Executive summary

Introduction

Chemotherapy-induced anaemia (CIA), characterised by a reduction in haemoglobin (Hb) levels, is a debilitating condition associated with increased morbidity and fatigue. It is a frequent complication of cancer treatment and can adversely affect disease and treatment outcomes. Patients who develop CIA during the course of cancer treatment often experience additional clinical, economic and health-related quality of life (HRQoL) burdens. Therefore, the primary aim of treatment for CIA is to increase Hb levels, in order to reduce morbidity and fatigue, and improve HRQoL. Within the UK, best supportive care (BSC) consists primarily of red blood cell transfusion (RBCT), but can also include adjustment to chemotherapy and iron supplementation. There are a number of limitations associated with use of RBCT for the management of CIA; they provide only a transient increase in Hb levels, are associated with transfusion reactions and are contraindicated in a number of co-morbid conditions. RBCTs are also costly and burdensome to administer. There is therefore a clear unmet need for clinically and cost-effective treatments, available to all patients with CIA in the UK, that address these limitations and optimise cancer therapy.

A range of erythropoiesis-stimulating agents (ESAs) are available in the UK for the treatment of CIA (darbepoetin alfa, epoetin alfa, epoetin beta, epoetin theta and epoetin zeta); used either with or without supplemental iron (depending on the presence of an iron deficiency). Initially ESAs, including darbepoetin alfa, were licensed for use at Hb levels ≤11 g/dl, with target Hb levels not exceeding 13 g/dl. However, data showing a consistent, unexplained, excess mortality in CIA patients treated with ESAs, prompted changes to the ESA class license; decreasing the Hb level for treatment initiation to≤10 g/dl and amending Hb targets to 10-12 g/dl. Current NICE guidance (TA 142) only recommends the use of ESAs ‘in combination with intravenous iron as an option for the management of CIA in women receiving platinum-based chemotherapy for ovarian cancer who have symptomatic anaemia with a Hb of 8 g/100 ml or lower, or in patients who cannot be given blood transfusions and who have profound CIA that is likely to have an impact on survival’. Therefore, currently, ESAs are rarely used for the treatment of CIA in the UK.

Darbepoetin alfa is an ESA indicated for ‘the treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies who are receiving chemotherapy’. It is biochemically distinct from other epoetins, with a longer half-life, which allows flexible dosing options of both once-a-week (QW) and once-every-3-weeks (Q3W) administration. Darbepoetin alfa effectively increases Hb, reduces the requirement for RBCTs, and is well tolerated. It is more convenient than RBCTs, as it does not require hospital attendance for administration, which aligns with NHS policy to reduce hospitalisations. Darbepoetin alfa should therefore be made available as a treatment option for all patients with CIA within the UK, in accordance with its licensed indication.

Two of the six ESAs licensed for the treatment of patients with CIA in the UK are biosimilars – Binocrit and Retacrit (both epoetin alfa biosimilars). It is important for the

Institute to recognise that biosimilars are not identical to originators and to ensure alignment with the recommendations of both the European Commission and Medicines and Healthcare products Regulatory Agency (MHRA) on biosimilars; with clear statements regarding safety, traceability and the need to avoid automatic substitution.

Selection of comparator

BSC is the relevant comparator for the broad CIA patient population. ESAs are only recommended by TA 142 in specific subgroups of CIA patients. However, UK patient numbers are small for each of these subgroups, with no available clinical evidence comparing darbepoetin alfa versus other ESAs. Therefore, for the purposes of this darbepoetin alfa submission, other ESAs are not considered a comparator to darbepoetin alfa.

Key clinical evidence

Summary of the evidence base: The key clinical evidence comes from nine randomised controlled trials (RCTs) evaluating darbepoetin alfa versus BSC (placebo, no treatment or usual care), of which four were new and not considered in the previous NICE TA 142. None of the darbepoetin alfa studies were entirely aligned with the current UK license, (specifically regarding the treatment initiation of ≤10 g/dl or the Hb treatment targets of 10–12 g/dl). Therefore, studies were included which used a licensed starting dose (500 µg or 6.75 µg/kg Q3W or 2.25 µg/kg QW) even if they did not align with other criteria stipulated by the current license regarding Hb levels. All nine trials evaluating darbepoetin alfa versus control fulfilled this criterion and formed the basis of the meta-analysis.

Meta-analysis – Anaemia-related outcomes: The meta-analysis of all darbepoetin alfa trials using a licensed starting dose indicated significant effects favouring darbepoetin alfa in comparison with BSC for anaemia-related outcomes: Haematological response - relative risk (RR) 3.67 (95% CI 2.73, 4.94, p <0.00001); Hb change - weighted mean difference (WMD) 1.06, (95% CI 0.86, 1.26, p <0.00001); Number of patients requiring a RBCT - RR 0.56, (95% CI 0.49, 0.64, p <0.00001) and the mean number of RBC units transfused WMD -1.25 (95% CI -1.84, -0.66, p <0.0001).

Meta-analysis – Tumour-related outcomes: A single darbepoetin alfa trial assessing complete response (CR) reported no significant difference from control with respect to CR (RR 0.99, 95% CI 0.89, 1.09, p=0.84). A meta-analysis of four darbepoetin alfa trials showed no significant differences between darbepoetin alfa and control for overall survival (HR 0.88, 95% CI 0.72 to 1.06, p=0.18), with no significant evidence that darbepoetin alfa resulted in an increased risk of death.

Safety analysis

To date, exposure to darbepoetin alfa worldwide is over 4.4 million patient-years, with a safety profile consistent with the current Summary of Product Characteristics (SmPC). A meta-analysis of key safety outcomes for darbepoetin alfa showed no significant differences from control in the RR of all adverse events (AEs); RR 1.03, (95% CI 0.95, 1.12, p=0.51) or of serious adverse events (SAEs) (RR 1.12, 95% CI 0.99, 1.28, p=0.08). However, there was a significant increase in RR of thrombotic events for darbepoetin alfa versus control (RR 2.15, 95% CI 1.41, 3.28, p <0.0004). These results are consistent with the information on expected adverse drug reactions contained within the darbepoetin alfa SmPC.

Although questions regarding safety have arisen in some studies conducted outside of the licensed indication or Hb recommendations for ESAs (including darbepoetin alfa), the weight of evidence supports that ESA benefits outweigh the risks of an increased risk of mortality or adverse tumour outcomes, when prescribed within the approved indication of anaemia in patients with non-myeloid malignancy receiving chemotherapy. Definitive studies to address these safety questions are ongoing. The Risk Management Plan (RMP) and current SmPC are considered sufficient by the regulators to address this potential risk in patients receiving ESAs (including darbepoetin alfa).

Conclusion

For the treatment of patients with CIA, the efficacy of darbepoetin alfa has been clearly demonstrated versus BSC, the current standard of care for patients with CIA in the UK; supported by evidence from a meta-analysis of nine relevant head-to-head RCTs. Safety data for darbepoetin alfa show a safety profile consistent with the current SmPC.