence that epoetin alfa (OR 0.18, 95% CI 0.05 to 0.59), epoetin beta (OR 0.09, 95% CI 0.02 to 0.38), darbepoetin alfa (OR 0.17, 95% CI 0.05 to 0.57), and methoxy polyethylene glycolepoetin beta (OR 0.15, 95% CI 0.03 to 0.70) prevented blood transfusions compared to placebo. The authors could not discern whether all ESAs were similar or different in their effects on preventing blood transfusions and confidence in the comparative effectiveness of different ESAs was generally very low.

CERA failed to show benefits on blood transfusion versus epoetin alfa or beta (5 trials, 1824 patients) Risk Ratio (IV, Random, 95% CI) 1.02 [0.72, 1.46](7).

ii. ADVERSE EFFECTS OF ESAs IN ANAEMIA IN CKD

A) All-cause mortality

A.1) ESAs versus placebo

Cody et al (2) demonstrated no significant increase in mortality in ESA-treated patients versus placebo RR, 95% CI: 0.6[0.13,2.88]. However, the four trials in the analysis were small with a combined N = 182.

There were no significant increases in all-cause mortality from any of the agents examined by Palmer et al(1), against placebo, nor against each other.

A.2) ESAs versus each other

Amato et al (11), comparing originator epoetin alfa with biosimilars found no significant difference in all-cause mortality (8 studies, 2294 patients) RR.94 (0.52–1.7) or 3 less per 1000 (from 23 less to 34 more). A comparison of epoetin alfa versus darbepoetin alfa found similarly little difference (7 studies, 1265 patients) RR: 1.11 (0.6–2.06) or 4 more per 1000 (from 13 less to 35 more).

In Hahn et al for Epoetin alpha weekly versus every two weeks using same total dose of epoetin, there was no significant difference in all-cause mortality (4 studies, 838 participants): RR 0.89, 95% CI 0.38 to 2.07). Epoetin alpha every two weeks versus every four weeks using same total dose of epoetin, there was no significant difference in all-cause mortality (3 studies, 724 participants): RR 0.95, 95% CI 0.33 to
2.75). Epoetin alpha versus other epoetins or biosimilars no significant differences were noted in all-cause mortality (288 participants): RR 2.46, 95% CI 0.29 to 20.77).

In Koulouridis et a(11)l, in the unadjusted analysis, higher first- 3-month mean ESA dose (per epoetin alfa–equivalent 10,000-U/wk increment) was associated with a higher rate of all-cause mortality (IRR, 1.42; 95% CI, 1.10–1.83).This association persisted after adjustment for the first-3-month achieved mean hemoglobin level (IRR, 1.48; 95% CI, 1.02–2.14). After adjustment for the target hemoglobin level, the association strengthened in magnitude but lost statistical significance (IRR, 1.71; 95% 10 CI, 0.90–3.24). A similar association was observed in the unadjusted analysis for the association of the total-study-period mean ESA dose and all-cause mortality (IRR, 1.09; 95% CI, 1.02– 1.18).

Palmer et al (5) found that Darbepoetin alfa had uncertain effects on all-cause mortality (3 studies, 1122 participants): RR 0.89, 95% CI 0.53 to 1.51; IQ = 3%).

B) <u>Cardiovascular mortality</u>

B.1) ESAs versus Placebo

The odds of cardiovascular mortality were uncertain for epoetin beta (2 studies, 260 participants): OR 0.45, 95% CI 0.06 to 3.75, IU = 0%) and darbepoetin alfa (1 study, 4038 participants): OR 1.05, 95% 0.87 to 1.26) when compared to placebo.(1) The odds of cardiovascular mortality were uncertain for epoetin beta (3 studies, 430 participants): OR 0.28, 95% CI 0.08 to 1.03; IU = 0%) when compared with no treatment.

B.2) ESAs versus each other

In the comparison darbepoetin α vs. methoxy polyethylene glycol-epoetin β (3 studies 938 patients), there was no significant difference – RR: 0.7 (0.33–1.46) or 11 less per 1000 (from 24 less to 17 more).
In the comparison epoetin α vs. darbepoetin α (2 studies, 487 patients) there was also no significantly different risk. RR 2.12 (0.32–14.23) or 8 more per 1000 (from 5 less to 91 more).(9)

In another systematic review the relationship between mean ESA dose and cardiovascular mortality was also not statistically significant(11).

When compared to placebo, Darbepoetin alfa had little or no effect on cardiovascular mortality (RR 1.04, 95% CI 0.89 to 1.23)(5). Versus epoetin, Darbepoetin alfa had uncertain effects on cardiovascular mortality in adults (2 studies, 487 participants): RR 0.47, 95% CI 0.07 to 3.17; IQ = 0%). Versus methoxy polyethylene glycol-epoetin, effects were also uncertain.

The relationship between mean ESA dose and cardiovascular mortality was in the same direction as with overall mortality, albeit not statistically significant. In unadjusted analyses, IRRs of the first-3-month and total-study-period mean ESA dose (per epoetin alfa–equivalent 10,000-U/wk increment) were 1.31 (95% CI, 0.92–1.86) and 1.07 (95% CI, 0.97–1.17), respectively(11). Adjusted analyses were limited due to the insufficient number of observations or collinearity between the predictor variables.

The odds of cardiovascular mortality were uncertain for epoetin alfa when compared to darbepoetin alfa (2 studies, 487 participants): OR 2.15, 95% CI 0.31 to 14.91; IU = 0%) or a biosimilar ESA (Analysis 1.5.5 (2 studies, 657 participants): OR 0.53, 95% CI 0.20 to 1.35; IU = 0%). The odds of cardiovascular mortality were uncertain for epoetin beta when compared to a biosimilar ESA (1 study, 290 participants): OR 0.34, 95% CI 0.04 to 2.82).

The odds of cardiovascular mortality were uncertain for darbepoetin alfa when compared to methoxy polyethylene glycol-epoetin beta (3 studies, 938 participants): OR 0.69, 95% CI 0.32 to 1.48; IU = 0%).

C) Progression to end-stage kidney disease

This was difficult to measure in many reviews, as the study durations were often too short to measure this as a primary outcome(2, 5, 11).

D) Worsening cardiovascular condition (i.e., worsening hypertension)

D.1) ESAs versus Placebo

No significant differences were found for hypertension where darbepoetin was compared with placebo, CERA, epoetin alfa.(5) Similar findings were had for methoxy polyethylene glycol-epoetin beta, compared to placebo, epoetin alfa and darbepoetin.(7)

D.2) ESAs versus each other

Amato et al (11), comparing originator epoetin alfa with biosimilars found no significant difference in hypertension (5 studies, 1571 patients); RR 1.62 (0.98–2.66) or 17 more per 1000 (from
1 less to 47 more). A comparison of epoetin alfa versus darbepoetin alfa found similarly little difference (6 studies, 1628 patients); RR: 0.95 (0.7–1.29) or 9 less per 1000 (from 53 less to 51 more).

In Hahn et al for Epoetin alpha weekly versus every two weeks using same total dose of epoetin, there was no significant difference in hypertension: Risk Ratio (M-H, Random, 95% CI) 0.85 [0.55, 1.32]. Epoetin alpha every two weeks versus every four weeks using same total dose of epoetin, there was no significant difference in all-cause mortality (3 studies, 724 participants: Risk Ratio (M-H, Random, 95% CI) 1.02 [0.62, 1.69].

E) Allo-immunisation

E.1 ESAs versus each other

Anti-erythropoietin antibodies, which can cause pure red cell aplasia, were assessed In only five studies in Hahn et al(10). In a study of epoetin alfa against a biosimilar, the compared the biosimilar HX575 epoetin alpha with epoetin alpha; both medications were administered subcutaneously. The study was ceased when two patients receiving HX575 developed antibodies to epoetin and pure red cell aplasia and HX575 epoetin alpha was withdrawn for subcutaneous administration. The change in Hb from baseline at 13 weeks did not differ between groups (HX575 2.2 ± 0.9 g/dL; epoetin alpha 2.2 ± 1.0 g/dL) but the data could not be included in meta-analyses since no denominators were provided and information could not be obtained from the authors.

iii. INTERNATIONAL GUIDELINE RECOMMENDATIONS

None of the international guidelines examined recommend one ESA over another or differentiate between the potential outcomes of one ESA versus another.

The KDIGO Guidelines (2012(12)) recommend that some patients will benefit from ESA in terms of quality of life improvement on the KDQ scale, mainly those starting with very low Hbs, and receiving high doses of EPO, targeting an Hb Level of 13.5-14.5g/dl. However, the recommendation is that this be balanced with consideration of the negative effects.

The National Guidelines Centre guidance (13) which has informed the NICE Guidance in the United Kingdom recommended “The GDG agreed that the evidence statements from the multisite RCT support the summary that there is no difference between darbepoetin and epoetin alfa for the outcomes measured, in a selected group of patients who were stable.” This review was not updated in the 2015 update, and so is dependent on reviews conducted in 2006.

The NICE Guideline update of 2021, on anaemia management in renal failure also did not update its searches or recommendations on ESAs. (14)

The Renal Association Guidelines update 2020 recommends that Anaemia be treated with ESAs – for CKD patients who are likely to benefit in terms of quality of life and physical function and to avoid blood transfusion; especially in patients considered suitable for transplantation. (1B) The choice of ESA is recommended that the decision on the choice of ESA is based on local availability of ESAs. (1B)(15)

The Anaemia working Group of European Renal Best Practice (ERBP)'s position statement on Anaemia management in patients with chronic kidney disease: 2009 update (16), also does not differentiate between choice of agent. However, the overall quality of this statement was questionable when interrogated in the AGREE II tool.

The Canadian Society of Nephrology also published Clinical Practice Guidelines for evidence-based use of erythropoietic-stimulating agents, but these have not been updated since 2008. Overall the guidance also scored low in the AGREE II assessment and was not referred to here.(16)

7. DOSING COMPARISONS

The systematic reviews offered little solid evidence in terms of dosing comparisons and overall dosing response, as ESA therapy tends to be initiated at recommended doses, and then adjusted according to response, based on haemoglobin levels, generally.

Table 1: The starting dose of these and other ESAs among patients receiving hemodialysis

Phase	**Epoetin Alfa**	**Epoetin Beta**	**Darbepoetin Alfa**	**Methoxy polyethylene glycol-epoetin beta**
Correction phase	Preferably by IV route (but may be SC where IV not readily available) Adult haemodialysis patients: 50IU/kg 3x/wk. adjust dose at 4 weekly intervals by 25IU/kg 3x/wk until Hb targets achieved	Can be administered SC or IV SC: 20IU/kg 3x/wk. May be increased every 4 weeks by 20IU/kg 3x/wk IV:40IU/Kg 3x/wk. Dose may be raised after 1 month to 80IU/kg 3x/wk with further increments of 20IU/Kg 3x/wk	SC use preferable for patients not in haemodialysis. 0.45mcg/kg SC/IV body weight as a single dose once weekly or 0.75mcg/kg every 2 weeks. Increase dose every 4 weeks by 25% if response inadequate	SC/IV according to clinical preference 0.6mcg/kg once every 2 weeks. Dose can be increased by 25% if Hb increase less than 1g/dl in 4 weeks. Further increase of 25% until target obtained.
Maintenance phase	Individual dosing to maintain target of 10-12g/dl. Recommended weekly dose of 75-300IU/kg in divided doses.	Maintain Hb target of 10-12g/dl – half the correction phase dose.	Dialysis patients convert to every second week dosing, titrating to Hb targets	
Switch from other agents			Initial weekly dose by Divide existing EPO dose (IU/wk) by 200.	See Table 2

The starting doses of ESAs presented above are based upon recommendations within the South African product literature. The Kidney Disease Outcomes Quality Initiative (KDOQI) and kidney disease: Improving Global Outcomes (KDIGO) anemia guidelines do not specify a starting dose but state that the dose should be individualized.

Table 2 Methoxy polyethylene glycol-epoetin beta **Starting Doses for Adult Patients Currently Receiving an ESA**

Previous Weekly Epoetin alfa Dose (units/week)	**Previous Weekly Darbepoetin alfa Dose (mcg/week)**	**Methoxy polyethylene glycol-epoetin beta Dose Once**	
		Monthly (mcg/month)	**Once Every Two Weeks (mcg/every two weeks)**
less than 8000	less than 40	120	60
8000 to 16000	40 to 80	200	100
more than 16000	more than 80	360	180

8. DOSING COSTING COMPARISONS

Table 3 Provides a cost comparison per unit of each different ESA based on available prices in March 2022 and estimated per month costs based on starting doses. Epoetin alfa and Epoetin Beta are currently on National state tender, with state tender prices, so pricing for both the private sector and public sector where applicable have been provided.

Table 3 Currently Available dosage forms, prices and prices per IU or ug of ESA

INN	Dosage form	Concentration	SEP* or Tender price**	Price per IU	Estimated monthly cost at starting dose
Epoetin Alfa	0.6ml pfs	6000 IU/0.6 ml	R452.78 SEP	R0.075	R 3 150.00
	0.4ml pfs	4000 IU/0.4 ml	R308.16 SEP	R0.077	R 3 234.00
	0.5ml pfs	2000 IU/0.5 ml	R159.79 SEP	R0.079	R 3 318.00
	1 ml injection	10 000 IU/ml – high doses general used in oncology	R1080.53 SEP	R0.108	R 4 536.00
Epoetin Beta	0.3ml pfs	6 000IU/ 0.3ml	R 509.26 SEP	0.0849	R 2851.86
	0.3ml pfs	4 000IU/ 0.3ml	R 346.67 SEP	0.0867	R 2 912.06
	0.3ml pfs	2 000IU/ 0.3ml	R 173.35 SEP	0.0867	R 2 912.06
	0.3ml pfs	2000IU/0.3ml	R50.32 Tender	0.025	R 840.00
	0.3ml pfs	10 000IU/0.3ml	R957.12 SEP	0.0957	R 4 019.88
Darbepoetin Alfa	0.4ml pfs	10mcg/0.4ml	R195.57 SEP	19.557	R 2 464.18
	0.4ml pfs	20mcg/0.4ml	R391.14 SEP	19.557	R 2 464.18
	0.4ml pfs	30mcg/0.4ml	R586.71 SEP	19.557	R 2 464.18
	0.4ml pfs	60mcg/0.4ml	R1173.44 SEP	19.557	R 2 464.18
	p0.4ml pfs	150mcg/0.4ml	R2933.54 SEP	19.557	R 2 464.18
	0.4ml pfs	300mcg/0.4ml	5867.07 SEP	19.557	R 2 464.18
	0.4ml pfs	100mcg/0.4ml	1051.75 SEP	10.51	R 2 464.18
Methoxy polyethylene glycol epoetin beta	0.3ml pfs	30mcg/0.3ml	726.31 SEP	24.210	R 2 033.64
	0.3ml pfs	50mcg/0.3ml	1255.07 SEP	25.101	R 2 108.48
	0.3ml pfs	75mcg/0.3ml	1882.61 SEP	25.101	R 2 108.48
	0.3ml pfs	100mcg/0.3ml	1902.53 SEP	19.025	R 1598.10
	0.3ml pfs	120mcg/0.3ml	3012.18 SEP	25.101	R 2 108.48
	0.3ml pfs	150mcg/0.3ml	3765.22 SEP	25.101	R 2 108.48
	0.3ml pfs	200mcg/0.3ml	3805.05 SEP	19.025	R 1598.10
	0.3ml pfs	250mcg/0.3ml	3805.05 SEP	15.22	R 1 278.48
	0.3ml pfs	360mcg/0.3ml	5752.42 SEP	15.98	R 1 278.48

Pfs=prefilled syringe; ml = milliliter; IU = international units

* SEP database, 31 December 2021

** Contract circular HP06-2021SVP/01

9. CONCLUSION

In this class review of existing erythropoiesis-stimulating agents (ESAs), including Epoetin alfa and Epoetin beta; methoxy polyethylene glycol epoetin beta; Darbepoetin alfa, we looked at systematic reviews of efficacy and safety of these agents (including against placebo and biosimilar agents) and interrogated existing international guidelines on the use of ESAs for anaemia in renal failure.

Epoetin alfa and epoetin beta; methoxy polyethylene glycol epoetin beta and darbepoetin alfa have all demonstrated efficacy versus placebo, as indicated by, haemoglobin responses or prevention of the need for transfusion.
Versus placebo or no treatment, haemoglobin increased by Mean difference D 1.90 g/dL, 95% CI 1.47 to 2.34: I2 =30%). Reduction in transfusions needed placebo was relatively consistent, however estimates vary, for epoetins where relative risk was lower than placebo by about 30% (3 studies, 111 participants): RR 0.32, 95% CI 0.12 to 0.83; I2 = 0%), to darbepoetin alfa versus versus alfa reduced need for one or more blood transfusions (RR 0.60, 95% CI 0.53 to 0.69). There were no notable differences in outcomes reported for quality of life, haemoglobin level improvements or prevention of the need for transfusion, between the agents examined, including when agents were compared at different dosage frequencies.

There were also no remarkable differences in adverse events such as all-cause mortality, cardiovascular related mortality, hypertension or alloimmunization. One systematic review drew from concerns of a biosimilar trial which was terminated early when two patients developed antibodies to their biosimilar epoetin.

International Guidelines also do not discriminate between the different ESAs on the basis of efficacy nor safety.

10.LIMITATIONS

It is important to reiterate that although this analysis examined both chronic renal failure patients on dialysis as well as not on dialysis, the current indication in the standard treatment guidelines is for patient on renal dialysis. Another PICO has been developed to examine the efficacy of ESAs in patients not yet on dialysis (broadening of STG indication). This analysis serves to inform the therapeutic interchange database for the purpose of tendering for the various agents. . It was not intended to adjudicate the efficacy of ESAs versus placebos or to compare one ESA agent specifically versus another.

This review was a review of the many systematic reviews available on the topic of ESAs in chronic renal failure, distinguishing more based on outcomes in the renal failure population than on the specifics of each patient subgroup e.g. dialysis versus non-dialysis; pre-existing conditions such as Type 2 diabetes , or iron status prior to ESA initiation. The studies included in the different systematic reviews had different primary outcomes, as well as examining trials where target Hb levels may have differed and dose escalations may also have been managed differently.

APPENDIX 1: SEARCH STRATEGIES IN PUBMED AND COCHRANE

Pubmed
((((erythropoietin OR epoetin alpha OR epoetin beta OR darbepoetin alpha OR EPO OR methoxy polyethylene glycol epoetin beta OR "Epoetin Alfa" OR "Erythropoietin" OR "epoetin beta") OR "continuous erythropoietin receptor activator") AND (end stage renal disease OR chronic renal failure OR "Renal Insufficiency, Chronic" OR "Renal Insufficiency, Chronic"))) Limited to Systematic Reviews and Meta-analyses
Cochrane Library
((renal insufficiency, chronic) OR (chronic renal disease) OR (kidney Failure)) AND ((erythropoietin) OR (epoetin) OR (darbopoetin) OR (methoxy polyethylene glycol-epoetin))

APPENDIX 2: SUMMARY OF SYSTEMATIC REVIEWS AN META-ANALYSIS INCLUDED IN THE ANALYSIS

Citation	Details of study	Population (n)	Comparators	Outcomes	Main Findings
Alsalimy, N., Awaisu, A. Methoxy polyethylene glycol-epoetin beta versus darbepoetin alfa for anemia in non-dialysis-dependent CKD: a systematic review. Int J Clin Pharm 36, 1115–1125 (2014). (8)https://doi.org/10.1007/s11096-014-0023-x	Systematic review of original studies examining Efficacy and tolerability of MPG-EPO compared with other erythropoiesis stimulating agents (in particular darbepoetin alfa) for the treatment of anemia in non-dialysis-dependent CKD patients.	The review ultimately included Four trials involving 1,155 patients were included in the review. Patients were all pre-dialysis.	Methoxy polyethylene glycol-epoetin beta versus darbepoetin alfa	• Changes in Hb Level from baseline • Proportion of patients requiring blood transfusions • Time to haemoglobin response • Incidence of serious adverse effects	The changes in hemoglobin level from the baseline reported by the reviewed studies demonstrate that MPG-EPO was clinically non-inferior to darbepoetin alfa. In addition, the studies documented that MPG-EPO-treated patients experienced a lower rate of hemoglobin level above the target range of 12–13 g/dL than darbepoetin-treated patients. The proportion of patients requiring RBC transfusion was higher among patients who received darbepoetin alfa than those who received MPG-EPO. However, the time to hemoglobin response was longer with MPG-EPO than with darbepoetin. The incidences of serious adverse events were similar between the two therapeutic agents. However, the authors concluded that the review was not conclusive due to limited number of studies.
Amato L, Addis A, Saulle R, Trotta F, Mitrova Z, Davoli M. Comparative efficacy and safety in ESA biosimilars vs. originators in adults with chronic kidney disease: a systematic review and meta-analysis. J Nephrol. 2018 Jun;31(3):321-332. doi: 10.1007/s40620-017-0419-5. Epub 2017 Jun 23. PMID: 28646375.(9)	Systematic literature search of CENTRAL, PubMed, and Embase through November 11, 2015. RCTs that evaluated the comparative effectiveness of different ESAs originators and/or biosimilar. 30 eligible studies including 7843 patients with CKD, and 21/30 studies included patients using hemodialysis or peritoneal dialysis.	The considered participants were adults aged 18 years or older with anemia due to CKD (on dialysis or not on dialysis)			Compared with ESA biosimilars, epoetin α did not statistically differ for any of the ten measured outcomes. The quality of evidence varied from low to very low. In the comparison between epoetin α vs. darbepoetin α, no differences were observed for all outcomes, but blood transfusions showed favorable results for darbepoetin α: RR 2.18 (1.31-3.62). The quality of evidence varied from low to very low. No differences were observed between epoetin β and methoxy polyethylene glycol-epoetin β, and between darbepoetin α and methoxy polyethylene glycol-epoetin β, the quality of evidence varied from moderate to very low.
Cody JD, Hodson EM.	Systematic review of randomised controlled trials	Patients with the anaemia of CKD who	ALL EPO interventions, regardless of dose and mode of delivery	1. Measures of progression of kidney failure:	There was an improvement in haemoglobin (MD 1.90 gm/L, 95% CI -2.34

Citation	Details of study	Population (n)	Comparators	Outcomes	Main Findings
Recombinant human erythropoietin versus placebo or no treatment for the anaemia of chronic kidney disease in people not requiring dialysis. Cochrane Database of Systematic Reviews 2016, Issue 1. Art. No.: CD003266.(2)	(RCTs) or quasi-RCTs comparing the use of rHuEPO with no treatment or placebo in predialysis patients. Nineteen studies (enrolling 993 participants) were included.	have not yet commenced dialysis were included. The definitions of anaemia and CKD used by each individual study were accepted. There were no age exclusions	were compared to placebo or no treatment.	time from start of rHuEPO to start of dialysis. numbers starting RRT in each group; glomerular filtration rate (GFR) at the end of the study; change in GFR; serum creatinine at the end of the study and change in creatinine in each group. 2. Measures of correction of anaemia: haemoglobin/haematocrit values; numbers of blood transfusions. 3. Quality of life measures, including changes in exercise capacity. 4. Measures of hypertension: systolic blood pressure; diastolic blood pressure; numbers with an increase or introduction of antihypertensive treatment. 5. Other adverse events: numbers discontinued due to adverse events; access problems for patients commenced on haemodialysis; seizures. 6. Mortality.	to -1.47) and haematocrit (MD 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 kidney disease showed no statistically significant difference. No significant increase in adverse events was identified.
Collister D, Komenda P, Hiebert B, Gunasekara R, Xu Y, Eng F, Lerner B, Macdonald K, Rigatto C, Tangri N. The Effect of Erythropoietin-Stimulating Agents on Health-Related Quality of Life in Anemia of Chronic Kidney Disease: A Systematic Review and Meta-analysis. Ann Intern Med. 2016 Apr	Systematic review of randomized, controlled trials that evaluated the treatment of anemia with ESAs, including erythropoietin and darbepoetin, targeted higher versus lower hemoglobin levels, and used validated HRQOL metrics. 17 Eligible studies were included.			Outcome measures were scores on the Short Form-36 Health Survey (SF-36), Kidney Dialysis Questionnaire (KDQ), and other tools.	Of 17 eligible studies, 13 reported SF-36 outcomes and 4 reported KDQ outcomes. Study populations consisted of patients not undergoing dialysis (n = 12), those undergoing dialysis (n = 4), or a mixed sample (n = 1). Only 4 studies had low risk of bias. Pooled analyses showed that higher hemoglobin targets resulted in no statistically or clinically significant differences in SF-36 or KDQ domains. Differences in HRQOL were further attenuated in studies at low risk of bias and in subgroups of dialysis recipients.

Citation	Details of study	Population (n)	Comparators	Outcomes	Main Findings
5;164(7):472-8. doi: 10.7326/M15-1839. Epub 2016 Feb 16. PMID: 26881842(3)					
Coronado Daza J, Martí-Carvajal AJ, Ariza García A, Rodelo Ceballos J, Yomayusa González N, Páez-Canro C, Loza Munárriz C, Urrútia G. Early versus delayed erythropoietin for the anaemia of end-stage kidney disease. Cochrane Database of Systematic Reviews 2015,(17)	Systematic review of randomised controlled trials (RCTs) and quasi-RCTs evaluating at the clinical benefits and harms of early versus delayed EPO for anaemia in patients with ESKD undergoing haemodialysis or peritoneal dialysis. .	Anaemic in patients with ESKD undergoing haemodialysis or peritoneal dialysis.	Studies comparing EPO with another EPO, placebo or no treatment were eligible for inclusion.	**Primary outcomes** 1. All-cause mortality 2. Cardiovascular mortality 3. Quality of life **Secondary outcomes** 1. Adverse events: hypertension 2. Myocardial infarction (fatal or non-fatal) 3. Stroke (ischaemic or haemorrhagic, either fatal or non-fatal) 4. Thrombotic events (deep venous thrombosis, peripheral arterial thrombotic events, and dialysis vascular access thrombosis) 5. Blood transfusions requirements 6. Haemoglobin level reached at end of study.	No Conclusions could be made as no trials matched the inclusion criteria
Hahn D, Esezobor CI, Elserafy N, Webster AC, Hodson EM. Short-acting erythropoiesis-stimulating agents for anaemia in predialysis patients. Cochrane Database of Systematic Reviews 2017(6)	All RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at epoetins (shortacting ESAs) for treatment of anaemia in patients with CKD not on dialysis.	Patients of any age (adults and children) with anaemia due to CKD (stages 2 to 5) of any severity, who were not receiving dialysis, were included. The definitions of CKD and anaemia used in individual studies were used.	Short-acting ESAs including epoetins alpha, beta, delt, epoetin theta and biosimilars of epoetin alpha, epoetin zeta • Short-acting ESAs including epoetins with different routes of administration • Short-acting ESAs including epoetins used at different frequencies of administration • Short-acting ESAs including epoetins used at different doses • Head-to-head comparisons of different short-acting ESAs.	**Primary outcomes** 1. Death • All-cause mortality • Mortality due to cardiac disease or cerebrovascular events 2. Measures of correction of anaemia • Values of Hb/HCT or change in Hb/HCT at the end of the study 3. Quality of life. **Secondary outcomes** 1. Hypertension and blood pressure outcomes 2. Cardiovascular morbidity 3. Cerebrovascular morbidity 4. Adverse effects 5. Kidney function measures (GFR, serum creatinine (SCr), doubling of SCr) as reported by the authors of primary studies 6. Need for iron supplementation.	See detailed description in text

Citation	Details of study	Population (n)	Comparators	Outcomes	Main Findings
Koulouridis I, Alfayez M, Trikalinos TA, Balk EM, Jaber BL. Dose of erythropoiesis-stimulating agents and adverse outcomes in CKD: a metaregression analysis. Am J Kidney Dis. 2013 Jan;61(1):44-56. doi: 10.1053/j.ajkd.2012.07.014. Epub 2012 Aug 22. PMID: 22921639; PMCID: PMC3525813.(11)	Review of published meta-analyses and selected randomized controlled trials assessing the efficacy of ESAs for treatment of anemia in adults with CKD, with minimum 3-month duration.	Adults with Anaemia from Chronic kidney disease.	Epoetin alfa, Epoetin Beta, darbepoetin	All-cause mortality Cardiovascular mortality, cardiovascular events, kidney disease progression or transfusion requirement.	All-cause mortality was associated with higher (per epoetin-alfa–equivalent 10,000-U/wk increment) first-3-month mean ESA dose (incidence rate ratio [IRR], 1.42; 95% CI, 1.10–1.83) and higher total-study-period mean ESA dose (IRR, 1.09; 95% CI, 1.02–1.18). First-3-month ESA dose remained significant after adjusting for first-3-month mean hemoglobin (IRR, 1.48; 95% CI, 1.02- 2.14), as did total-study-period mean ESA dose adjusting for target hemoglobin (IRR, 2 1.41; 95% CI, 1.08–1.82). Parameter estimates between ESA dose and cardiovascular mortality were similar in magnitude and direction but not statistically significant. Higher total-study-period mean ESA dose was also associated with increased rate of hypertension, stroke, and thrombotic events including dialysis vascular access related thrombotic events.
Palmer_SC, Saglimbene_V, Mavridis_D, Salanti_G, Craig_JC, Tonelli_M, Wiebe_N, Strippoli_GFM. Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2014, Issue 12. Art. No.: CD010590. DOI: 10.1002/14651858.CD010590.pub2.(1)	Systematic Review of Randomised controlled trials (RCTs) that included a comparison of an ESA (epoetin alfa, epoetin beta, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta, or biosimilar ESA) with another ESA, placebo or no treatment in adults with CKD and that reported prespecified patient-relevant outcomes were considered for inclusion. Identified 56 eligible studies involving 15,596 adults with CKD.	Studies in adults aged 18 years or older with anaemia due to CKD were included. CKD was characterised by clinically relevant proteinuria, haematuria, and/or structural kidney disease with or without estimated glomerular filtration rate (eGFR) < 60 mL/ min/1.73 mU, recipients of a kidney transplant, and people with Stage 5 CKD treated with dialysis (KDIGO 2013).	ESAs - epoetin alfa, epoetin beta, darbepoetin beta, methoxy polyethylene glycol-epoetin beta, biosimilar administered via any route (IV or SC), compared with each other, placebo or no treatment. Dose adaptation of ESAs and non-randomised iron supplementation depending on haematological response were allowed. We included studies in which iron was administered as a randomised intervention in all arms of the study.	Primary outcomes **Response to treatment** • Preventing blood transfusion Safety • All-cause mortality. **Secondary outcomes** Response to treatment • Fatigue (as defined by study authors) • Dyspnoea (as defined by study authors) • Cardiovascular mortality • Fatal or nonfatal MI • Fatal or nonfatal stroke • Vascular access thrombosis • Major adverse cardiovascular event (as adjudicated by investigators) • End-stage kidney disease (ESKD).	In network analyses, there was moderate to low confidence that epoetin alfa (OR 0.18, 95% CI 0.05 to 0.59), epoetin beta (OR 0.09, 95% CI 0.02 to 0.38), darbepoetin alfa (OR 0.17, 95% CI 0.05 to 0.57), and methoxy polyethylene glycolepoetin beta (OR 0.15, 95% CI 0.03 to 0.70) prevented blood transfusions compared to placebo. The comparative effects of ESAs compared with another ESA, placebo or no treatment on all-cause mortality were imprecise. All proprietary ESAs increased the odds of hypertension compared to placebo (epoetin alfa OR 2.31, 95% CI 1.27 to 4.23; epoetin beta OR 2.57, 95% CI 1.23 to 5.39; darbepoetin alfa OR 1.83, 95% CI 1.05 to 3.21; methoxy polyethylene glycol-epoetin beta OR 1.96, 95% CI 0.98

Citation	Details of study	Population (n)	Comparators	Outcomes	Main Findings
					to 3.92). The comparative effects of all ESAs on cardiovascular mortality, myocardial infarction (MI), stroke, and vascular access thrombosis were uncertain and network analyses for major cardiovascular events, end-stage kidney disease (ESKD), fatigue and breathlessness were not possible.
Palmer SC, Saglimbene V, Craig JC, Navaneethan SD, Strippoli GFM. Darbepoetin for the anaemia of chronic kidney disease. Cochrane Database of Systematic Reviews. 2014(3).	Systematic review of RCTs and quasi-RCTs of darbepoetin alpha alone or in combination with other nonrandomized co-interventions (e.g., iron supplementation, or red cell transfusion) in individuals with anaemia and CKD (ESA-naïve patients and conversion from other ESAs) were included. The first period of randomised cross-over studies was also considered. Studies were considered without language restriction. Studies were of at least three months in duration.	Individuals with stage 3, 4, and 5 CKD (including patients on dialysis) as defined by the NKF-KDOQI guidelines. * Stage 3: glomerular filtration rate (GFR) 30 to 59 mL/min/1.73 mQ * Stage 4: GFR 16 to 29 mL/min/1.73 mQ * Stage 5: GFR < 15 mL/min/1.73 mQ * Stage 5D: GFR < 15 mL/min/1.73 mQ (treated with dialysis) • Kidney transplant recipients • Adults and children	Studies of darbepoetin alfa by any route (SC or IV) or dose, compared with epoetin alfa or beta, methoxy polyethylene glycolepoetin beta, placebo, or no treatment were included.	The following parameters were analysed for each planned treatment comparison. * Number of individuals achieving the recommended Hb levels during the study period • Progression of CKD in patients not yet requiring renal replacement therapy (RRT: haemodialysis, peritoneal dialysis or kidney transplantation). • Clinical outcomes including cardiovascular events, Hospital admissions, Cardiovascular mortality, All-cause mortality, Vascular access thrombosis, Cancer: onset of new documented cancer, or as defined by the investigators • Quality of life	See individual summaries in text
Saglimbene VM, Palmer SC, Ruospo M, Natale P, Craig JC, Strippoli GF. Continuous erythropoiesis receptor activator (CERA) for the anaemia of chronic kidney disease. Cochrane Database Syst Rev. 2017;8(8):Cd009904.(7)	All RCTs and quasi-RCTs (RCTs looking at CERA alone or in combination with other non-randomised co-interventions (such as iron supplementation or red cell transfusion) in were included. Studies of at least three months' follow-up duration were included.	People with CKD (any stage) and anaemia	CERA versus placebo or no treatment • CERA versus darbepoetin alfa • CERA versus epoetin alfa or beta • CERA versus CERA with diLering strategies for administration (For example: higher versus lower doses; IV versus SC administration; longer versus shorter dosing intervals; higher versus lower target haemoglobin levels).	**Primary outcomes** • Clinical outcomes • Quality of life • Adverse events **Secondary outcomes** • Achieving and maintaining haemoglobin levels/iron status	There was low certainty evidence that CERA had little or no effects on mortality (RR 1.07, 95% CI 0.73 to 1.57; RR 1.11, 95% CI 0.75 to 1.65), major adverse cardiovascular events (RR 5.09, 95% CI 0.25 to 105.23; RR 5.56, 95% CI 0.99 to 31.30), hypertension (RR 1.01, 95% CI 0.75 to 1.37; RR 1.00, 95% CI 0.79 to 1.28), need for blood transfusion (RR 1.02, 95% CI 0.72 to 1.46; RR 0.94, 95% CI 0.55 to 1.61), or additional iron therapy (RR 1.03, 95% CI 0.91 to 1.15; RR 0.99, 95% CI 0.95 to 1.03) compared to epoetin alfa/beta or darbepoetin alfa respectively.

Citation	Details of study	Population (n)	Comparators	Outcomes	Main Findings
					There was insufficient evidence to compare the effect of CERA to placebo on clinical outcomes. Only one low quality study reported that CERA compared to placebo might lead to little or no difference in the risk of major cardiovascular events (RR 2.97, 95% CI 0.31 to 28.18) and hypertension ((RR 0.73, 95% CI 0.35 to 1.52). There was low certainty evidence that different doses (higher versus lower) or frequency (twice versus once monthly) of CERA administration had little or no different effect on all-cause mortality (RR 3.95, 95% CI 0.17 to 91.61; RR 0.97, 95% CI 0.56 to 1.66), hypertension (RR 0.45, 95% CI 0.08 to 2.52; RR 0.85, 95% CI 0.60 to 1.21), and blood cell transfusions (RR 4.16, 95% CI 0.89 to 19.53; RR 0.91, 95% CI 0.51 to 1.62). No studies reported comparative treatment effects of different ESAs on health-related quality of life.

APPENDIX 3: SUMMARY OF INTERNATIONAL GUIDANCE ON THE USE OF ESAS IN CHRONIC RENAL DISEASE

Guidelines	Source of information for recommendations	AGREE II Assessment	Recommendation for ESA Choice	Recommendations in relation to ESAs
KIDIGO Clinical practice Guideline for Anaemia in chronic kidney disease. (12)	Systematic review of specifically identified topics, using POCO methodology with the application of the GRADE system of evidence and evaluation of overall study quality. The COGS Checklist was used to evaluate the final reporting of the Guideline	Overall score of 6 – high quality systematic reviews, evidence grading, and declarations of interest. Largely physicians on the working group and little attention to patient preferences.	3.11.1: We recommend choosing an ESA based on the balance of pharmacodynamics, safety information, clinical outcome data, costs, and availability. (1D) 3.11.2: We suggest using only ESAs that have been approved by an independent regulatory agency. Specifically, for 'copy' versions of ESAs, true biosimilar products should be used. (2D)	At present, there is no evidence that any given ESA brand is superior to another in terms of patient outcomes, with the historical exception of the temporary increase in the incidence of antibody-mediated pure red cell aplasia (PRCA) about 10–20 years ago, which was associated with SC administration of an epoetin-alfa formulation available in Europe, but not in the United States. It is the considered opinion of the Work Group that the likelihood of differences in clinical outcomes among ESA brands is low, although there is no robust evidence supporting this assumption.
National Clinical Guideline Centre, United Kingdom. Final version, June 2015 Anaemia Management in Chronic Kidney Disease Partial update 2015. (13)	Followed the NICE methodology – systematic reviews for selected clinical issues – some recommendations were not updated as a result and still reference the previous updates in 2006 and 2009.	Overall score of 6 – high quality systematic revies addressing specific questions. Lower score on editorial independence and Applicability	The GDG agreed that the evidence statements from the multisite RCT support the summary that there is no difference between darbepoetin and epoetin alfa for the outcomes measured, in a selected group of patients who were stable Evidence statements on efficacy suggest that both darbepoetin and epoetin beta effectively maintain target haemoglobin levels. ESAs are made available to NHS trusts through a system of tendering for local supply contracts. Costs therefore vary between locations and over time. The recommendation 10 below outlines the considerations in agreeing on a first choice ESA rather than specifying a particular 11 agent for all patients. This is intended to allow flexibility for local units over the lifetime of the 12 guidelines while providing useful advice in selecting the best treatment for the patient.	The recommendations were still based on the original reviews from 2006 (not repeated in this update of the guideline) – Update evidence reviews focused on optimizing iron doses in renal patients and some other questions which address the clinical management of the disease, rather than the clinical comparative efficacy of the ESAs.
The Renal Association: Clinical Practice Guideline Anaemia of Chronic Kidney Disease Updated: February 2020(15)	Systematic reviews of evidence for specific issues as well as reference to existing guidelines (NICE, KDIGO, KDOQI, ERBP)	Overall score of 5. Valid methodology but lacking in consideration of patient preferences, and some declaration of interests issues. Includes auditing measures	Guideline 3.1 - Treatment of Anaemia - Erythropoiesis Stimulating Agents We recommend that treatment with Erythropoiesis Stimulating Agents (ESAs) should be offered to patients with anaemia of CKD who are likely to benefit in terms of quality of life and physical function and to avoid blood transfusion; especially in patients considered suitable for transplantation. (1B) Guideline 3.2 - Treatment of Anaemia - Choice of ESA We recommend that the decision on the choice of ESA is based on local availability of ESAs. (1B)	No differentiation between agents – choice based on local availability.
Anaemia management in patients with chronic	Not clear – reads like a narrative review	Overall score of 2 because of low quality	Use new EPOS as other rHuEPOs CERA Starting dose: 0.6 µg/kg	There is no preference given to any specific ESA – dosing is per recommended use and IV versus SC not differentiated

Guidelines	Source of information for recommendations	AGREE II Assessment	Recommendation for ESA Choice	Recommendations in relation to ESAs
kidney disease: a position statement by the Anaemia Working Group of European Renal Best Practice (ERBP) – 2009 update(18)		of evidence reporting and translation of evidence into recommendation framework	Frequency: once every 2 weeks for correction; once every 4 weeks for maintenance Administration route: i.v. or s.c. Biosimilars Use as originator compounds, strict post marketing surveillance, only IV administration biosimilars and Epoetin zeta – – Use as epoetin alpha; strict post-marketing surveillance CKD patients with cancer– – Use caution; do not aim for Hb >12 g/dl	
Canadian Society of Nephrology - Clinical Practice Guidelines for evidence-based use of erythropoietic-stimulating agents 2008(16)	Not clear - narrative			

APPENDIX 4: EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High: [ ] Moderate: [X] Low: [ ] Very low: [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	All ESAs have demonstrated moderate certainty evidence of benefit in increasing Hb levels, and reducing the need for blood transfusions versus placebo, however there is little evidence of differences between the different ESAs. Impacts on quality of life are uncertain, even versus placebo. Versus placebo or no treatment, haemoglobin increased, mean difference 1.90 g/dL, 95% CI 1.47 to 2.34: I2 =30%. Reduction in transfusions needed placebo was relatively consistent, however estimates vary, for recombinant erythropoietins where relative risk was lower than placebo by about 70% (3 studies, 111 participants): RR 0.32, 95% CI 0.12 to 0.83; I2 = 0%), to darbepoetin alfa versus versus placebo- 40% reduction in need for one or more blood transfusions (RR 0.60, 95% CI 0.53 to 0.69).
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large: [ ] Moderate: [ ] Small: [ ] None: [X]	Very little difference was noted between the different ESAs, when compared to placebo. Studies have indicated at least an increase of 1g/dl improvement versus placebo. No notable differences in Hb improvements between the difference active treatments. Blood transfusions were reduced by up to 70% versus placebo in the largest meta-anaysis in this review.
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High: [ ] Moderate: [ ] Low: [X] Very low: [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	The evidence is relatively weak. Grade Assessments were performed in most of the Systematic reviews, the confidence in the evidence evidence was low to very low, Evidence for negative cardiovascular outcomes of one ESA versus the others is very weak, with little demonstrable differences between agents and different dosing regimens of the same agents. No significant differences reported for hypertension development between agents. Increase in all-cause mortality has been reported versus placebo, however this seems to be related more to higher initial doses of ESAs, than any particular ESA
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large: [ ] Moderate: [ ] Small: [ ] None: [X]	The risk of cardiovascular events and all-cause mortality among the various formulations of ESAs (compared to placebo) including the ones dosed less frequently, appears to be comparable, although the confidence in the information is very low. In comparison to each other, ESAs appear to have no significant risks above others, although confidence intervals were wide.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favour's intervention: [ ] Favour's control: [ ] Intervention = Control *or* Uncertain: [X]	ESA agents have similar effects when compared to placebo
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes: [x] No: [ ]	Epoetin alfa and Epoetin beta; methoxy polyethylene glycol epoetin beta and Darbepoetin alfa Specific exclusion from the group: None
FEASABILITY	**Is implementation of this recommendation feasible?** Yes: [x] No: [ ] Uncertain: [ ]	Epoetin is already being provided to dialysis patients as part of the Standard Treatment Guidelines – issues have been experienced with availability of the products on tender, hence the request for a class review.
RESOURCE USE	**How large are the resource requirements?** More intensive: [ ] Less intensive: [ ] Uncertain: [X] **Note:** This judgement is for the current indication of anaemia of CKD in dialysed patients only	**Price of medicines:** **Medicine** / **SEP (ZAR)** / **Contract price** Epoetin alfa, 6000IU injection: R452.78: N/A Epoetin alfa, 4000IU injection: R308.16: N/A Epoetin alfa, 2000IU injection: R159.79: NA Epoetin beta, 6000IU injection: R509.26: NA Epoetin beta, 4000IU injection: R346.67: NA Epoetin beta, 2000IU injection: R173.35: R50.32

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS

Darbepoetin alfa 10mcg prefilled syringe	R195.57	NA
Darbepoetin alfa 20mcg prefilled syringe	R391.14	NA
Darbepoetin alfa 30mcg prefilled syringe	R586.71	NA
Darbepoetin alfa 60mcg prefilled syringe	R1173.44	NA
Darbepoetin alfa 150mcg prefilled syringe	R2933.54	NA
Darbepoetin alfa 300mcg prefilled syringe	R5867.07	NA
Methoxy polyethylene glycol epoetin beta, 50mcg prefilled syringe	R1255.07	NA
Methoxy polyethylene glycol epoetin beta, 75mcg prefilled syringe	R1882.61	NA
Methoxy polyethylene glycol epoetin beta, 100mcg prefilled syringe	R1902.53	NA
Methoxy polyethylene glycol epoetin beta, 120mcg prefilled syringe	R3012.18	NA
Methoxy polyethylene glycol epoetin beta, 150mcg prefilled syringe	R3765.22	NA
Methoxy polyethylene glycol epoetin beta, 200mcg prefilled syringe	R3805.05	NA
Methoxy polyethylene glycol epoetin beta, 250mcg prefilled syringe	R3805.05	NA
Methoxy polyethylene glycol epoetin beta, 360mcg prefilled syringe	R5752.42	NA

*SEP database, 24 December 2021

Rough Estimates at recommended initiation doses (70kg patient, at starting doses
NOTE – two products are already on national tender and available at prices substantially less than SEP

Medicine	Price (ZAR)
Epoetin alfa - 3500IU 3x a week (10 500)	R3 234 per month SEP
Epoetin beta, 1400IU 3x a week (SC) (4200); 2800IU 3x a week (IV) (8400)	R2 912.06 per month SEP
	R1 056.72 per month tender (only 2000IU of epo beta available)
Methoxy polyethylene glycol epoetin beta, 42 mcg every second week	R2 108 per month SEP
Darbepoetin alfa 0.45mcg/ kg weekly (31.5)	R 2 464.18 per month SEP

VALUES, PREFERENCES, ACCEPTABILITY

Is there important uncertainty or variability about how much people value the options?

Minor	Major	Uncertain
X		

Is the option acceptable to key stakeholders?

Yes	No	Uncertain
X		

Already available on tender and in use in units – so acceptable.

Subcutaneous and intravenous administration were examined in the trials, with few differences between these routes of administration.

EQUITY

Would there be an impact on health inequity?

Yes	No	Uncertain
	X	

Unlikely to have an impact on equity, if available at secondary level.

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