(1) Does the application adequately address the issue of the public health need for the medicine?

Yes ☒ No ☐

Please provide brief details:

Chronic kidney disease is a worldwide public health issue affects approximately 8-16% of the adult population worldwide. The overall lifetime incidence of chronic kidney disease rises with age, with approximately 50% of Stage 3a+ incidents occurred after age 70 years. The overall lifetime incidence of end-stage renal disease has been estimated at 3.6%. The incidence and prevalence of chronic kidney disease seem remarkably consistent globally, though not always well documented, whereas the distribution of those receiving renal replacement therapies (dialysis and transplantation) varies by country. About 2.2 million people receive dialysis globally, projected to be 5.4 million by 2030.

Anemia is common in patients with chronic kidney disease. The landmark study by Obrador et al showed that among predialysis patients, 68% of those with advanced chronic kidney disease who required renal replacement therapy had a haematocrit less than 30 mg/dL; of these, 51% of patients had a haematocrit less than 28 mg/dL. Furthermore, although anemia is not as common in earlier stages of chronic kidney disease, patients with stage III disease have a prevalence of concurrent anemia of 5.2%, whereas those with stage IV disease have a prevalence of concurrent anemia of 44.1%. Prevalence of anemia by stage of chronic kidney disease (CKD), adapted from Stauffer 2014 is Stage 1- 8.4%, Stage 2- 12.2%, Stage 3 -17.4%, Stage 4 - 50.3%, and Stage 5 - 53.4%

Chronic kidney disease is associated with decreases in cardiac and renal functions, quality of life, and poses a significant clinical and economic burden on healthcare systems. Anemia is also associated with a high prevalence of cardiovascular diseases in renal patients, and their consequent higher morbidity and mortality. Anemia has been shown to be an independent risk factor for increased cardiovascular morbidity and mortality and cardiovascular diseases are reported to account for more than 50% of deaths in these patients. In children iron deficiency and Hb lower than 11.8 g/dL (118 g/L) have also been associated with impairment in cognition function.

Severe anemia of chronic renal failure is associated with left ventricular dilation, possibly left ventricular hypertrophy (LVH), and high output cardiac failure. Left ventricular geometry and LVH are important predictors of subsequent mortality and cardiac complications. Correction of anemia with erythropoietin (EPO) has been shown to significantly improve quality of life, exercise tolerance, work capacity, and LVH.
In summary, if haemoglobin levels are maintained at the recommended target goals, these translate into decreased LVH, decreased hospitalizations related to cardiovascular disease, and decreased mortality from cardiovascular disease. Aside from these findings, however, higher quality of life (QOL) scores are also obtained: less easy fatigability and fatigue symptoms, improved physical well-being and exercise tolerance, and improved functional well-being.

(2) Have all important studies/evidence of which you are aware been included in the application?
   Yes ☒ No ☐

   Please provide brief comments on any relevant studies that have not been included:
   No relevant studies not included in this application, interestingly in this application, not only looked available evidence in literatures, but conducted their own systematic review on available randomized control trials and other relevant data sources, to retrieve this evidence, search performed in MedLine, EMBASE, and the Cochrane Library up to November 2016, using the search strategies reported. Included up-to-date systematic reviews of randomized controlled trials (RCTs) and other types of evidence syntheses (e.g. health technology assessment [HTA] reports, clinical guidelines if developed following a systematic approach) and pharmacoeconomic analyses comparing erythropoietin’s (epoetin alfa, beta, theta, zeta), darbepoetin alfa, and CERA. The evidence on the effectiveness and safety of ESAs, including branded medicinal products and biosimilars, for the treatment of anemia in end-stage renal disease, including evidence on adults and children with anemia due to stage 5 chronic kidney disease undergoing dialysis. The findings prepared per the GRADE approach for assessment of evidence quality and strength of recommendations (GRADE 2016), this approach improved the quality of evidence in the application.

(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?
   Yes ☒ No ☐

   (a) Briefly summarise the reported benefits (e.g. clinical versus surrogate) and comment, where possible, on the actual magnitude of benefit associated with use of the medicine:

   In Adult
   Comparing epoetin alfa and beta Vs. placebo/no treatment/standard care the review demonstrated that there are no differences in all-cause mortality and major cardiovascular events (stroke, myocardial infarction) presumably because of a paucity of data on these outcomes. Epoetin alfa and beta consistently reduced the risk of requiring blood transfusions. Epoetin alfa and beta do not appear to affect the risk of vascular access thrombosis but increase the risk of hypertension. The quality of evidence was low for all-cause mortality, major cardiovascular events, and vascular access thrombosis attributed by unclear risk of selection bias and the imprecision of the estimates, however, the effect of epoetin alfa and beta in reducing the number of blood transfusions and increasing risk of
hypertension was supported by high-quality evidence; the results seem to be consistent with industry-sponsored and other sponsorship trials. There was no evidence of a difference between darbepoetin and other ESAs (epoetin alfa, beta, CERA) in terms of all-cause mortality, major cardiovascular events (stroke, myocardial infarction), hypertension, vascular access thrombosis and Hb levels, however demonstrated trend that darbepoetin reduces the risk of requiring blood transfusions compared to epoetin alfa but not to CERA, the quality of evidence was very low to moderate mainly because of the unclear risk of selection bias, the imprecision of the estimates and the suspicion of selective reporting of outcomes. Noteworthy, the benefit of darbepoetin in reducing blood transfusions was high-quality evidence. These results should be interpreted cautiously due to the fact were largely driven by industry-sponsored trials. CERA appears to be like epoetin alfa and beta in terms of all the outcomes evaluated. However, the quality of evidence supporting these findings was very low and low because of the unclear risk of selection bias, the imprecision of the estimates and the suspicion of selective reporting of outcomes. These results were largely driven by industry-sponsored trials. There were no differences between the originator epoetin alfa and its biosimilars in terms of all-cause mortality, major cardiovascular events (stroke, myocardial infarction), blood transfusions, and vascular access thrombosis. The risk of hypertension seemed lower with biosimilars. The quality of evidence was low because of the unclear risk of selection bias and the imprecision of the estimates, apart from the findings on hypertension, showed evidence of moderate quality due to unclear risk of selection bias only. These results appear to be consistent between industry-sponsored and other sponsorship trials.

In Children
Generally, evidence in children scarce and of low quality, and extrapolated from evidence in adults, providers caring for adult and pediatric patients with chronic kidney disease largely share the same concerns regarding the diagnosis and management of anemia. Morris et al compared ESA therapy (target Hb >10 g/dL) or placebo in a blinded crossover trial of 11 children aged between 2.3 and 12.3 years, undergoing peritoneal or hemodialysis. ESA therapy was associated with partial correction of an elevated cardiac index by six months and a significant reduction in left ventricular mass by 12 months. The most robust evidence for using ESA products in children is related to erythropoietin alfa and beta, with some preliminary data on darbepoetin. In children with chronic kidney disease stages 4 and 5, darbepoetin alfa compared to epoetin had uncertain effects on the need for blood transfusion and risk of progression to renal replacement therapy, all-cause mortality, hypertension, dialysis vascular access thrombosis, exceeding Hb target level and injection site pain, as well as Hb levels during treatment (Palmer 2014-darbe).

Children in the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) database from 1992 to 2001 with Hb lower than 9.9 g/dL compared with those with Hb more than 9.9 g/dL had a high risk for mortality (adjusted relative risk, 1.52; 95% confidence interval [CI], 1.03 to 2.26). Patients with more severe anemia also had an increased risk of hospitalization.
In a multicenter single-arm interventional trial evaluating 22 children with chronic kidney
disease (4 months to 16 years) treatment of anemia with recombinant erythropoietin was
associated with a significant increase in intelligence quotient, although the relative increase
in Hb levels was small (Hb baseline, 9.2 ± 1.6 versus final, 9.7 ± 1.7 g/dL) (Burke 1995 and
KDOQI 2006)

(b) Is there evidence of efficacy in diverse settings and/or populations? Please
provide brief details:

In this application not find evidence of efficacy in diverse settings and/or populations except
on targeted population.

(4) Has the application adequately considered the safety and adverse effects of
the medicine? Are there any adverse effects of concern, or that may require
special monitoring?

Yes ☒ No ☐

Please provide brief details:
There is concern of developing PRCA and severe anemia, with or without cytopenia,
associated with neutralizing antibodies to erythropoietin has been reported, the findings
prompted the FDA to issue a warning in all the proprietary ESAs. Recommended
multinational, National surveillance of adverse effects

(5) Please comment on the overall benefit to risk ratio of the medicine (e.g.,
favourable, uncertain etc).

All ESAs are effective in correcting the anemia of end-stage renal disease in patients on
dialysis especially in terms of reducing the number of blood transfusions. All ESAs,
including biosimilars, appears to have similar benefit/adverse profile

ADDITIONAL CONSIDERATIONS:

(6) Are there special requirements or training needed for the safe, effective
and/or appropriate use of the medicine?

Yes ☒ No ☐

Please provide brief details:
ESAs are administered at hospital/clinic settings, requiring close monitoring to achieve
treatment haemoglobin goal target with dose adjustment accordingly, as well surveillance of
adverse effects
Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)

Yes ☐ No ☒

Please provide brief details:

ESAs are licensed globally indicated for “treatment of symptomatic anemia associated with chronic kidney disease” Regulatory Authority in Australia, Canada, European Union and US emphasising specific information on the pediatric indication. Biosimilar erythropoietins are available in the market after expiry of patent protection for epoetin alfa in Europe in 2007, Currently registered in Europe, US, Canada, Australia and India.

Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?

Yes ☒ No ☐

Please provide brief details:

Included on guideline for treatment of Anaemia in chronic kidney disease in adult and children

Please comment briefly on issues regarding cost and affordability of this medicine.

The cost of originators is high; however, expected that with availability of the biosimilars of epoetin in the market mighty have an impact on drug prices. Price differences between biosimilars and originators has been broadly estimated between 10 and 34%, although current evidence is limited Cost-saving should be weighted and evaluated considering the different penetration of biosimilars in different countries

Any additional comments? No

Please frame the decisions and recommendations that the Expert Committee could make.

Chronic kidney disease is a worldwide public health issue affects approximately 8-16% of the adult population worldwide Anemia is one of the most serious complications of chronic kidney disease and end-stage renal disease. Anemia is also associated with a high prevalence of cardiovascular diseases in renal patients, and their consequent higher morbidity and mortality. Anemia has been shown to be an independent risk factor for increased cardiovascular morbidity and mortality and
cardiovascular diseases are reported to account for more than 50% of deaths in these patients.

Maintaining haemoglobin levels at the recommended target goals, these translate into decreased LVH, decreased hospitalizations related to cardiovascular disease, and decreased mortality from cardiovascular disease. Moreover, higher quality of life (QOL) scores are also obtained: less easy fatigability and fatigue symptoms, improved physical well-being and exercise tolerance, and improved functional well-being.

The high quality of clinical evidence on the effect of all ESAs in reducing the number of blood transfusions, and lack of statistically significant difference in all-cause mortality, major cardiovascular events (stroke, myocardial infarction), hypertension, vascular access thrombosis and Hb levels. All ESAs including biosimilars are effective in correcting the anemia of end-stage renal disease in patients on dialysis and significantly reduce the number of blood transfusions, with comparative similar benefit/adverse profile.

I support application request including erythropoietin-stimulating agents (ESA) in the WHO Model List of Essential Medicines (EML) and Model List of Essential Medicines for Children (EMLc) for the treatment of anemia in children, young people and adult patients with end-stage renal disease requiring dialysis.

(12) References (if required)