Erythropoiesis-stimulating agents

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.5. Supportive medicines

EMLc | ATC codes: B03XA01 B03XA02

Indication	Drug-induced aplastic anaemia ICD11 code: 3A70.10
INN	Epoetin alfa
Medicine type	Chemical agent
List type	Complementary (EML) (EMLc)
Formulations	Parenteral > General injections > unspecified: 2000 IU per mL in vial (single-dose) ; 3000 IU per mL in vial (single-dose) ; 4000 IU per mL in vial (single-dose) ; 10000 IU per mL in vial (single-dose) ; 40000 IU per mL in vial (single-dose) ; 20000 IU per mL in vial (multiple-dose) ; 20000 IU per 2 mL in vial (multiple-dose)
EML status history	Application rejected in 2025 (TRS 1064)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	epoetin alfa (ATC codes: B03XA01) epoetin beta (ATC codes: B03XA01) darbepoetin alfa (ATC codes: B03XA02)
Patent information	Patents have expired in most jurisdictions Read more about patents.
Tags	Biological
Wikipedia	Erythropoiesis-stimulating agents
DrugBank	Erythropoiesis-stimulating agents (Erythropoietin)

Expert Committee recommendation

The Expert Committee acknowledged that anaemia is a relatively common complication of chemotherapy treatment and is associated with reduced quality of life and functional capacity for patients. The Committee noted that judicious use of erythropoiesis-stimulating agents in patients with chemotherapy-induced anaemia has been shown to improve haemoglobin levels, may reduce transfusion requirements and may be associated with improvements in quality of life. However, their use has not been shown to improve overall survival, with some studies reporting inferior survival and worse cancer outcomes as these medicines might stimulate tumour growth directly or affect the tumour microenvironment limiting effective immune responses. The Committee also noted that guidelines from professional societies (e.g. the American Society of Clinical Oncology and the European Society of Medical Oncology) recommend careful patient selection, informed consent about risks and conservative dosing – factors that are important limitations in terms of feasibility in the use of this class of medicines. Therefore, the Expert Committee did not recommend the expansion of the indications for erythropoiesis-stimulating agents on the EML and EMLc to include supportive management of chemotherapy-induced anaemia, based on evidence of a potentially unfavourable long-term benefit-to-harm profile.

Background

Erythropoiesis-stimulating agents have not previously been evaluated for inclusion on the Model Lists for the proposed indication.

Erythropoiesis-stimulating agents (including biosimilars) have been included on the Model Lists since 2017 for the treatment of adults and children with anaemia of chronic kidney disease (1).

Public health relevance

Anaemia is a condition characterized by deficiency of red blood cells or haemoglobin, which diminishes the capacity of the blood to carry oxygen necessary for tissues and organs (2). It is a common adverse effect of myelosuppressive chemotherapy and affects around 80% of patients undergoing treatment (2, 3). Symptoms include fatigue, drowsiness, depression, dyspnoea, tachycardia and dizziness. Chemotherapy-induced anaemia can have a negative effect on quality of life, and it is associated with substantial economic burden and medical costs (4–6). Chemotherapy-induced anaemia may be treated using red blood cell transfusions. In low- and middle-income countries, availability of high-quality blood transfusion services for anaemia management may be limited. The WHO Global Status Report on Blood Safety and Availability 2021 reported lower rates of whole blood donations per 1000 population in low- and middle-income countries, as well as higher rates of blood donations with positive/reactive results for transfusion-transmissible infections on screening tests (7).

Benefits

The application did not report having conducted a systematic search of the literature and did not provide an adequate summary of the evidence to support the comparative effectiveness of erythropoiesis-stimulating agents in the treatment of chemotherapy-induced anaemia.

Harms

The application did not report having conducted a systematic search of the literature and did not provide an adequate summary of the evidence to support the comparative safety of erythropoiesis-stimulating agents in the treatment of chemotherapy-induced anaemia. The application stated that the use of erythropoiesis-stimulating agents has been associated with increased risk of thromboembolic events (particularly when haemoglobin levels are higher than 12 g/dL) and increased risk of tumour progression (8, 9).

Additional evidence

The following evidence was identified during the application review period. A 2012 Cochrane systematic review of 91 randomized controlled trials (20 102 participants) assessed the effects of erythropoiesis-stimulating agents for the prevention or treatment of anaemia in cancer patients (10). Only one of the trials evaluated erythropoiesis-stimulating agents in children. The review found that the use of erythropoietin or darbepoetin significantly reduced the risk of requiring red blood cell transfusions (risk ratio (RR) 0.65, 95% confidence interval (CI) 0.62 to 0.68; 70 trials, 15 935 participants). Additionally, participants receiving erythropoiesis-stimulating agents received fewer units of blood if transfused than controls (mean difference (MD) −0.98 units, 95% CI −1.17 to −0.78; 19 trials, 4715 participants). More participants receiving erythropoiesis-stimulating agents achieved a haematological response – defined as the proportion of patients with an increase in haemoglobin level of 2 g/dL or more, or an increase in haematocrit of 6% points or more – (RR 3.93, 95% CI 3.10 to 3.71; 31 trials, 6413 participants). There was low-certainty evidence that erythropoiesis-stimulating agents may improve quality of life. There was high-certainty evidence that erythropoiesis-stimulating agents may decrease overall survival (hazard ratio (HR) 1.05, 95% CI 1.00 to 1.11; 78 trials, 19 003 participants) and increase the risk of death (HR 1.17, 95% CI 1.06 to 1.29; 70 trials, 15 935 participants). Mortality risk was higher in patients with higher baseline haemoglobin levels > 12 g/dL (HR 1.37, 95% CI 1.12 to 1.68; 13 trials, 3923 participants). Erythropoiesis-stimulating agents were also associated with an increased risk of thromboembolic complications (RR 1.52, 95% CI 1.34 to 1.74, 57 trials, 15 498 participants), hypertension (RR 1.30, 95% CI 1.08 to 1.56; 31 trials 7228 participants) and thrombocytopenia/haemorrhage (RR 1.21, 95% CI 1.04 to 1.42, 21 trials, 4507 participants). A 2009 meta-analysis of 53 randomized controlled trials (13 933 participants) evaluated mortality risk of recombinant human erythropoiesis-stimulating agents in patients with cancer (11). In 38/53 (72%) trials, patients received chemotherapy, while in 5/53 (9%) trials, patient received radio-chemotherapy. The remaining trials did not include the use of chemotherapy. Median follow-up was 3.7 months and 3.9 months in the erythropoiesis-stimulating agents and control groups, respectively. Across all trials, treatment with erythropoiesis-stimulating agents was associated with an increased mortality risk (HR 1.17, 95% CI 1.06 to 1.30). Considering only the chemotherapy trials, the mortality risk remained increased, albeit slightly lower (HR 1.10, 95% CI 0.98 to 1.24).

Cost / cost effectiveness

The application stated that the cost of erythropoiesis-stimulating agents varies across regions. Prices can be higher in low- and middle-income countries than in high-income countries due to import and supply chain costs. The introduction of biosimilars has helped to reduce costs (12). The application identified several cost–effectiveness analyses for erythropoiesis-stimulating agents in the treatment of chemotherapy-induced anaemia (13–18), but highlighted their limitations as they were all conducted in high-income countries only and were not published recently.

WHO guidelines

WHO guidelines for the treatment of chemotherapy-induced anaemia are not available. In clinical guidelines from various oncology and haematology organizations, recommendations for the use of erythropoiesis-stimulating agents include: to consider using only in patients with symptomatic chemotherapy-induced anaemia when haemoglobin levels are lower than 10 g/dL; cautioning against use in patients receiving chemotherapy with curative intent; discussing the potential risks and benefits with patients and obtaining informed consent; regular monitoring; and using the lowest effective dose to achieve target haemoglobin levels.

Availability

Erythropoiesis-stimulating agents, including biosimilars, are widely available in high-income countries but may be less widely available and accessible in resource-constrained countries.

Other considerations

The cancer team within the Department of Noncommunicable Diseases, Rehabilitation and Disability reviewed and provided comments on the application. The technical team supported the inclusion of erythropoiesis-stimulating agents on the Model Lists for chemotherapy-induced anaemia in a carefully defined subset of patients who were adhering to established supportive care standards and were under the close supervision of trained health-care professionals to ensure safe and effective use. The technical team noted that although data do not support a survival benefit from these medicines, their use may be justified in selected patients to reduce red blood cell transfusions and improve quality of life.

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