Application for Inclusion of Selected Erythropoesis-Stimulating Agents in the WHO Essential Medicines List for Adults and Children

Proposal: Extension of current EML listing to include Chemotherapy-Induced Anemia

Submitted by Resonance

For communications related to this submission, please contact
Scott Howard
CEO, Resonance
scott.howard@resonancehealth.org
Mobile and Whatsapp +1 (901) 608-5086

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1. SUMMARY STATEMENT OF THE PROPOSAL

Summary of the application

Anemia is a common complication in cancer patients receiving chemotherapy, affecting approximately 30–90% of cases, depending on cancer type, stage, and treatment regimen. Chemotherapy-induced anemia significantly impairs quality of life, causing fatigue, dyspnea, and cardiovascular strain. In LMICs, blood transfusions for anemia management are often limited, increasing the need for alternative interventions such as ESAs.

Erythropoiesis-Stimulating Agents (ESAs), specifically **epoetin alfa, epoetin beta** and **darbepoetin alfa**, are recommended for inclusion on the WHO Essential Medicines List (EML) for the treatment of **chemotherapy-induced anemia (CIA)** in patients with non-myeloid malignancies undergoing myelosuppressive chemotherapy.[1-9]

At present, ESAs are approved and widely used in high-income countries and LMICs for anemia of chronic disease[7,10-16] and chemotherapy-induced anemia.[17-22] However, in the WHO EML they are currently (TRA 1006) only listed for anemia of chronic kidney disease, which could lead some regulatory agencies and ministries of health to limit their use to this indication. Therefore, this application requests that CIA be added to the list of uses of these agents.[1-9,17-22]

The aim is to improve quality of life, reduce transfusion dependency, and manage anemia-related symptoms. These ESAs are widely available in North America, Europe, parts of Asia, and Latin America, with biosimilars increasingly accessible in low- and middle-income countries (LMICs).

Erythropoiesis-stimulating agents are a therapeutic group

Listing is requested as an example of the **therapeutic group of erythropoiesis-stimulating agents** for the treatment of chemotherapy-induced anemia. Medicines in the ESA therapeutic group that are approved for CIA by the FDA, EMA, and regulatory agencies of various other countries include: Epoetin Alfa, Epoetin Beta, Darbepoetin Alfa and their biosimilars.[15,23-25]

Importance of ESAs in LMICs

In high-income countries, ESAs are standard treatment for managing CIA in patients with non-myeloid malignancies. Their use reduces transfusion dependence, alleviates symptoms of anemia, and improves quality of life. However, in LMICs, ESA availability and affordability are limited, and transfusion services may be unreliable. Including ESAs in the EML could improve anemia management and reduce reliance on transfusion services in these regions, where maintaining high-quality transfusion services may be problematic.

Cost-effectiveness of ESAs

Even before biosimilars came to market and lowered prices, ESAs were cost-effective for CIA.[26-31] Biosimilar competition is now widely available, so downward price pressures and will only increase.[25,28,32-37]

In summary, ESAs effectively treat CIA, are approved by regulators in many countries for CKD and CIA but need to have CIA listed as a WHO EML approved indication to maximize access.

2. CONSULTATION WITH WHO TECHNICAL DEPARTMENTS

The submitter has engaged with the WHO NCD (Cancer) Section in consideration of preparation of the current submission and sought the advice of the WHO EML Section with respect to content that may be useful in support of the application.

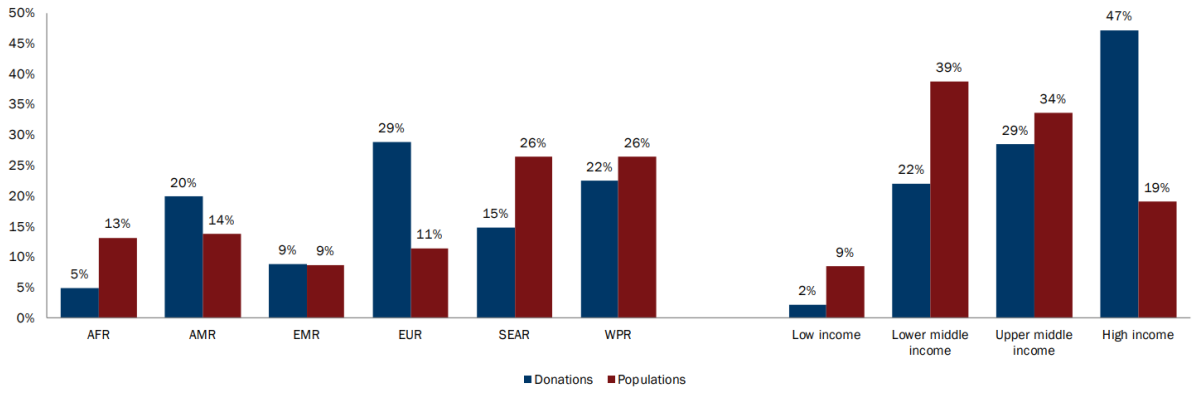
3. OTHER ORGANISATIONS CONSULTED AND/ OR SUPPORTING THE SUBMISSION

Not applicable.

4. KEY INFORMATION SUMMARY FOR THE PROPOSED MEDICINE

Introduction

Erythropoiesis-Stimulating Agents (ESAs) are biologic drugs that stimulate the bone marrow to produce more red blood cells. They are primarily used to treat **anemia** associated with conditions like **chronic kidney disease (CKD)**, **HIV/AIDS**, and **chemotherapy-induced anemia (CIA)**. CIA is a common side effect of cancer treatment, especially in patients receiving myelosuppressive chemotherapy, which damages the bone marrow's ability to produce blood cells. ESAs can help reduce the need for blood transfusions in these patients by increasing hemoglobin levels and alleviating symptoms of anemia, such as fatigue and weakness. Decreasing the need for blood transfusion is especially important in LMICs, where blood donations, blood product safety, and blood product access may be limited (**Figures 1, 2 and 3**).



AFR: African Region; AMR: Region of the Americas; EMR: Eastern Mediterranean Region; EUR: European Region; SEAR: South-East Asia Region; WPR: Western Pacific Region

Figure 1. Regional distribution of population and blood donations by WHO region and World Bank income group, 2013. *WHO Global Status Report on Blood Safety and Availability*

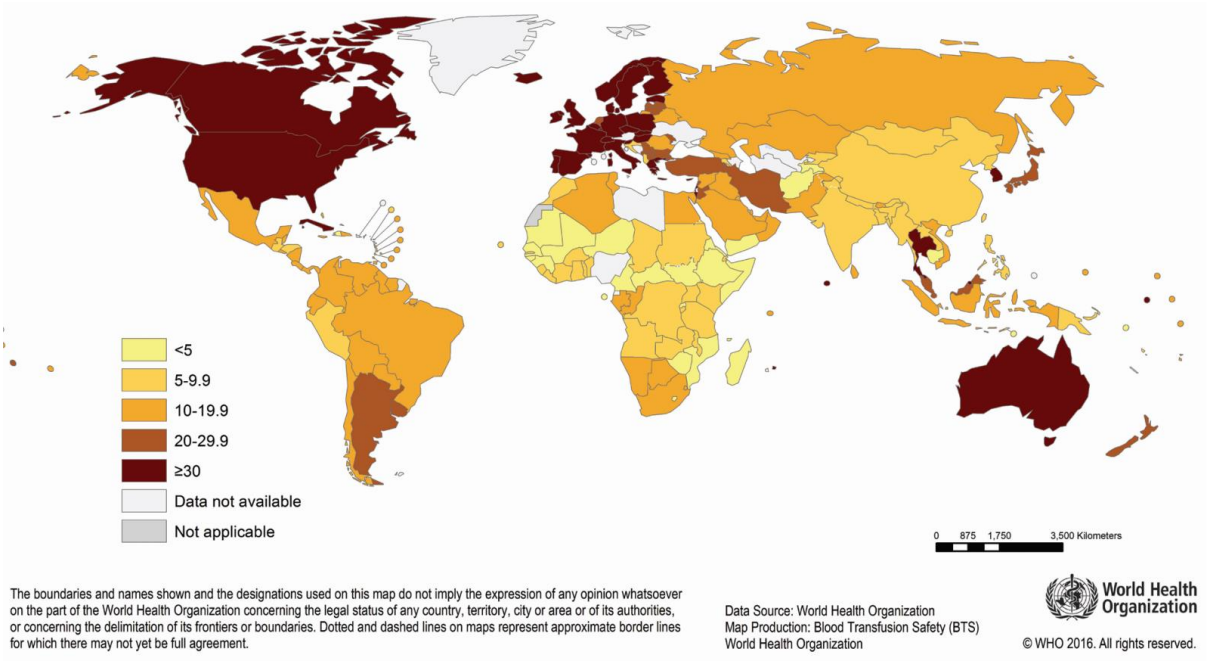


Figure 2. Whole blood donations per 1000 population, 2013. ***WHO Global Status Report on Blood Safety and Availability***

Income group	Proportion of blood donations with positive/reactive results (median and interquartile range, %)			
	HIV	HBV	HCV	Syphilis
High	0.003 (<0.001–0.04)	0.03 (0.008–0.18)	0.02 (0.003–0.16)	0.05 (0.005–0.26)
Upper middle	0.08 (0.006–0.2)	0.39 (0.16–0.69)	0.21 (0.05–0.42)	0.31 (0.12–1.07)
Lower middle	0.20 (0.05–0.44)	1.60 (0.94–4.13)	0.40 (0.19–1.50)	0.58 (0.18–1.47)
Low	1.08 (0.56–2.69)	3.70 (3.34–8.47)	1.03 (0.67–1.80)	0.90 (0.31–1.88)

Figure 3. Proportion of blood donations with positive results on screening tests for transmissible infectious diseases. ***WHO Global Status Report on Blood Safety and Availability***

HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus

In summary, blood product availability and safety are much lower in LMICs than HICs, so use of ESAs is likely to be even more cost-effective in LMICs.

Overview of Common ESAs and Their Mechanisms

ESAs are synthetic forms of erythropoetin, a hormone that regulates red blood cell production. The main ESAs used clinically include:

- Epoetin Alfa: A recombinant form of erythropoietin, available under several brand names (e.g., EPOGEN®, Procrit®).

- Darbepoetin Alfa: A modified form of erythropoietin with a longer half-life, branded as Aranesp®.
- Epoetin Beta: Another recombinant erythropoietin, sold as NeoRecormon® or Mircera® in some regions.

These agents are already on the WHO EML but are only listed for anemia of chronic kidney disease. This application proposes to add chemotherapy-induced anemia to their listed indications for branded and biosimilar ESAs in this therapeutic group.[25,28,32-37]

International non-proprietary name (INN) of the proposed medicine(s)

- Darbepoetin alfa
- Epoetin alfa
- Epoetin beta
    - Epoetin beta is not approved by the FDA for CIA, but is approved by the EMA for that indication. We propose the therapeutic group in general, but member states should consider all global approvals, as well as cost and other factors when deciding which to procure for each indication. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125164s089lbl.pdf
    - EMA: Treatment of symptomatic anaemia in adult patients with non-myeloid malignancies receiving chemotherapy. https://www.ema.europa.eu/en/documents/product-information/neorecormon-epar-product-information_en.pdf

Anatomical therapeutic chemical (ATC) code of the proposed medicine(s)

ATC Code: B03XA01. **Erythropoietin**. Pharmacotherapeutic group: Anti-anaemic preparations, other anti-anaemic preparations.

- https://atcddd.fhi.no/atc_ddd_index/?showdescription=yes&code=B03XA01

ATC Code: B03XA02. **Darbepoetin**. Pharmacotherapeutic group: Anti-anaemic preparations, other anti-anaemic preparations.

- https://atcddd.fhi.no/atc_ddd_index/?code=B03XA02&showdescription=yes

Indication to be added with this submission

Treatment of Anemia in Cancer Patients Receiving Chemotherapy

Inclusion of adults and children in EML listing

Both adults and children with chemotherapy-induced anemia benefit from ESAs. Different products have different indications and ages of inclusion.

For example, Epoetin alfa is indicated for use in adults and children for CIA (FDA label):

- https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103234s5363s5366lbl.pdf

However, in Europe it is indicated for use in adults (SmPC; EMA): Epoetin alfa is indicated in adults receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, and at risk of transfusion as assessed by the patient's general status (e.g. cardiovascular status, pre-existing anaemia at the start of chemotherapy) for the treatment of anaemia and reduction of transfusion requirements

- https://www.ema.europa.eu/en/documents/product-information/epoetin-alfa-hexal-epar-product-information_en.pdf

Epoetin beta is not indicated for CIA use in any population included in the FDA label:

- https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125164s089lbl.pdf

Epoetin beta is indicated for use in adults in the EMA SmPC for treatment of symptomatic anaemia in adult patients with non-myeloid malignancies receiving chemotherapy:

- https://www.ema.europa.eu/en/documents/product-information/neorecormon-epar-product-information_en.pdf

In the case of darbepoetin alfa, no age limits are listed in the FDA or the EMA label:

- https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/103951s5378lbl.pdf
- https://www.ema.europa.eu/en/documents/product-information/aranesp-epar-product-information_en.pdf

Dosage form(s) and strength(s) of the proposed medicine(s)

There are many different dose forms and strengths of ESAs (e.g. 32 for darbepoetin alfa, 13 for epoetin alfa, and 9 for epoetin beta). The relevant regulatory labels should be consulted for full details.

Epoetin alfa:

EPOGEN/ PROCRIT

2,000 Units/mL, single-dose vial

3,000 Units/mL, single-dose vial

4,000 Units/mL single-dose vial

10,000 Units/mL single-dose vial

20,000 Units/2 mL multiple-dose vials

20,000 Units/mL multiple-dose vials

RETACRIT

2,000 Units/mL, single-dose vial

3,000 Units/mL, single-dose vial

4,000 Units/mL single-dose vial

10,000 Units/mL single-dose vial

40,000 Units/mL single-dose vial

20,000 Units/2 mL multiple-dose vials

20,000 Units/mL multiple-dose vials

Epoetin beta:

500 IU solution for injection in pre-filled syringe

2000 IU solution for injection in pre-filled syringe

3000 IU solution for injection in pre-filled syringe

4000 IU solution for injection in pre-filled syringe

5000 IU solution for injection in pre-filled syringe

6000 IU solution for injection in pre-filled syringe

10,000 IU solution for injection in pre-filled syringe

20,000 IU solution for injection in pre-filled syringe

30,000 IU solution for injection in pre-filled syringe

Darbepoetin alfa

10 micrograms solution for injection in pre-filled syringe.

15 micrograms solution for injection in pre-filled syringe.

20 micrograms solution for injection in pre-filled syringe.

30 micrograms solution for injection in pre-filled syringe.

40 micrograms solution for injection in pre-filled syringe.

50 micrograms solution for injection in pre-filled syringe.

60 micrograms solution for injection in pre-filled syringe.

80 micrograms solution for injection in pre-filled syringe.

100 micrograms solution for injection in pre-filled syringe.

130 micrograms solution for injection in pre-filled syringe.

150 micrograms solution for injection in pre-filled syringe.

300 micrograms solution for injection in pre-filled syringe.

500 micrograms solution for injection in pre-filled syringe.

10 micrograms solution for injection in pre-filled pen.

15 micrograms solution for injection in pre-filled pen.

20 micrograms solution for injection in pre-filled pen.

30 micrograms solution for injection in pre-filled pen.

40 micrograms solution for injection in pre-filled pen.

50 micrograms solution for injection in pre-filled pen.

60 micrograms solution for injection in pre-filled pen.

80 micrograms solution for injection in pre-filled pen.

100 micrograms solution for injection in pre-filled pen.

130 micrograms solution for injection in pre-filled pen.

150 micrograms solution for injection in pre-filled pen.

300 micrograms solution for injection in pre-filled pen.

500 micrograms solution for injection in pre-filled pen.

25 micrograms solution for injection in vial.

40 micrograms solution for injection in vial.

60 micrograms solution for injection in vial.

100 micrograms solution for injection in vial.

200 micrograms solution for injection in vial.

300 micrograms solution for injection in vial.

Target list (EML/EMLc)

Epoetin alfa, epoetin beta, darbepoetin alfa, and other relevant ESAs and biosimilars considered to be therapeutically equivalent) are proposed for the same categorization as the current listings for ESAs for 'Anemia due to chronic disease'. That is:

- Complementary (EML)
- EML for Children

5. LISTING AS AN INDIVUAL MEDICINE OR REPRESENTATIVE OF A CLASS/

Therapeutic group

It is proposed to include ESAs for CIA as a therapeutically equivalent group, with acknowledgement of the distinct approvals for each specific product by regulator and age group. Epoetin alfa, epoetin beta and darbepoetin alfa have indications for use in chemotherapy-induced anemia, but this varies between regulatory jurisdictions.

6. INFORMATION SUPPORTING THE PUBLIC HEALTH RELEVANCE

Proposed indication(s) and target population(s)

EMA label: Treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy.

Epidemiology

Anemia is a common adverse effect of myelosuppressive chemotherapy, and the development of chemotherapy-induced anemia (CIA) is common.[6] Anemia is a common complication of myelosuppressive chemotherapy that results in a decreased functional capacity and quality of life (QOL) for cancer patients.[38] Severe anemia is treated with red blood cell transfusions, but mild-to-moderate anemia in patients receiving chemotherapy has traditionally been managed

conservatively on the basis of the perception that it was clinically unimportant. This practice has been reflected in the relative inattention to standardized and complete reporting of all degrees of chemotherapy-induced anemia.[8] Patients with non-Hodgkin lymphoma (NHL) from a large managed care organization in California. were examined from 2000 to 2013. All data were collected from Kaiser Permanente Southern California electronic health records. Of 699 chemotherapy-treated patients, 36.9% developed moderate (hemoglobin < 10 g/dL) and 11.6% severe (hemoglobin < 8 g/dL) CIA during chemotherapy. Proportions of moderate CIA events treated with erythropoiesis-stimulating agents (ESAs) decreased from 2000 to 2013: 34% in phase 1 (January 1, 2000, to December 31, 2006), 22% in phase 2 (January 1, 2007, to March 24, 2010), and 6% in phase 3 (March 25, 2010, to June 30, 2013). An increasing trend of red blood cell transfusion was observed: 12% in phase 1, 22% in phase 2, and 27% in phase 3. Similar calendar trends were observed for management of severe CIA events. Thus, this common problem, occurring in more than a third of cancer patients, can be managed with ESAs or red blood cell transfusions. Unfortunately, in LMICs, blood banking infrastructure and blood product safety can make this option less appealing.

Alternative medicines currently included on the Model Lists for the proposed indication

No ESAs or other medicines are currently included on the EML for chemotherapy-induced anemia.

7. TREATMENT DETAILS

Management of chemotherapy-induced anemia

The following information relates to treatment details from the relevant regulatory approvals for each medicine:

A. Epoetin alfa – patients on cancer chemotherapy (FDA label)

Initiate [Epogen] in patients on cancer chemotherapy only if the hemoglobin is less than 10 g/dL, and if there is a minimum of two additional months of planned chemotherapy.

Use the lowest dose of [Epogen] necessary to avoid RBC transfusions.

Recommended Starting Dose Adults:

- 150 Units/kg subcutaneously 3 times per week until completion of a chemotherapy course or
- 40,000 Units subcutaneously weekly until completion of a chemotherapy course.

Pediatric Patients (5 to 18 years):

- 600 Units/kg intravenously weekly until completion of a chemotherapy course.

Dose Reduction

Reduce dose by 25% if:

- Hemoglobin increases greater than 1 g/dL in any 2-week period or
- Hemoglobin reaches a level needed to avoid RBC transfusion.

Withhold dose if hemoglobin exceeds a level needed to avoid RBC transfusion. Reinitiate at a dose 25% below the previous dose when hemoglobin approaches a level where RBC transfusions may be required.

Dose Increase

After the initial 4 weeks of [Epogen] therapy, if hemoglobin increases by less than 1 g/dL and remains below 10 g/dL, increase dose to:

- 300 Units/kg three times per week in adults or
- 60,000 Units weekly in adults
- 900 Units/kg (maximum 60,000 Units) weekly in pediatric patients

After 8 weeks of therapy, if there is no response as measured by hemoglobin levels or if RBC transfusions are still required, discontinue [Epogen].

B. Epoetin alfa (EMA)

Anaemia symptoms and sequelae may vary with age, gender, and overall burden of disease; a physician's evaluation of the individual patient's clinical course and condition is necessary.

Epoetin alfa should be administered to patients with anaemia (e.g. haemoglobin concentration ≤ 10 g/dL (6.2 mmol/L)).

The initial dose is 150 IU/kg subcutaneously, 3 times per week.

Alternatively, Epoetin alfa can be administered at an initial dose of 450 IU/kg subcutaneously once weekly.

Appropriate adjustment of the dose should be made in order to maintain haemoglobin concentrations within the desired concentration range between 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L).

Due to intra-patient variability, occasional individual haemoglobin concentrations for a patient above and below the desired haemoglobin concentration range may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the desired

haemoglobin concentration range between 10 g/dL (6.2 mmol/L) to 12 g/dL (7.5 mmol/L). A sustained haemoglobin concentration of greater than 12 g/dL (7.5 mmol/L) should be avoided; guidance for appropriate dose adjustment for when haemoglobin concentrations exceed 12 g/dL (7.5 mmol/L) is described below.

- If the haemoglobin concentration has increased by at least 1 g/dL (0.62 mmol/L) or the reticulocyte count has increased > 40,000 cells/μL above baseline after 4 weeks of treatment, the dose should remain at 150 IU/kg 3 times per week or 450 IU/kg once weekly.
- If the haemoglobin concentration increase is < 1 g/dL (< 0.62 mmol/L) and the reticulocyte count has increased < 40,000 cells/μL above baseline, increase the dose to 300 IU/kg 3 times per week. If after an additional 4 weeks of therapy at 300 IU/kg 3 times per week, the haemoglobin concentration has increased > 1 g/dL (> 0.62 mmol/L) or the reticulocyte count has increased > 40,000 cells/μL, the dose should remain at 300 IU/kg 3 times per week.
- If the haemoglobin concentration has increased < 1 g/dL (< 0.62 mmol/L) and the reticulocyte count has increased < 40 000 cells/μL above baseline, response is unlikely and treatment should be discontinued.

Dose adjustment to maintain haemoglobin concentrations between 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L)

- If the haemoglobin concentration is increasing by more than 2 g/dL (1.25 mmol/L) per month, or if the haemoglobin concentration level exceeds 12 g/dL (7.5 mmol/L), reduce the Epoetin alfa dose by about 25% to 50%.
- If the haemoglobin concentration level exceeds 13 g/dL (8.1 mmol/L), discontinue therapy until it falls below 12 g/dL (7.5 mmol/L) and then reinitiate Epoetin alfa therapy at a dose 25% below the previous dose.

Patients should be monitored closely to ensure that the lowest approved dose of ESA is used to provide adequate control of the symptoms of anaemia.

Epoetin alfa therapy should continue until one month after the end of chemotherapy.

C. Epoetin beta (EMA)

[NeoRecormon] should be administered by the subcutaneous route to patients with anaemia (e.g. haemoglobin concentration ≤ 10g/dl (6.21 mmol/l). Anaemia symptoms and sequelae may vary with age, gender, and overall burden of disease; a physician's evaluation of the individual patient's clinical course and condition is necessary.

The weekly dose can be given as one injection per week or in divided doses 3 to 7 times per week.

The recommended initial dose is 30,000 IU per week (corresponding to approximately 450 IU/kg body weight per week, based on an average weighted patient).

Due to intra-patient variability, occasional individual haemoglobin values for a patient above and below the desired haemoglobin level may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin target range of 10 g/dl (6.21 mmol/l) to 12 g/dl (7.45 mmol/l). A sustained haemoglobin level of greater than 12 g/dl (7.45 mmol/l) should be avoided; guidance for appropriate dose adjustment for when haemoglobin values exceeding 12 g/dl (7.45 mmol/l) are observed are described below.

If, after 4 weeks of therapy, the haemoglobin value has increased by at least 1 g/dl (0.62 mmol/l), the current dose should be continued. If the haemoglobin value has not increased by at least 1 g/dl (0.62 mmol/l), a doubling of the weekly dose should be considered. If, after 8 weeks of therapy, the haemoglobin value has not increased by at least 1 g/dl (0.62 mmol/l), response is unlikely, and treatment should be discontinued.

The therapy should be continued for up to 4 weeks after the end of chemotherapy.

The maximum dose should not exceed 60,000 IU per week.

Once the therapeutic objective for an individual patient has been achieved, the dose should be reduced by 25 to 50% to maintain haemoglobin at that level. Appropriate dose titration should be considered.

If the haemoglobin exceeds 12 g/dl (7.45 mmol/l), the dose should be reduced by approximately 25 to 50%. Treatment with [NeoRecormon] should be temporarily discontinued if haemoglobin levels exceed 13 g/dl (8.1 mmol/l). Therapy should be reinitiated at approximately 25% lower than the previous dose after haemoglobin levels fall to 12 g/dl (7.45 mmol/l) or below.

If the rise in haemoglobin is greater than 2 g/dl (1.3 mmol/l) in 4 weeks, the dose should be reduced by 25 to 50%. Patients should be monitored closely to ensure that the lowest approved dose of [NeoRecormon] is used to provide adequate control of the symptoms of anaemia.

D. Darbepoetin alfa (FDA)

Initiate [Aranesp] in patients on cancer chemotherapy only if the hemoglobin is less than 10 g/dL, and if there is a minimum of two additional months of planned chemotherapy. Use the lowest dose of [Aranesp] necessary to avoid RBC transfusions.

Recommended Starting Dose

The recommended starting dose and schedules are:

- 2.25 mcg/kg every week subcutaneously until completion of a chemotherapy course.
- 500 mcg every 3 weeks subcutaneously until completion of a chemotherapy course.

Dose adjustment

If hemoglobin increases greater than 1 g/dL in any 2-week period OR if hemoglobin reaches a level needed to avoid RBC transfusion:

- Weekly schedule - reduce dose by 40%
- Every 3 week schedule - reduce dose by 40%

If hemoglobin exceeds a level needed to avoid RBC transfusion

- Weekly schedule
    - Withhold dose until hemoglobin approaches a level where RBC transfusions may be required
    - Reinitiate at a dose 40% below the previous dose
- Every 3 week schedule
    - Withhold dose until hemoglobin approaches a level where RBC transfusions may be required
    - Reinitiate at a dose 40% below the previous dose
- If hemoglobin increases by less than 1 g/dL and remains below 10 g/dL after 6 weeks of therapy
    - Weekly schedule - increase dose to 4.5 mcg/kg/week
    - Every 3 week schedule – no dose adjustment
- If there is no response as measured by hemoglobin levels or if RBC transfusions are still required after 8 weeks of therapy OR Following completion of a chemotherapy course
    - Weekly schedule – discontinue [Aranesp]
    - Every 3 week schedule – discontinue [Aranesp]

E. Darbepoetin alfa (EMA)

[Aranesp] should be administered by the subcutaneous route to patients with anaemia (e.g. haemoglobin concentration ≤ 10 g/dL (6.2 mmol/L)) to increase haemoglobin to not greater than 12 g/dL (7.5 mmol/L). Anaemia symptoms and sequelae may vary with age, gender, and overall burden of disease; a physician's evaluation of the individual patient's clinical course and condition is necessary.

Due to intra-patient variability, occasional individual haemoglobin values for a patient above and below the desired haemoglobin level may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin target range of 10 g/dL (6.2 mmol/L) to 12 g/dL (7.5 mmol/L). A sustained haemoglobin level of greater than 12 g/dL (7.5 mmol/L) should be avoided; guidance for appropriate dose adjustments for when haemoglobin values exceeding 12 g/dL (7.5 mmol/L) are observed are described below.

The recommended initial dose is 500 mcg (6.75 mcg/kg) given once every three weeks, or once weekly dosing can be given at 2.25 mcg/kg body weight. If the clinical response of the patient (fatigue, haemoglobin response) is inadequate after nine weeks, further therapy may not be effective. [Aranesp] therapy should be discontinued approximately four weeks after the end of chemotherapy.

Once the therapeutic objective for an individual patient has been achieved, the dose should be reduced by 25 to 50% in order to ensure that the lowest approved dose of [Aranesp] is used to maintain haemoglobin at a level that controls the symptoms of anaemia. Appropriate dose titration between 500 mcg, 300 mcg, and 150 mcg should be considered.

Patients should be monitored closely, if the haemoglobin exceeds 12 g/dL (7.5 mmol/L), the dose should be reduced by approximately 25 to 50%. Treatment with [Aranesp] should be temporarily discontinued if haemoglobin levels exceed 13 g/dL (8.1 mmol/L). Therapy should be reinitiated at approximately 25% lower than the previous dose after haemoglobin levels fall to 12 g/dL (7.5 mmol/L) or below.

If the rise in haemoglobin is greater than 2 g/dL (1.25 mmol/L) in 4 weeks, the dose should be reduced by 25 to 50%.

Requirements to ensure appropriate use of medicines

ESAs require no special equipment or laboratory testing. Routine complete blood counts or hemoglobin levels are sufficient to adjust doses and determine the duration of therapy needed.

8. REVIEW OF EVIDENCE FOR BENEFITS AND HARMS

Summary of available evidence for comparative effectiveness and comparative safety

Comparative effectiveness:

Compared to red blood cell transfusions, ESAs provide sustained hemoglobin elevation without the logistical and infection risks associated with transfusion. ESAs can be administered in outpatient settings, making them practical for both high-resource and resource-constrained environments.[3,7,19]

Multiple studies and meta-analyses have evaluated the effectiveness of ESAs in managing chemotherapy-induced anemia. For example:

- Epoetin alfa significantly reduced transfusion requirements and improved hemoglobin levels in CIA patients.[39]
- Bohlius et al.[40] showed that darbepoetin alfa and epoetin alfa reduce transfusion dependence with a manageable safety profile.

Comparative safety

Safety issues with ESAs include the following:

- **Thromboembolic risks**: Increased risk of thromboembolism, especially when hemoglobin levels exceed 12 g/dL. Clinical guidelines recommend starting treatment when hemoglobin falls below 10 g/dL and maintaining levels within a safe range.
- **Tumor progression risk**: Some studies suggest a potential association between ESAs and tumor progression in specific cancers. Therefore, ESAs are recommended primarily for palliative care or when transfusions are impractical, including patients with various types of metastatic cancer.[3,40-42]

Meta-analyses found that while there are safety concerns associated with ESA use, adherence to clinical guidelines minimizes risks.[40,41] The risk-benefit ratio supports ESA use in symptomatic CIA where transfusions are unavailable or unsuitable.

In the open-label, multi-center EPO-ANE-3010 study, 2,098 anemic women with metastatic breast cancer who received first line or second line chemotherapy were randomized to receive epoetin alfa plus standard of care (SOC) as compared with SOC alone.[42] This non inferiority study was designed to rule out a 15% risk increase in tumour progression or death with use of epoetin. The median progression free survival (PFS) was 7.4 months in each arm (HR 1.09, 95% CI: 0.99, 1.20), indicating no increased disease progression with epoetin alfa. Significantly fewer patients received RBC transfusions in the epoetin alfa plus SOC arm (5.8% versus 11.4%); however, significantly more patients had thrombotic vascular events in the epoetin alfa plus SOC arm (2.8% versus 1.4%). At the final analysis, 1,653 deaths were reported. Median overall survival in the epoetin alfa plus SOC group was 17.8 months compared with 18.0 months in the SOC alone group (HR 1.07, 95% CI: 0.97, 1.18). The median time to progression (TTP) based on investigator-determined progressive disease (PD) was 7.5 months in the epoetin alfa plus SOC group and 7.5 months in the SOC group (HR 1.099, 95% CI: 0.998, 1.210). The median TTP based on IRC determined PD was 8.0 months in the epoetin alfa plus SOC group and 8.3 months in the SOC group (HR 1.033, 95% CI: 0.924, 1.156).

Safety Considerations

The use of ESAs in **chemotherapy-induced anemia** has been subject to considerable scrutiny due to associated risks:

- **Thromboembolic events**: ESAs have been linked to an increased risk of blood clots, especially when hemoglobin levels rise above 12 g/dL.
- **Tumor progression**: Studies have indicated that ESAs might potentially accelerate tumor growth in some cancers, leading to strict guidelines to mitigate these risks.

Due to these risks, ESAs are recommended only when:

- **Hemoglobin** levels fall below 10 g/dL.
- **Dose adjustments** are made based on hemoglobin response.
- **Frequent monitoring** is conducted to avoid hemoglobin levels rising excessively.

As with any medicine, the regulatory labels provide the most up-to-date wording with respect to safety language. While there are specific comments with respect to ESAs and their safety requirements, the fact that they have regulatory approval in many countries (and for many years) suggests that regulatory agencies remain satisfied that the benefit-risk ratio is acceptable for the designated use populations.

Assessment of applicability of the available evidence across diverse populations and settings

ESAs are used wherever cancer patients have access to cytotoxic therapy.

9. SUMMARY OF RECOMMENDATIONS IN CURRENT CLINICAL GUIDELINES

Recommendations in existing WHO guidelines

Not applicable for CIA.

Recommendations in other current clinical guidelines

The use of erythropoiesis-stimulating agents (ESAs) for managing chemotherapy-induced anemia (CIA) is supported by clinical guidelines from several major oncology and hematology organizations. These guidelines provide evidence-based recommendations on the use of ESAs to minimize transfusion requirements and manage anemia-related symptoms while addressing potential risks associated with ESA therapy. Here are some of the most relevant clinical guidelines:

1. American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH) Guidelines

- Guideline Title: "Use of Erythropoiesis-Stimulating Agents in Patients with Cancer"
- Key Recommendations:
    - ESAs are recommended for patients with CIA who have hemoglobin levels below 10 g/dL to reduce the need for transfusions.
    - ESA therapy should be used cautiously due to potential risks, including thromboembolism and potential impacts on survival.
    - ESAs should not be used in patients receiving chemotherapy with curative intent.

- Latest Update: These guidelines are periodically updated, with the latest versions emphasizing safety and patient selection criteria

. https://pmc.ncbi.nlm.nih.gov/articles/PMC6482353/

2. National Comprehensive Cancer Network (NCCN) Guidelines

- Guideline Title: "NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Cancer- and Chemotherapy-Induced Anemia"
- Key Recommendations:
    - ESA treatment is recommended for cancer patients undergoing myelosuppressive chemotherapy with hemoglobin below 10 g/dL.
    - Close monitoring of hemoglobin levels is advised to avoid exceeding 12 g/dL, which may increase thromboembolic risk.
    - The NCCN guidelines recommend discussing the potential risks and benefits of ESA therapy with patients.
- Latest Update: Updated annually or biannually, NCCN guidelines incorporate the latest research findings and FDA updates on ESA use.

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3. European Society for Medical Oncology (ESMO) Guidelines

- Guideline Title: "Management of Cancer-Related Anemia in Adult Patients: ESMO Clinical Practice Guidelines"
- Key Recommendations:
    - ESAs may be used in cancer patients with symptomatic anemia undergoing chemotherapy, particularly if hemoglobin levels fall below 10 g/dL.
    - ESMO guidelines caution against ESA use in patients with curative treatment goals due to concerns about tumor progression.
    - Risk of thromboembolic events should be discussed, and alternative options, such as transfusion, should be considered if appropriate.
- Latest Update: Regular updates, with emphasis on safety and evidence-based risk-benefit analysis for ESA use

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4. British Committee for Standards in Haematology (BCSH) Guidelines

- Guideline Title: "Guidelines for the Use of Erythropoiesis-Stimulating Agents (ESAs) in the Management of Anaemia in Patients with Cancer"
- Key Recommendations:

- ESAs should be considered in patients with symptomatic anemia due to chemotherapy when hemoglobin levels fall below 10 g/dL.
- BCSH guidelines emphasize the need for patient-informed consent due to potential adverse effects and recommend regular monitoring.
- Suggests using the lowest effective dose to achieve target hemoglobin levels and minimize risks.

- Latest Update: Provides evidence-based, region-specific recommendations for ESA administration and monitoring in oncology patients

5. Canadian Association of Provincial Cancer Agencies (CAPCA) Guidelines

- Guideline Title: "Guidelines on the Use of Erythropoiesis-Stimulating Agents for the Management of Anemia in Adult Cancer Patients"
- Key Recommendations:
  - ESAs are recommended for non-curative cancer patients with CIA to reduce transfusion needs, provided hemoglobin is below 10 g/dL.
  - Cautions against exceeding target hemoglobin levels and highlights the importance of discussing risks with patients.
  - CAPCA guidelines are aligned with the principles of balancing anemia management with the minimization of potential harms.
- Latest Update: Updated as new evidence emerges, particularly with biosimilar availability in Canada

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Previous safety concerns and mitigating factors in place

The risks of ESAs prompted multiple regulatory actions by the US Food and Drug Administration (FDA) between 2004 and 2009. In 2010, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for ESA use in patients with cancer. In 2017, the FDA determined that the REMS was no longer necessary because prescribers demonstrated acceptable knowledge of the risks of ESAs and the need to counsel patients about the risks, and utilization data suggested an increase in appropriate prescribing practices.

The information below is extracted directly from the FDA website, and summarizes the FDA determination regarding the ESA Risk Evaluation and Mitigation Strategy (REMS), which was limited to the use of epoetin alfa (Epogen/Procrit) and darbepoetin alfa (Aranesp) to treat patients with anemia due to associated myelosuppressive chemotherapy:

- *The results from surveyed prescribers demonstrate acceptable knowledge of the product risks of decreased survival and/or the increased risk of tumor progression or recurrence and the need to counsel patients about these risks.*

- *The drug utilization data indicates appropriate prescribing of ESAs consistent with the intended use as a treatment alternative to RBC transfusion for anemia associated with myelosuppressive chemotherapy*

The FDA further note the following, which outlines information that is consistent with the guidelines for use in regulatory labelling:

- *While the REMS is no longer necessary to ensure the benefits outweigh the risks, the serious risks of shortened overall survival and/or increased risk of tumor progression or recurrence associated with these drugs remain. The prescribing information continues to note an increased risk of tumor progression or recurrence, as well as death, myocardial infarction, stroke, venous thromboembolism, and thrombosis of vascular access. Health care providers are encouraged to discuss the risks and benefits of using ESAs with each patient before initiating use.*

Clinical paper describing trends following REMS: https://pubmed.ncbi.nlm.nih.gov/33534188/

General Themes Across Guidelines

- Patient Selection: ESAs are primarily indicated for CIA in patients with non-curative treatment intent and hemoglobin levels below 10 g/dL.
- Safety Concerns: All guidelines highlight the risks of thromboembolic events and the potential for tumor progression, particularly in certain cancers.
- Monitoring and Dosing: Guidelines recommend using the lowest effective dose, frequent hemoglobin monitoring, and avoiding levels above 12 g/dL to reduce adverse events.
- Informed Consent: Guidelines stress the need for patient education on ESA risks and
- benefits, ensuring informed decision-making.

These guidelines reflect a balanced approach to ESA use in CIA, aimed at reducing transfusion dependence while carefully managing the associated risks. The recommendations provided by ASCO/ASH, NCCN, ESMO, BCSH, and CAPCA offer comprehensive frameworks that healthcare providers in different regions can adapt based on local healthcare resources and patient needs.

10. SUMMARY OF AVAILABLE DATA ON COMPARATIVE COST AND COST-EFFECTIVENESS (NEW MEDICINE(S) / INDICATION(S))

Range of Costs of the Proposed Medicine

The cost of ESAs varies significantly across regions and formulations. Epoetin alfa costs **$10–20 per 1,000 IU** in high-income countries, while prices can be higher in LMICs due to import and supply chain costs. Biosimilars have reduce ESA costs, making them more accessible.[25,28,32,33,35-37]

In the European Union G5 countries, the costs of epoetin alpha (originator [Eprex(R)] and biosimilar [Binocrit(R)]; once weekly), epoetin beta (NeoRecormon(R); once weekly), and

darbepoetin alpha (Aranesp(R); once weekly or once every 3 weeks) were evaluated under different scenarios of fixed and weight-based dosing in the management of chemotherapy-[28] induced anemia. Direct costs of ESA treatment were calculated for one patient with cancer undergoing chemotherapy (six cycles at 3-week intervals) with ESA initiated at week 4 and continued for 15 weeks. Five scenarios were developed under fixed and weight-based dosing: continuous standard dose for 15 weeks; sustained dose escalation to 1.5x or double the standard dose at week 7, continued for 12 weeks; and discontinued dose escalation to 1.5x or double the standard dose at week 7 for a 3-week period, then 9 weeks of standard dose.

Under fixed dosing, the average cost of biosimilar epoetin alpha treatment across scenarios was €4643 (30,000 IU) or €6178 (40,000 IU). Corresponding estimates were €7168 for originator epoetin alpha, €7389 for epoetin beta, €8299 for darbepoetin alpha once weekly, and €9221 for darbepoetin alpha once every 3 weeks. Under weight-based dosing, the average cost of biosimilar epoetin alpha treatment across scenarios was €4726. Corresponding estimates were €5484 for originator epoetin alpha, €5652 for epoetin beta, and €8465 for both darbepoetin alpha once weekly and once every three weeks.

In summary, managing chemotherapy-induced anemia with biosimilar epoetin alpha is consistently cost efficient over treatment with originator epoetin alpha, epoetin beta, and darbepoetin alpha under both fixed and weight-based dosing scenarios.[43] Indeed, costs were low and cost-effectiveness high regardless of the ESA used. In any case, this application proposes to add chemotherapy-induced anemia as an indication for ESAs as a therapeutic group.

Comparative Cost-Effectiveness

There are a range of cost-effectiveness analyses for ESAs in chemotherapy-induced anemia. A major concern with the relevance of these studies is the period of analysis/ period of publication, given many years have passed since the introduction of these medicines for this indication.[31,44-49] Unsurprisingly, many of the cost-effectiveness studies have been published in high-income country contexts, and as such may have little relevance for how LMICs may consider procurement if added to the EML for this extension of indication. Nikolaidi et al.[50] published a budget impact analysis within the Greek healthcare context and found that biosimilar ESAs appeared to be cost-saving option over originator medicines. Studies in Europe showed that total and anemia-related costs were lowest in patients receiving darbepoetin vs either epoetin alfa or beta.[27,51]

The most important point to consider is that ESAs exist in a competitive environment and are many years away from their original listings, with biosimilars evident. As costs have come down through branded and biosimilar competition, the cost-effectiveness has increased for all ESA indications. When considering the need for better outcomes for people with cancer in LMICs, who will be most likely to benefit from a change in EML status extending the indication of these medicines to include CIA, the context must be considered, including potential for less availability of same blood products for transfusion and excess utilization of scare healthcare services.[52-56]

11. REGULATORY STATUS, MARKET AVAILABILITY AND PHARMACOPOEIAL STANDARDS

Regulatory status of the proposed medicine(s)

The use of ESAs in **chemotherapy-induced anemia** is subject to additional regulatory approval based on studies in people receiving chemotherapy for cancer and are only incorporated into clinical guidelines after clinical trial results allayed concerns about safety in people with cancer, including potential risks of thromboembolic events and increased risk of tumor progression that could hypothetically be mediated by stimulation of EPO receptors. In general, regulatory approvals are evident in mostly high-income countries, as well as some middle-income countries. Given the WHO Essential Medicines List is a significant influencer of whether or not a medicine has regulatory approval in LMICs, it is unsurprising that ESAs do not have regulatory approval in most LMICs. Below are details of ESAs approved for CIA, along with their brand names and regions where they are approved:

1. Epoetin Alfa

- **United States**
    - **Brand Names**: **EPOGEN®** (Amgen), **Procrit®** (Janssen), and **Retacrit®** (biosimilar).
    - **Regulatory Authority**: **FDA**
    - **Indication**: Approved for use in chemotherapy-induced anemia in patients with non-myeloid malignancies to reduce the need for blood transfusions. The FDA guidelines suggest initiating treatment only when hemoglobin levels fall below 10 g/dL to minimize risks.
- **European Union**
    - **Brand Name**: **Various**
    - **Regulatory Authority**: **EMA**
    - **Indication**: Approved for chemotherapy-induced anemia in adult cancer patients. Similar to the U.S., it is used to manage anemia to reduce transfusion needs, with restrictions to monitor safety.
- **Canada**
    - **Brand Name**: **Eprex®**
    - **Regulatory Authority**: **Health Canada**
    - **Indication**: Approved for anemia in cancer patients undergoing chemotherapy, with usage guidelines similar to those in the U.S. and EU.

2. Darbepoetin Alfa

- **United States**:

- **Brand Name**: **Aranesp®**
- **Regulatory Authority**: **FDA**
- **Indication**: Approved for CIA in non-myeloid malignancies. Darbepoetin has a longer half-life than epoetin alfa, allowing for less frequent dosing, which may benefit patient compliance.

- **European Union**:
  - **Brand Name**: **Aranesp®**
  - **Regulatory Authority**: **EMA**
  - **Indication**: Similar to the U.S., approved for chemotherapy-induced anemia to reduce transfusions. Treatment initiation and monitoring guidelines are also in place to minimize adverse effects.
- **Australia**:
  - **Brand Name**: **Aranesp®**
  - **Regulatory Authority**: **Therapeutic Goods Administration (TGA)**
  - **Indication**: Approved for use in CIA to reduce transfusion requirements, with dosing guidance and close monitoring recommended.

3. Epoetin Beta

- **European Union**:
  - **Brand Name**: **Various**
  - **Regulatory Authority**: **EMA**
  - **Indication**: Approved for chemotherapy-induced anemia. This ESA has a similar function to epoetin alfa but is marketed separately in Europe.
- **Other Regions**: Epoetin beta is approved for use in various countries within Latin America, Asia, and Africa under similar brand names, primarily in settings where cost and access to alternative treatments may be limited.

Market availability of the proposed medicines

ESAs are widely available in high-income countries. Given the indications for use in chronic kidney disease, and the EML listing for this indication, market availability is possible in many LMICs, although the presence or absence of Universal Health Coverage (or health insurance) and the availability of health infrastructure may reduce access opportunities, especially in rural areas.

The possibility of broader availability in LMICs if a recommendation for addition of relevant ESAs to the Essential Medicines List for chemotherapy-induced anemia is made cannot be ignored.

Pharmacopial standards

ESAs are approved by regulatory agencies around the world, and if approved by those regulatory agencies are able to meet relevant pharmacopial standards.

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