# 10. Medicines affecting the blood

## 10.1. Antianaemia medicines

### Erythropoiesis-stimulating agents

- **ATC codes:** B03XA03 B03XA01 B03XA02

<table>
<thead>
<tr>
<th>Indication</th>
<th>Anaemia due to chronic disease</th>
<th>ICD11 code: 3A71</th>
</tr>
</thead>
<tbody>
<tr>
<td>INN</td>
<td>Epoetin alfa</td>
<td></td>
</tr>
<tr>
<td>Medicine type</td>
<td>Chemical agent</td>
<td></td>
</tr>
<tr>
<td>List type</td>
<td>Complementary (EML)</td>
<td></td>
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<tr>
<td></td>
<td>(EMLc)</td>
<td></td>
</tr>
<tr>
<td>Formulations</td>
<td>Parenteral &gt; General injections &gt; unspecified: 1000 IU per 0.5 mL pre-filled syringe; 2000 IU per 0.5 mL pre-filled syringe; 3000 IU per 0.3 mL pre-filled syringe; 4000 IU per 0.4 mL pre-filled syringe; 5000 IU per 0.5 mL pre-filled syringe; 6000 IU per 0.6 mL pre-filled syringe; 8000 IU per 0.8 mL pre-filled syringe; 10000 IU per 1 mL pre-filled syringe; 20000 IU per 0.5 mL pre-filled syringe; 40000 IU per 1 mL pre-filled syringe</td>
<td></td>
</tr>
<tr>
<td>EML status history</td>
<td>First added in 2017 (TRS 1006)</td>
<td></td>
</tr>
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<td>Sex</td>
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<td></td>
</tr>
<tr>
<td>Age</td>
<td>Also recommended for children</td>
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</tr>
<tr>
<td>Therapeutic alternatives</td>
<td>epoetin alfa (ATC codes: B03XA01)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>epoetin beta (ATC codes: B03XA01)</td>
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<td></td>
<td>epoetin theta (ATC codes: B03XA01)</td>
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<tr>
<td></td>
<td>darbepoetin alfa (ATC codes: B03XA02)</td>
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<td></td>
<td>methoxy polyethylene glycol-epoetin beta (ATC codes: B03XA03)</td>
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</tr>
<tr>
<td>Patent information</td>
<td>Patents have expired in most jurisdictions</td>
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<td>Wikipedia</td>
<td>Erythropoiesis-stimulating agents</td>
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<tr>
<td>DrugBank</td>
<td>Erythropoiesis-stimulating agents (Erythropoietin)</td>
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</tbody>
</table>

### Expert Committee recommendation

The Expert Committee noted that erythropoiesis-stimulating agents have been shown to be an effective medication for treating anaemia in children, young people and adults with chronic renal disease requiring dialysis and that there are no alternative medicines already included in the EML and EMLc for this indication. It also noted that biosimilars for erythropoiesis-stimulating agents have been shown to be a valid alternative to the reference products. Considering all important clinical outcomes, the Committee considered that there is a relevant benefit resulting from erythropoiesis-stimulating agents. Based on the positive evaluation, the Committee therefore recommended erythropoiesis-stimulating agents be included in the complementary list of the EML and EMLc. The Expert Committee recommended listing erythropoiesis-stimulating agents with a square box to represent the class and inclusion of a note limiting alternatives to epoetin alfa, beta and theta, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta and their respective biosimilars (EML) and epoetin alfa, beta and theta, darbepoetin alfa, and their respective biosimilars (EMLc).

### Background

The antianaemia medicines currently included in the EML are: ferrous salt, ferrous salt + folic acid, folic acid, and hydroxocobalamin (4).
Chronic kidney disease is defined as the presence of kidney damage (usually detected as urinary albumin excretion $\geq 30$ mg/day, or equivalent) or reduced kidney function (defined as estimated glomerular filtration rate (GFR) $< 60$ mL/min per 1.73 m$^2$) for 3 or more months, irrespective of the cause. The prognosis for chronic kidney disease and the need for renal replacement therapy (either dialysis or kidney transplant) depend on: the cause of chronic kidney disease; GFR category; albuminuria category; and other risk factors and comorbid conditions (e.g. hypertension, hyperglycaemia, dyslipidaemia, smoking, obesity, history of cardiovascular disease) (2). End-stage renal disease refers to people with stage 5 chronic kidney disease undergoing dialysis and to recipients of kidney transplants. The KDIGO (Kidney Disease: Improving Global Outcomes) initiative recommends beginning dialysis as soon as life-threatening changes occur in fluid, electrolyte and acid–base balance; these usually happen when GFR is $5–10$ mL/min per 1.73 m$^2$. Specifically, starting dialysis is suggested when at least one of the following occurs: • signs or symptoms of renal failure, such as serositis, acid–base or electrolyte abnormalities, pruritus • inability to control volume status • inability to control blood pressure • malnutrition not responsive to dietary interventions • cognitive impairment. Anaemia is one of the most serious complications of chronic kidney disease and end-stage renal disease. Normochromic normocytic anaemia is due mainly to erythropoietin deficiency which itself is caused principally by reduced renal erythropoietin production, presumably reflecting the reduction in the number of erythropoietin-producing cells in the kidneys. To a lesser degree, it is caused by the shortened red cell lifespan. Erythropoietin is the hormone responsible for maintaining the proliferation and differentiation of erythroid progenitor cells in the bone marrow, and renal anaemia can thus be regarded as a hormone deficiency state. According to WHO (5) anaemia is to be diagnosed when Hb falls below: • $13$ g/dL ($130$ g/L) in men $\geq 15$ years old • $12$ g/dL ($120$ g/L) in non-pregnant women $\geq 15$ years old or adolescents aged 12–14 years • $11.5$ g/dL ($115$ g/L) in children aged 5–11 years • $11$ g/dL ($110$ g/L) in pregnant women, or children aged 6–59 months. If left untreated, anaemia in chronic kidney disease may cause deterioration in cardiac function, poor cognition and mental acuity, and fatigue. There are also associations with an increased risk of morbidity and mortality, principally due to cardiac disease and stroke (6). Chronic kidney disease affects approximately 8–16% of the adult population worldwide (7). The overall lifetime incidence of chronic kidney disease rises with age, with approximately 50% of Stage $3a$+ incidents occurring after age 70 years. The overall lifetime incidence of end-stage renal disease has been estimated at 3.6% (8). The incidence and prevalence of chronic kidney disease seem remarkably consistent globally, if not always well documented, whereas the distribution of those receiving renal replacement therapies (dialysis and transplantation) varies by country. About 2.2 million people receive dialysis globally, projected to be 5.4 million by 2030 (9). Anaemia is one of the several complications of chronic kidney disease. Its prevalence (from any cause) in patients with renal failure is about 15% in USA (10). In chronic kidney diseases end stages, about half of all patients are severely anaemic. The main impact of anaemia on organ function is reduced oxygen delivery to tissues, leading to debilitating symptoms such as fatigue, exercise intolerance, impaired cognitive function, sleep disorder, altered haemostasis, and depressed immune function. Anaemia in patients with chronic kidney disease is associated with decreases in cardiac and renal functions and impaired quality of life and poses a significant clinical and economic burden on health-care systems. Anaemia is also associated with a high prevalence of cardiovascular diseases in renal patients, with consequent higher morbidity and mortality: cardiovascular diseases are reported to account for more than 50% of deaths in these patients (11). In children, iron deficiency and Hb lower than 11.8 g/dL ($118$ g/L) have also been associated with cognitive impairment (12).

**Benefits**

The application summarizes evidence on the effectiveness and safety of ESAs, including branded medicinal products and biosimilars, for the treatment of anaemia in end-stage chronic kidney disease in adults and children undergoing dialysis. The review includes up-to-date systematic reviews of randomized controlled trials (RCTs) and other types of evidence syntheses (e.g. health technology assessment (HTA) reports, clinical guidelines if developed following a systematic approach) and pharmacoeconomic analyses comparing erythropoietins (epoetin alfa, beta, theta, zeta), darbepoetin alfa, and CERA with: • no intervention, placebo, standard care • other ESAs • other interventions (e.g. iron supplementation, androgen) • different dosages and administration schedules of the same ESA • branded versus biosimilar products. Eight systematic reviews (13–20), three clinical guidelines (1, 6, 21), two HTA reports (22, 23), five cost-analyses (described in the Costs section), one RCT published in 2015 but not included in the evidence synthesis reports (24) and one meta-regression study (25) were included. Adults Several sources of information provided useful information (16, 18, 20, 24), but the main source was a 2014 network meta-analysis that summarizes 56 studies for a total of 15 596 participants (17). This compared the efficacy and safety of different ESAs (epoetin alfa and beta, darbepoetin, ...
which include non-randomized studies and data from registries (21). Guidelines and clinical practice recommendations for anemia in chronic kidney disease issued by the National Kidney Foundation, the same authors included one additional study on darbepoetin (28). Additional information can be found in the Clinical practice guidelines and management of anaemia. Since evidence in children is generally scarce and of low quality, generalization from evidence in adults is unavoidable. A 2010 review identified two RCTs in children with end-stage renal disease (26, 27); a 2014 review by the National Kidney Foundation, which include non-randomized studies and data from registries (21). The most robust evidence for using ESA products in children is......
related to epoetin alfa and beta, with some preliminary data on darbepoetin. Compared with epoetin in children with chronic kidney disease stages 4 and 5, darbepoetin alfa had uncertain effects on the need for blood transfusion and risk of progression to renal replacement therapy, all-cause mortality, hypertension, dialysis vascular access thrombosis, exceeding Hb target level and injection site pain, as well as Hb levels during treatment (18). Children in the North American Pediatric Renal Transplant Cooperative Study database from 1992 to 2001 with Hb lower than 9.9 g/dL compared with those with Hb more than 9.9 g/dL had a high risk for mortality (adjusted relative risk, 1.52; 95% CI 1.03–2.26). Patients with more severe anaemia also had an increased risk of hospitalization. In a multicentre single-arm interventional trial evaluating 22 children (4 months to 16 years) with chronic kidney disease, treatment of anaemia with recombinant erythropoietin was associated with a significant increase in intelligence quotient, although the relative increase in Hb levels was small (Hb baseline 9.2 ± 1.6 vs final 9.7 ± 1.7 g/dL) (21, 29).

### Harms

The main safety concern linked to the use of ESAs in patients with chronic kidney disease is increases in the risk of death, myocardial infarction, stroke and other serious cardiovascular events. This is related to ESA doses targeting Hb of 11 g/dL and above. No trial has identified a Hb target level, ESA dose or dosing strategy that does not raise these risks. The lowest effective dose is therefore recommended (30). All proprietary ESAs raised the odds of hypertension compared with placebo, while the effect of biosimilar ESAs on hypertension was less certain (17). Since 2000, cases of aplasia (i.e., pure red cell aplasia, PRCA) and severe anaemia, with or without cytopenia, associated with neutralizing antibodies to erythropoietin, were reported in Europe and in USA, primarily in patients with chronic kidney disease given the medicine by SC injection. This was probably due to the interaction of stabilizing agent and part of the pre-filled syringes. Despite modifications in the pre-filled syringes new cases of antibody-associated PRCA are still reported, although the size of the phenomenon is limited (31). Based on time of exposure, PRCA incidence was 35.8/100 000 patient-years (95% CI 7.4–104.7) for epoetin alfa, 14.0/100 000 patient-years (95% CI 1.7–50.6) for epoetin beta and darbepoetin (11). No cases of PRCA emerged from the clinical development of biosimilars of epoetin alfa. However, sudden loss of efficacy and confirmed cases of PRCA were reported in a cluster of 23 Thai patients receiving regionally manufactured SC epoetin not approved in Europe (32, 33). High doses of erythropoietin may be associated with nephrogenic fibrosing dermopathy (34). A major issue in ESA use relates to the Hb target. It is generally known that targeting higher Hb levels in chronic kidney disease raises the risks for stroke, hypertension and vascular access thrombosis and probably increases the risks of death, serious cardiovascular events and end-stage renal disease (19). A systematic review with meta-regression of RCTs of ESAs in patients with chronic kidney disease examined whether a gradient of doses was associated with these potential harms, adjusting for the target or achieved Hb level (25). The authors identified an association between the first 3-month and total study period mean ESA dose and all-cause mortality, both in unadjusted models and models adjusting for target Hb. When restricting the analyses to dialysis patients, the association persisted in both the unadjusted and adjusted analyses. The lack of adjustment for other factors such as comorbidities and inflammatory markers, and inadequate control for treatment-by-indication bias and ecological fallacy, are limitations of this meta-regression analysis. In any case, these findings support the widely accepted use of more conservative dosing regimens for the treatment of patients with chronic kidney disease. Recent systematic reviews have suggested that aiming at Hb levels similar to those in healthy adults involves a significantly higher risk of all-cause mortality (16, 19). The first-generation ESAs (epoetin alfa and epoetin beta) have to be administered frequently, up to three times a week. This led to development of ESA agents with longer half-life (darbepoetin alfa, CERA) and consequent lower dosing frequency. The dosing schedules of darbepoetin once a week or once every 2 weeks and of CERA once a month offer many potential advantages to both patients and caregivers (35). However, the impact of these advantage should be considered in the light of the frequency of dialysis, which for most patients is three times a week. It remains unclear whether the new, longer-acting ESAs, given less frequently, offer the same efficacy and safety as older ESAs. A Cochrane systematic review updated in 2013 (16) sought to establish the optimal frequency of ESA administration. The review included 33 studies involving 5526 participants and concluded that longer-acting ESA (darbepoetin and CERA) given at 1–4-week intervals were non-inferior to ESA given 1–3 times a week in terms of achieving Hb targets, without any significant differences in adverse events in haemodialysis patients. The rapidly growing clinical experience with biosimilars has confirmed that their safety profile is in line with that of the reference products in terms of cardiovascular and thromboembolic events and immunogenicity data. In general, the known safety profile of ESAs as a class can be extended to biosimilars (36).

### Cost / cost effectiveness

The application identified five cost-analyses. Four of them (37–40) and two HTA reports (22, 23) form the basis of the evidence.
Availability

ESAs are licensed globally for treatment of symptomatic anaemia associated with chronic kidney disease. With the expiry of patent protection for epoetin alfa in Europe in 2007, biosimilar erythropoietins – e.g. epoetin alfa (Binocrit, Abseamed, Epoetin alfa Hexal), epoetin zeta (Retacrit, Silapo) – were introduced on the market (36). The patents on darbepoetin (Aranesp) expired in Europe in 2016 and will expire in USA in 2024 (42). Darbepoetin alfa “similar biologic” drugs (Actorise, Cresp, Darbatitor) are available in India (42). To be licensed in countries with stringent regulatory agencies, such as USA and countries of the European Union, a new epoetin claimed to be similar to a reference marketed product needs to undergo a proper comparability exercise, i.e. the head-to-head comparison, to establish similarity in quality, safety and efficacy (44). The stringent regulatory criteria and the need to provide a comprehensive data package have often been seen as putting an unnecessary burden (and cost) on the development and licensing processes, leading to delays in access to biosimilars. On the other hand, these criteria are meant to provide a sufficient level of evidence and extrapolation to reduce the concerns of both patients and health-care professionals about the use of biosimilars. Nevertheless, the adoption of such criteria is a matter of debate in clinical practice, with particular regard to the acceptability of switching from a reference drug to its biosimilars. However, pre-marketing trials and, above all, post-marketing drug-utilization data have helped, consolidating not only the therapeutic equivalence of the two products but also the safety of switching from reference to biosimilar products (45–47).

Other considerations

The application did not include peginesatide because of the safety concerns reported post-marketing, including serious hypersensitivity reactions such as anaphylaxis, which may be life-threatening or fatal. In 2013, the FDA recalled all lots of injectable peginesatide (Omontys) because of 19 reports of anaphylaxis (including three deaths) after the first dose in patients receiving dialysis (48).

4. The selection and use of essential medicines. Report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of...


