I.5 Erythropoiesis stimulating agents – EML and EMLc

Reviewer summary	☐ Supportive of the proposal ☒ Not supportive of the proposal Justification (based on considerations of the dimensions described below): Anemia is commonly encountered in cancer patients, especially in those undergoing active chemotherapy with or without radiation therapy. Anemia affects 30–90% of cancer patients, and 40% of patients undergoing chemotherapy and followed for 6 months were found to be anemic with Hb<10.0 g/Dl. Overall, less than half of these patients were treated, mostly with erythropoietin-stimulating agents (ESA) or blood transfusion, which remain necessary when Hgb falls below 7–8 g/dL The pathogenesis of cancer-induced anemia (CIA) is complex and is often multifactorial. Disease-related blood loss can be encountered in gastrointestinal, genitourinary and gynecological cancers. Both radiotherapy and chemotherapy can inhibit erythropoiesis and may cause different degree of anemia. But significant portion of cancer patients with anemia have no identifiable cause; the anemia in this situation is classified as anemia of chronic illness, with activation of cytokines such as Interferon-γ, Interleukin-1 and tissue necrosis factor. These cytokines may suppress endogenous erythropoietin (EPO) production, impair iron absorption and utilization, and reduce erythroid precursor proliferation. Anemia, caused by the tumor or its therapy, can lead to reduced oxygen carrying capacity of the blood, further contributing to tumor hypoxia. It is well known that hypoxia may affect proliferation kinetics and cell cycle position. Studies have shown that sustained tumor hypoxia can additionally enhance malignant progression and may increase aggressiveness through clonal selection and genome changes. Additionally, cytotoxicity induced by radiotherapy and chemotherapy requires adequate oxygen levels, thus, tumor hypoxia can be a contributing factor in failure of the tumor to respond as it makes tumors resistant to both radiation and chemotherapy. Anemia, in cancer patients, can cause a wide range of symptoms. The severity of such symptoms depends on the degree of anemia, rapidity of its onset and existing comorbidities. Fatigue, one of the most common symptoms encountered in cancer patients, while cancer fatigue has different pathogenetic mechanisms, it is believed that anemia is a significant contributing factor and may adversely affect patients' quality of life (QOL). Aside from its important role in QOL issues, many studies have suggested that anemia is an independent factor that can adversely affect survival in cancer patients. The impact of anemia on survival can be attributed to delay in initiating or failure to complete chemotherapy regimens in a timely manner, but data regarding improved survival with correction of anemia is conflicting. Prior to the introduction of ESA, red blood cell (RBC) transfusion has been the only method of anemia treatment. Its benefit is marked in patients who are present with severe symptomatic anemia or bleeding, especially in patients undergoing surgery. In addition to cancer surgery, patients with severe anemia, usually at Hb level around 8.0 g/dL are commonly transfused. However, the decision to transfuse is not based on Hb level only. Existing comorbidities, rapidity of Hb decline and the nature and intensity of ongoing or planned chemotherapy or radiotherapy are important factors. The safety of blood transfusion has improved significantly over recent years. However, the risk of transmitting a known or an emerging pathogen is not zero. Furthermore, allogeneic blood may induce thrombotic as well as inflammatory responses; both may result in serious adverse events. Association between transfusions and both venous and arterial thromboembolism in hospitalized patients with cancer was highlighted in many studies. Indeed, the additional risk of RBC transfusion, in multivariate analysis, was significantly and independently associated with an increased risk of venous and arterial thromboembolism in comparison with the population who did not receive transfusion. Also, in large population-based studies and meta-analysis, RBC transfusions was found to be associated with an increased risk of cancer recurrence in comparison with matched not-transfused ones, and in some retrospective studies with a decreased overall survival. The ESAs are biological analogues of human erythropoietin. These agents mimic the action of EPO, by binding to EPO receptors on erythroid progenitors in the bone marrow, stimulating the proliferation and maturation of red blood cells. Major goals of ESAs use in CIA are sustained correction of anemia, improvement in QOL, and reducing need for RBC transfusions. Currently different short- and long-acting

	formulations of ESAs are available and were approved for CIA by FDA in 1993 (epoetin alfa) and 2002 (darbepoetin alfa). Many randomized clinical trials have shown that ESAs increased Hb values and reduced the number of RBC transfusions in CIA. Additionally, several studies and meta-analyses had shown that treatment with ESAs resulted in a statistically significant improvement in fatigue-related symptoms and QOL, was associated with fewer RBC transfusions and higher Hb rise than placebo. This was supported by a large Cochrane meta analysis, that analyzed more than 20.000 patients from 91 randomized clinical trials, which evaluated ESAs for therapy of CIA. Despite those clinical benefits of ESAs for CIA, on another side, several randomized clinical studies and systematic reviews demonstrated a **significantly higher risk of thromboembolic events** in patients receiving ESAs for CIA than in the placebo groups, **an inferior survival and worse cancer outcomes**. A meta-analysis found that ESA use was associated with a **higher mortality risk**, with a combined hazard ratio of 1.17 (95% CI 1.06–1.30). This was more significant in patients with higher baseline Hb values (i.e. Hb>10.0 g/ dL). Accordingly, in 2007, FDA published a **warning statement** limiting ESA use only when antineoplastic therapy is given for **palliative intent**. The FDA also mandates that ESA use requires informed patient consent under the Risk Evaluation and Mitigation Strategy (REMS) program. According to the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), the American Society of Hematology (ASH), guidelines ESAs are recommended for patients receiving palliative chemotherapy to reduce transfusion requirements and alleviate anemia symptoms. Guidelines recommend using the lowest effective dose of ESA (in combination with iron supplementation), for patients undergoing non-curative chemotherapy with Hgb levels below 10 g/dL. ESAs are not recommended for patients receiving curative chemotherapy due to the increased risks of thrombosis, tumor progression, and mortality. Even if, in 2017, the FDA determined that the REMS was no longer necessary because prescribers demonstrated acceptable knowledge of the risks of ESAs, FAD still published on website "*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".*

Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (**https://list.essentialmeds.org/**)	☐ Yes ☒ No ☒ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;)	☐ Yes ☒ No ☐ Not applicable
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;)	☒ Yes ☒ No ☐ Not applicable
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms?	☐ Yes ☒ No ☐ Not applicable

Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable
Are there any issues regarding price, cost-effectiveness and budget implications in different settings?	☒ Yes ☐ No ☐ Not applicable
Is the medicine available and accessible across countries? (e.g. shortages, generics and biosimilars, pooled procurement programmes, access programmes)	☒ Yes ☐ No ☐ Not applicable
Does the medicine have wide regulatory approval?	☐ Yes, for the proposed indication ☒ Yes, but only for other indications (off-label for proposed indication) ☐ No ☒ Not applicable