PUBLIC SUMMARY DOCUMENT
Product: Methoxy polyethylene glycol-epoetin beta, solution for injection, 30 micrograms in 0.3 mL, 50 micrograms in 0.3 mL, 75 micrograms in 0.3 mL, 100 micrograms in 0.3 mL, 120 micrograms in 0.3 mL, 200 micrograms in 0.3 mL and 360 micrograms in 0.6 mL, single use pre-filled syringe, Mircera®
Sponsor: Roche Products Pty Limited
Date of PBAC Consideration: November 2009

1. Purpose of Application

To request a Section 100 (Highly Specialised Drugs Program) listing for treatment of anaemia requiring transfusion, defined as a haemoglobin level of less than 100 g per litre, where intrinsic renal disease, as assessed by a nephrologist, is the primary cause of the anaemia.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Methoxy polyethylene glycol-epoetin beta was registered by the TGA on 28 July 2009 for the treatment of anaemia associated with chronic kidney disease (CKD).

4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drugs) Private hospital authority required
Treatment of anaemia requiring transfusion, defined as a haemoglobin level of less than 100g per litre, where intrinsic renal disease, as assessed by a nephrologist, is the primary cause of the anaemia.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Chronic kidney disease (CKD) is marked by long-term and usually irreversible loss of kidney function and may further deteriorate into end-stage kidney disease, and renal replacement therapy in the form of dialysis or transplantation is required for survival. Anaemia is a complication of chronic kidney disease.

Methoxy polyethylene glycol-epoetin beta would provide an alternative treatment for anaemia associated with CKD.

6. Comparator

The submission nominated darbepoetin alfa as the main comparator and epoetin alfa and epoetin beta as the secondary comparators. The PBAC considered this appropriate.

7. Clinical Trials

The submission presented six randomised trials comparing methoxy polyethylene glycol-epoetin beta (MPGE) and existing Erythropoiesis Stimulating Agents (ESAs) over 24 to 36

weeks in patients with anaemia of chronic kidney disease. Two are correction trials (BA16736, BA16738) in pre-dialysis patients or patients new to dialysis, and four are maintenance trials (BA16739, BA16740, BA17283, BA17284) in patients already on treatment with an existing ESA. Two trials (BA16738, BA17283) used darbepoetin as control, and the other four trials used epoetin alfa or beta.

The table below details the published trials presented in the submission:

Trial ID / First author	Protocol title / Publication title	Publication citation
Direct randomised trials		
BA16736 Klinger M,et al	Efficacy of intravenous methoxy polyethylene glycol-epoetin beta administered every 2 weeks compared with epoetin administered 3 times weekly in patients treated by haemodialysis or peritoneal dialysis: A randomised trial	American Journal of Kidney Disease 2007;50(6):989-1000
BA16738 Macdougall IC, et al.	CERA corrects anaemia in patients with chronic kidney disease not on dialysis: results of a randomised clinical trial.	Clinical Journal of the American Society of Nephrology 2008;3(2):337-347
BA16739 Levin NW, et al	Intravenous methoxy polyethylene glycol-epoetin beta for haemoglobin control in patients with chronic kidney disease who are on dialysis: a randomised non-inferiority trial (MAXIMA).	Lancet 2007;370:1415-1421
BA16740 Sulowicz W, et al.	Once-monthly subcutaneous CERA maintains stable haemoglobin control in patients with chronic kidney disease on dialysis and converted directly from epoetin one to three times weekly.	Clinical Journal of the American Society of Nephrology 2007;2: 637-646
BA17283 Canaud B, et al.	Intravenous CERA maintains stable haemoglobin levels in patients on dialysis previously treated with darbepoetin alfa: results from STRIATA, a randomised phase III study.	Nephrology Dialysis Transplantation 2008;23:3654-3661
B17284 Spinowitz B, et al.	CERA maintains stable control of haemoglobin in patients with chronic kidney disease on dialysis when administered once every two weeks.	American Journal of Nephrology 2008;28 (2):280-289

8. Results of Trials

The primary outcome in the correction trials was the proportion with a haemoglobin response (defined as a Hb increase of at least 1.0 g/dL to a level of at least 11 g/dL). The primary outcome in the maintenance trials was a change in Hb level; differences between MPGE and other ESAs were tested using a non-inferiority margin of -0.75 g/dL. Results were pooled using a random effects meta-analysis. Trial BA16738 used both Hb response rate and change in Hb as primary outcomes.

There were no statistically significant differences in responder rates and relative risk between MPGE and the comparator ESAs (epoetin in Trial BA 16736 and darbepoetin in Trial BA16738).

In all trial comparisons the mean difference in the change in Hb exceeded the non-inferiority margin of -0.75 g/dL.

There was no difference between MPGE and control ESA in the need for transfusion in the trials. In the correction trials there was slower time-to-target haemoglobin with MPGE (57 days vs 31 days in Trial BA16736; and 43 days vs 29 days in Trial 16738, both $p<0.0001$, using the log rank test).

The toxicity profiles of MPGE and the comparator ESAs were generally similar. However, it was also noted that MPGE may be associated with more serious gastro-intestinal bleeds, as there was an excess of serious gastrointestinal haemorrhage events with MPGE (21/1789 vs 2/948).

For PBAC's view see Recommendation and Reasons.

9. Clinical Claim

The submission described MPGE as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over marketed erythropoietin stimulating agents.

For PBAC's view see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis. Equi-effective doses were presented separately using darbepoetin as comparator and using epoetin as comparator and were derived from the clinical trial data.

Where data were derived from more than one trial, estimates were weighted by trial size.

For PBAC's view see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year accounting for market share was estimated to be 10,000 – 50,000 in Year 5.

The net financial cost per year to the PBS was estimated to be zero based on the assumption that MPGE is substituted for existing ESAs and a market share approach is used to allocate prices based on equi-effective doses.

12. Recommendation and Reasons

The PBAC recommended the listing of methoxy-polyethylene glycol-epoetin beta (MPGE) under Section 100 (Highly Specialised Drugs Program) for treatment of anaemia requiring transfusion, defined as a haemoglobin level of less than 100 g per litre, where intrinsic renal disease, as assessed by a nephrologist, is the primary cause of anaemia, on a cost minimisation basis compared with darbepoetin alfa and epoetin.

The calculation of equi-effective doses depends on the clinical setting (correction vs maintenance) and route of administration. The PBAC considered that there is substantial uncertainty in these estimations of equi-effective doses as they differ depending on the setting (correction versus maintenance), the comparator used, and the trials used. These trial data give rise to dose relativities for darbepoetin and epoetin that are different from those previously accepted by the PBAC. The PBAC recommended that the cost per day for the

Erythropoeisis Stimulating Agents (ESAs) should be the same, taking into account the different settings of use.

The PBAC noted that, because there is less frequent dosing with MPGE, it takes longer to achieve target haemoglobin level (longer half-life enables once-monthly dosing regimen) which was not regarded as a clinically important difference. Patients treated with MPGE may need to take more iron supplements (greater incidence of relative iron deficiency for MPGE treated patients compared to other ESAs; although in this clinical context almost all patients are on iron supplementation. It was also noted that MPGE may be associated with more serious gastro-intestinal bleeds.

Recommendation:
METHOXY-POLYETHYLENE GLYCOL-EPOETIN BETA, solution for injection, 30 micrograms in 0.3 mL, 50 micrograms in 0.3 mL, 75 micrograms in 0.3 mL, 100 micrograms in 0.3 mL, 120 micrograms in 0.3 mL, 200 micrograms in 0.3 mL and 360 micrograms in 0.6 mL, single use pre-filled syringe

Restriction:	Section 100 (Highly Specialised Drugs Program) Private hospital authority required Treatment of anaemia requiring transfusion, defined as a haemoglobin level of less than 100 g per L, where intrinsic renal disease, as assessed by a nephrologist, is the primary cause of the anaemia.
Pack size:	1

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor has no further comment.