

# 5. ERYTHROPOIESIS STIMULATING AGENTS

Erythropoiesis stimulating agents (ESAs) boost the production of red blood cells and as such may play a role in optimising red cell mass (PBM Pillar 1) in specific groups of patients.

## Key messages

- ESAs are a method of optimising red cell mass (PBM Pillar 1)
- ESAs are an Authority item on the Pharmaceutical Benefits Scheme (PBS) with a limited indication.<sup>1</sup>
- ESAs have FDA prescribed Boxed Warnings for Chronic Kidney Disease (CKD), cancer and perisurgical use.<sup>2,3</sup>

## Clinical implications

- Routine use of ESAs are not recommended for cancer patients<sup>4</sup> or in the critically ill.<sup>5</sup>
- ESAs have been recommended or suggested in:
  - patients with Chronic Kidney Disease (CKD) and anaemia to avoid transfusion and relieve fatigue.<sup>4,7</sup>
  - surgical patients with anaemia of chronic disease.<sup>6,7</sup>
- Where an ESA is used, it must be combined with iron therapy.<sup>6</sup>
- In patients with CKD, ESAs to target a haemoglobin level of greater than 110 g/L increases the risk of serious adverse cardiovascular events and has not been shown to provide additional patient benefit.<sup>4</sup>
- If ESA therapy is prescribed outside the PBS indication, 'Individual Patient Approval' may be required.
- If ESA therapy is made locally available for management of patients with anaemia in the perioperative setting, a [local clinical guideline](#)<sup>6</sup> which includes indications, dosage, administration and monitoring should be developed.

## Background

ESAs include recombinant human erythropoietin (EPO) derivatives: epoetin alfa (Eprex®), epoetin beta (Neorecormon®), and epoetin lambda (Novicrit®); and chemically modified forms of EPO such as methoxy polyethylene glycol-epoetin beta (Mircera®) and darbepoetin alfa (Aranesp®).

In Australia, ESAs are available on the PBS as an Authority item for the "treatment of anaemia requiring transfusion, defined as a haemoglobin level of less than 100 g/L, where intrinsic renal disease, as assessed by a nephrologist, is the primary cause of the anaemia".<sup>1</sup> 'Individual Patient Approval' may be required if patients fall outside these guidelines.

In June 2011, the U.S. Food and Drug Administration (FDA) informed healthcare professionals of modified recommendations for more conservative dosing of ESAs in patients with CKD to improve the safe use of these drugs. FDA has made these recommendations because of data showing increased risks of cardiovascular events (stroke, thrombosis and death) with ESAs in this patient population.<sup>2</sup> Previous warnings exist for use in cancer patients and in the perisurgical setting.<sup>3</sup>

## FDA Boxed Warnings for ESAs:

### **WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE**

#### **Chronic Kidney Disease:**

- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL.
- No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.
- Use the lowest ESA dose sufficient to reduce the need for red blood cell (RBC) transfusions [see *Warnings and Precautions*].

#### **Cancer:**

- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers [see *Warnings and Precautions*].
- Because of these risks, prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology program to prescribe and/or dispense ESA to patients with cancer. To enroll in the ESA APPRISE Oncology Program, visit [www.esa-apprise.com](http://www.esa-apprise.com) or call 1-866-284-8089 for further assistance [see *Warnings and Precautions*].
- To decrease these risks, as well as the risk of serious cardiovascular and thromboembolic reactions, use the lowest dose needed to avoid RBC transfusions [see *Dosage and Administration*].
- Use ESAs only for anemia from myelosuppressive chemotherapy [see *Indications and Usage*].
- ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure [see *Indications and Usage*].
- Discontinue following the completion of a chemotherapy course [see *Dosage and Administration*].

#### **Perisurgery (EPOGEN/PROCRIT only):**

- Due to increased risk of Deep Venous Thrombosis (DVT), DVT prophylaxis is recommended [see *Dosage and Administration and Warnings and Precautions*].

## ESAs in cancer

In cancer patients with anaemia, the routine use of ESAs is not recommended because of the increased risks of mortality and thromboembolic events (MED-R2). If ESAs are used, iron status should be evaluated to guide adjuvant iron therapy (MED-PP12). ESAs are not currently listed on the PBS for reimbursement for patients with cancer.<sup>3</sup>

## ESAs in chronic heart failure

At the time of the systematic reviews for the PBM guidelines: Module 3 – Medical, there was evidence of reduced mortality with ESA therapy in a group of patients, including a large subset with diabetes and congestive cardiac failure.<sup>3</sup> In a separate systematic review the incidence of thromboembolic events, mortality and heart failure-related hospitalisations were not affected by ESAs<sup>4</sup> but there was a significant improvement in exercise tolerance. ESAs are not currently listed on the PBS for reimbursement for patients with cardiac failure.

## ESAs in chronic kidney disease

In anaemic patients with CKD, ESA therapy to a low to intermediate Hb target may be used to avoid RBC transfusion (MED-R4), and/or to relieve fatigue (MED-R5), after consideration of risks and benefits for the individual patient.<sup>4</sup> However a target Hb >130 g/L is not recommended because of increased morbidity (MED-R6). The CARI guidelines recommend a Hb target between 100–115 g/L.<sup>8</sup> The FDA warning advises that using ESAs to target a haemoglobin level of greater than 110 g/L increases the risk of serious adverse cardiovascular events and has not been shown to provide additional patient benefit.<sup>2</sup> In anaemic patients with non-dialysis dependent CKD, type 2 diabetes and a history of malignancy, the routine use of ESAs is not recommended because of the increased risk of cancer-related mortality (MED-R7).<sup>4</sup> ESA use is less effective in patients with chronic renal failure who have absolute or functional iron deficiency (MED-PP13).<sup>4</sup> For comprehensive information about ESA and iron therapy in patients with CKD, refer to [CARI iron guidelines](#) (MED-PP14).<sup>4</sup> Refer also to the [FDA warnings](#).<sup>2,3</sup>

## ESAs in critically ill patients

ESAs should not be routinely used in critically ill anaemic patients (CC-R2)<sup>4</sup>. This recommendation is based on the lack of effect of ESAs on mortality in a heterogeneous population of critically ill patients.<sup>4</sup>

## ESAs in perioperative patients

In surgical patients with anaemia of chronic disease (also known as anaemia of inflammation), ESAs may be indicated (PO-PP7).<sup>5</sup> Where indicated, it must be combined with iron therapy (PO-R5).<sup>5</sup> International guidelines recommend ESAs for orthopaedic surgery patients with anaemia, in whom nutritional deficiencies are absent or have been corrected.<sup>6</sup> FDA Boxed Warnings and local Product Information advise use of DVT prophylaxis in the perisurgical setting. However they are not currently listed on the PBS for this indication in Australia.

---

### References

1. The Schedule of Pharmaceutical Benefits. Accessed 10 September 2013. Available at: <http://www.pbs.gov.au/pbs/home>
2. FDA Drug Safety Communication: [Modified dosing recommendations to improve the safe use of Erythropoiesis-Stimulating Agents \(ESAs\) in chronic kidney disease](#).
3. Important Prescribing Information. [Updated Aranesp® \(darbepoetin alfa\) and EPOGEN®/PROCRIT® \(epoetin alfa\) United States Prescribing Information \(USPI\)](#). Accessed 14 October 2013.
4. National Blood Authority. [Patient Blood Management Guidelines: Module 3 – Medical](#). Australia, 2012.

5. National Blood Authority. [Patient Blood Management Guidelines: Module 4 – Critical Care](#). Australia, 2012.
6. National Blood Authority. [Patient Blood Management Guidelines: Module 2 – Perioperative](#). Australia, 2012.
7. Kozek-Langenecker SA, Afshari A, Albaladejo P, Santullano CA, De Robertis E, et al. [Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology](#). Eur J Anaesthesiol. 2013;30:270-382
8. McMahon LP, MacGinley R. KHA-CARI guideline: [biochemical and haematological targets: haemoglobin concentrations in patients using erythropoietin-stimulating agents](#). Nephrology 2012; 17(1):17-9.
9. WA Health. Patient Blood Management Program. [Erythropoietic Stimulating Agents: general guidelines \(PDF 157KB\)](#)

#### Additional Resources

- Council of Australian Therapeutic Advisory Groups (CATAC): Guiding Principles for the quality use of off-label medicines. Nov 2013 <http://www.catag.org.au/rethinking-medicines-decision-making/>